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Advancing Drug Delivery in Colorectal Cancer: A Comprehensive Exploration of Nanotechnology, Experimental Models, and Production Process Simulation

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Abstract

Colorectal cancer (CRC) remains a major global health challenge as the third most common cancer worldwide. Survival relies heavily on early diagnosis and treatment before progression to metastasis. Employing nanotechnology for targeted drug delivery shows promise to enhance therapeutic efficacy and tolerability in CRC. Diverse nanoparticle platforms offer unique advantages as CRC drug carriers with tunable properties like improved pharmacokinetics, stability, sustained release, and tumor cell uptake through endocytosis or transcytosis. Key platforms highlighted include liposomes, polymeric micelles, solid lipid nanoparticles, nanodiscs, cubosomes, and polysaccharide particles. In vivo testing is warranted to translate multiparameter optimized carrier designs to clinical applications. Simulations help predict carrier localization, biodistribution, controlled release, and optimal formulations. Overall, nanomedicine promises more targeted therapeutic delivery to improve survival for CRC patients, especially those with advanced or metastatic disease. However, realizing this potential requires additional pharmacodynamic studies alongside mechanistic clarification and carrier optimization to progress designs to clinical evaluation. Advancing personalized, targeted nanotechnology-enabled treatment options remains imperative.

Keywords: *Nanoparticles, Drug delivery, Colorectal cancer, Experimental models, Bioprocess simulation, Manufacturing, Simulation software*

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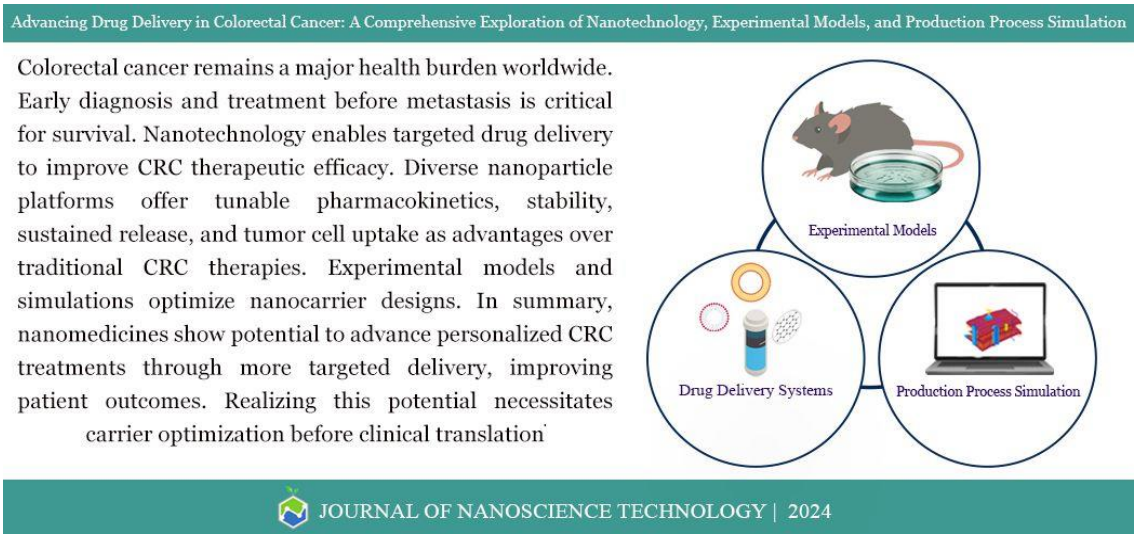

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant gastrointestinal tumors, ranking as the third most diagnosed cancer globally and the fourth leading cause of cancer mortality [1, 2]. In the United States, CRC is the second leading cause of cancer deaths, with an estimated 153,000 new cases and 52,500 deaths projected for 2023 [3]. Survival rates depend significantly on stage at diagnosis, along with factors like age, sex, and genetics [4, 5]. Older patients tend to have poorer CRC prognoses owing to greater treatment toxicity risks from age-related changes and co-morbidities [6].

CRC prognosis relies upon three key elements – TNM staging, molecular biomarkers, and histological features. The universally utilized TNM system stages tumors based on the degree of bowel wall invasion (T), lymph node involvement (N), and presence of metastases (M) [7-13]. T stage correlates directly with 5-year overall survival, while nodal involvement reduces 5-year overall survival by 30-60% compared to node-negative disease [9-11]. Metastatic disease at diagnosis confers a <10% 5-year survival rate [8, 13]. Molecular prognostic biomarkers in CRC include KRAS, BRAF, MSI status, and CDX2 expression levels. Mutated KRAS and BRAF mediate aberrant MAPK signaling, enabling pathways involved in proliferation, apoptosis, and viability [14-16]. MSI status denotes frameshift mutations in microsatellites, with ~15% of CRCs exhibiting high MSI (MSI-H) that may predict the prognosis and efficacy of adjuvant therapy [17-19]. The homeobox transcription factor CDX2 exhibits tumor suppressor functions in the adult colon [20-22]. Histological features like tumor size, location, budding, and lymph node yield also influence outcomes [23-26].

When caught early, CRC has highly favorable treatment outcomes [27]. However, the prognosis for metastatic or recurrent disease remains extremely poor [28]. First-line therapy for advanced CRC includes oxaliplatin, fluoropyrimidines like 5-fluorouracil (5-FU) capecitabine, or topoisomerase inhibitors such as irinotecan [29, 30]. Platinum agents like oxaliplatin damage DNA, 5-FU inhibits thymidylate synthesis, and irinotecan induces DNA Damage [31-34]. Targeted therapies now used additionally or instead include the anti-angiogenesis agents bevacizumab and panitumumab, the anti-proliferative cetuximab, as well as the immunotherapy agent pembrolizumab [35-39]. Predictive molecular analyses and imaging may help guide optimal therapy [40]. While numerous advances have improved localized CRC, combatting recurrent and metastatic disease remains an ongoing challenge [41, 42]. Furthermore, patients experience substantial toxicity risks including mucositis, hair loss, neuropathy, and myelosuppression [43-46]. Developing improved chemotherapy agents and delivery systems to enhance efficacy and tolerability therefore remains a high priority.

Drug delivery systems (DDSs) have been explored as carriers to enhance the delivery of chemotherapeutic agents in cancer treatment [45]. Conventional chemotherapy delivery lacks selectivity, distributing agents systemically and causing toxicity to healthy cells [47]. In contrast, controlled DDSs can guide drugs specifically to tumor sites, increasing concentration in cancerous tissues while averting toxicity in normal cells [48, 49]. DDSs also protect drugs from degradation and clearance, helpful for the delivery of biologics like proteins and nucleic acids [50]. Controlled DDSs therefore show promise to improve the efficacy and tolerability of CRC treatment by enhancing tumor-selective delivery.

2. Nanoparticles used in colon cancer

Nanoscale drug delivery systems (DDSs) can improve bioavailability and pharmacokinetics through sustained release while avoiding reticuloendothelial system clearance [45, 51]. Various nanoparticle platforms offer unique advantages for DDSs, though combinations help overcome inherent limitations. We survey key lipid and polysaccharide nanoparticles being explored for colon cancer. Figure 1 shows the main types of nano delivery systems which are used in the treatment of colorectal cancer.

