

# Nanotechnology-Driven Delivery of Capecitabine for Advanced Colon Cancer Therapy: A Review

Apeksha Saraf, Gajendra Pratap Choudhary, Nidhi Dubey, Lokesh Pancholi\*

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshila Parisar, Indore, Madhya Pradesh 452001

Corresponding Author\*

Mail id - lp1995lokesh@gmail.com

## Abstract

Colon cancer continues to be a significant international health challenge, ranking as the third most frequently diagnosed cancer and a principal cause of cancer-related deaths worldwide. capecitabine, an oral prodrug of 5-fluorouracil (5-FU), plays a critical role in treatment plans for both adjuvant and metastatic colon cancer. Nevertheless, its clinical effectiveness is markedly hindered by its irregular oral absorption, rapid systemic metabolism, dose-dependent side effects (particularly hand-foot syndrome, diarrhea, and myelosuppression), and the unavoidable onset of chemoresistance. The introduction of nanotechnology in oncology has sparked a significant shift, providing advanced solutions to these persistent issues. Nanotechnology driven drug delivery systems (NDDS) designed for capecitabine such as polymeric nanoparticles, lipid-based carriers, inorganic nanostructures, dendrimers, and micellar systems offer improved drug stability, enhanced pharmacokinetic properties and therapeutic efficacy. This comprehensive review critically examines the design strategies, mechanistic advantages, and therapeutic outcomes associated with various capecitabine-loaded nanocarrier systems for colon cancer treatment.

**Keywords:** Capecitabine, Colon Cancer, Nanotechnology, Targeted Drug Delivery, Nanocarriers.

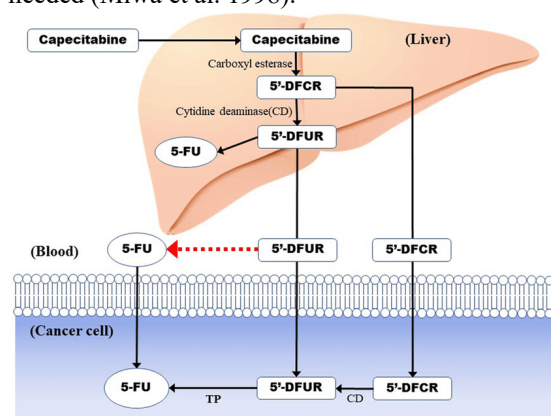
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## 1. Introduction

Colorectal cancer (CRC) poses a significant global challenge in oncology. The latest GLOBOCAN data shows approximately 1.93 million new cases and 935,000 annual deaths, reaffirming its status as the third most common cancer and the second leading cause of cancer-related deaths worldwide (Sung et al., 2021; Bray et al., 2018). The treatment approach for colon cancer is diverse, with surgical removal providing a potential cure for localized disease. However, for cases that are advanced, metastatic, or recurrent, systemic chemotherapy is essential (Van Cutsem et al., 2016). In this setting, fluoropyrimidines primarily 5-fluorouracil (5-FU) and its orally available prodrug, capecitabine, serve as the cornerstone of therapy, either as a standalone treatment or in combination regimens like XELOX (with oxaliplatin) or XELIRI (with irinotecan) (Twelves et al., 2005; Schmoll et al., 2007).

Capecitabine (N<sup>4</sup>-pentylloxycarbonyl-5'-deoxy-5-fluorocytidine) is a well-designed prodrug activated by tumors. It undergoes a sequential triple-enzymatic conversion in the body to produce its active form, 5-FU. This process is intentionally structured for selectivity toward tumors wherein hepatic carboxylesterase first transforms capecitabine into 5'-deoxy-5-fluorocytidine (5'-DFCR) (Fig.1). Next, cytidine deaminase, which is found in both the liver and tumors, converts it to 5'-deoxy-5-fluorouridine (5'-DFUR) (Schuller et al. 2000). The final and crucial step is conducted by thymidine phosphorylase (dThdPase), an enzyme that is often overexpressed in colon cancer and other solid tumors, leading to the formation of the active

and cytotoxic drug, 5-FU. This targeted activation approach aims to enhance the therapeutic index by focusing the generation of 5-FU where it is most needed (Miwa et al. 1998).



**Fig.1 Depiction of Mechanism of Capecitabine**

Despite its sophisticated biochemical design, the clinical effectiveness of capecitabine is considerably limited by several inherent challenges. Firstly, its oral administration results in inconsistent and incomplete bioavailability (roughly 70-80%), influenced by individual variations related to diet, gastrointestinal dynamics, and extensive first-pass metabolism (Gieschke et al. 2003; Reigner et al. 1998). Secondly, the nonspecific systemic distribution of capecitabine and its metabolites can cause serious, dose-limiting side effects. Moreover, the hand-foot syndrome (palmar-plantar erythrodysesthesia) occurs in a significant number of patients (up to 60%) and other common issues

such as diarrhoea, myelosuppression, and fatigue often require dose adjustments or halting treatment, which can diminish treatment effectiveness (Cassidy et al. 2002; Hoff et al. 2001). Thirdly, the pathophysiological tumor microenvironment (TME) is characterized by low oxygen levels, increased interstitial fluid pressure (IFP), abnormal blood vessels, and a dense extracellular matrix (ECM) that creates significant physical obstacles, hindering uniform drug penetration and distribution (Jain 2013 and Heldin et al. 2004). Lastly, the emergence of intrinsic and acquired resistance mechanisms, including the upregulation of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and ATP-binding cassette (ABC) efflux transporters, often leads tumors to become resistant to treatment, resulting in therapeutic failure (Salonga et al. 2000 and Longley et al. 2006).

The emergence of nanotechnology within the field of biomedical science has marked the beginning of a significant shift in oncology therapies. Nanotechnology-based drug delivery systems (NDDS) serve as advanced carriers for therapeutic agents (Etheridge et al. 2013). This review offers an in-depth and critical analysis of the latest advancements in NDDS designed for the targeted delivery of capecitabine in colon cancer.

