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REVIEW

Localized Drug Delivery in Different Gastrointestinal Cancers: Navigating Challenges and Advancing Nanotechnological Solutions

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Abstract: Different types of cancers affect the gastrointestinal tract (GIT), starting from the oral cavity and extending to the colon. In general, most of the current research focuses on the systemic delivery of the therapeutic agents, which leads to undesired side effects and a limited enhancement in the therapeutic outcomes. As a result, localized delivery within gastrointestinal (GI) cancers is favorable in overcoming these limitations. However, the localized delivery via oral administration faces many challenges related to the complex structure of GIT (varied pH levels and transit times) as well as the harsh environment within tumor cells (hypoxia, efflux pumps, and acidity). To overcome these obstacles, nano-drug delivery systems (NDDs) have been designed and proved their potential by exploiting these challenges in favor of offering a specific delivery to the desired target. The current review begins with an overview of different GI cancers and their impact globally. Then, it discusses the current treatment approaches and their corresponding limitations. Additionally, the different challenges associated with localized drug delivery for GI cancers are summarized. Finally, the review discusses in detail the recent therapeutic and diagnostic applications of NDDs that have been conducted in oral, esophageal, gastric, colon, and liver cancers, aiming to offer valuable insights into the current and future state of utilizing NDDs for the local treatment of GI cancers.

Keywords: gastrointestinal cancer, localized delivery, stimuli-responsive nanomaterials, gastro-retentive delivery systems

Introduction

The GIT is an essential system responsible for digestion and nutrient absorption. Among the different diseases that affect the GIT, GI cancers represent a major health challenge owing to the negative impact on the quality of life and the remarkably higher rates of mortality and morbidity.[1] According to recent GLOBOCAN estimates, GI cancers account for 22.8% of global cancer-related mortality and 19.4% of newly diagnosed cases. These figures highlight the pressing need for effective strategies in the management and treatment of these diseases worldwide.[2] Despite the advances in the diverse current treatment modalities, many limitations remain.

Treatment of GI cancers poses various challenges for traditional delivery systems designed for oral or systemic delivery. The systemic delivery for such localized GI tumors does not seem to be a favorable option, as it cannot enhance drug concentration within the tumor site. Also, using higher systemic doses to reach GI tumors effectively will aggravate the undesired side effects and may result in a limited enhancement in therapeutic outcomes. In contrast, local delivery via

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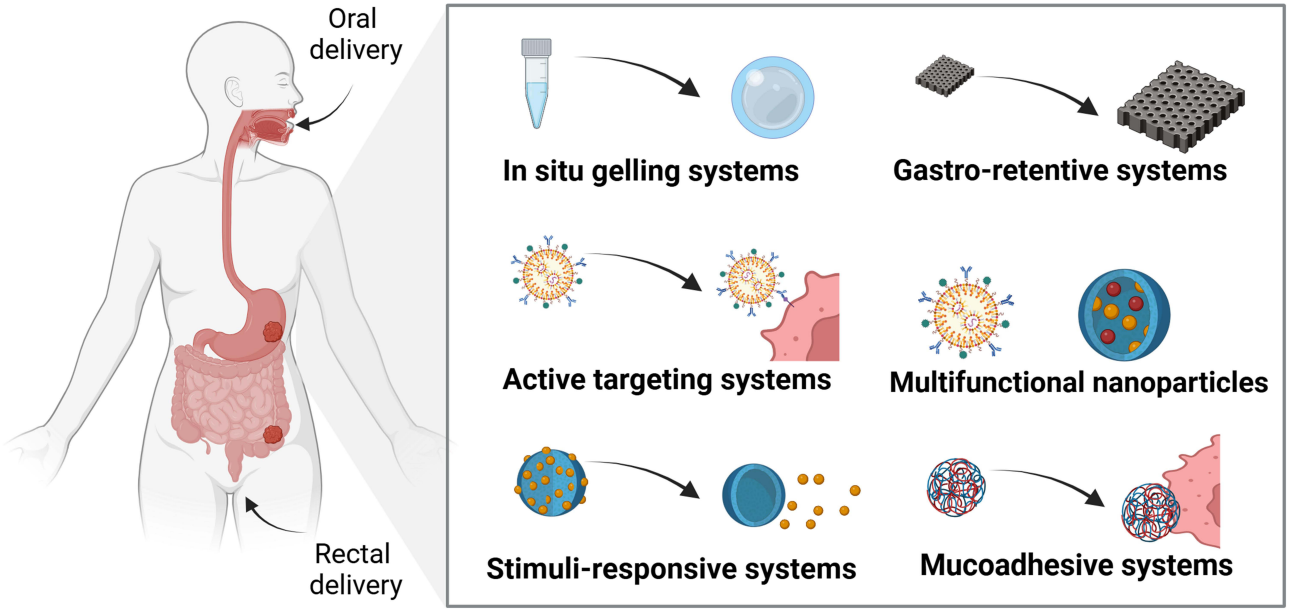
Graphical Abstract



oral administration can overcome these limitations by enhancing the drug localization within tumors, minimizing the undesired systemic side effects.[3]

In addition to oral administration, rectal administration is an alternative local delivery method, particularly for treating colon tumors. Rectal administration offers direct delivery to the disease site, reducing systemic exposure and minimizing side effects. However, effective local treatment, whether by oral or rectal administration, must overcome numerous barriers, including the complex physiological attributes of GIT and the harsh tumor microenvironment.[4] Additionally, the inadequate physicochemical properties of most anticancer agents present further challenges.[5]

The unique physiology of the GI tract renders the treatment of gastrointestinal cancers difficult. The local treatment through oral administration is subjected to different obstacles during the passage of the drug across GIT segments. These limitations involve the physiological variations between GIT segments. Changes in pH levels, enzymatic activity, and mucus barriers within different GIT segments can degrade anticancer drugs during delivery to the targeted tumor site. Variable transit times and peristaltic movements further limit drug contact time with the tumor, hindering therapeutic efficacy.[6] Besides, suppose the drugs even do well in reaching the supposed destination or target site. In that case, some other difficulties will still be encountered based on the harsh tumor microenvironment. Hypoxia, acidity, dense extracellular matrix (ECM), and efflux pumps characterize the tumor microenvironment, contributing to drug resistance.[7] Consequently, due to these different challenges, it is essential to have innovative delivery strategies for improving drug stability, prolonging contact time, and enhancing localized action specifically for GI cancers.

Nanotechnology-based systems have many advantages, making them good delivery platforms for bypassing tumor and GIT physiological barriers. They should be modified with different ligands to deliver the drugs specifically to the targeted tumor site, thus decreasing systemic toxicities and increasing treatment efficiencies. These carriers can save the loaded substances from a diversity of pH and enzyme levels.[8] Interestingly, it is possible to develop NDDs that will improve the mucoadhesive abilities to counteract various transit periods and increase the time drugs stay in contact with mucus membrane.[9] These systems can also capitalize on diverse characteristics of GI segments by producing pH, time, or enzyme-sensitive NDDs for selective delivery at particular sites. All these advantages have made NDDs the principal focus of current investigations which aim at effective management of GI cancers.[10–12] In conclusion, incorporating

nanotechnology into GI cancer treatment can override existing treatments' limitations and address specific hurdles related to the GIT.

The main purpose of the present review is to provide a comprehensive survey of localized nanotechnology-based drug delivery systems for efficient treatment of GI cancers, in different areas of the GIT. Herein, a concise overview of the global prevalence and impact of different GI cancers are discussed. Then, the review summarizes the current treatment modalities, their limitations, and the different challenges associated with drug delivery related to physiological GIT and tumor characteristics. Finally, the review discusses the advantages and applications of different nanotechnology approaches for overcoming these obstacles. Analyzing current studies and potential future directions is anticipated to inspire new ideas and increase innovation in developing effective therapies for GI malignancies.

Gastrointestinal Cancers

Many malignancies affect GIT, starting from the oral cavity to the colon (Figure 1). These malignancies pose a significant public health concern because global morbidity and mortality rates are significantly higher. They also significantly impact the healthcare system and quality of life.

The physiology of cancerous tissues significantly differs from that of normal tissues, presenting distinct challenges for localized drug delivery. The tumor microenvironment is characterized by hypoxia and acidity, along with altered pH gradients that affect drug stability and efficacy.[13] In normal tissues, cells generally exhibit adequate oxygenation and a neutral pH, facilitating the optimal efficacy of various therapeutic agents. In tumors, low oxygen levels and elevated acidity (pH ~6.5–7.0) can reduce the effectiveness of drugs, especially those sensitive to pH or requiring oxygen for activation.

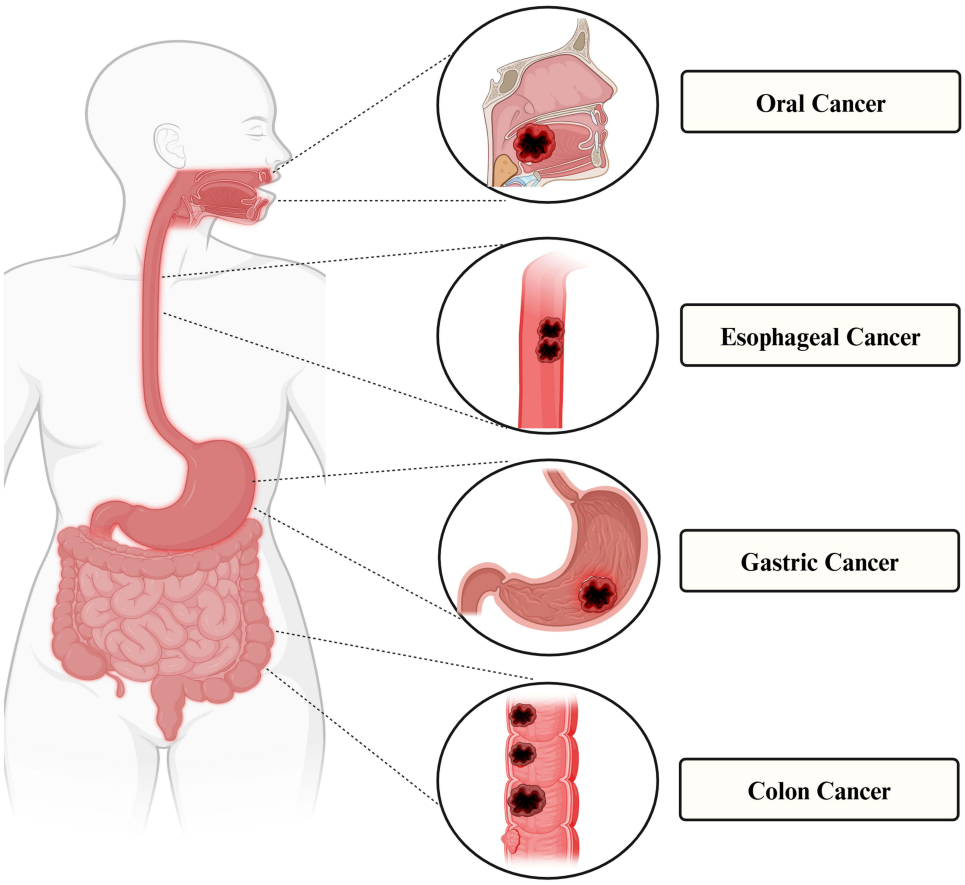


Figure 1 Illustration diagram of the different malignancies affecting the gastrointestinal tract, including oral, esophageal, gastric, and colon cancers. Created in BioRender. Kira, A. (2024) https://BioRender.com/o93m427.