Liposomal nanoparticles were the first generation of DDSs. Conventional liposomes display limited circulation times and tumor accumulation [52]. Long-circulating liposomes exhibit extended half-lives [53], while active-targeting liposomes feature surface ligands binding cancer cell receptors [54]. Stimuli-sensitive liposomes release contents in response to tumor conditions like low pH [55]. Cationic liposomes have positively charged surfaces that better attach to

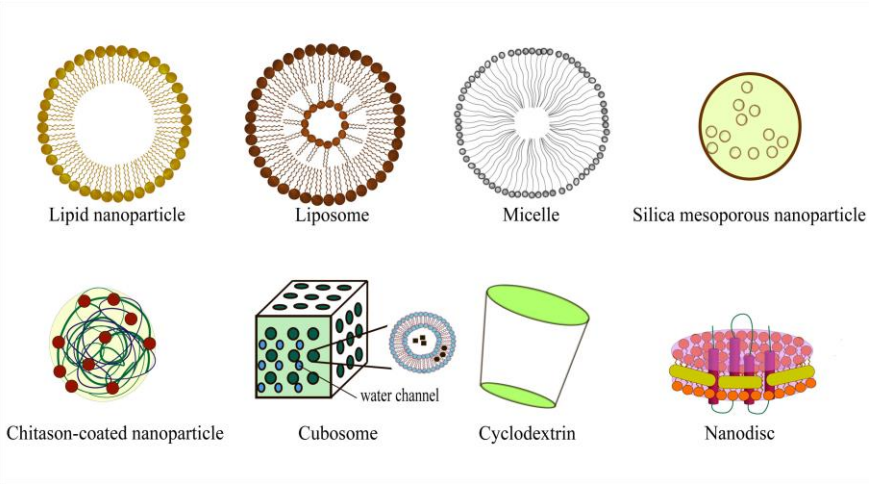

Figure 1. The main types of nano delivery systems used in treatment colorectal cancer

negatively charged cancer cell membranes [56]. Advantages of liposomal DDSs include biocompatibility, low toxicity, improved pharmacokinetics, and encapsulation of both hydrophobic drugs like doxorubicin and hydrophilic drugs like 5-fluorouracil (5-FU) [57-59]. However, hydrophilic drug encapsulation remains challenging due to dissolution into the external aqueous phase during production [60].

Polymeric micelles offer small sizes for enhanced permeation and retention (EPR), stability, scalability, surface functionality, and hydrophobic core domains for carrying poorly soluble chemotherapeutics like paclitaxel [61]. Solid lipid nanoparticles (SLNs) provide sustained matrix release of drugs like doxorubicin while protecting unstable agents [62-64]. However, SLNs weakly encapsulate hydrophilic medications [65, 66]. Nanodiscs comprise discoidal lipid bilayers encircled by polymer “belts”, allowing the delivery of membrane protein complexes, lipophilic drugs, and combination therapies [67, 68]. Cubic phase nanoparticles known as cubosomes or nano-cubosomes offer ultralow viscosity and high stability for binding membrane proteins [69-71]. Encapsulated cubic phase cisplatin displayed cytotoxic synergy with metformin in colon cancer models. Mesoporous silica nanoparticles (MSNs) enable oral chemotherapy regimens through increased hydrophobic drug solubility, protection from degradation, controlled release, and mucus penetration [72-79].

Polysaccharide platforms leverage biological properties like biodegradability, nonimmunogenicity, and bioadhesion [80-85]. Chitosan nanoparticles open epithelial tight junctions for enhanced hydrophilic drug transport [80, 83, 85], while cyclodextrins improve drug solubility, dissolution, and bioavailability through host-guest interactions in their hydrophobic interiors [86, 87].

In summary, numerous emerging nanoparticle DDS technologies offer promising opportunities to improve pharmacokinetics, drug synergies, delivery mechanisms, and tolerability profiles for colon cancer therapeutics. Further development and optimization are warranted to translate these platforms into clinical applications.

Table 1 shows the number of drugs used in colorectal cancer and the nanoplatforms used in them.

3. Experimental models and nanotechnology

Nanotechnology's foray into colon cancer treatment employs diverse experimental models, spanning from in vitro cell models to in vivo animal models. These models form the bedrock for evaluating the effectiveness and safety of treatments rooted in

Table 1. Several drugs used in colorectal cancer and their feature.

Drug name	Type of nano platform (Formulation)	Model	Main outcome(s)	Ref.
Doxorubicin	Liposomal (PEGylated liposomal)	In vitro	Reduced colon cancer mortality	[88]
Folic acid	Liposomal (Formulation of 5FU liposomes with phosphatidylcholine (PC))	In vitro and in vivo	Liposomes with a specific target induce cell death through the mitochondrial pathway. Targeted liposome results in vivo demonstrated a significant reduction in tumor volume.	[89]
Retinoic acid, prednisone, and doxorubicin	Micelles (Core-shell polymeric micelles)	In vitro	BPM Doxorubicin treatment induces apoptosis, allowing targeted in vivo delivery of lipophilic medications to inflammatory colon tissue and mucosa.	[90]
Doxorubicin	Micelles (Polymeric micelles)	Colon tumor-bearing models, in situ surgery transplantation models, in BALB/c mice.	The DOX delivery system enhanced tumor tissue accumulation and antitumor activity in three tumor models.	[91]
Docetaxel	SLNs (Cationic SLNs)	In vivo and In vitro	Low-dose oral treatment daily Reduced toxicity of chemotherapeutics Stopped the development of existing malignancies Prevented tumor development	[92]
sHDL-DOX	Nanodiscs	In vitro	Low cytotoxicity is related to delayed drug uptake and release, Increasing CRT expression on CT26 and MC38 cells, Increasing the release of HMGB1 within tumors	[68]
sHDL-DOX	Nanodiscs	In vitro	sHDL-DOX treatment significantly slows tumor growth without toxicity, weight loss, or damage to cardiac or liver tissue.	[68]
Cisplatin-metformin-loaded nano-cubosomes	Nano-cubosome	In vitro	Compared to unformulated cisplatin, nano-cubosomes have a significant antitumor effect. The inhibition of metabolic pathways associated with tumorigenesis led to an increase in apoptosis. They can increase cisplatin's cytotoxicity by combining it with metformin, an indirect mTOR inhibitor.	[93]
5-fluorouracil	Chitosan-coated liposomes	In vitro	Improved 5-fluorouracil's cytotoxicity towards CRC cells	[94]
5-fluorouracil	MSN	In vitro	Guar gum capping as an efficient enzyme-responsive carrier in an adenocarcinoma cell line	[95]
Doxorubicin	MSN	In vitro	High drug loading capacity (~785,7 mg/g), Exceptional compatibility, Excellent pH-triggered response	[79]

nanomedicine. In colon cancer, nanoparticles emerge as harbingers of hope, demonstrating their potential to precisely target cancer cells, bolster drug stability, and curtail adverse effects. Their prowess lies in amplifying therapeutic efficiency while sparing healthy cells from harm [96]. Animal models, encompassing xenografts, genetically engineered models, and chemically induced models, serve as vanguards in gauging the efficacy of potential chemopreventive agents and nanoformulations against cancer [97]. The realm of nanotechnology, facilitated by nanoparticles, harbors the potential to revolutionize the early detection and treatment landscape of colorectal cancer. For instance, gold nanoparticles can be harnessed to seek out and adhere to cancer cells, potentially facilitating their detection and removal [98]. Nanotechnology's interventions in colorectal cancer extend to the screening of tumors using nanomaterials and tailoring precise targeted drug deliveries [99]. Moreover, integrating nanoparticles within animal models for cancer treatment yields promising results, manifesting in notable tumor reduction [100]. These revelations underscore the substantial potential of experimental models within nanotechnology, paving the way for strides in advancing colon cancer treatment.