## **2. Limitations of Conventional Therapies containing Capecitabine**

### **2.1. Pharmacokinetic and Biodistribution Challenges**

After oral ingestion, capecitabine is mainly absorbed through passive diffusion across the intestinal lining, with possible assistance from nucleoside transporters (Mackean et al. 1998). Its bioavailability is not only incomplete but also shows significant variability among patients (Twelves et al. 1999). The 5-FU undergoes extensive metabolic conversion in both the liver and peripheral tissues leading to the systemic distribution of the drug and its active byproducts (Reigner et al., 1999). Its plasma half-life remains exceedingly brief approximately 10 to 20 minutes. This rapid clearance necessitates sustained intratumoral drug exposure to maximize anticancer efficacy. In addition, conventional bolus or intermittent dosing strategies are fundamentally incapable of meeting this requirement and as a result they generate a paradoxical and clinically problematic pharmacokinetic profile characterized by dangerously elevated peak concentrations, toxicity and subtherapeutic trough levels that compromise therapeutic effect (Diasio and Harris, 1989).

### **2.2. Spectrum of Dose-Limiting Toxicities**

The anticancer activity of capecitabine is ultimately mediated through its active metabolite, 5-fluorouracil (5-FU), which exerts its cytotoxic effects via well-established molecular mechanisms. The cytotoxic effects of 5-FU stem from its two-fold mechanism of action: (i) the incorrect incorporation

of its metabolites viz. fluorouridine triphosphate (FUTP) and fluorodeoxyuridine triphosphate (FdUTP) into RNA and DNA, which disrupts the normal functioning of nucleic acids and leads to strand breakage; and (ii) the strong inhibition of thymidylate synthase (TS) by fluorodeoxyuridine monophosphate (FdUMP), resulting in the depletion of intracellular thymidine levels that are crucial for DNA replication and repair (Parker and Cheng, 1990 and Santi et al. 1974). Since these mechanisms are essential for all rapidly dividing cells, collateral damage to healthy tissues that have high turnover rates such as the bone marrow, gastrointestinal lining, and skin is unavoidable. Hand-foot syndrome, a specific skin toxicity linked to capecitabine, is believed to occur due to the leakage of the drug or its metabolites into the capillaries of the palms and soles, leading to localized inflammation, redness, peeling, and pain, which significantly affects patient's quality of life and their willingness to adhere to treatment (Nagore et al. 2000).

### **2.3. Tumor Microenvironment as a Formidable Barrier**

Solid tumors consist of more than just collections of malignant cells; they represent intricate, diverse ecosystems that include cancer-associated fibroblasts (CAFs), immune cells, disorganized and abnormal blood vessels and a densely packed, cross-linked extracellular matrix (ECM) (Joyce and Fearon, 2015). This abnormal structure leads to significantly increased interstitial fluid pressure (IFP), which hinders the movement of therapeutic agents from the bloodstream into the tumor tissue (Jain, 1987). The areas of low oxygen and uneven blood flow create refuge spots where drug infiltration is limited, allowing evolution of resistant cell populations (Vaupeul et al. 1989).

### **2.4. Molecular Underpinnings of Chemoresistance**

**Modifications in Drug Metabolism:** Increased levels of dihydropyrimidine dehydrogenase (DPD), which is the primary enzyme responsible for the breakdown of 5-FU, lead to faster inactivation of the drug (Di Paolo, 2004). The higher concentrations of thymidylate synthase (TS) or mutations that decrease the binding affinity of FdUMP reduce the effectiveness of TS inhibition (Popat et al. 2004).

**Improved DNA Damage Repair:** The increased activity of essential DNA repair mechanisms, such as base-excision repair (BER) and mismatch repair (MMR), can mitigate the DNA-damaging impact of 5-FU incorporation (Meyers et al. 2001).

**Disruption of Apoptotic Mechanisms:** The genetic and epigenetic changes that interfere with pro-apoptotic signaling (such as TP53 mutations and overexpression of Bcl-2) allow cancer cells to dodge the programmed cell death induced by chemotherapy.

**Active Drug Efflux:** The upregulation of ATP-binding cassette (ABC) efflux transporters, notably P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP), effectively pumps drugs out of cancer cells, representing a key mechanism of multidrug resistance (MDR) (Gottesman et al., 2002).

Nanotechnology-based drug delivery systems are specifically designed to address these limitations. The nanocarriers can enclose and protect CAP during its travel through the body, significantly modify its distribution to prioritize accumulation in tumors, improve its ability to penetrate the tumor microenvironment, and can be combined with agents that directly address particular resistance mechanisms (Torchilin, 2012 and Ferrari, 2005).

### 3. Nanotechnology based drug delivery system (NDDS)

Nanotechnology-based drug delivery systems (NDDS) are tiny carriers, ranging from 1 to 1000 nanometers in size, that encapsulate, protect, and deliver therapeutic agents precisely to target sites within the body. Their application in cancer therapy offers several strategic benefits over conventional chemotherapy. A primary advantage lies in augmenting the dissolution and systemic absorption of hydrophobic compounds like capecitabine, ensuring that pharmacologically active levels are consistently attained (Peer et al., 2007). Nanocarriers physically shield encapsulated drugs from enzymatic breakdown and chemical degradation, extending circulation half-life and minimizing first-pass metabolism. The structural anomalies of tumor vasculature, characterized by extensive fenestrations and compromised lymphatic clearance, facilitate the passive homing of these nanocarriers, resulting in a marked 3- to 8-fold increase in tumoral drug deposition relative to healthy parenchyma (Matsumura & Maeda, 1986). Furthermore, functionalization with high-affinity moieties, such as folate, monoclonal antibodies, or RGD peptides, significantly elevates tumor selectivity by initiating receptor-mediated internalization, thereby circumventing membrane-bound drug efflux mechanisms (Low & Kularatne, 2009). "Intelligent" nanoconstructs equipped with stimuli-labile components responsive to acidic pH gradients, enzymatic overexpression, redox imbalances, or exogenous physical stimuli ensure that cytotoxic payloads are liberated almost exclusively at the pathological site, drastically curtailing systemic adverse events (Mura et al., 2013). Additionally, these platforms permit the simultaneous transport of combinatorial drug regimens or siRNA molecules to extinguish resistance pathways (Davis et al., 2010) and the incorporation of contrast agents allowing non-invasive surveillance of drug biodistribution and therapeutic outcomes (Kelkar & Reineke, 2011).