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Cancerous tissues demonstrate a disorganized ECM compared to normal tissue, which is generally more structured and less dense. The tumor ECM is frequently characterized by increased rigidity, which can create a physical barrier that hinders the effective penetration of therapeutic agents.[14] Cancer cells frequently exhibit modified cellular characteristics, including heightened expression of efflux pumps that actively expel drugs from the cell, thereby diminishing their intracellular concentrations.[15] These pumps, including ATP-binding cassette (ABC) transporter family members, are overexpressed in many tumors, contributing to drug resistance.

Additionally, The vascular system in tumors is frequently abnormal, characterized by tortuous and leaky blood vessels that lead to increased permeability. The enhanced permeability and retention (EPR) effect can be utilized by drug delivery systems aimed at selectively accumulating in tumor tissues.[16] The irregular and often inadequate blood supply can limit the uniform distribution of drugs within the tumor, presenting a challenge for localized drug delivery.

Oral Cancer

Oral cancer develops as a malignant neoplasm within the oral cavity. The term refers traditionally to squamous cell carcinoma (SCC), which occurs in the thin, flat cells lining the oral cavity. SCC is the major type of oral cancer, accounting for more than 90% of all oral cancer cases.[17] Squamous cells are present in the mucosal lining of the mouth, and during malignant changes, they can invade deeper tissues and spread to other areas of the body, such as lymph nodes.[18]

The World Health Organization estimates a high annual incidence rate of oral cancer worldwide, with more than 300,000 new cases diagnosed each year. Additionally, the annual mortality rate from oral cancer is estimated to be approximately 145,000.[2] The late-stage diagnosis is one of the major issues facing effective oral cancer management. It is often detected after spreading to distant organs.[19]

Numerous risk factors are correlated with the development of oral SCC. Approximately 75% of oral cancer cases are caused by tobacco use, which is the most significant risk factor.[20] The combined effects of tobacco and alcohol further aggravate the risk. The risk of oropharyngeal malignancies has been increasingly acknowledged as a result of human papillomavirus (HPV) infection, particularly with HPV-16.[21]

Esophageal Cancer

Esophageal adenocarcinoma (EAC) is a cancer that starts in the glandular cells lining the lower esophagus, where it meets the stomach. Due to persistent gastroesophageal reflux disease (GERD), Barrett's esophagus replaces the normal squamous epithelium with columnar epithelium, which often leads to this malignancy.[22,23] EAC is characterized by its aggressive nature and ability to metastasize early, making early detection and treatment challenging.

EAC is becoming more common, especially in Western countries.[24] Over the past few decades, patient prognoses have improved slightly, yet only 20% of Western patients survive five years; this is worse than other malignancies.[25,26] In 2022, an estimated 511,054 new cases of esophageal cancer were diagnosed globally, resulting in 445,391 deaths, representing a significant global health burden.[27]

EAC occurs due to certain risk factors. Chronic GERD is a major risk factor.[28] Another major risk factor for GERD is obesity, particularly abdominal obesity.[29] Smoking and high alcohol use also increase the risk.[30,31] EAC is also associated with diet, such as low fruit and vegetable intake and excessive processed meat and fatty food consumption.[32]

Stomach Cancer

Gastric cancer, or stomach cancer, is a malignant tumor that forms in the stomach lining. The stomach lining's glandular cells cause adenocarcinoma, the most prevalent stomach cancer. Other rare forms include lymphomas and gastrointestinal stromal tumors.[33] Invasive stomach cancer spreads to lymph nodes, liver, pancreas, and other organs. Due to its slow onset and late presentation, it has a high mortality rate.[34] According to GLOBOCAN estimates, there were 968,350 new cases of stomach cancer and 659,853 associated deaths worldwide.[2] These statistics underscore the urgent need for effective management and treatment strategies for stomach cancer on a global scale.

Several risk factors cause stomach cancer. Helicobacter pylori, which colonizes the stomach lining and produces chronic inflammation and atrophic gastritis, can lead to cancer.[35] Stomach cancer risk increases with a diet high in salted, smoked, and pickled foods and low in fruits and vegetables. Smoking and heavy alcohol consumption further elevate the risk.[36] Chronic

atrophic gastritis, intestinal metaplasia, and pernicious anemia are also recognized as conditions that increase the risk of developing stomach cancer.

Colon Cancer

Colon cancer (CRC) is a cancerous tumor of the large intestine. It usually starts as a noncancerous polyp on the colon or rectum. The polyps might become malignant over time. Early polyp discovery and excision are essential for prevention and treatment since the disease can spread to other organs.

While regional incidence and prevalence vary, CRC is one of the most diagnosed malignancies worldwide. According to GLOBOCAN estimates, CRC ranks third in terms of incidence, with 1,926,118 new cases globally, accounting for 9.6% of all cancer cases. It is also the second leading cause of cancer-related deaths, with 903,859 deaths, representing 9.3% of all cancer fatalities.[2] These figures emphasize the critical need for enhanced prevention, early detection, and treatment strategies for CRC worldwide.

CRC has several risk factors. Age matters, with most occurrences happening in those over 50 years old.[37] CRC risk is also enhanced by lifestyle variables such as red and processed meat consumption, low physical activity, obesity, smoking, and heavy alcohol usage.[38] Additionally, inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are important risk factors.[39]

Current Treatment Modalities and Their Limitations

GI cancer treatments aim to reduce tumor development, relieve symptoms, and improve survival. Surgery, radiation therapy, chemotherapy, immunotherapy, and immunotherapy are the main treatments. These modalities are often employed together or sequentially depending on the cancer's location, stage, and patient health and treatment goals. In addition to these established clinical therapies, emerging treatments like gene therapy and photodynamic therapy (PDT) are being actively researched. Despite advances in GI cancer treatment, these approaches have limitations (Figure 2). Understanding these limits is essential for improving and developing more effective therapy strategies.

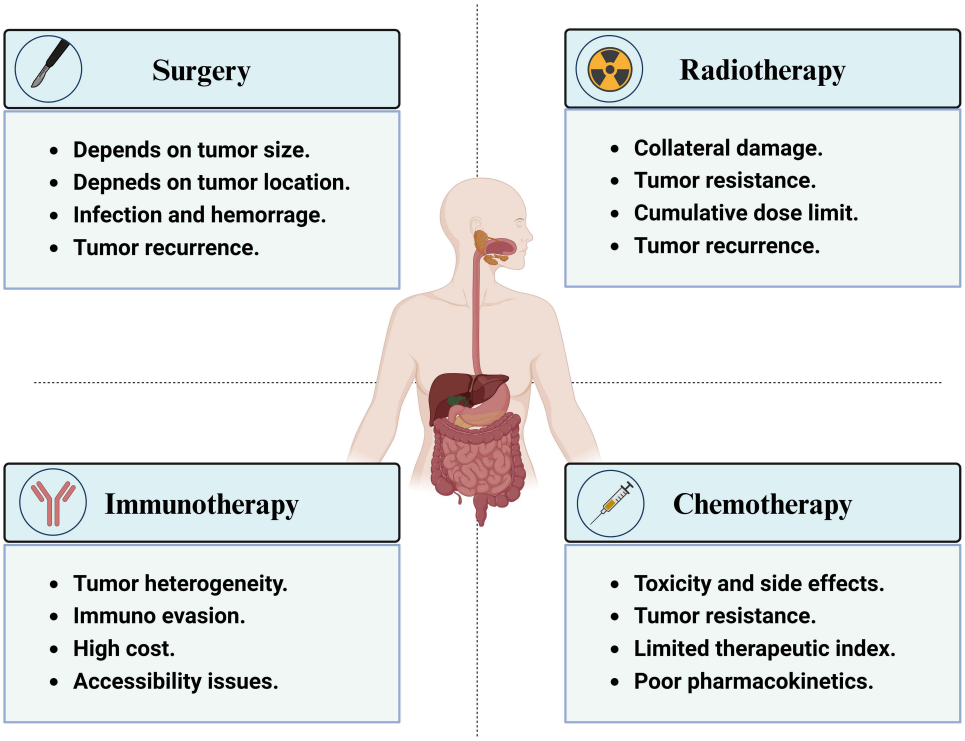

Figure 2 The current treatment modalities of gastrointestinal cancers and their corresponding limitations. Created in BioRender. Kira, A. (2024) https://BioRender.com/j25w368.

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Surgery

Surgery continues as the primary curative treatment for many GI cancers. Surgical removal of isolated tumors and lymph nodes can cure many GI malignancies. Surgery may be the best treatment for early-stage malignancies.[40] Surgery to remove the tumor and lymph nodes is typical in CRC. Gastric cancer surgery might include partial or total gastrectomy, depending on tumor location and extent.[41] Advanced techniques such as laparoscopic offer limited recovery times and fewer complications compared to traditional open surgery.

Despite its benefits, GI cancer surgery has limitations. The tumor's location, size, and invasion determine surgical resection feasibility. Some cancers are unresectable due to being near to vital structures or widespread metastasis. Furthermore, postoperative consequences include infection, hemorrhage, and organ dysfunction. Also, surgery may not eliminate microscopic disease, causing recurrence.[42]

Radiation Therapy

Radiation involves the usage of high-energy beams to destroy cancer cells. It is often used in multimodal treatments to decrease tumors before surgery (neoadjuvant), eradicate remaining cancer cells after surgery (adjuvant).[43] Radiation therapy works well for GI malignancies near critical structures or when surgery is not possible. Radiation therapy alone or in conjunction with chemotherapy (chemoradiation) can improve local tumor control and surgical resection in esophageal cancer.[44]

Radiation therapy has limitations, notably in terms of its effects on healthy tissues and organs. While technological developments have enabled more precise targeting of tumors and protection of normal tissues, radiation therapy can still cause collateral damage to surrounding structures, resulting in acute and chronic adverse effects.[45] Additionally, some tumors may show resistance to radiation, reducing their effectiveness.[46] Radiotherapy involves specific equipment and expertise, which may not be available in all healthcare settings, restricting its accessibility for some patients.