3.1 In-vitro cell models

In-vitro cellular models have played an integral role in research on the treatment of colon cancer, enabling scientists to examine the effects of various treatments and identify potential targets for pharmaceuticals. In-vitro cell lines refer to cells cultivated outside their natural environment, such as in a laboratory dish. They are employed in cancer research to investigate diverse aspects of the disease, encompassing its molecular intricacies, genetic abnormalities, and responses to treatment. These cell lines originate from cancerous tissues and offer valuable means to scrutinize cancer biology, advance drug development, and explore personalized medicine. They facilitate the efficient screening of potential anti-cancer compounds, leading to the creation of novel therapeutic agents. Additionally, in-vitro cell lines play a crucial role in comprehending cancer heterogeneity and testing the effectiveness of different treatment strategies. Although in-vitro models have limitations, they remain an indispensable component of cancer research, actively contributing to ongoing endeavors to combat this intricate ailment. Cell lines occupy a significant position in exploring cancer biology, pharmaceutical assessments, and personalized treatment approaches [101, 102].

3.1.1 HCT116, HT29, and H508 cell lines

HCT116 is a cell line with high aggressiveness commonly utilized in cancer biology, toxicology, and therapeutic development. This cell line originated from colon cancer and possesses an epithelial morphology with a diameter ranging from 150 to 400 µm. Furthermore, it is noteworthy for its lack of differentiation capacity [103-105]. HT29, on the other hand, is another cell line derived from colon cancer. It proves valuable in medical development research and the fields of cancer biology, bioavailability, and food digestion. Differing from HCT116, this cell line can differentiate into enterocytes and mucin-expressing cell lines. HT29 serves as an in-vitro model for multiple research purposes. These purposes include transport studies, the creation of permeability models, analyzing the impact of mucus on drug permeation, investigating the molecular mechanisms of biological activity, studying the pivotal players involved in intestinal iron absorption, and assessing receptor and internalization transporter functions of toxins in recent years. Additionally, researchers employ HT29 cells to examine the intestinal immune response to bacterial infection, assess the survival, adhesion, or invasion of microorganisms, and evaluate the effects of food compounds. The cell line is also utilized to investigate the impact of different compounds on mucin secretion and evaluate transepithelial absorption through the use of Transwell® inserts [106].

H508 cell lines serve as a prime example of cell lines utilized in cancer research. Specifically, H508 denotes a cell line derived from colon cancer, possessing the VTI1A-TCF7L2 fusion gene. This gene encodes the VTI1A-TCF4 fusion protein, containing a truncated TCF4. The VTI1A-TCF4 fusion protein functions as a dominant negative regulator of the Wnt signaling pathway, effectively hindering its activity. The effects of this fusion protein on Wnt signaling were investigated in both NCI-H508 and LS174T colon cancer cell lines. In the case of NCI-H508, no active Wnt signaling was observed. Conversely, when the VTI1A-TCF4 fusion protein and a Wnt signaling luciferase reporter plasmid were overexpressed in

LS174T cells, a notable inhibition of Wnt signaling activity was detected [107].

3.1.2 SW480, SW620, and SW837 cell lines

The SW480 cell line is frequently utilized in cancer research originating from primary colon adenocarcinoma. It possesses stable resistant traits, including multi-drug resistance and resistance to chemotherapy drugs such as oxaliplatin (L-OHP) and Adriamycin. Researchers have extensively employed the SW480 cell line to study drug resistance in colorectal cancer. For instance, they have established oxaliplatin and adriamycin-resistant cell lines derived from SW480 to investigate resistance mechanisms and potential strategies to reverse drug resistance [108, 109]. Furthermore, the SW480 cell line has been instrumental in studying Epithelial-Mesenchymal Transition (EMT), a process involved in cancer metastasis. Studies have demonstrated that the SW480 cell line undergoes TGF-β-induced EMT, and researchers have explored the underlying epigenetic mechanisms, thereby revealing insights into the molecular mechanisms of EMT in colorectal cancer [110]. This cell line has also been utilized to establish anoikis-resistant cell lines, enabling investigations into the biological characteristics of anoikis resistance. These investigations encompass apoptosis, cell proliferation, migration, invasion abilities, and the expression of EMT markers, offering valuable insights into the mechanisms of anoikis resistance in colorectal cancer [111].

Furthermore, the SW620 and SW837 cell lines are other notable examples contributing to cancer research. SW620 is derived from a metastatic site of human colon adenocarcinoma, while SW837 is derived from a primary tumor site. Various studies have utilized these cell lines to explore diverse aspects of cancer, including molecular characteristics and drug responses. These cell lines exhibit unique molecular characteristics influencing their behavior and treatment response. For example, a study on breast cancer subtypes identified distinct tumor-specific expression subtypes that potentially link to these cell lines' molecular characteristics. Additionally, a study on the gut microbiota in patients with gastric cancer compared the microbiota of patients with healthy individuals, highlighting the potential impact of molecular differences on cancer development and progression [112, 113].

Understanding the drug response of SW620 and SW837 is vital in cancer research. Researchers have focused on investigating how these cell lines react to various treatments. For instance, a study examining the effects of the HSP90 inhibitor 17-DMAG on the SW620 cell line demonstrated its influence on cell proliferation and apoptosis, offering valuable insights into potential therapeutic strategies [114]. Furthermore, establishing a patient-derived tumor organoid biobank has facilitated the development of an integrated database of chemotherapeutic drug response using deep learning-based imaging methods, which could be applied to study the drug response of these cell lines [115].

3.1.3 Caco-2 and Colo205 cell lines

The cell lines Caco-2 and Colo205 are frequently employed in cancer research. Caco-2, in particular, is a cell line derived from a human colon adenocarcinoma and serves as a widely accepted model for studying intestinal absorption and toxicity. Colo205, on the other hand, is also derived from a human colon adenocarcinoma. However, it is used explicitly in cancer research to examine the impacts of different treatments on colon cancer cells. These cell lines have been utilized in studies investigating the influence of diverse compounds on cancer cells. For instance, one study discovered that sheep whey proteins isolated from sheep colostrum have apoptotic and anticarcinogenic effects on the Caco-2 cancer cell line, significantly hindering tumor cell growth [116]. Another study exhibited that Salvia syriaca essential oil contains noteworthy phytochemicals, which may prove beneficial in cancer treatment due to their relatively cytotoxic and apoptotic activities when applied to Caco-2 cells [117]. Moreover, a study revealed that the induction of apoptosis in colon cancer COLO205 cells involves the Wnt/β-catenin signaling pathway through the use of oridonin [118].