Despite these marked advantages, translational bottlenecks persist. The propensity for nanomaterials to sequester in reticuloendothelial organs raises concerns regarding chronic hepatotoxicity, splenic damage, nephropathy and uncertainties about the long-term clearance of non-biodegradable inorganic cores (Oberdorster et al., 2005). Reproducible large-scale production under stringent GMP conditions remains a formidable technical barrier, as minor deviations in synthesis drastically affect batch uniformity, particle size distribution and drug encapsulation efficiency (Barenholz, 2012). Meanwhile, regulatory pathways lack standardized characterization protocols, creating ambiguity in quality control benchmarks and extending the timeline for clinical endorsement (Soares et al., 2018). Immunological recognition of carrier components, notably the development of anti-PEG antibodies, frequently compromises the "stealth" functionality, leading to accelerated blood clearance and potential infusion-related reactions (Immordino et al., 2006). Although several challenges exist but still the rational design and clinical integration of nanomedicine based delivery systems hold immense promise for transforming colon cancer therapy.

### 4. Nanocarrier Architectures for Capecitabine Delivery

A wide range of nanomaterial platforms have been explored for the delivery of capecitabine, with each providing unique benefits regarding drug loading, release rates, biocompatibility, and potential for functionalization.

#### 4.1 Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles are solid colloidal particles that can either dissolve, trap, encapsulate, or be covalently linked to a polymeric matrix with the drug (Fig. 2). They are among the most widely studied carriers for the controlled delivery of capecitabine (Soppimath et al. 2001).

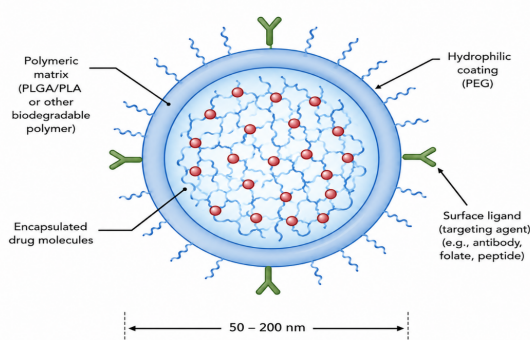
**Poly(lactic-co-glycolic acid) (PLGA) PNPs:** PLGA, a biocompatible and biodegradable copolymer, approved by the FDA, is regarded as a standard material for the fabrication of polymeric nanoparticles, (Makadia and Siegel, 2011). Astete and Sabliov (2006) had synthesized the capecitabine-loaded PLGA nanoparticles using methods such as emulsion-solvent evaporation and nanoprecipitation method. They exhibit sustained and controlled release profiles lasting from days to weeks, effectively safeguarding capecitabine against early degradation. Gref et al. (1994) developed a strategy by modifying the surface of PNPs with polyethylene glycol (PEG) known as PEGylation to impart "stealth" characteristics whereby minimizing opsonization and subsequent elimination by the mononuclear phagocyte system (MPS), which considerably prolongs systemic circulation time of PNPs. Swami et al. (2015) conducted *in vivo* studies on BALB/c mice with CT26 colon carcinoma and

revealed that capecitabine encapsulated PLGA nanoparticles exhibited significantly higher tumor growth inhibition (TGI >70%) compared to free capecitabine, along with noticeably diminished systemic toxicity, which was evident by stable body weight and normalized serum biochemical markers indicating hepatic and renal function. Among the most extensively investigated platforms for capecitabine encapsulation are polymeric nanoparticles fabricated from biodegradable copolymers. Pandey et al. (2017) developed Eudragit S100-PLGA nanoparticles using double emulsification-solvent evaporation method, yielding a mean particle size of 179.25 nm with 71.27% entrapment efficiency and sustained drug release of 81.82% over 72 hours. Cytotoxicity studies demonstrated that the nanoparticle formulation exhibited dose-dependent anticancer activity, with cellular uptake completely achieved within 2–4 hours in HT-29 adenocarcinoma cells. More recently, CAP and thymoquinone-loaded galactosylated PLGA nanoparticles coated with Eudragit-S-100 were engineered for pH-triggered colonic release following oral administration, with galactosylation facilitating galectin-mediated endocytosis and demonstrating enhanced cytotoxicity and apoptosis compared to free drug. Chen et al. (2022) designed a compound capecitabine colon-targeted microparticle (COPMP) utilizing coaxial electrospray technology, featuring a core-shell architecture composed of a CAP/osimertinib-loaded PLGA core enveloped by an Eudragit S100 outer layer. This strategically engineered construct exhibited a size of  $1.87 \pm 0.23 \mu\text{m}$  with drug loadings of 4.93% and 4.95% for capecitabine and osimertinib, respectively. The release profile demonstrated minimal drug release at gastric pH (pH 1.0), less than 50% release between 3–5 hours at intestinal pH (6.8), and sustained release exceeding 80% between 6–48 hours at colonic pH (7.4), thereby ensuring preferential drug liberation at the target site. In a colon tumor model, oral administration of COPMP achieved a remarkable tumor inhibition rate of 94% within one week, with CAP and OSI demonstrating a synergistic effect on HCT-116 cell.