Chemotherapy

Cytotoxic drugs are used in chemotherapy to eradicate cancer cells rapidly dividing throughout the body. It is critically important in treating GI cancers, both as a monotherapy and in combination with other approaches such as radiation and surgery. Chemotherapy regimens are customized to the patient's overall health, the type, and the stage of cancer. For instance, chemotherapy regimens such as FOLFOX (folinic acid, fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, irinotecan) are frequently employed in advanced CRC to reduce tumors, delay disease progression, and enhance survival outcomes.[47,48]

Chemotherapy, as is well-known, presents numerous obstacles, such as its extraordinary toxicity and adverse effects. While acting on malignant cells, chemotherapy drugs can also impact healthy, normal cells. Chemotherapy is linked to side effects, including hair loss, vertigo, vomiting, and suppression of bone marrow. The quality of life and adherence to treatment of patients can be significantly impacted by these adverse effects.[49] Drug resistance, which can develop over time, is another well-known challenge that can lead to treatment failure.[50] Additionally, many chemotherapeutic drugs face an additional challenge due to their poor pharmacokinetics and limited therapeutic index, necessitating monitoring and dose adjustment to guarantee efficacy.

Immunotherapy

Immunotherapy utilizes the body's immune system to eliminate cancer cells. It has emerged as a promising treatment option for specific GI malignancies, particularly those with elevated levels of immune checkpoint proteins. Pembrolizumab and nivolumab, immune checkpoint inhibitors, have recently been revealed to be effective in the treatment of metastatic CRC and stomach cancer after failing standard treatment options.[51] The combination of immunotherapy with other modalities is also being investigated to improve response and survival rates.[52]

Many factors, including immune evasion mechanisms and tumor heterogeneity, can hinder the efficacy of immunotherapy.[53] Immunotherapy does not work for all patients; biomarkers predicting treatment response are still in progress. Immune-related adverse events, such as autoimmune reactions, can also occur.[54] Furthermore, immunotherapy medications are expensive and difficult to obtain, especially in resource-limited regions where innovative therapeutics are scarce.

Gene Therapy

Gene therapy is a novel method for treating GI cancers, which involves introducing or altering genetic material within a patient's cells to treat or prevent disease. This therapy seeks to correct or substitute defective genes implicated in tumorigenesis, either through direct modification of tumor cells or by modifying the immune microenvironment to bolster anti-cancer immune responses.[55] Gene therapy strategies typically involve viral vector-based delivery systems, including adenoviruses, lentiviruses, and retroviruses, as well as advanced techniques such as CRISPR/Cas9 genome editing.[56] These strategies facilitate the targeted delivery of therapeutic genes to the tumor location, potentially allowing for the correction of genetic defects or the inhibition of oncogene expression.

Gene therapy shows significant potential in treating GI cancers, especially in instances resistant to standard therapies like chemotherapy or radiation. The possibility of integrating gene therapy with treatments such as chemotherapy or immunotherapy is currently under investigation in clinical trials to enhance treatment outcomes. Gene therapy encounters numerous substantial limitations that impede its broad clinical application. Viral vectors have demonstrated efficacy in gene delivery to specific cells; however, issues related to immune responses, potential off-target effects, and genetic integration leading to unintended mutations restrict their clinical use.

Photodynamic Therapy

Photodynamic therapy (PDT) is a localized treatment approach that employs light-sensitive agents, termed photosensitizers, to target and eliminate cancer cells specifically. Photosensitizers, when activated by a specific wavelength of light, produce reactive oxygen species that elicit cytotoxic effects in cancer cells.[57] PDT has been investigated mainly for superficial tumors or those accessible to light, rendering it especially beneficial for treating GIT cancers, mainly when surgical options are not viable. Besides its direct cytotoxic effect on tumors, PDT can also induce vascular damage and trigger an inflammatory response, which further contributes to tumor destruction.[58] PDT may be utilized as an independent treatment or in conjunction with other modalities, including chemotherapy and radiation, to enhance effectiveness.

PDT presents several significant limitations that constrain its clinical application. Light penetration poses a considerable challenge, particularly for deep-seated tumors. PDT demonstrates efficacy for superficial or endoscopically accessible tumors; however, its effectiveness diminishes significantly for tumors situated more profound within the GIT. This limitation confines the application of PDT to particular cancer types or tumor stages. Photosensitizer-induced skin photosensitivity represents a significant adverse effect, necessitating that patients avoid direct sunlight for several days post-treatment, which can be burdensome and adversely affect their quality of life.[59] PDT is frequently constrained by its effectiveness in addressing larger or more aggressive tumors.

Challenges in Drug Delivery for GI Cancers

Effective drug delivery for GI cancers encounters several challenges that significantly impact therapeutic efficacy. Two main categories of barriers complicate this process. First, physiological barriers in the GIT, such as the varied pH levels, and second, the unique tumor microenvironment within the GIT presents additional obstacles. Understanding and addressing these barriers is crucial for improving drug delivery strategies.

Physiological Barriers in the GIT

GIT is a complex system with many anatomical and physiological variations across its segments (Table 1). As a result, the passage of drug molecules along the GIT will encounter many challenges that hinder drug delivery (Figure 3). Specific challenges in each section require customized approaches to enhance the effectiveness of drug delivery for GI malignancies. The presence of saliva, enzymatic breakdown, and mechanical activities provide problems within the oral cavity. The esophagus exhibits fast passage time and a restricted surface area for absorption. The stomach contains a very acidic environment. The colon and rectum possess a compact layer of mucus.

Table 1 Physiological Features of Different Segments Within GIT

Segment	pH	Membrane	Surface area	Transit Time	Microbiota	References
Oral cavity	6.5–7.5	Thin (50–100 μm)	Relatively small (~214 cm^2)	Short (seconds to minutes)	Diverse (~10^8 CFU/mL)	[60–62]
Esophagus	6–7	Relatively thick (300–500 μm)	Small (~100 cm^2)	Very short (10 seconds)	Minimal (~10^3 CFU/mL)	[63–65]
Stomach	1–3	Thick (500–1000 μm)	Relatively large due to rugae (~0.1–0.2 m^2)	1–3 h	Limited (~10^1 –10^3 CFU/mL)	[66–68]
Small intestine	5.9–7.8	Relatively thin (200–300 μm)	Extremely large due to villi and microvilli (30–40 m^2)	3–4 h	Increasing diversity (~10^4–10^8 CFU/mL)	[69,70]
Large intestine	5–8	Thicker than small intestine (300–500 μm)	Large due to surface folds (~2 m^2)	6–70 h	Abundant and diverse (~10^{11}–10^{12} CFU/mL)	[71,72]

Barriers in the Oral Cavity

The complex and dynamic oral cavity presents unique challenges for drug delivery in treating oral cancer. It is anatomically composed of various structures, including the lips, buccal mucosa, hard and soft palates, mouth floor, and the tongue's anterior two-thirds. Each of these structures has a distinct type of either keratinized or non-keratinized mucosa that shields them.[73]

The oral cavity also contains additional barriers, such as saliva and mechanical actions. To uphold oral hydration and aid digestion, saliva is produced continuously.[74] Nevertheless, this ongoing flow of fluid dilutes and washes down drugs, hence compromising the residence time they should have in the body to be effective for therapy. Moreover, amylase and

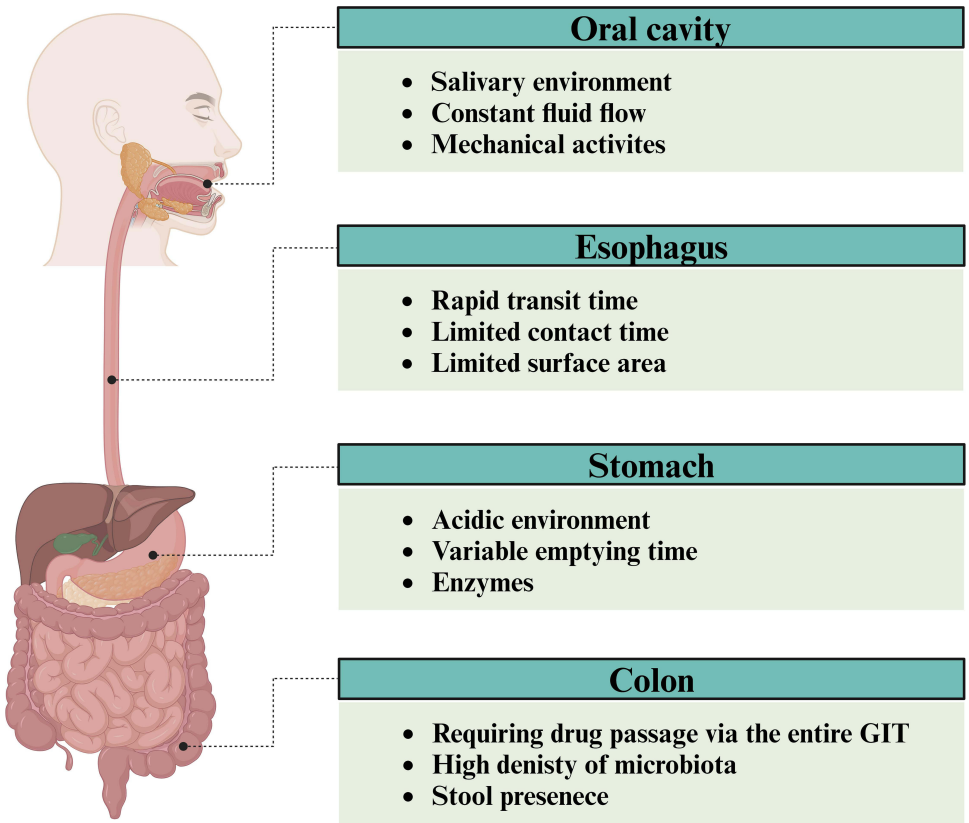

Figure 3 Schematic representation of physiological barriers to localized drug delivery within the gastrointestinal tract. Created in BioRender. Kira, A. (2024) https://BioRender.com/r26v629.

lysozyme enzymes found in saliva affect the stability of drugs.[75] Consequently, developing delivery systems that can withstand fluid dynamics and enzymatic activity in the mouth is a challenge. Another barrier is speech and swallowing, which leads to dynamic movements within the oral cavity.

Barriers in the Esophagus

A few problems have been encountered regarding the anatomy of the esophagus regarding the use of localized delivery for EAC treatment. One such factor is the rapid transit time. The esophagus is a muscular tube that swiftly propels food from mouth to stomach through peristaltic movements. Because of these quick movements, drugs have a very short residence period, nearly 10 seconds, resulting in low drug concentration and retention at the tumor site.[76] There is a restricted surface area for drug application in the esophagus as well. It lowers the potential places for drugs to attach and penetrate because the mucosal surface of the esophagus is smaller than that of the stomach or intestines.[77] Therefore, drug formulations that effectively stick to and pierce the epithelial layers around EAC are necessary to ensure localized treatment options.