Notably, specific variances exist between the Caco-2 and Colo205 cell lines. Caco-2 cells are derived from a human colon adenocarcinoma, while Colo205 cells originate from a metastatic human colon adenocarcinoma. Caco-2 cells possess the ability to differentiate into polarized cells that resemble the intestinal epithelium, unlike Colo205 cells, which do not undergo differentiation during cultivation. Additionally, Caco-2 cells are predominantly utilized in studying intestinal absorption and toxicity, whereas

Colo205 cells are employed to investigate the effects of various treatments, specifically on colon cancer cells [119].

3.1.4 LS174T, SNU-C4, and DLD-1 cell lines

LS174T, SNU-C4, and DLD-1 are three cell lines that have been utilized in various cancer research endeavors. To exemplify, LS174T has been employed in establishing the LS174T/5-Fu, a multi-drug resistant cell line that exhibits resistance to 5-fluorouracil (5-Fu). The development of LS174T/5-Fu, derived from human colon cancer, has served as an essential launching pad for further investigations into the mechanisms underlying multi-drug resistance induced by 5-fluorouracil in colon cancer patients [120]. SNU-C4, another cell line derived from human colorectal cancer, has extensively scrutinized the anti-cancer properties of oligomeric proanthocyanidins (OPC). These OPCs have demonstrated the ability to induce apoptosis in SNU-C4 cells by activating caspase signaling pathways, laying the groundwork for potential therapeutic interventions in human colorectal cancer [121]. Similarly, DLD-1, a cell line derived from human colorectal cancer, has proven invaluable in exploring the impact of miRNAs on the emergence of chemoresistance-induced EMT. Downregulation of miRNA-200 family members in DLD-1 cells has been linked to the occurrence of EMT, enabling a deeper understanding of the molecular basis behind chemoresistance in colorectal cancer [122].

These three cell lines have contributed significantly to our knowledge of various aspects of cancer research, encompassing drug resistance, apoptosis, cell cycle distribution, binding characteristics, and miRNA expression.

Utilizing all these cell lines has proven instrumental in comprehending the intricacies of colon cancer, including drug resistance, the impact of natural compounds on cytotoxicity, and the potential synergistic effects of treatment combinations. Each cell line possesses distinctive characteristics and holds immense value in addressing specific research questions. To illustrate, HCT116 and HT29 have primarily been leveraged to investigate drug resistance, while SW480 and LS174T have served as tools to explore the effects of nanoparticles and potential treatment combinations, respectively. In summary, the broad applications of these cell lines in colon cancer research attest to their indispensable role in advancing our knowledge of the disease and formulating potential therapeutic strategies. Each cell line contributes uniquely to the comprehensive study of colon cancer, and their comparative analysis yields valuable insights into diverse aspects of the disease.

3.2 In-vivo animal models

Utilizing in-vivo animal models in exploring colon cancer drugs is an intricate and multifaceted subject. Animal models are indispensable in investigating the underlying mechanisms of cancer and testing the effectiveness of potential drug candidates. While in-vivo animal models have been pivotal in deepening our understanding of how drugs work, historically, there has been a weak correlation between their efficacy in animal models and their performance in clinical trials [123]. This inconsistency has led to the necessity for innovative in vitro and in-vivo models that better replicate the complexity and diversity of colorectal cancer (CRC) [124]. Despite this, animal models remain essential in comprehending and tracking the progression of colon cancer, and they are crucial in improving and discovering new methods of prevention and treatment [125].

Compared to in-vitro models, in-vivo animal models can more accurately reflect the intricate interactions within a living organism, including the tumor microenvironment, immune response, and drug metabolism. Even so, in-vitro models, such as patient-derived organoids, have increasingly gained recognition for their ability to mimic the complexity and diversity of CRC, providing valuable data for drug screening and treatment prediction. Furthermore, the employment of patient-derived in vitro models, such as conditional reprogramming-based cell cultures, has emerged as a promising approach for drug discovery in colorectal carcinoma [124]. Moreover, the advancement of organoid technology has provided an intermediary model between cancer cell lines in vitro and xenografts, enabling high-throughput drug screening and the discovery of novel therapeutic approaches [126].

In conclusion, while in-vivo animal models continue to be essential in understanding the progression of colon cancer and testing the effectiveness of potential drug candidates, there is a recognized need for innovative in vitro models that more accurately replicate the

complexity and diversity of the disease. Both in-vivo and in-vitro models serve complementary roles in colon cancer drug discovery, and their ongoing development and optimization are vital for advancing effective treatments. The following sections provide in-vivo animal models that can be used in CRC research.

3.2.1 Animals with spontaneous CRC

These particular species of animals can serve as a suitable instrument for CRC research; nevertheless, they may be constrained by the low prevalence of CRC within their population. Dogs are widely utilized among these species due to their resemblance to humans regarding CRC. Dogs are a fitting tool for examining the WNT signaling pathway, given the pathway's similarity in both dogs and humans. However, a significant divergence between dogs and humans lies in the occurrence of TP53 mutations alongside CRC in dogs [127].

Another dependable model to consider is sheep, whose CRC shares numerous characteristics with humans. In ordinary adult sheep, the rate of CRC incidence stands at 1.6%, surpassing that of dogs (less than 1%). However, using sheep as a human CRC model is marred by certain limitations. Firstly, all sheep-related adenocarcinomas exclusively occur in the small intestines, and secondly, their unique ruminant anatomy renders them considerably weak in this context [127].

Another example worth mentioning is Saguinus Oedipus, where the mortality rate associated with CRC reaches 39%, and the average span of years with CRC-related deaths ranges from 5 to 7 years within this species. Saguinus Oedipus proves to be an apt animal model for human CRC research due to its striking similarity and high incidence rate. Nevertheless, challenges such as delayed carcinogenesis, ethical concerns, and high financial costs pose constraints when utilizing these species [127].

3.2.2 Exogenous-induced CRC models

These models comprise animals with CRC induced by various exogenous factors. Amongst these factors, diet holds significant importance. Previous studies have shown that a specific diet known as the Western diet can lead to the development of this type of animal model. The Western diet is characterized by a low percentage of fiber and a high percentage of fat. However, this approach for developing CRC models needs to be sufficiently suitable due to the low frequency of development and the extended time required to produce such models. Despite these limitations, this method remains appealing compared to spontaneous CRC models [127, 128].

Another approach to developing exogenous-induced CRC models involves employing chemicals with mutagenesis capabilities. The most commonly used chemicals for this purpose include 1,2-dimethylhydrazine (DMH), azoxymethane (AOM), 2-amino-1-methyl-6-phenylimidozo [4,5-b] pyridine (PhIP), N-methyl-N-nitro-N-nitrosoguanidine (MNNG), and N-methyl-N-nitrosourea (NMU or MNU). These chemical substances are utilized as carcinogenic agents in rodents. However, current studies are underway to determine which substance exhibits the highest carcinogenic potential [127, 128].