**Chitosan-based PNPs:** Chitosan, a natural polysaccharide with a cationic charge obtained from chitin, demonstrates favorable properties such as biocompatibility, biodegradability, and mucoadhesion (Rinaudo 2006). Its positive charge allows it to interact with negatively charged cell membranes and mucosal surfaces, which can enhance cellular uptake and facilitate paracellular transport by momentarily opening tight junctions between epithelial cells (Bernkop-Schnurch and Dunnhaupt, 2012). The characteristic that makes chitosan nanoparticles particularly suitable for oral delivery methods is attributed to their favorable physicochemical properties, such as high drug-

loading capacity, stability in gastrointestinal fluids, and the ability to improve the oral bioavailability of poorly absorbed therapeutics. For targeting specifically to the colon, chitosan can be chemically modified with azo-aromatic compounds or covered with pH-sensitive polymers like Eudragit® S100, which dissolves at a colonic pH (>7.0), whereby promoting drug release specifically in the colon due to changes in pH or enzymatic activity from colonic bacterial azoreductases (Chourasia and Jain, 2003). Chitosan-based nanocarriers have also gained considerable attention showing the mucoadhesive properties and biocompatibility. Bhattacharya et al. (2024) formulated capecitabine-loaded potato starch-chitosan nanoparticles using ultrasonication and ionotropic gelation, achieving a mean size of 245 nm, positive zeta potential (+30 mV), high loading efficacy (76%), and sustained release (92% over 100 hours). In vivo studies in DMH-induced Balb/c mice demonstrated superior colon histology, reduced tumor scores, and inhibition of VEGD and CD31 expression compared to free capecitabine. Gomathi et al. (2024) developed chitosan-lysine nanoparticles via ionic gelation for sustained capecitabine delivery, with comprehensive characterization employing FTIR, XRD, SEM, TEM, and UV spectroscopy to elucidate the physicochemical properties of the nanosystem. The incorporation of lysine into the chitosan matrix imparted additional functionality, potentially enhancing cellular uptake and therapeutic efficacy through improved electrostatic interactions with negatively charged cell membranes. Furthermore, the strategic conjugation of targeting moieties has been explored to augment tumor specificity. Shankar et al. (2024) formulated folic acid-conjugated chitosan nanoparticles (FA-CS-NPs) wherein folic acid was associated with the nanoparticles through electrostatic interactions, capitalizing on the overexpression of folate receptors on colorectal cancer cells to facilitate receptor-mediated endocytosis and enhance intracellular drug accumulation.

**Other Polymeric Matrices:** Poly( $\epsilon$ -caprolactone) (PCL), recognized for its slower degradation rate, and poly(alkyl cyanoacrylates) (PACAs), known for their rapid enzymatic breakdown, have also been investigated for delivering capecitabine (Sinha et al. 2004). Furthermore, nanoparticles based on albumin (such as those utilizing endogenous serum albumin) present a naturally biocompatible platform with potential for receptor-mediated tumor targeting (e.g., via gp60/SPARC) (Kratz, 2008).



**Fig.2**  
**Polymeric nanoparticles**

#### 4.2 Lipid-Based Nanocarriers

**Liposomes:** Liposomes first reported by Bangham et al. (1965), are vesicular structures comprising one or multiple concentric phospholipid bilayers that surround an internal aqueous compartment. The amphiphilic lipid molecules spontaneously self-assemble into bilayer configurations, positioning their hydrophilic head groups toward the aqueous phases while their hydrophobic fatty acyl chains are directed inward (Lasic, 1998; Allen & Cullis, 2013). This distinctive structural arrangement enables the entrapment of water-soluble drugs such as capecitabine within the internal aqueous core, whereas lipophilic agents can be accommodated within the hydrophobic domain of the lipid bilayer. Their size, charge, and membrane properties can be modified by altering lipid composition and preparation methods. However, conventional liposomes are rapidly cleared by the mononuclear phagocytic system (Immordino et al., 2006). PEGylation prolongs circulation time and promotes passive tumor accumulation via the EPR effect, as demonstrated by Doxil® (Gabizon et al., 2003). Liposomes also protect capecitabine from premature degradation and can be surface-functionalized with ligands for targeted colon cancer therapy, although challenges related to stability and drug loading still exist (Stella et al., 2000).

Barenholz et al. (2012) have reviewed that although preclinical data for capecitabine nanomedicines appear robust and encouraging but their clinical translation lags behind. Established oncology nanotherapeutics like liposomal doxorubicin (Doxil®/Caelyx®) and albumin-bound paclitaxel nanoparticles (Abraxane®) have led the field while capecitabine specific nanoformulations remain largely confined to preclinical studies or early clinical trials. Certain Phase I/II clinical trials have investigated liposomal capecitabine formulations, mainly to enhance tolerability and mitigate toxicities such as hand-foot syndrome. Major formulation hurdles involve attaining adequate drug

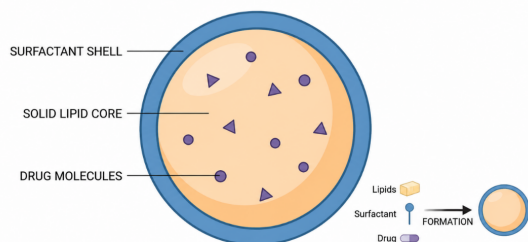
encapsulation in the aqueous core and maintaining long-term liposomal stability.

Padmasree and Vishwanath (2022) developed PEGylated stealth liposomal formulations of capecitabine employing the thin film hydration method, utilizing various combinations of phospholipids including DSPC and PE-PEG 2000 to impart prolonged circulation characteristics. The prepared stealth liposomes underwent comprehensive characterization for particle size analysis, zeta potential determination, entrapment efficiency assessment, and drug release studies, with Fourier transform infrared spectroscopy confirming drug–excipient compatibility. The average particle size of capecitabine-loaded stealth liposomes ranged from 110 to 201 nm, while the percentage entrapment efficiency was found to vary between 54% and 73% across different formulations.