Barriers in the Stomach

Some major physiological obstacles must be overcome in order to achieve effective intragastric delivery. One of the primary barriers is the highly acidic gastric fluid, which has a pH ranging from 1 to 3. This acidic microenvironment can degrade therapeutic agents before reaching tumor cells, necessitating drug formulations that can withstand such harsh conditions.[78] Also, the different GIT enzymes that break down proteins and other substances entering the stomach can affect drug stability, decreasing its efficacy.[79] Additionally, the variable gastric emptying time, as well as the dynamic movements of the stomach, can affect the residence time of drugs, expelling drugs from the application site.[80] Collectively, these challenges required a delivery system that can increase the retention time of drugs within the stomach and simultaneously protect the entrapped drug from acidic and enzymatic degradation.

Barriers in the Colon

The localized delivery for CRC management requires drug passage across different GIT segments, and as mentioned, each segment represents its challenges. A heterogeneous distribution of acidity characterizes GIT. The stomach exhibits an acidic environment (pH 1–3). In contrast, the small intestine shifts to a slightly acidic to neutral environment (pH 5.9–7.8). Finally, the colonic environment demonstrates further variation (pH 5–8), posing challenges for pH-sensitive delivery systems.[81] Additionally, the mucosal protective functions of the colon can affect drug penetration into colonic tumors.[82]

Moreover, the colon is characterized by a significantly longer retention time (6–70 h) compared to the stomach and small intestine.[83] Although this property can be favorable for delivery systems, it increases the exposure time to the high microbiota environments of the colon, affecting drug stability and bioavailability[84] As a result, advanced NDDs should be designed to protect drugs from gastric enzymes and pH and prevent earlier release in the small intestine while ensuring effective drug release in the colon to maximize therapeutic efficacy against CRC.

Tumor Microenvironment Barriers in the GIT

The harsh tumor microenvironment poses an additional challenge to effectively treating GI cancers. This environment has different components, including hypoxia, acidity, efflux pumps, and dense ECM that cooperate dynamically to resist drug penetration, negatively impacting the therapeutic outcomes (Figure 4).

The dense EXM is a physical barrier surrounding tumor tissues, limiting drug penetration into tumors. Collagen fibers and other ECM components can impede drug diffusion and distribution within the tumor, reducing the efficacy of localized treatments.[85] Abnormal blood vessel formation and impaired angiogenesis are also an important challenge in tumors such as those resulting in the development of tortuous and leaky vessels and high interstitial pressure that can affect drug retention and penetration into tumor cells.[86]

Efflux proteins, for example ATP-binding cassette (ABC) transporters, are involved in active prevention of therapeutic agents from entering cancerous cells thereby lowering intracellular drug concentrations and causing multidrug resistance accompanied by the acidic and hypoxic conditions of tumors.[15] Also, an additional challenge for localized drug delivery is represented by the heterogeneous nature of tumors in the GIT as there may be variations in genetic profiles and biological activities occurring in different parts of the tumor; hence therapies targeting specific features of cancer cells could be ineffective because such cells

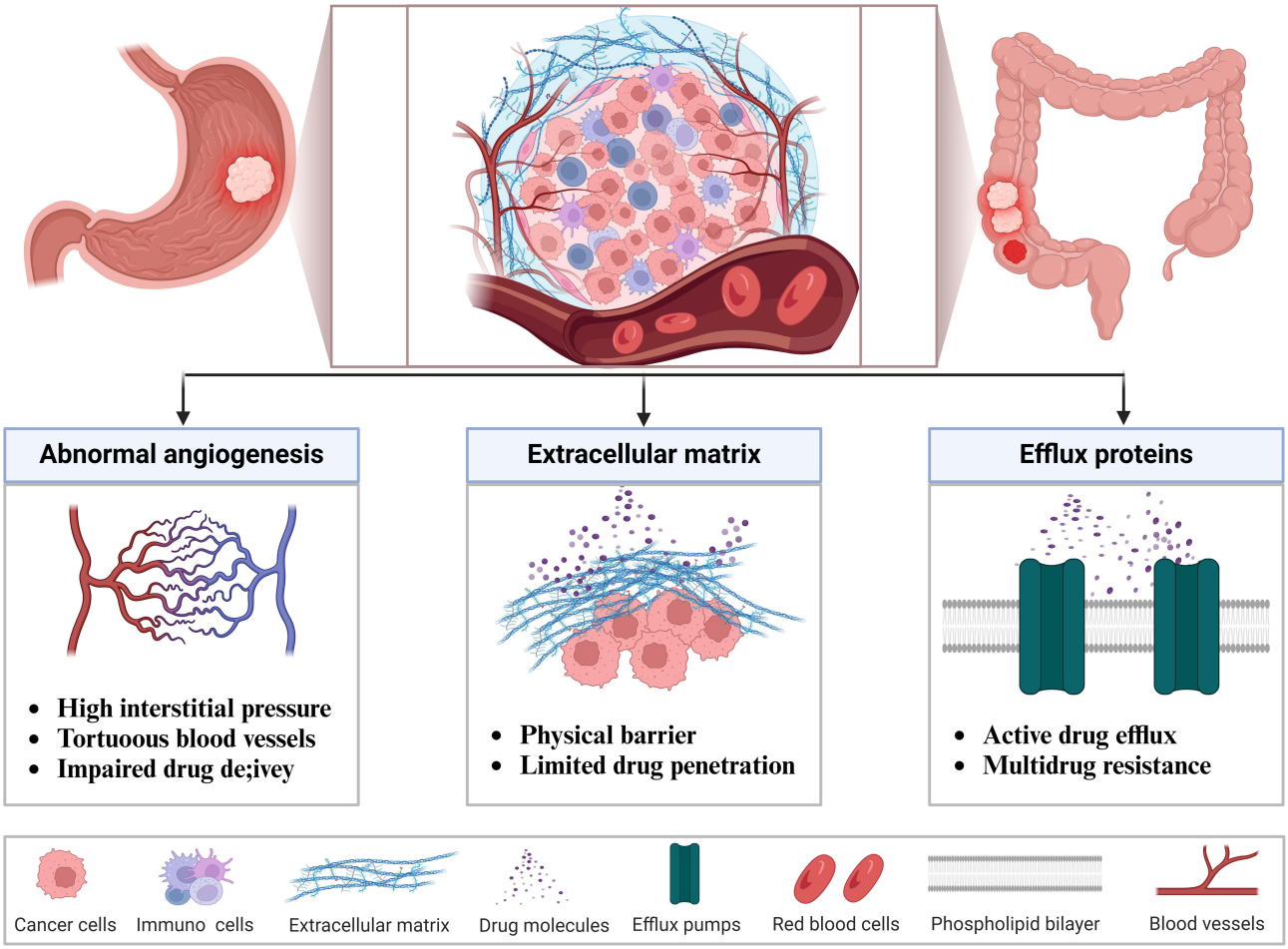

Figure 4 Key components of the tumor microenvironment in gastrointestinal cancers that negatively impact localized drug delivery. Created in BioRender. Kira, A. (2024) https://BioRender.com/m54v888.

might develop resistance to them.[87] Another problem with the utilization of such drugs is that they have severe negative effects and are also toxic.[88]

Localized Nano-Drug Delivery Approaches

The disadvantages of current GI cancer treatments and the physiological challenges to the GIT and tumor microenvironment that restrict localized drug delivery have been explored, hence there is a need for novel drug delivery systems to overcome these obstacles. By targeting and localizing therapeutic substances, NDDs could overcome such issues.[89] These systems offer the potential for improved drug stability, enhanced penetration of the dense tumor microenvironment, and reduced systemic toxicity. By utilizing the unique characteristics of NPs, such as their size, surface charge, and ability to be modified with targeting ligands, NDDs can achieve specific and effective treatment for GI cancers, including oral, esophageal, gastric, and colon cancers.

Nano-Drug Delivery Systems for Oral Cancer

One significant advantage of nanomedicine is its ability to overcome the anatomical and physiological barriers of the oral cavity using different approaches, such as mucoadhesive, in situ gelling, and active targeting systems (Figure 5). Different studies have been conducted to achieve localized delivery within the oral cavity utilizing NDDs (Table 2).

NDDs can be engineered to enhance mucoadhesion, ensuring a prolonged residence time of the drug in contact with the tumor. Mucoadhesive drug delivery systems have generated significant interest due to their capacity to deliver medications to a specific site precisely. These systems attach to the mucosal membrane utilizing interfacial interactions.[97]

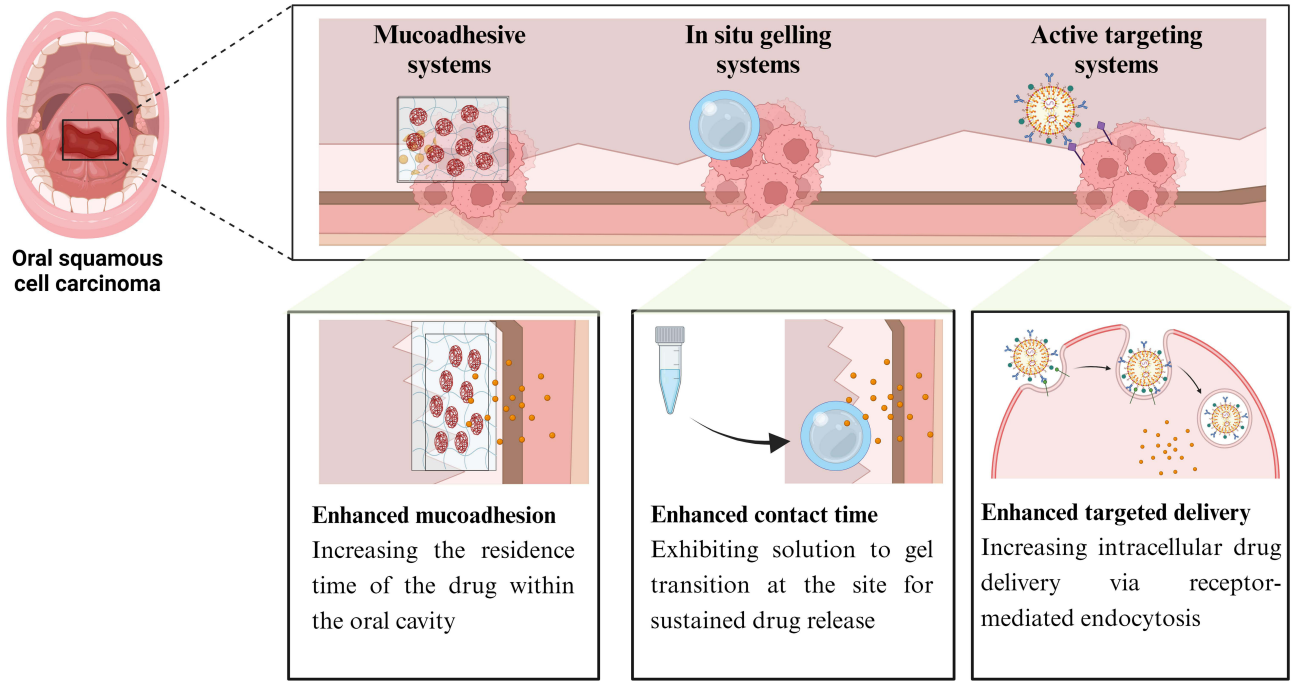

Figure 5 Schematic representation of nanotechnology-based strategies for localized delivery in oral cancer. Created in BioRender. Kira, A. (2024) https://BioRender.com/z10n113.