3.2.3 Mutant animals as a CRC model

Developing advanced gene manipulation techniques, such as the CRISPR/Cas system, has led to significant advancements in creating mutant animal models. While these models have a few drawbacks, such as potential metastasis, they are still considered practical tools for cancer study [129]. These models are created by introducing mutations into specific genes, including APC, KRAS, Ctnb1, Msh2, TGFβR2, Fbxw7, SMAD4, and TP53 [127, 128, 130]. These types of animal models have been widely utilized in colon cancer research to investigate the mechanisms of cancer development and progression and to test novel therapies. Additionally, mutant animal models have been employed in developing and assessing therapies for hepatocellular carcinoma, providing valuable preclinical evidence before evaluating human safety and effectiveness outcomes [131]. The main advantage of these models over other models is their ability to individually induce the development of colorectal neoplasias without multiple inducing models. This makes them particularly suitable for colorectal research [128].

3.2.4 Patient-derived tumor xenograft (PDX) models

PDX models are preclinical models used in cancer research to study precision medicine and drug

discovery. PDX models involve the transplantation of tumor tissue from a cancer patient into an immunodeficient mouse, preserving the genetic and histological characteristics of the original tumor. PDX-induced pluripotent stem cells, precision-cut liver slices, patient-derived organoids, and patient-derived tumor spheroids are widely utilized to maintain tumor heterogeneity outside the body and investigate precision medicine in diverse types of cancer. They are frequently employed as patient surrogates in preclinical and translational oncology studies to screen for drug efficacy and sensitivity at a population level. Consequently, sizable collections of PDX models have been constructed from various cancer types over the past decade [132, 133]. These PDX models have emerged as a potent tool for assessing the effectiveness of drugs and their degree of sensitivity, known as PDX clinical trials. Numerous investigations have evaluated the response rates of different drugs to different cancers using PDX models, revealing that the response rates of these models to a given drug are correlated with clinical outcomes [134].

Furthermore, these models have successfully been employed to construct 3D in vitro screening methods. They have enabled more efficient screening procedures and have facilitated the development of in vitro/in vivo pairs of models that maintain genomic, histopathological, and pharmacological characteristics [133]. Moreover, PDX models have proven invaluable in studying drug resistance and discovering novel therapeutic targets for various cancers, including acute leukemia [135].

PDX models faithfully recapitulate the primary features of the original tumors and exhibit considerable stability throughout successive passages. This makes them an ideal tool for investigating tumor heterogeneity, clonal evolution, the tumor microenvironment, drug resistance mechanisms, biomarker identification, and the development of drug screening methods [136]. However, it is essential to acknowledge their limitations. For instance, PDX models lack an immune-competent environment, which may impact their ability to predict clinical responses accurately [137].

4. Simulation of drug delivery and therapeutic

Simulation software plays a pivotal role in medicine, specifically in drug delivery and the pioneering development of new drugs. These simulations serve a multifaceted purpose: aiding in procedural training, dissecting biological systems at the atomic level, and crafting tailored medical devices. They allow scientists to model and prognosticate drug behavior within the human body. For instance, physiologically based pharmacokinetic (PBPK) models, instrumental in simulating drug absorption, distribution, metabolism, and excretion (ADME), offer invaluable insights into human pharmacokinetics (PK), contributing significantly to the innovation of inhalable drug formulations [138].

A recent emergence in the simulator platforms domain is the integration of Virtual Reality (VR) and Augmented Reality (AR) for Procedural Training. These simulations, deployed across various medical disciplines like radiology, bolster procedural aptitude and amplify patient outcomes. Noteworthy instances include enhancing performance among novices in ultrasound-guided percutaneous renal access through an AR simulator and the commendation received by a fluoroscopy-guided lumbar puncture simulator for its anatomical and procedural realism [139].

Another stalwart procedure in this sphere is Molecular Dynamics (MD) Simulations. Tools like LAMMPS have surfaced as potent instruments in biomedical research, facilitating profound explorations of biological systems at the atomic scale. Their applications span protein folding, drug design, biomaterials, and cellular processes [140]. Employing Newton's laws, these simulations scrutinize the motions of diverse molecules and macromolecules within biological settings. They unravel the intricacies of biological systems encompassing water molecules, ions, small compounds, and macromolecules like proteins and viruses. Particularly pivotal in discerning ligand-protein or protein-protein recognition patterns, MD simulations furnish insights into structural cavities crucial for devising novel structures with heightened affinity to the target. They refine the three-dimensional structure of targets in drug design, enhance the sampling of binding poses, and yield more reliable affinity values. Furthermore, they decipher hot spots, elucidate structural nuances within protein sites, and expunge structural anomalies. These simulations find application in various spheres, including drug design, protein folding, and identifying potential fusion inhibitors for SARS-CoV-2 [141-143].

In simulating therapeutics, 3D Printing and Personalized Medical Devices hold paramount importance. 3D printing has contributed to fabricating tailored medical devices such as drug-eluting coronary stents and bone wedges. The efficacy of drug release hinges on factors like surface area, coated polymer, drug concentration, and coat thickness [144]. Diverse 3D printing technologies—powder bed fusion, material extrusion, VAT photopolymerization, material jetting, and binder jetting—find utility in medical applications, with commonly used materials including thermoplastics, photopolymers, and metals like titanium alloys [145].

Beyond these platforms, numerous software applications function as simulators, offering myriad advantages over laboratory experiments. Simulating drug delivery and therapeutic efficacy through software tools proves more cost-effective, obviating the need for expensive equipment and minimizing resource and time investments. Moreover, these tools accelerate simulations, enabling testing of a broader array of scenarios and parameters within shorter timeframes. Their accuracy lies in their capacity to encompass diverse factors—drug properties, patient specifics, and physiological conditions. Easily adaptable, they facilitate the exploration of varied possibilities to optimize drug delivery and therapeutic efficacy. Using software tools ensures safety by eliminating exposure risks to hazardous substances inherent in physical experimentation. Overall, software tools designed for simulating drug delivery and therapeutic effectiveness present a cost-effective, efficient, accurate, adaptable, and safe means to optimize therapeutic interventions [146]. Some of the practical and recent simulation software are discussed below.

4.1 eBrain

eBrain emerges as a sophisticated three-dimensional tool meticulously crafted for unraveling the intricacies of drug delivery within the brain. It stands as a testament to ingenuity, translating MRI data into an interactive 3D model, where the enchantment unfolds by overlaying simulated drug diffusion and tissue uptake gleaned from MRI insights. This tool orchestrates a symphony of benefits, showcasing prowess in integrating patient-specific MRI data from diverse temporal junctures and sources. Its prowess extends to monitoring treatment effects and guiding clinicians in tailoring treatments that resonate most profoundly. eBrain's potential echoes through the halls of precision medicine, sculpting the landscape of clinical trial design, illuminating educational pathways, and empowering patients in their treatment journey. Crafted upon the scaffolding of 3D graphic technologies, it seamlessly weaves physiological nuances, medical imagery, and empirical wisdom, birthing outputs steeped in clinical relevance. This virtuoso supports a ballet of in-silico analyses, adapting effortlessly to varying conditions and individuals. Its promise lies in sculpting more effective treatment paradigms, transcending the confines of standardized medical approaches [147].