Shewale et al. (2024) developed capecitabine and celecoxib co-encapsulated liposomes for combination therapy, demonstrating a monodisperse particle population with an average size of 142 nm, surface potential of  $-6.93$  mV, and entrapment efficiencies of  $52.39 \pm 0.94\%$  for capecitabine and  $77.13 \pm 0.74\%$  for celecoxib. The incorporation of PEG into the liposomal carrier system has been established to extend blood circulation time by reducing opsonization and subsequent clearance by the mononuclear phagocyte system, thereby enhancing the passive accumulation of the nanocarriers at tumor sites via the enhanced permeability and retention effect.

**Solid Lipid Nanoparticles (SLNs):** Muller et al. (2000) are colloidal drug carriers fabricated from physiologically compatible lipids that maintain a solid state at body temperature like triglycerides, fatty acids, and waxes (Fig.3) (Mehnert & Mader, 2012). These nanocarriers feature a rigid crystalline or amorphous lipid core that provides stable encapsulation of therapeutic agents, effective shielding of labile drugs from enzymatic degradation and chemical breakdown during systemic circulation. SLNs offer several advantageous characteristics, including controlled drug release kinetics, excellent physical stability, remarkable biocompatibility, and the feasibility of large-scale production through high-pressure homogenization techniques (Muller et al., 2000). Unlike conventional emulsion-based systems, SLNs avoid the use of organic solvents during fabrication, minimizing toxicity issues and enhancing patient safety. Their solid matrix at physiological temperatures significantly reduces drug leakage and enables sustained release profiles, making them particularly attractive for oral delivery of lipophilic drugs. Furthermore, the surface of SLNs can be modified with targeting ligands like including folic acid or monoclonal antibodies, (active tumor targeting) or coated with mucoadhesive polymers (prolong gastrointestinal residence time and

improve oral bioavailability) (Mehnert & Mader, 2012). Collectively, these attributes establish SLNs as a versatile and promising nanocarriers for enhancing the therapeutic efficacy of chemotherapeutic agents in colon cancer management.



**Fig. 3 Schematic representation of solid lipid nanoparticles**

Jana et al. (2025) fabricated capecitabine-loaded SLNs utilizing a modified nanoprecipitation method, systematically optimizing formulation parameters to achieve desirable physicochemical attributes. Transmission electron microscopy revealed transparent, nearly spherical nanoparticles with mean particle sizes ranging from  $13.06 \pm 0.09$  to  $86.10 \pm 0.15$  nm, while the optimized F-3 formulation demonstrated the highest drug entrapment efficiency of  $45.49 \pm 0.28\%$  and drug loading of  $31.27 \pm 0.53\%$ . Zeta potential measurements ranging from  $-15.53 \pm 0.17$  to  $17.55 \pm 0.18$  mV confirmed adequate colloidal stability, with polydispersity indices between 0.1356 and 0.2678 indicating a relatively uniform particle size distribution. Fourier transform infrared spectroscopy confirmed drug–excipient compatibility, while differential scanning calorimetry and X-ray diffraction studies revealed the conversion of capecitabine to an amorphous form within the lipid matrix, a transformation that can enhance drug dissolution and bioavailability.

Dudhipala et al. (2018) employed a microemulsion method to prepare capecitabine-loaded SLNs, achieving an optimized formulation with a particle size of  $145.6 \pm 3.6$  nm, zeta potential of  $-26.9 \pm 2.7$  mV, and notably higher entrapment efficiency of  $88.33 \pm 3.74\%$ . The divergent entrapment efficiencies observed across these studies underscore the profound influence of preparation methodology on the encapsulation capacity of SLNs, with the microemulsion technique yielding superior drug loading compared to the nanoprecipitation approach.

#### 4.3 Inorganic Nanoparticles

Inorganic nanoparticles offer distinct benefits like structural stability, adjustable porosity, magnetic features, and optical properties, facilitating various multifunctional uses, as highlighted by Giner-Casares et al. (2016).

**Mesoporous Silica Nanoparticles (MSNs):** Mesoporous silica nanoparticles (MSNs) have

emerged as highly promising inorganic nanocarriers for cancer drug delivery, owing to their unique structural and physicochemical characteristics (Vallet-Regí et al. 2001). MSNs possess an exceptionally high surface area exceeding  $1000 \text{ m}^2/\text{g}$ , uniform and tunable pore diameters ranging from 2 to 10 nm, and substantial pore volumes, collectively enabling remarkably high drug loading capacities. The particle surface is densely populated with reactive silanol ( $-\text{SiOH}$ ) groups, that enables straightforward functionalization through silane coupling chemistry, allowing the attachment of various targeting ligands, polymers, or stimuli-responsive moieties (Slowing et al., 2008). A particularly innovative strategy for achieving controlled drug release involves the application of stimuli-responsive "gatekeepers" that cap the nanopores (Tarn et al. 2013). These gatekeepers can be pH-sensitive polymers like chitosan, acetal-based crosslinkers, or supramolecular assemblies which act as molecular switches that remain tightly closed under physiological conditions (pH 7.4), effectively preventing premature drug leakage during systemic circulation. However, upon reaching the tumor microenvironment, which is characterized by mild acidity (pH  $\sim 6.5$ – $6.8$ ) or upon cellular internalization into acidic endosomal and lysosomal compartments (pH 4.5–5.5), these gatekeepers undergo conformational changes, bond cleavage, or dissolution, thereby opening the pores and triggering rapid site-specific drug release. This pH-responsive gating mechanism ensures that the encapsulated therapeutic agent, such as capecitabine, is selectively liberated within the tumor tissues or intracellular compartments, significantly enhancing therapeutic efficacy while minimizing off-target toxicity. Collectively, these attributes position MSNs as highly versatile and efficient nanocarriers for precision oncology applications.