Some of the main mechanisms involved in enhancing mucoadhesion include, electrostatic Interactions, surface modification, and gelation mechanisms.

The surface properties of NDDs can be modified to improve mucoadhesion via functionalization. Coating NPs with catechol-based molecules or thiol groups enhances adhesion to mucus through the formation of covalent bonds with

Table 2 Applications of Nanotechnology-Based Drug Delivery Systems for Oral Cancer Therapy

Nanomaterial	Drug	Model	Key Findings	References
PLGA nanofibers	Diclofenac	In vivo	The nanofibers' local application significantly reduced tumor recurrence and improved survival over 7 weeks following tumor resection in a mouse oral cancer model.	[90]
Solid lipid NPs	Idarubicin	In vitro	The formulation showed excellent hemocompatibility and higher intracellular uptake in oral squamous cell carcinoma (OSCC) compared to bolus administration.	[91]
Poloxamer hydrogel, loaded with chitosan-coated NPs	Simvastatin	In vitro	The hydrogel showed enhanced stability, sustained drug release, and increased apoptosis in tongue carcinoma cells (HSC-3), offering a promising approach for localized therapy of oral carcinoma.	[92]
PLGA NPs	Resveratrol	In vitro and in vivo	The NPs resulted in a dose-dependent decrease in cell proliferation and invasion in human oral cancer cells. Furthermore, they effectively suppressed proliferation and angiogenesis by blocking the action of cytokines in an in vivo mouse model of oral cancer.	[93]
Chitosan-coated polycaprolactone NPs	Curcumin	In vitro	Coated NPs exhibited high mucoadhesive characteristics via electrostatic interactions, implying their potential as a local delivery system. Also, coated NPs dramatically reduced the survival of human oral cancer cells (SCC-9) by triggering apoptosis.	[94]

(*Continued*)

Table 2 (Continued).

Nanomaterial	Drug	Model	Key Findings	References
Liposomal-loaded thermosensitive pluronic gel	Paclitaxel	In vitro	The liposomal gel demonstrated significantly longer drug-release duration, stronger cytotoxicity, increased intercellular fluorescence intensity, and more drug concentration in human oral cancer KB cells compared to conventional liposomes.	[95]
α-tocopherol-modified PLGA NPs	5-fluorouracil	In vitro	The surface-modified NPs exhibited a significant level of cellular uptake, indicating the target moiety's potential to penetrate cancer cells and demonstrating advanced targeted delivery against OSCC.	[96]

mucin, which possesses thiol groups.[98] The chemical bonding enhances the interaction between the drug delivery system and the mucosal surface.

Moreover, NDDs can be designed to undergo in situ gelation or swelling upon contact with the aqueous environment of the mucus. This increases the viscosity of the NDD formulation, providing better contact with the mucosal surface and ensuring prolonged residence time at the application site. This mechanism is advantageous in the design of gastro-retentive and mucoadhesive formulations for oral and gastrointestinal drug delivery.

NDDs can be engineered with mucoadhesive polymers, such as chitosan, hyaluronic acid, or gelatin, that interact with the mucus layer through hydrogen bonding, electrostatic interactions, and Van der Waals forces.[99] These polymers contain functional groups (such as amino and carboxyl groups) that form non-covalent bonds with the glycoproteins in mucin, a key component of the mucus layer. This interaction increases the adhesive strength and prolongs the retention time of the NDDs at the target site.

Additionally, The surface charge of NPs can also influence mucoadhesion. Positively charged NPs (eg, those functionalized with cationic chitosan or other cationic polymers) interact with the negatively charged mucosal components, such as mucin, through electrostatic forces.[100] This interaction further stabilizes the adhesion of the NDDs to the mucosal surface, improving drug retention and targeted delivery.

Zhang et al recently developed nanofiber-based mucoadhesive patches as a local delivery system of astaxanthin (ASX) to treat oral premalignant lesions (OPL).[101] These patches were fabricated using polycaprolactone and gelatin via the electrospinning method and subsequently encapsulated within a saliva-insoluble polycaprolactone (PCL) backing. The PCL was made a bit easier to use in preventing the drug from being lost through the mouth when applied. Additionally, the films stuck well and maintained contact with the tongue mucosa of rats, resulting in an approximate 2h adhesion time, which ensured favorable local delivery of ASX. Moreover, it is important to note that in vivo studies revealed that these mucoadhesive patches played a crucial role in restoring OPL without causing any side effects. This suggests an avenue where the mucoadhesive technique can be employed to overcome drug delivery challenges within the oral cavity. Compared to conventional localized drug delivery systems, Zhang et al's nanofiber-based mucoadhesive patches offer several key advantages. These patches provide enhanced mucoadhesion, ensuring prolonged contact with the mucosal surface, which is typically shorter for conventional gels or creams. The controlled drug release from the nanofiber structure ensures more consistent delivery of ASX to the target site, reducing the need for frequent reapplication. Furthermore, the saliva-insoluble PCL backing prevents drug loss, improving bioavailability and minimizing systemic side effects. This suggests an avenue for the mucoadhesive technique to overcome drug delivery challenges within the oral cavity.

Among the many nanomaterials available, a unique set of mucoadhesive nanomaterials can be designed to establish long-lasting covalent bonds with mucin glycoprotein through surface modification of NDDs. This can be done by configuring NPs, which consist of catechols or thiols and acrylates so that there is strong chemical bonding through nucleophilic adduction.[102]

Pornpitchanarong et al developed chitosan/hyaluronic acid NPs modified with catechol (Cat-NPs) for local doxorubicin (DOX) delivery into oral cancerous cells.[103] Cat-NPs showed high mucoadhesion on porcine buccal mucosa

compared to unmodified NPs, indicating that Cat groups enhance mucoadhesive properties via various pathways by creating a strong covalent bond. Further, the DOX-loaded NPs demonstrated a more potent cytotoxic effect and significantly higher cellular uptake, approximately five times greater than the plain drug.

Moreover, NDDS can be modified by different targeting ligands such as antibodies, peptides, or small molecules that bind overexpressed receptors on tumor cells. This active targeting enhances the specific uptake of NPs by tumor cells and increases the chance of treatment success while minimizing off-target side effects and overall safety.[104] For example, NPs modified with folic acid residues can target folate receptors, which are frequently expressed in different types of cancers.

Recently, Gharat et al developed a drug delivery system combining both mucoadhesive and active targeting approaches for localized delivery of resveratrol (RES) to OSCC.[105] The delivery system comprised folate-modified chitosan lipidic NPs (FA-LP-NPs) dispersed in a Carbopol 971P as a mucoadhesive oro-gel. Mucoadhesiveness testing was carried out on the buccal mucosa of goats, showing that the gel could stick to the buccal mucosa for a period of 2 h and, thus, indicate its potential for maintaining long-term adhesion in patients. The NPs that were prepared inhibited OSCC effectively by arresting cell division at the G0/G1 phase through a cell culture study with an apoptotic rate of 58.08%. Additionally, a binding interaction analysis showed that the drug binds tightly to folate receptors. These findings indicate the potential for using mucoadhesive properties with active targeting approaches in site-specific delivery systems for OSCC treatment.

Srivastava et al reported the application of α-tocopherol as a targeted ligand for PLGA NPs loaded with 5-fluorouracil as a delivery system into OSCC.[96] The modified and unmodified formulations were examined with respect to their cellular uptake, cytotoxicity, and apoptosis on human tongue cancer cell lines. The results indicated that α-t-modified NPs significantly suppressed the growth of cells, with higher inhibition rate and apoptosis than those obtained in unmodified NPs. Furthermore, the developed NPs resulted in high cellular uptake, which indicated that targeting moiety efficiently adhered to the surface of tumor cells, leading to an improved selective drug delivery against OSCC. Thus, this study has demonstrated that this targeted polymeric nanoformulation is a possible platform for site-specific drug release systems to enable trigger-mediated therapy for oral cancer.

In situ gelling systems are another approach that can improve the localization of drugs in the oral cavity and overcome the limitations, as mentioned earlier. Once administered, these systems undergo a transition from sol to gel when affected by specific stimuli like temperature. The concentration of polymers or their type largely determines the mechanism behind gelation.[106] The main merit of using an in-situ hydrogel is greater contact with mucosa. This happens when there is an increased viscosity as well as a change from liquid (sol) to semisolid (gel), which then allows for controlled drug release.[107]

Kurakula and Naveen developed and optimized a thermosensitive gel composed of Carbopol 934 P and Poloxamer 407, loaded with a mucoadhesive polymer, chitosan-coated simvastatin quercetin NPs (SIM–QRC NPs), and evaluated its efficacy against the human tongue squamous carcinoma cell line (HSC-3).[92] The optimized formulation exhibited a gelation temperature of 34.1°C and a significant increase in viscosity from 1.57 to 15.19 cP upon gelation. The gel formulation significantly increased apoptosis and enhanced tumor suppressor protein levels. The presence of quercetin enhanced the biological activity of simvastatin due to the synergistic interaction between the drug and polymer. This proposed formulation offers a promising approach for overcoming the limitations of systemic chemotherapy by the localized delivery within the oral cavity.

Ortega et al developed a mucoadhesive, thermosensitive gel system composed of Hydroxypropyl methylcellulose and Poloxamer® 407, incorporating curcumin-loaded lipid-core nanocapsules coated with chitosan and in vitro investigated this system for potential OSCC treatment.[108] The in vitro evaluation revealed that the hydrogels underwent sol-gel transition at temperatures below 37 °C. Using a porcine buccal mucosa, the hydrogels exhibited superior mucoadhesion, remaining attached to the mucous membrane for almost 8 h. Also, the hydrogel formulation demonstrated a significant reduction in cell viability of the oral cancer cell line across all tested groups. These results suggest that combining nanoencapsulation with thermosensitive hydrogel development yields a promising formulation with desirable characteristics for treating oral cancer via buccal mucosa administration.

Another promising advantage of NDDs in oral cancer therapy is the ability to entrap multiple therapeutic agents within a single NPs system. This co-therapy approach allows for the simultaneous delivery of different agents, which can

target multiple pathways involved in cancer progression and resistance.[109] By encapsulating chemotherapeutic agents, gene therapy vectors, and even immunomodulatory compounds together, NPs can provide a synergistic effect that enhances overall treatment efficacy. This method maximizes the therapeutic outcome and also minimizes the side effects by using lower doses for each loaded drug.