4.2 GastroPlus

GastroPlus® emerges as virtuoso software, choreographing an intricate in silico dance to model and simulate the labyrinthine landscape of gastrointestinal absorption, pharmacokinetics, and biopharmaceutical properties within the human domain. Its symphony resonates in predicting oral absorption patterns, unfurling the tapestry of pharmacokinetics, and decoding the biopharmaceutics tale of diverse compounds. This software orchestrates a sonnet of exploration, unraveling the physicochemical secrets of compounds like mangiferin and forecasting pharmacokinetic odysseys. Its stellar performances grace the realm of research, optimizing the birth of novel medications and enriching the minds of aspiring pharmacists. GastroPlus® is a virtuoso, painting an in silico canvas of in vitro–in vivo correlation (IVIVC) and molding formulations for class II drugs. Its merits abound, prognosticating physicochemical properties, simulating gastrointestinal absorption, and sculpting the selection of biorelevant dissolution conditions in perfect harmony with IVIVC. This luminary educates and optimizes the genesis of generic medications, breathing life into the absorption dreams of bioactive compounds [148-150].

4.3 Simcyp™ PBPK Simulator

Simcyp™ stands tall as a software platform tailored for population-based Physiologically Based Pharmacokinetic (PBPK) modeling and simulation. This avant-garde tool is meticulously crafted to prophesize the fate of drugs within the human corpus,

deciphering their interactions with other medications, disease states, and demographic specifics. Leveraging clinical data, Simcyp™ births and hones PBPK models of drugs, verifying their authenticity and envisioning the canvas of drug-drug interactions (DDIs) and diverse outcomes. Renowned for its mechanistic finesse, this simulator paints a more vivid, lifelike portrayal of drug disposition in vivo, eclipsing traditional models. Its prowess extends to linking PBPK models with Pharmacodynamic (PD) models, unfurling a tapestry that predicts pharmacokinetics and pharmacodynamics, thus foretelling drug efficacy and response. The Simcyp PBPK Simulator unfurls a plethora of advantages: guiding pivotal drug development choices, fortifying regulatory submissions, and mitigating the protracted and exorbitant nature of clinical trials. Furthermore, it navigates clinical scenarios adeptly, lending its support to pivotal drug-label decisions. Esteemed in the pharmaceutical realm, it is an invaluable asset for model-driven drug evolution and scholarly exploration [151, 152].

4.4 COMSOL Multiphysics

COMSOL Multiphysics emerges as a vanguard in finite element analysis software, empowering users to simulate and model intricate physical systems across diverse domains like engineering, physics, chemistry, and biology. Its repertoire spans a myriad of physical phenomena—from heat transfer to fluid flow, electromagnetics, and structural mechanics. The accolades it gathers stem from its dexterity, precision, and adeptness in handling labyrinthine geometries and multiphysics quandaries. User-friendly and bolstered by a thriving community, COMSOL Multiphysics showcases its prowess in various arenas, from simulating microswimmers to modeling heat exchangers and monitoring cleanroom air quality [153-155]. However, its enchantment extends to pharmaceutical sciences as well. Here, it wields its prowess in crafting drug delivery systems, navigating microfluidics, and sculpting pharmacokinetics. It paints a canvas where drug release from diverse delivery systems dances, delves into drug behavior within the human corpus, and orchestrates optimizing microfluidic tools for pharmaceutical ends. Additionally, it lends its expertise to design and refine drug formulations and medical devices. The software's adeptness in modeling multiphysics phenomena heralds a new era in understanding complex pharmaceutical processes and products [156, 157].

4.5 ADMEWORKS Predictor

ADMEWORKS Predictor emerges as a stalwart in the prediction realm, decoding the pharmacokinetic destiny of potential drug candidates. Its prowess spans the simulation of crucial aspects—absorption, distribution, metabolism, and excretion (ADME)—acting as a beacon in deciphering the efficacy and safety of drug delivery systems. For instance, an article published in the Pharmaceutics journal employed ADMEWORKS Predictor to unravel the transport dynamics of antibiotic drugs from hydrogel drug delivery systems within a 3D eye model [156]; this software unraveled the systemic absorption patterns and disposition of the drug from nanocomposites, bestowing invaluable insights into drug release kinetics and behavior [158].

4.6 MATLAB

MATLAB is a commanding high-level programming language and environment revered for its numerical computing, data analysis, and visualization prowess. Within the realm of drug delivery and therapeutics, MATLAB finds its canvas in simulating an array of drug delivery systems, encompassing nanocarriers and sensors. An illustrative paper sculpted a mathematical model leveraging MATLAB's prowess, unraveling nanodevices for cancer diagnosis and automated drug delivery systems. This exposition showcased MATLAB's finesse in birthing neural network-based nano-bio sensors for diagnosing cancer, unveiling their potential to navigate complex drug delivery systems [159].

4.7 Integration of ADMEWORKS Predictor and MATLAB

The convergence of ADMEWORKS Predictor and MATLAB presents an all-encompassing frontier for predictive modeling and simulation in drug delivery and therapeutics. A scholarly delve witnessed the fusion of Python modules into a MATLAB-centric predictive analytics toolset for healthcare, unfurling the feasibility of extending MATLAB's armory with functionalities from diverse programming languages.

This fusion promises seamless data exchange and harnesses the sophisticated predictive modeling techniques innate to both ADMEWORKS Predictor and MATLAB [160].

In colon cancer, the alliance of ADMEWORKS Predictor and MATLAB assumes paramount importance in simulating the targeted delivery of anticancer drugs. An elucidating study pitched a fusion of imaging and analysis methodologies to scrutinize the release of anticancer drugs from nanocarriers within colon cancer cells. This pioneering effort illuminates the potential for simulating drug delivery dynamics in the realm of cancer therapeutics [161]. The discourse on multiphysics simulation's role in drug development and delivery, highlighted in an editorial, underscores the significance of advanced simulation techniques in refining treatment efficacy [162].

In conclusion, the utilization of ADMEWORKS Predictor and MATLAB in simulating drug delivery and therapeutics, notably in the context of colon cancer, heralds a promising epoch in shaping effective drug delivery systems and treatment strategies. This fusion of tools paves the way for an all-encompassing platform in predictive modeling and simulation, endowing researchers with profound insights into the comportment of drug delivery systems and their potential applications in cancer therapeutics.

5. Evaluation of the production process of drug delivery and therapeutics

Manufacturing of drug substances and products are the two key steps comprising the pharmaceutical manufacturing process. A drug product is a completed dosage form, such as a tablet, capsule, or solution, that typically, but not always, includes one or more additional substances [163]. Nevertheless, a possible public health risk arises from the pharmaceutical manufacturing industry's lack of adaptability, flexibility, and resilience. Production facility failures resulting in poor-quality goods can cause medicine shortages [164]. Moreover, as estimated by the government, the price of medications has decreased, despite the pharmaceutical industry's greater profits.

Consequently, pharmaceutical companies today face a challenge to reduce costs by modernizing and improving their production techniques. The pharmaceutical industries' production procedures allow various product quality options [165]. Thus, choosing the proper process and engineering that process to gain high-quality products with the lowest cost is necessary.