Narayan et al. (2021) developed glycosylated pH-sensitive MSNs for colorectal cancer targeting, employing a modified Stöber's method to synthesize nanoparticles possessing an average pore diameter of  $8.12 \pm 0.43$  nm, pore volume of  $0.73 \pm 0.21 \text{ cm}^3/\text{g}$ , and particle size of  $245.24 \pm 5.75$  nm. A remarkably high drug loading capacity of  $180.51 \pm 5.23 \text{ mg/g}$  was achieved, attributed to the larger pore volume that facilitates extensive drug accommodation within the mesoporous channels. The surface of drug-loaded MSNs was subsequently capped with a chitosan-glucuronic acid (CHS-GCA) conjugate, strategically combining pH-sensitive release characteristics with lectin receptor-mediated uptake for enhanced tumor specificity.

Tripathi et al. (2024) designed PLGA-capped mesoporous silica nanoparticles functionalized with folic acid (FoA) for pH-sensitive controlled release within the acidic tumor microenvironment. Comprehensive physicochemical characterization utilizing transmission electron microscopy, atomic

force microscopy, zeta potential analysis, thermogravimetric analysis, Fourier transform infrared spectroscopy, Brunauer-Emmett-Teller analysis, and dynamic light scattering confirmed the successful fabrication of the nanoformulations, with the final PLGA-FoA-MSN-CAP construct exhibiting a particle size of  $164.5 \pm 1.8$  nm. Morphological evaluation and elemental analysis further validated the proper capping and tagging of PLGA and folic acid moieties, establishing a robust platform for targeted capecitabine delivery.

**Gold nanoparticles (AuNPs):** Gold nanoparticles (AuNPs) have garnered significant attention in cancer nanomedicine due to their remarkable biocompatibility, tunable surface plasmon resonance properties, and facile surface functionalization through stable thiol-gold interactions (Daniel & Astruc, 2004). These unique optical characteristics enable AuNPs to absorb and scatter near-infrared (NIR) light efficiently, converting it into localized heat, which forms the basis for photothermal therapy (PTT). Although capecitabine is not conventionally delivered as a primary therapeutic agent using bare AuNPs, these metallic nanostructures serve as excellent core templates for constructing multifunctional composite nanoplateforms. For instance, encapsulating capecitabine within biodegradable polymer shells such as PLGA and coating them onto AuNP cores enables concurrent chemotherapy and photothermal therapy (Huang et al., 2007). Upon NIR laser irradiation, the AuNP core generates localized hyperthermia, which not only induces thermal ablation of cancer cells but also triggers rapid drug release from the heat-sensitive polymeric coating, thereby achieving synergistic antitumor effects. Additionally, AuNPs can be surface-decorated with targeting ligands, including folic acid or peptides, to facilitate active tumor recognition and enhance cellular uptake (Dreaden et al., 2012). Collectively, these versatile attributes position AuNPs as promising multifunctional nanoplateforms for integrating imaging, targeted chemotherapy, and photothermal ablation in colon cancer treatment.

**Superparamagnetic Iron Oxide Nanoparticles (SPIONs):** Superparamagnetic iron oxide nanoparticles (SPIONs), typically composed of magnetite ( $\text{Fe}_3\text{O}_4$ ) or maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ), have emerged as versatile theranostic nanoplateforms in cancer nanomedicine (Gupta & Gupta, 2005). These nanostructures exhibit superparamagnetic behavior, meaning they become magnetized only in the presence of an external magnetic field and rapidly demagnetize upon its removal, thus preventing particle aggregation and ensuring colloidal stability. For drug delivery applications, capecitabine can be attached to SPIONs coated with biocompatible polymers such as dextran, polyethylene glycol (PEG), or chitosan, which provide functional groups for drug conjugation and enhance circulation time

by reducing opsonization. By applying an external magnetic field localized at the tumor site, these magnetic nanocarriers can be actively directed and retained within the target tissue, substantially elevating the local drug concentration while minimizing systemic exposure and associated off-target toxicities (Pankhurst et al., 2009). Additionally, SPIONs can generate localized hyperthermia when exposed to an alternating magnetic field (AMF), inducing controlled heating that sensitizes cancer cells to chemotherapy, thereby enabling a combined magnetic hyperthermia and chemotherapy approach (Sun et al., 2008). Furthermore, the surface of SPIONs can be functionalized with targeting ligands, such as antibodies or peptides, to enhance tumor-specific recognition and cellular uptake. Besides, the incorporation of fluorescent dyes enables optical imaging, creating truly multifunctional platforms that integrate diagnostics, targeted drug delivery, and therapeutic monitoring (Lee et al., 2009). These multifaceted attributes collectively establish SPIONs as powerful theranostic tools for advancing capecitabine-based colon cancer therapy.

Anbarasan et al. (2015) synthesized  $\text{Fe}_3\text{O}_4$  nanoparticles via chemical precipitation methodology, subsequently coating the magnetic cores with PLGA-PEG polymers to impart biocompatibility and stealth properties prior to capecitabine loading. Comprehensive physicochemical characterization employing X-ray diffraction, Fourier transform infrared spectroscopy, vibrating sample magnetometry, particle size analysis, and scanning electron microscopy confirmed the successful fabrication of the magnetic nanocarrier system.

Erdag et al. (2025) engineered a sophisticated multifunctional system wherein superparamagnetic iron oxide nanoclusters were coated with mesoporous silica, functionalized with folic acid, and co-loaded with curcumin and capecitabine, creating a smart theranostic platform with particle size optimization and controlled surface functionality. The incorporation of folic acid as a targeting ligand exploits the overexpression of folate receptors on cancer cells, facilitating receptor-mediated endocytosis and enhancing tumor-specific accumulation.