Recently, Kim et al conducted an innovative study on combined chemo-dynamic therapy for oral cancer, employing cellular glutathione and glucose-responsive, flash-dissolving nanofibers.[110] In this study, the authors developed polyvinyl alcohol nanofibers co-loaded with glucose oxidase, MnO_2, and rapamycin. The combination of glucose oxidase, MnO_2, and rapamycin in the nanofiber mat demonstrated synergistic effects in oral cancer cells. Glucose oxidase decomposed excess glucose, generating H_2O_2. Mn^{2+} transformed H_2O_2 into hydroxyl radicals, and MnO_2 decreased cellular glutathione levels, generating oxygen, which positively affected the hypoxia environment. These catalytic reactions resulted in a cascade that allowed rapamycin to exert a significant additional antiproliferative effect, alleviating oral cancer. These findings highlight the potential of nanomaterials to offer multi-therapy carriers that can effectively manage oral cancer.

In summary, Recent studies have demonstrated the effectiveness of various NDDs for oral cancer through innovative approaches. Mucoadhesive NDDs demonstrate enhanced retention within the oral cavity. In situ gelling systems, including thermosensitive hydrogels, have garnered interest for their capacity to facilitate sustained release by converting from liquid to gel upon interaction with mucosal surfaces, thereby ensuring extended drug residence time. Multifunctional NDDs that integrate mucoadhesion and active targeting strategies demonstrate the potential to enhance specificity and therapeutic outcomes by facilitating targeted drug delivery while ensuring localized treatment.

Despite the encouraging results, numerous challenges remain. The oral environment, characterized by variable pH levels and saliva presence, presents challenges for drug delivery systems' stability and prolonged retention. The mucosal barrier restricts the penetration of specific NDDs, thereby diminishing their efficacy in deeper tissues. The variability in the structure of the oral cavity and salivary flow rates complicates the development of consistent and dependable systems for localized drug delivery. Oral cancer poses distinct challenges beyond the oral cavity, notably tumor heterogeneity and drug resistance.

Future research must concentrate on improving multifunctional NDDs that incorporate mucoadhesion, active targeting, and stimuli-responsive systems to address the previously mentioned challenges. The development of smart nanocarriers that respond to tumor-specific characteristics, including hypoxia or acidic pH, can potentially improve drug release within the tumor microenvironment while minimizing systemic side effects. Furthermore, integrating NPs with in situ gelling formulations may facilitate more controlled and sustained drug release, thereby enhancing patient adherence and therapeutic outcomes. Future strategies must address drug resistance mechanisms and tumor heterogeneity by incorporating combination therapies targeting multiple pathways in cancer progression.

Furthermore, although NDDs have been studied through ex vivo analyses of tissue and saliva samples and in vivo experiments using animal models, additional research is required before these technologies can be implemented. Nanobiosensors are expected to play an increasingly important role in electroanalytical science in the near future. Research is essential for developing techniques for producing and functionalizing NPs for clinical applications. The main effects appear to involve the early detection of diseases, genetic modifications, and biological targets. Biosensors that incorporate nanomaterials provide rapid and sensitive detection mechanisms for cancer, potentially functioning as valuable tools in anticancer biosensor research.

Nano-Drug Delivery Systems for Esophageal Cancer

The utilization of NDDs to target the esophagus is currently in the initial investigation phase. Among the few available studies, the majority primarily examine the use of intravenous administration, while only a small number of studies specifically investigate the local application. As mentioned in this review, the esophagus presents a substantial obstacle for drug administration, particularly for local drug delivery, because of the rapid transit time (10 seconds) and the thick membrane that renders this organ impermeable to substances. In this section, we provide limited trials that utilize localized esophageal drug delivery systems.

Huang et al developed chitosan-coated hyaluronic acid-modified polycaprolactone NPs as an esophageal-targeted delivery system to improve the anticancer efficacy of paclitaxel.[111] The cumulative percentage release of paclitaxel from the chitosan-coated NPs was investigated at pH range (3–7.4). Almost 20% of paclitaxel was released from the coated NPs within 48 h for all examined pH values. While the uncoated NPs showed a significantly higher release (80%) within 48 h generated by

incorporating hyaluronidase-1 in the release medium as it is abundant within tumor cells, indicating the specific release within cancer cells. Also, the prepared NPs enhanced the drug's cellular uptake and cytotoxic efficacy using an esophageal carcinoma cell line (EC109). Furthermore, in vivo evaluation of the orally administrated NPs into EC109-bearing mice revealed the ability of NPs to exhibit targeted- delivery of PTX within the tumor, enhancing its efficacy with few side effects.

Recently, Mai et al fabricated a bioadhesive nanosystem composed of polylactic acid-hyperbranched-polyglycerol NPs as a specific drug delivery system for the esophagus.[112] The prepared formulation exhibited a prolonged residence time and a significant degree of adhesion within the ex vivo rat and human tissues. The adhesion to esophageal tissue was not influenced by simulated gastric fluid (SGF), which corroborates the bioadhesive properties of this formulation in acidic microenvironments induced by certain diseases, such as GERD. Additionally, the in vivo investigation showed that the rat's esophagus retained 73% and 30% of the bioadhesive nanosystem for 2 and 10 hours, respectively, post-administration. In vivo, oral administration of NPs did not cause intestinal, hepatic, or splenic toxicity. These findings highlight the capability of bioadhesive systems for offering a localized drug delivery for the esophagus, which can enhance therapeutic efficacy outcomes for esophageal cancer as well as reduce systemic side effects of chemotherapy.

The potential of NDDs for esophageal cancer is acknowledged; however, substantial challenges impede their clinical application. Esophageal cancer presents treatment challenges due to the rapid transit time through the esophagus, which restricts the duration of contact between drug delivery systems and the tumor. The thick, impermeable esophageal mucosa is a barrier to drug penetration, thereby diminishing the efficacy of localized treatments. Moreover, the challenges associated with this aspect have resulted in an insufficient number of studies, hindering progress in the development of NDDs for the treatment of esophageal cancer. The absence of standardization in preclinical models and the disease's complexity impedes the advancement of effective therapies.

Further research is required to improve the residence time of NDDs in the esophagus. Future research should prioritize the development of advanced strategies to enhance drug retention in the esophageal region. Strategies including magnetic targeting and ultrasound-triggered release represent promising strategies that may be integrated with NDDs to address rapid transit and improve drug delivery efficiency in esophageal cancer.

Moreover, multiple studies required for the clinical translation of these platforms involve comprehensive assessments of efficacy, safety, and pharmacokinetics in suitable animal disease models. Mice and rats are commonly used for preclinical evaluation; however, it is crucial to recognize that their esophagus contains keratinized squamous epithelium, presenting an additional barrier, in contrast to the non-keratinized epithelium found in humans.[113] The esophagus of pigs shows significant similarities to that of humans in terms of length, transit duration, and characteristics,[114] therefore, it should be utilized for in vivo studies when possible.

Nano-Drug Delivery Systems for Gastric Cancer

NDDs proved their potential in addressing the difficulties associated with gastric oral delivery, offering a promising platform for gastric cancer management (Table 3). Particularly, gastro-retentive NDDs have proven to be ideal. It is possible to achieve targeted drug release over a longer period with the help of these systems because of their prolonged stomach retention time and regulated drug release input.[115] Extensive research has been conducted on gastro-retentive NDDs, which are a subject of interest because they have the potential to deliver controlled drugs to the specific location

Table 3 Summary of Nanotechnology-Based Approaches for Local Treatment of Gastric Cancer

Nanomaterial	Drug	Model	Key Findings	References
Fucose-modified chitosan NPs	Epigallocatechin-3-gallate	In vitro and in vivo	NPs successfully guaranteed the specific release of the drug within via active targeting, inhibiting the growth of gastric cancer cells in vitro and in vivo.	[116]
Magnetic-graphitic-nanocapsules	Doxorubicin	In vitro and in vivo	Nanocapsules enhanced gastric residence time and mucus penetration. Also, oral administration of the formulation exhibited enhanced cancer cell killing and improved drug penetration in vivo.	[117]

(*Continued*)

https://doi.org/10.2147/IJN.S502833

Table 3 (Continued).

Nanomaterial	Drug	Model	Key Findings	References
Nanomicelles-loaded floating mucoadhesive beads	Emodin	In vitro and in vivo	The beads delivered the drug directly to the stomach, prolonged its retention time, and effectively inhibited gastric cancer cells.	[118]
Gastro-retentive nanofibers	5-fluorouracil	In vitro and in vivo	The nanofibers showed higher mucoadhesive and floating ability. Also, it enhanced cytotoxicity and showed better tumor regression and pharmacokinetics than the plain drug, offering an effective approach for localized gastric cancer treatment	[119]
Estrogen-modified PEGyltaed liposomes	Oxaliplatin	In vitro and in vivo	The modified liposomes enhanced drug concentration within tumor sites via active targeting, showing the strongest inhibition of tumor growth. Additionally, the formulation improved oxaliplatin's pharmacokinetics profile and reduced its toxicity	[120]
β-casein NPs	Paclitaxel	In vitro	In vitro studies using human gastric cancer cell lines revealed that casein NPs were not cytotoxic to gastric cancer cells, protecting the upper GIT and effectively releasing the drug into the stomach.	[121]
Cyclic peptides nanotubes	Cisplatin	In vitro and in vivo	The prepared nanotubes demonstrated excellent mucosal permeability and specific uptake by cancer cells after oral administration, inhibiting angiogenesis and proliferation in gastric cancer	[122]

being targeted. Through the mechanisms of mucoadhesion, flotation, and expansion, it is possible to achieve the controlled retention of NDDs in the stomach (Figure 6).

The development of gastro-retentive floating systems is a significant method for enhancing the drug's efficacy by prolonging its residence within the stomach. Being with a low density, floating systems can remain buoyant for an extended period regardless of the emptying rate of the stomach[123] While the system is suspended on the gastric contents,

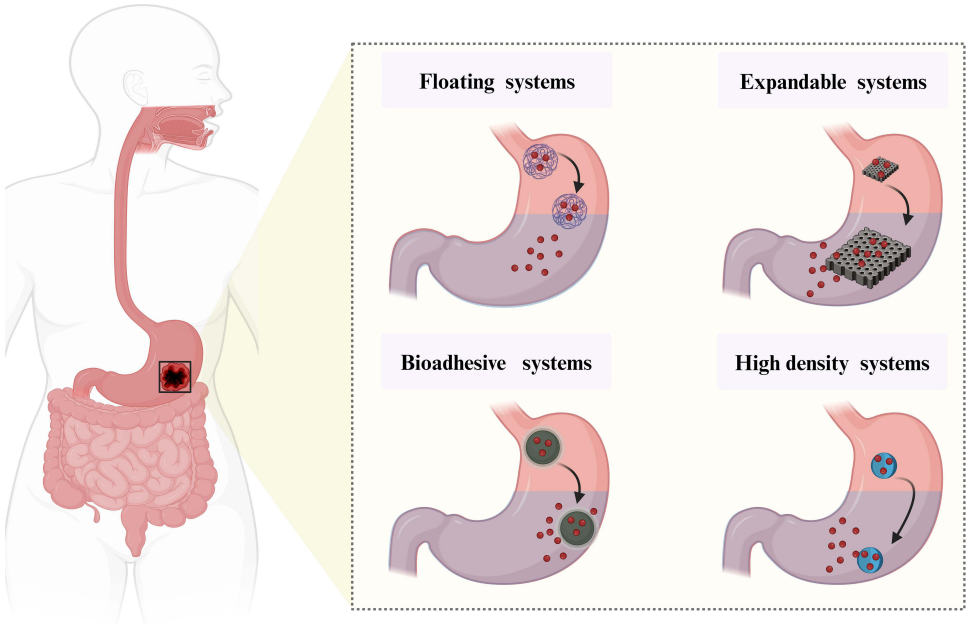

Figure 6 Schematic representation of various gastro-retentive systems for localized drug delivery in gastric cancer. Created in BioRender. Kira, A. (2024) https://BioRender.com/d56q951.

the drug is released at a controlled rate, and then the residual system is eliminated from the stomach following the drug's discharge. This extends the duration of the residence.