Particles with sizes between one to one hundred nanometers are known as nanoparticles [166]. Due to their special characteristics have become important in many sectors, including health and environmental science [167, 168]. Nanoparticles have been exploited as drug delivery systems since they may more easily permeate cells and tissues according to their small size. Additionally, specific functional groups can be added to them using chemical reagents. Then they can be linked to pharmaceuticals through covalent or non-covalent interactions [168]. In addition, studies have demonstrated that cellular uptake can be affected by nanoparticle size, shape, stiffness, and surface chemistry [166]. Furthermore, nanoparticles have been demonstrated to speed up the biodegradation of several substances, including low-density polyethylene. However, in some circumstances, their toxicity to microorganisms may restrict their efficacy [167]. Another distinctive characteristic of nanoparticles is the formation of a protein corona. In biological media, nanoparticles may interact with proteins to generate a protein corona that can influence their in vivo behavior. Designing secure and efficient nanomedicines requires an understanding of the protein corona. Control repeat experiments are crucial to adequately assess the distinctions and parallels between comparable systems because inadequate experimental design might result in biased results [169].

Due to the above characteristics, nanoparticles have many uses in industry and research. Their numerous industrial uses include serving as catalysts in various industrial processes, producing electronic devices, creating coatings with distinctive features, and using them in medication delivery systems, cancer therapy, medical imaging, and energy storage and conversion [170]. These particles have numerous uses in research as well. Nanoparticles are used in research for various purposes, such as the creation of new materials with special properties, the investigation of biological systems, the investigation of environmental systems, and the creation of new electronic devices with special features [170].

5.1 Processing of nanoparticle production

The scaling up of nanoparticle manufacturing from tiny to big numbers is a difficult process. However, it is required to meet the growing need for nanoparticles in numerous applications and products [171]. Different procedures and methods are used for producing nanoparticles. They can be created as solutions or powders. Top-down and Bottom-up approaches are the two main approaches for processing nanoparticles [170].

5.2 Top-down approach synthesis methods

The top-down strategy entails dismantling big structures into smaller ones, such as when patterns are etched onto a surface using lithography. The two benefits of the bottom-up method are the ability to build complex structures with fine control over their attributes and the potential for scalability. It can, however, also be more difficult to implement than the top-down strategy [172]. Many top-down synthesis methods can be utilized in nanoparticle production.

Lithography. To create patterns with nanoscale resolution, this method selectively exposes a surface to light or other types of energy using a mask. Spintronics and Nanoelectronics, which can increase the efficiency and speed of electronic devices, are made using lithography [171, 173].

Etching. The material is removed from a surface selectively during this process using chemicals or physical methods. Microelectromechanical systems (MEMS) are made using surfaces with nanoscale features created on them through etching [171].

Deposition. This method deposits material onto a surface by physical or chemical processes, including chemical vapor deposition or sputtering. When producing thin layers of materials with exact management of their properties, such as when making computer chips, deposition is utilized [171].

Nanopatterning. Employing nanoscale characteristics to make patterns on a surface, like using block copolymers to make self-assembled patterns. Using nanopatterning, one can produce tiny devices and sensors with particular characteristics [171].

Templated synthesis. This method entails using a template to direct the synthesis of nanoscale structures, such as producing nanowires utilizing porous membranes. Templated synthesis is used when producing nanomaterials with specialized properties, such as catalysts and sensors [171].

Mechanical milling. Mechanical milling is a practical method for creating materials at the nanoscale from bulk materials. To create blends of various phases and nanocomposites, mechanical milling is a useful technique. Aluminum alloys that have been strengthened by oxide and carbide, spray coatings that are resistant to wear, nanoalloys based on aluminum, nickel, magnesium, and copper, and a variety of other nanocomposite materials can all be created for mechanical milling [173].

Electrospinning. One of the easiest top-down techniques for creating nanostructured materials is electrospinning. Typically, it is used to create nanofibers from various materials, most often polymers. Core-shell and hollow polymer, organic, inorganic, and hybrid materials have all been developed using this technique [173].

Sputtering. By hitting solid surfaces with high-energy particles like plasma or gas, sputtering allows for nanomaterials to be produced. Sputtering is a useful technique for creating thin nanomaterial films. During the sputtering deposition process, intense gaseous ions hit the target surface and, depending on the incident gaseous-ion energy, physically expel tiny atom clusters [173].

The arc discharge method. The arc discharge technique is effective for producing a range of nanostructured materials. Amorphous spherical carbon nanoparticles, fullerenes, carbon nanohorns (CNHs), carbon nanotubes, few-layer graphene (FLG), and other carbon-based compounds are among those it is best known for creating. The arc discharge technique is crucial for producing fullerene nanoparticles [173].

Parallelization of multiple transferred arcs. Parallelization of multiple transferred arcs is one of the top-down approach techniques used in nanoparticle production. This approach involves parallelizing multiple transferred arcs, which have been individually optimized for nanoparticle generation. It has successfully scaled up the production rate of pure metal nanoparticles while maintaining their nanoscale size [174].

Laser beam ablation. Laser ablation synthesis produces nanoparticles by striking the target material with a strong laser beam. Due to the high energy of the laser irradiation used in the laser ablation process, the source material or precursor vaporizes, causing the production of nanoparticles. Since no stabilizing agents or other chemicals are required, using laser ablation to create noble metal nanoparticles can be considered green. This method can create various nanomaterials, including metal nanoparticles, carbon nanomaterials, oxide composites, and ceramics [173].

Overall, top-down approaches in nanotechnology involve breaking down larger structures into smaller ones, using lithography, etching, deposition, nanopatterning, and templated synthesis to create nanoscale structures with specific properties. These approaches have numerous applications in various fields, including medicine and health, energy and environment, information technology, national security and defense, and textiles and clothing.

5.3 Bottom-up approach synthesis methods

Building structures from the bottom up, or at the molecular or atomic level, is known as the bottom-up approach in nanotechnology. This method uses various methods, such as self-assembly, to build larger objects with particular features [171]. The most common industrial synthesis route for nanoparticle production is the bottom-up approach. This approach starts with nucleation, forming small particles, followed by particle growth through condensation and coagulation [170]. This approach consists of many synthesis methods that are described below.

Self-assembly. In this method, molecules or nanoparticles dynamically organize themselves into the required configuration without the assistance of outside forces [171].

Molecular beam epitaxy method. A thin film of materials can be grown with atomic accuracy by molecular beam epitaxy. In this bottom-up method, atoms or molecules are deposited onto a substrate placed in a vacuum chamber and then allowed to self-assemble into the desired structure [171].

DNA nanotechnology. This method builds nanoscale structures using DNA molecules as the building blocks. In this approach, DNA strands can be guided to self-assemble in particular configurations [171].

Colloidal self-assembly. This method produces ordered structures using colloidal particles, including nanoparticles. The intended interaction between the particles enables them to eventually self-assemble into the appropriate structure [172].

Hydrothermal method. In hydrothermal processes, chemicals that are insoluble at normal temperature and pressure are converted into nanoparticle crystals by a heterogeneous reaction that takes place under high temperature and high pressure. Crystal development is carried out in an apparatus made of a steel pressure vessel called an autoclave, where nutrients and water are fed. Normally, hydrothermal synthesis takes place at temperatures below 300 °C. Due to the acceleration of the reaction rate and significant supersaturation based on the nucleation theory, the critical condition provides a favorable reaction field for the production of nanoparticles. Metal oxide nanoparticles in supercritical water and semiconductor nanoparticles have been created using this technique [175].