#### 4.4 Dendrimers

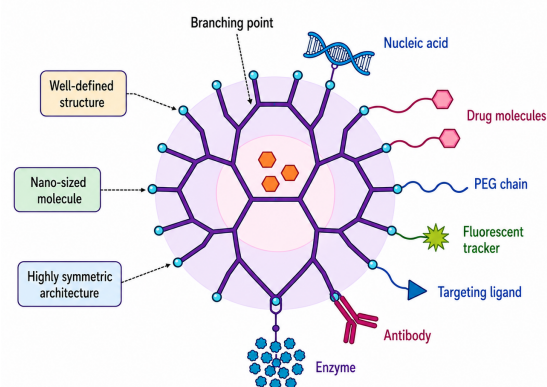
Dendrimers represent a distinctive class of synthetic macromolecules characterized by their highly branched, three-dimensional, and monodisperse architecture. These nanoscale carriers possess a unique tree-like structure composed of a central core followed by repetitive branching layers referred to as generations and an outer shell densely populated with functional groups available for chemical conjugation. Their well-defined molecular weight, controlled geometry, and narrow polydispersity index distinguish dendrimers from conventional

linear polymers and confer several advantageous properties for drug delivery applications. Among the various dendrimer families, poly(amidoamine) (PAMAM) dendrimers have emerged as the most extensively investigated class in pharmaceutical research, offering exceptional biocompatibility, abundant surface amine groups for covalent attachment of therapeutic agents, targeting ligands, and imaging moieties (Fig. 4) (Tomalia et al., 1985; Svenson & Tomalia, 2012).

The therapeutic potential of PAMAM dendrimers for capecitabine delivery has been substantiated through preclinical investigations. In a pivotal study, Nabavizadeh et al. (2016) evaluated the ability of PAMAM dendrimers to improve the therapeutic index of capecitabine while mitigating its adverse effects on healthy tissues in a mouse model of colon adenocarcinoma induced by azoxymethane. The capecitabine-dendrimer complex demonstrated superior antitumor activity compared to free capecitabine, with significant tumor size reduction observed in treated animals. Importantly, the dendrimer formulation effectively decreased drug-induced side effects on non-target organs, particularly the liver and bone marrow. Mechanistically, the capecitabine-PAMAM dendrimer complex has been shown to modulate apoptotic pathways by increasing Bax protein gene expression and reducing Bcl-2 protein expression, thereby promoting programmed cell death in cancer cells. Menjoge et al. (2010) further highlighted that the multifunctional surface of dendrimers enables simultaneous attachment of targeting ligands, imaging agents, and therapeutic molecules, creating comprehensive theranostic platforms for concurrent diagnosis, targeted delivery, and treatment monitoring.

Beyond PAMAM-based systems, innovative dendrimer architectures continue to emerge for capecitabine delivery. Recent advancements include dendrimer-modified nanosheets incorporating pH- and thermosensitive polymers, which achieve controlled drug release—approximately 88% capecitabine release over 6 hours at pH 5.6 and 45°C with further enhancement upon near-infrared laser irradiation (Norouzzadeh Chegini et al., 2022). These externally triggerable systems represent a promising frontier for achieving precise spatiotemporal control over drug liberation. Collectively, dendrimers offer a versatile and precision-engineered platform for capecitabine delivery, combining high drug loading capacity, site-specific targeting potential, and multifunctional capabilities. Their ability to improve therapeutic efficacy while reducing off-target toxicity positions them as valuable contributors to the evolving landscape of nanomedicine for colon cancer therapy (Nabavizadeh et al., 2016; Svenson & Tomalia, 2012). Norouzzadeh Chegini et al. (2022) pioneered a novel pH/thermosensitive nanocarrier wherein

dendrimers were grown from the surface of modified tungsten disulfide (WS<sub>2</sub>) nanosheets to encapsulate capecitabine. Comprehensive characterization of the obtained nanoparticles was performed using various analytical techniques, with multiple formulation parameters systematically optimized. Drug release experiments conducted at different temperatures and pH values revealed that the release rate of capecitabine at pH 5.6 was remarkably higher than that at pH 7.4, and the nanocarrier could release more than 90% of the drug at 45°C in pH 5.6 within 6 hours. The release curves demonstrated strong dependence on near-infrared (NIR) laser irradiation, establishing an externally triggerable delivery system. Cytotoxicity evaluation via MTT assay against MCF-7 breast cancer cells indicated that the pH/thermosensitive nanocarrier significantly increased the rate of cell death in the cancer cell line compared to normal breast cells. Jafari et al. (2019) demonstrated that the capecitabine-PAMAM dendrimer complex reduced the size of axillary implanted tumors, lowered serum levels of liver enzymes (AST and ALP), and decreased drug-induced adverse effects on other body organs, while also improving blood cell counts compared to free capecitabine.



**Fig. 4 Structure of dendrimers**

#### 4.5 Polymeric Micelles

Polymeric micelles represent a well-established class of nanocarriers prepared by the spontaneous self-assembly of amphiphilic block copolymers in aqueous environments when concentrations exceed their critical micelle concentration (CMC). These supramolecular structures feature a distinct core-shell architecture, a hydrophobic inner core that serves as a reservoir for poorly water-soluble therapeutic agents and a well-established hydrophilic outer shell, which provides steric stabilization and prolongs the systemic circulation (Torchilin et al. 2001). This dynamic nature of micelles exists in a reversible equilibrium between single structures and assembled structures which