Chen et al fabricated a floating mucoadhesive system composed of chitosan-coated nanomicelles-loaded in Na-carboxymethylcellulose (CMC) beads as a gastro-retentive system for emodin and in vitro investigated its efficacy against human gastric carcinoma cell line.[118] The in vitro floating ability study, which utilized SGF, demonstrated that 60% of the beads with a CMC: nanomicelles ratio of 5:1 remained afloat in the gastric fluid for 8 h, indicating a high level of floating ability. The investigation of the mucoadhesive characteristics using isolated gastric mucosa of mice revealed that beads with higher ratios of CMC exhibited high mucoadhesive ability (90%) owing to the ability of CMC to form strong H-bonds with the mucin of the gastric mucosa. The potential gastro-retentive ability of the prepared system was indicated by the beads' appearance in the rabbit stomach 15 minutes after oral administration and their retention for a minimum of 8 hours, as disclosed by the results of X-ray radiography. Furthermore, the in vitro cytotoxicity assay demonstrated that the emodin-loaded nanomicelles exhibited a significantly higher cytotoxic effect compared to the emodin suspension. This indicates that the developed system can enhance the anti-tumor efficacy of emodin.

Anothra et al developed a gastro-retentive Eudragit S-100 nanofibrous film via an electrospinning approach to improving the chemotherapeutics efficacy of 5-fluorouracil against stomach cancer.[119] The prepared film showed a higher encapsulation efficiency of 5-FU (98%), a slower degradation rate (≈16% weight loss) after 10 days of incubation in GSF, and a controlled release of 5-FU in SGF, achieving almost complete dissolution within 12 h. In contrast, the plain drug showed a complete dissolution after 1 h. The nanofibers also showed better mucoadhesive properties as a force of 100 gm/cm^2 was required to separate the 5FU-nanofibrous film from the goat mucosa. In addition, the study on the in vitro floating ability of the prepared nanofibers showed that the 5FU-nanofibers floated immediately without any delay and remained floating for 48 h within SGF. The X-ray scanning revealed the improved nanofibers retained in the stomach for 12 h and confirmed the position of fibers in the upper stomach, assuring the carrier's ultralow density and floating behavior. Moreover, the developed nanofibers enhanced the pharmacokinetic profile of the drug (*Cmax, tmax*, and *AUC*) after oral administration, resulting in a significant reduction in the tumor volume compared to plain drug against Ehrlich Ascites Carcinoma-induced rat model.

Regarding the expandable gastro-retentive systems, they are easy to swallow and expand to a substantially larger size in the stomach due to unfolding or swelling processes that extend their retention time in the stomach. After the release of the drug, their dimensions are diminished as they are evacuated from the stomach.[124] By combining considerable dimensions with a high level of rigidity in the delivery system, the gastric retention time is increased to accommodate the stomach's mechanical contractility and peristalsis. Numerous studies have found that expandable systems improve gastric retention time.

Cai et al have exploited a method for controlling the shape of magnetic-graphitic-nanocapsules needle assembly (MNA) using a combination of magnetic fields and endogenous pepsin aiming to improve the gastric retention time and mucus penetration.[117] The fabricated magnetic NPs demonstrated high stability within acidic conditions, and distinctive needle shapes were developed upon contact with gastric pepsin. These MNAs exhibit exceptional magnetic-driven capacity to cross the stomach mucus barrier. Molecular dynamics simulations demonstrate the specific ways in which magnetic NPs bind to amino acid residues on both sides of pepsin, suggesting that pepsin serves as a "bridge" that enables effective interaction between NPs and promotes needle formation. Furthermore, MNAs enhanced cellular uptake and endocytosis of doxorubicin in malignant gastric carcinoma cells (MGC-803). In vivo, MNAs successfully reached the targeted stomach regions with a significant level of drug efficacy. This magnetically driven delivery system demonstrated a powerful ability to penetrate mucus and increased the stomach retention time of the drug to a period of 12 h after oral administration.

Gastro-retentive systems effectively enhance drug retention in the stomach; however, tissue permeability poses a significant challenge for drugs that necessitate deeper penetration into the stomach lining and tumor tissue. Numerous pharmaceuticals encounter difficulties traversing the gastric mucosal barrier, diminishing their effectiveness in treating gastric tumors. Scalability and reproducibility present considerable challenges in the production of NDDs. The development of manufacturing processes that guarantee the consistent quality of gastro-retentive systems for large-scale clinical application continues to pose a challenge.

Future research should prioritize improving drug penetration into gastric tissues, especially for deeper tumors. A promising direction involves the development of penetration-enhancing NDDs capable of overcoming the gastric

mucosal barrier. Incorporating penetration enhancers, including enzymes or surfactants, may temporarily modify the permeability of the stomach lining to promote deeper drug diffusion. Furthermore, NPs engineered to target tight junctions or employ transcytosis mechanisms may enhance drug delivery beyond superficial mucosal layers, thereby improving the bioavailability of the drug at the tumor site.

In addition to enhancing drug delivery, scalability presents a significant challenge in the clinical application of these advanced NDDs. Future research should concentrate on high-throughput manufacturing technologies, including automated NPs synthesis and 3D printing, to facilitate cost-effective and reproducible large-scale production. Consistent manufacturing of these systems at a reasonable cost is essential for their widespread clinical adoption and practical therapeutic application.

Nano-Drug Delivery Systems for Colon Cancer

The colon is usually reached orally or rectally. Rectal administration is an efficient method for colon-targeted drug therapy, as it allows higher doses to be delivered directly to the colon, thereby avoiding the pharmacokinetic issues related to GI motility, pH fluctuations, and hepatic first-pass metabolism associated with oral administration.[125,126] Moreover, systemic exposure is significantly diminished with rectal administration compared to oral and intravenous routes, hence substantially mitigating the risk of side effects.

Nevertheless, rectal administration struggles to target the proximal colon effectively, and self-administration poses challenges for patients, potentially leading to discomfort and reduced compliance.[127] Furthermore, despite their efficacy, the practical application of injectable medications has been impeded by the procedural demands and particular injection procedures.[128]

Oral dosage forms necessitate non-sterile production standards, exhibit low manufacturing costs, are user-friendly for patients, and are distinguished by precise dosing, stability, and storage. Additionally, oral targeted delivery systems can enhance intratumoral drug concentrations, mitigate side effects, and augment therapeutic efficacy. Consequently, oral administration is typically regarded as the most preferable and appropriate method for the treatment of colon cancer. However, regular oral administration can destroy drugs through varied pH levels, and enzyme activity.

NDDs can overcome these limitations by exploiting the different physiological characteristics of GIT. These systems can use time-dependent, pH-dependent, and microbiota enzyme-dependent methods to deliver drugs specifically for the colon. A significant number of applications have been developed, highlighting the therapeutic potential of these systems for CRC (Table 4).

Samprasit et al developed a mucoadhesive, pH-sensitive nanocarrier loaded with the anti-cancer drug alpha-mangostin.[135] The authors utilized Eudragit L100 as a pH-sensitive coating material and employed chitosan and alginate

Table 4 Summary of Nanomaterials Applications for Local Treatment of Colon Cancer

Nanomaterial	Mechanism	Drug	Model	Key Findings	References
Dextran NPs	Enzyme-responsive system	5- fluorouracil	In vitro	The NPs selectively released the drug in the colon tissues without any drug release in the stomach and small intestine simulating fluids. Also, NPs showed dextranase-triggered cytotoxicity in colon cancer cells	[129]
Folate and dextran-modified solid lipid NPs	Enzyme-responsive and active targeting system	Doxorubicin	In vitro and in vivo	Both in vitro and in vivo studies confirmed that dextran shells on NPs delayed cellular transport in the small intestine and enhanced colon residence. The folate ligands improved cellular uptake. Oral administration of the NPs effectively inhibited primary colon tumors without systemic side effects.	[130]

(*Continued*)

Table 4 (Continued).

Nanomaterial	Mechanism	Drug	Model	Key Findings	References
Lactoferrin-modified NPs-based microbeads	pH-responsive, co-loaded, and active targeting system	Indomethacin and quercetin	In vitro and in vivo	Among the different simulated gastrointestinal fluids, the microbeads effectively released the drugs only within the colon. The lactoferrin ligands enhanced the cytotoxicity and cellular uptake of NPs. Additionally, the prepared microbeads demonstrated outstanding in vivo antitumor efficacy with a low mortality rate.	[131]
Lysozyme-hyaluronan composite colloidal NPs	pH-responsive and co-loaded system	5-fluorouracil and curcumin	In vitro and in vivo	The prepared NPs enhanced higher cellular uptake and increased cytotoxicity on colorectal tumor growth compared to the control. In vivo, NPs reduced tumor volume in mice and showed synergistic effects on apoptosis and proliferation.	[132]
Eudragit S100-coated triphenylphosphine-modified nanodiamond-based NPs	pH-responsive, photothermal, and active targeting system	Doxorubicin	In vitro and in vivo	The Eudragit coating prevented drug leakage before reaching the colon. NPs showed exceptional photothermal conversion, inducing apoptosis. The triphenylphosphine ligand enhanced cellular uptake and mitochondrial targeting, showing maximum cytotoxicity. In vivo, combining chemotherapy with photothermal therapy showed the greatest inhibitory effect on tumor growth.	[133]
Folate-modified guar gum NPs	pH-, time-dependent, and active targeting system	Methotrexate	In vitro and in vivo	The folate-modified NPs showed enhanced growth inhibition of colon cancer cells, indicating folate receptor-mediated uptake. In vivo studies demonstrated preferential uptake in the colon.	[134]

as mucoadhesive polymeric NPs. The in vitro release study revealed that uncoated chitosan NPs exhibited almost 50% drug release within SGF, indicating the chitosan NPs cannot withstand the gastric acidic microenvironment after oral administration. However, coating NPs with Eudragit L100 resulted in a substantial decrease in drug release within SGF, a nearly 2.5-fold reduction, indicating the potential of Eudragit L100 as a pH-responsive coating material that can protect NP degradation in the stomach and increase drug localization in the colon. Furthermore, using chitosan NPs with Eudragit L100 coating demonstrated mucoadhesive properties, retaining the drug at the colon location and also demonstrated anti-tumor activity against colorectal cancer cells.