Biological synthesis. Nanotechnology and biotechnology are connected through the green chemistry method known as the biological production of nanoparticles. Biological nanoparticles are stable, yet despite this, they are not monodispersed, and the rate of synthesis is slow. The polydispersity of nanoparticles and the ensuing slowdown in the synthesis rate are caused by the fluctuating concentration of synthesized macromolecules or components involved in the nucleation of particles throughout time. A combinatorial strategy, such as photobiological methods, may overcome these issues [176].

One-step desolvation. This approach is used to prepare gelatine nanoparticles (GNPs) and involves using a commercially available gelatine type. Controlled stirring conditions and ultrafiltration are used to achieve large-scale production of nanoparticles of up to 2.6 g per batch. Particle size distributions are conserved and comparable to those determined for two-step desolvation on a small scale [177].

The sol-gel method. A wet-chemical approach called the sol-gel method is widely employed for the creation of nanomaterials. This technique is utilized to create a variety of premium metal-oxide-based nanomaterials. This process is known as a sol-gel method because the liquid precursor is changed into a sol during the production of the metal-oxide nanoparticles, and the

sol is then changed into a network structure known as a gel [173].

Chemical vapor deposition technique (CVD). A chemical reaction on or near a typically heated substrate surface produces a solid material that is then deposited from vapor in a process known as chemical vapor deposition. The resulting solid substance can be a single crystal, a thin layer, or both [178]. The appropriate catalyst and carbon supply are used in the CVD process. This is a productive way to create carbon nanotubes. This technique produced dispersed graphene sheaths with improper alignment and a disorganized morphology because of the poor crystallinity of the carbon nanotubes produced by this technique [179]. This method has three different process models: photo-induced CVD, plasma-enhanced CVD, and thermally activated CVD [180].

Overall, the bottom-up approach in nanotechnology involves building structures from the bottom, or at the molecular or atomic level, using self-assembly and other techniques to create larger structures with specific properties.

5.4 Bioprocess simulation

Bioprocess simulation is a computational approach to model and analyze biological processes, particularly those involving microorganisms or cells, to optimize and control biotechnological production systems. It uses mathematical models and algorithms to represent the complex interactions between biological components, such as cells, enzymes, and substrates, and the physical and chemical conditions within a bioreactor or other bioprocess equipment [181]. This simulation can be very useful in the nanoparticle industry. Bioprocess simulation in nanoparticle manufacturing involves applying simulation modeling techniques to understand and optimize various aspects of the manufacturing process, including synthesis, characterization, assembly, and sintering. These simulations can aid in improving process efficiency, product quality, and the development of novel nanoparticle-based materials and technologies [182, 183].

Researchers and engineers can determine the ideal operating variables, such as temperature, pH, nutrient concentrations, and agitation rates, to maximize product yield and reduce production costs by modeling various process scenarios [184]. It can also create control plans to preserve desirable process parameters and guarantee product quality. This could lower batch-to-batch variability and enhance overall process performance by preventing failures [184]. Moreover, Utilizing bioprocess modeling, one can assess the economic viability of a particular bioprocess by estimating the costs and revenues associated with various process configurations [185]. Additionally, to plan and implement industrial-scale production systems, it is vital to forecast how bioprocesses will perform at higher scales. This may facilitate risk reduction, speed up process scaling, and lower costs [186]. Furthermore, bioprocess engineering ideas and methods can be taught to students and professionals using simulation tools, enabling them to get a deeper grasp of the intricate connections and dynamics present in biological systems [184].

There are many bioprocess software in the market. However, the most widely used among scientists that can be used in nanoparticle production simulation are:

Aspen Batch Plus. This software can perform particular simulation tasks and is appropriate for simulating industrial biotechnology processes. It is most effective for process management, which may be used to answer scheduling queries, investigate equipment replacements, and compute cost information [192].

BioMASS. Users can access a ready-to-use, expressive visual modeling tool through BioMASS. The continuous stirred tank reactor (CSTR) with biomass recycle and the CSTR with an additional stream in the second stage are only a few of its bioprocess configurations and subroutines. The simulation's results can be seen graphically [193].

Intelligen SuperPro. This program can carry out particular simulation tasks for industrial biotechnology processes, much like Aspen Batch Plus. Additionally, it works well for process management, where scheduling issues can be resolved utilizing material and energy balances [192].

MATLAB-based bioprocess simulation tool. This simple mathematical modeling tool was created using the MATLAB programming language. It is appropriate for describing the dynamic behavior of diverse enzyme, fermentation, and environmental bioreaction

Table 2. Examples of process simulation in nanoparticle-based pharmaceuticals.

Nanoparticle type	Simulation	Results	Software	Ref.
Magnetic nanoparticles (magnetite (Fe_3O_4) nanoparticles)	Reducing energy consumption and increasing revenue in a processing facility with a particular focus on improving the heat exchanger (HX-102) that can cut operating expenses by up to 90% and save $3,300 annually	The most economical and feasible approach was found, payback period and return on investment were estimated	Superpro student version 9	[187]
Lignin nanoparticles (nanolignin, NL)	Manipulation of lignin concentration	When lignin content reaches 6%, production costs decrease to 2.46 USD/kg.	SuperPro Designer v 9.5	[188]
Monodisperse nanoparticles	This research sheds light on the two stages of Ostwald ripening and the impact of monomer concentration at low D/k ratios on batch nanoparticle formation, indicating that this simulation can successfully direct diffusional growth	Mathematical analysis of batch nanoparticle	Matlab	[189]
Metallic nanoparticles (MNPs)	Calculations related to the extraction, green synthesis steps, and microalgae cultivation	Process designing in 7 steps	SuperPro Designer v 8.0	[190]
Magnetotactic bacteria (MTB)-derived nanomagnets	Modeling and simulation of the process in single-stage fed-batch and semicontinuous situations, as well as the suggested changes, are considered in sensitivity assessments.	Process designing and breaking down costs in fed-batch and semicontinuous situations	SuperPro Designer v 9.0	[191]

systems in bioprocess engineering simulations. The software can solve differential equation systems using a simple graphical interface [194].

SuperPro Designer. Numerous industrial applications make use of this adaptable computational tool. From a computational perspective, it can assess the production of different biological products, such as Ganoderma lucidum, in large-scale growing cultures. The program can recognize process yields and suggest adjustments to boost productivity [195].

Examples of process simulation in nanoparticle-based pharmaceuticals are summarized in Table 2.

6. Conclusion

In conclusion, colorectal cancer poses ongoing treatment challenges, especially for advanced and metastatic diseases where the prognosis remains poor. A diverse range of nanoplatforms offer unique advantages as CRC therapeutic carriers, including liposomes, polymeric micelles, solid lipid nanoparticles, and polysaccharide particles. Optimization and surface functionalization can tailor nanoparticle properties for improved stability, circulation, cell uptake, and controlled drug release specifically at tumor sites. Evaluating these nanocarriers relies heavily on appropriate experimental models, spanning cancer cell lines, xenografts, genetically engineered mice, and patient-derived organoids/spheroids to assess biodistribution, efficacy, and transport mechanisms in settings mimicking human tumors. Further pharmacokinetic and pharmacodynamic testing in vivo is warranted alongside mechanistic elucidation and rational design refinement through simulation tools. Overall, advanced nanoparticle delivery systems harbor promising potential to progress personalized targeted treatment options into clinical evaluations and ultimately clinical practice, improving outcomes and quality of life for CRC patients.

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