helps to initiate rapid disassembly upon dilution or environmental changes and also facilitates drug release at target sites, as observed by (Kwon et al. 2003). Moreover, the small size of micelles, usually below 100 nm, confers significant advantages including enhanced tumor penetration through the dense extracellular matrix, extended blood circulation, and efficient extravasation through leaky tumor vasculature via the EPR effect (Cabral and Kataoka et al. 2014). Although capecitabine itself does not exhibit strong hydrophobicity, it can be chemically derivatized into lipophilic prodrugs or co-encapsulated with hydrophobic adjuvants to facilitate incorporation into the micellar core. Notably, certain amphiphilic block copolymers such as D- $\alpha$ -tocopheryl polyethylene glycol succinate (TPGS) and Pluronic® block copolymers (such as Pluronic® P85) possess inherent biological activity beyond their carrier functions. They effectively inhibit ATP-dependent drug efflux pumps, particularly P-glycoprotein (P-gp), through ATPase inhibition and cellular ATP depletion (Collnot et al., 2007). Building upon this property, Kabanov et al. (2002) pioneered a strategy wherein capecitabine-loaded micelles fabricated with these multifunctional polymers not only deliver the chemotherapeutic agent effectively to tumor cells but also concurrently sensitize multidrug-resistant (MDR) cancer cells by circumventing efflux-mediated drug expulsion.

### 5. Nanocarrier Strategies

A major benefit of nano-systems is their capacity to avoid multidrug resistance, often mediated by efflux transporters like P-glycoprotein. Nanoparticles evade these pumps via endocytic uptake and can co-deliver chemosensitizers to revive drug susceptibility, thereby increasing intracellular retention while minimizing off-target toxicity (Holohan et al., 2013).

#### Evasion & Inhibition of efflux pumps

Nanocarriers enter cancer cells via endocytic pathways (e.g., clathrin-mediated endocytosis and macropinocytosis), which sequester the drug within endosomal/lysosomal compartments. This intracellular confinement physically separates the payload from plasma membrane-anchored efflux pumps like P-gp, thereby evading immediate extrusion and enhancing drug retention (Sahay et al., 2010). Beyond this passive evasion, specific carrier components such as Pluronic® P85 and TPGS actively counteract resistance by inhibiting P-gp ATPase activity and depleting intracellular ATP, thus impairing the pump's energy supply (Batrakova et al., 2003). Through this dual mechanism i.e., endocytic bypass coupled with direct inhibition of the efflux machinery, these multifunctional nanocarriers effectively restore drug sensitivity in multidrug-resistant tumors, offering a potent strategy against refractory cancers.

#### Co-delivery of synergistic therapeutic agents

Nanocarriers can transport multiple therapeutic agents simultaneously to the same cell population. This allows for precisely controlled, pre-calculated drug ratios that maximize therapeutic impact. These systems enhance treatment synergy and efficiency by enabling high concentration of payload at the target.

Combination chemotherapy can be enhanced by loading multiple drugs, such as capecitabine and oxaliplatin or irinotecan, into a single PLGA nanoparticle. This method synchronizes drug's pharmacokinetics and biodistribution, resolving common challenges like varying solubility, stability, and clearance rates associated with administering free drugs in combination. Consequently, both agents arrive at the tumor simultaneously, which can produce a truly synergistic cytotoxic effect. Research in chemoresistant colon cancer models shows that such co-encapsulated nanoparticles induce significantly greater tumor regression and extend survival more effectively than combinations of free drugs or individual agents alone.

Nanoparticles can be engineered to co-deliver the chemotherapeutic agent capecitabine along with RNA interference molecules like siRNA or miRNA, which are designed to silence specific drug-resistance genes (such as TYMS, BCL2, or MDR1). This strategy simultaneously downregulates the expression of these genes within cancer cells, effectively reversing chemoresistance and resensitizing the tumor to treatment. Davis et al. (2010) showed that nanocarriers utilize cationic materials to bind and encapsulate the negatively charged nucleic acids, facilitating their efficient packaging and delivery into the target cells.

Kroemer et al. (2013) described a mechanism wherein combining capecitabine with immunomodulatory agents, such as Toll-like receptor agonists or checkpoint inhibitors, within a single nanoparticle can counteract the immunosuppressive tumor microenvironment. This strategy creates an "in situ vaccination" effect, where the chemotherapy-induced immunogenic cell death is synergized with local immune stimulation to generate potent, systemic anti-tumor immunity and long-lasting immunological memory.

### 6. Future Prospects

Nanotechnology-driven delivery of capecitabine has the potential to redefine the therapeutic development in the treatment of colon cancer by next-generation, precision-engineered nanocarriers and personalized drug delivery systems. Furthermore, the advance strategies such as surface functionalized/ligand targeting, combination therapies with gene/immunotherapeutics, smart responsive nanocarriers, etc., would bridge the gap between experimental research to the clinical application while reducing toxicity and improving patient compliance. In addition, upon addressing the challenges related to scalability, long term bio-

safety and regulatory issues, nanotechnology-based capecitabine formulations are expected to become a paradigm in advanced colon cancer treatment.

## 7. Conclusion

The integration of nanotechnology with the well-established chemotherapeutic agent capecitabine signifies a major advancement in the therapeutic landscape for colon cancer. By systematically addressing the inherent pharmacokinetic limitations, nonspecific cytotoxicity, and molecular resistance mechanisms of traditional capecitabine therapy, nanocarriers ranging from conventional polymeric and lipid-based systems to advanced, actively targeted and stimuli-responsive platforms have exhibited exceptional promise in preclinical investigations. These nanocarriers effectively convert a broadly acting cytotoxic drug into a precision-guided therapeutic system with superior tumor targeting and controlled intracellular release. Despite the intricate path from preclinical innovation to clinical implementation which involves scientific validation, scalable manufacturing, regulatory navigation, feasibility the momentum of their progress remains undeniable. With continuous interdisciplinary advancements in refining nanocarrier engineering, while elucidating nano-bio interactions and optimizing production scalability, nanotechnology based capecitabine delivery is steadily evolving from phase of an experimental prototype to a clinical reality. This ongoing transformation holds immense potential to improve survival rates, enhance patient quality of life, and drive more personalized and efficacious treatment strategies in combatting colon cancer.

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