Using a single approach, either pH or time or enzyme-dependent system may be accompanied by limitations, resulting in compromised drug delivery to the colon. The pH-dependent system may bypass the stomach but not the small intestine, while the time-dependent system cannot survive the varied pH gradient within GIT. Also, it is affected by the irregular and varied transit times across the GIT. Moreover, microflora enzymes-sensitive systems such as natural polysaccharides are generally hydrophilic and cannot control drug release within GIT.[136,137] Advanced technologies, including di-dependent systems, have been developed to enhance colon-targeted delivery.[138] These systems employ dual control mechanisms to release the drug payload, including parameters like pH and time or pH and enzymes found in the colon's microflora (Figure 7).

In this context, a dual pH- and time-dependent system was fabricated by Taymouri et al to enhance the anticancer efficacy of simvastatin (SEM) against CRC.[139] The anti-solvent crystallization approach was utilized to prepare a nanosuspension of SEM to enhance its solubility. Then, the lyophilized NPs were filled within gelatin capsules coated with ethyl cellulose and Eudragit S100. The role of ethyl cellulose is to offer a controlled release pattern, while Eudragit S100 acts as a pH-dependent polymer. The coated capsules enhanced the drug release within the simulated colonic fluid (≈70%). In contrast, no release was observed within SGF, highlighting the ability of this system to offer a specific

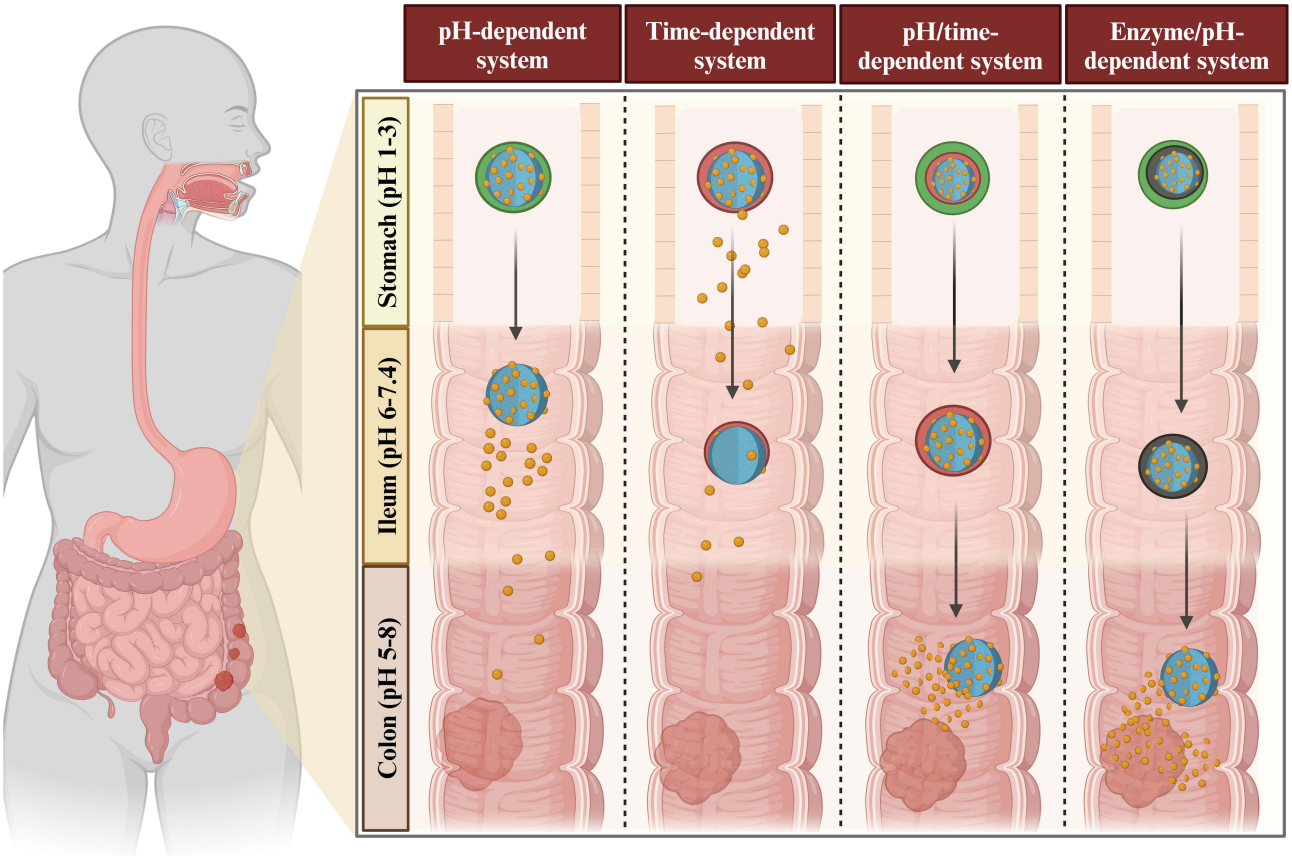

Figure 7 Comparison of stimuli-sensitive nano-delivery systems for localized colon cancer treatment. pH-dependent systems bypass the stomach but exhibit low drug concentration in the colon due to premature release in the small intestine. Time-dependent systems are susceptible to the GIT's pH variations, leading to burst drug release and reduced colon drug levels. Dual pH/time-dependent systems prevent premature release, enhancing colon drug concentration. Dual enzyme/pH-dependent systems resist pH fluctuations, targeting drug release to the colon's specific enzyme environment, maximizing drug efficacy. Created in BioRender. Kira, A. (2024) https://BioRender.com/o75c515.

delivery to the colon. Furthermore, SEM NPs showed a significantly higher cytotoxic effect against HT-29 colorectal cancer cells compared to free SEM. According to these findings, combining time, pH-dependent, and nanotechnology can offer a potential for enhancing drug concentration and cytotoxic efficacy against CRC.

Regarding microbiota enzyme-dependent systems, the colon contains a high density of microbial flora compared to other GIT segments. NDDs can utilize the GI microbiota to achieve selective drug release. Naeem et al developed a dual pH and enzyme-dependent system as a specific delivery system for the colon.[140] The system consisted of polymeric NPs of azo-polyurethane and Eudragit S100 (AZO-ES NPs). Azo-polyurethane acted as an enzyme-dependent polymer that targets azoreductase enzymes within colon tissues, while Eudragit S100 served as a pH-sensitive polymer that can protect payload within harsh acidic environments. The in vitro release study showed that the AZO-ES NPs displayed a more controlled release at ileal pH (pH 7.4) compared to ES NPs, indicative of its potential for specific colon delivery without bursting at a small intestinal level. Besides, AZO-ES NPs demonstrated significantly higher release when rat cecal contents were introduced into the release medium thus indicating that Azo-polyurethane was responsive to enzyme. Additionally, localization of AZO-ES NPs within GIT was done through an in vivo distribution study, and it was found that this drug was concentrated in the colon with 5.5 times more than that of ES NPs.

To enhance the targeting of NDDs to a greater extent, multifunctional targeted delivery systems that incorporate various targeting mechanisms have been developed. Shen et al fabricated multifunctional NPs composed of dextran/folic acid-coated solid lipid NPs as a colon-specific delivery system for doxorubicin for the local treatment of colon cancer.[130] Folic acid molecules act as a targeting ligand for folate receptors that are expressed within tumor cells, while dextran is an enzyme-dependent polysaccharide that targets dextranase enzyme within the colon. When combined with solid lipid

NPs, this dual-targeted mechanism can help treat colon cancer in several ways, such as delivering doxorubicin directly to the colon, improving drug efficacy, controlling drug release, and lowering side effects. The dextran shells on solid lipid NPs remained intact till reaching the colon. Enzymatic breakdown and degradation of the dextran coating occurred by dextranase enzymes, uncovering the folic acid ligands that interacted specifically with the overexpressed folate receptor on tumor cells, thus enhancing the specific targeting and absorption of the NPs at the cellular level within colon cancer. In vivo, NPs significantly reduced the size of the colon tumors without observing any adverse effects.

Additionally, Hou et al designed a multifunctional oral colon-targeted drug delivery system utilizing paclitaxel-loaded double-targeted NPs to treat orthotopic colon cancer.[141] These NPs were engineered with a dual-layer structure: an inulin-modified outer layer, a polylactic acid-polyethyleneimine, and a hyaluronic acid-modified inner core. The inulin shell, resistant to degradation in the upper gastrointestinal tract, ensures the safe passage of NPs to the colon, where colon-specific bacteria selectively break it down. This enzymatic degradation exposes the hyaluronic acid residues, which facilitate receptor-mediated endocytosis via CD44 overexpression on colon cancer cells, thus enabling active targeting of tumor tissues. In addition, the inner polyethyleneimine layer enhances drug release through the proton sponge effect, promoting efficient drug delivery to the target site. In vitro studies demonstrated that these NPs significantly improved cellular uptake, enhanced cytotoxicity, and induced apoptosis in colon cancer cells compared to free drug, while in vivo experiments confirmed their ability to accumulate at tumor sites and exert therapeutic effects with a favorable safety profile, with no significant cytotoxicity observed in normal tissues.

Besides their potential as an effective strategy for localized oral delivery in colon cancer, NDDs also hold promise for targeted delivery via rectal administration. Seo et al developed a novel thermosensitive and bioadhesive nanomicelle-based drug delivery system for the rectal administration of docetaxel, intending to enhance its localization within the colon and improve chemotherapeutic efficacy.[142] The system demonstrated significant gelation properties and bioadhesive strength, facilitating prolonged contact with the rectal mucosa. The properties improved the drug's retention in the rectum and promoted absorption. In vivo studies demonstrated that rectally administered nanomicelles resulted in a notable enhancement in rectal bioavailability (29%) relative to oral administration, during which the drug rapidly attained subtherapeutic levels. The nanomicelles formulation demonstrated significant therapeutic efficacy, evidenced by a notable reduction in tumor size (200 mm^3) in tumor-bearing mice, in contrast to the larger tumor volumes recorded in the oral group (950 mm^3). Histological analysis further confirmed the safety of the nanomicelles, revealing no indications of irritation or damage to the rectal mucosa.

Recently, Saleem et al created a thermosensitive liquid suppository to enhance the bioavailability and therapeutic efficacy of the multi-target kinase inhibitor regorafenib for treating CRC.[143] Regorafenib exhibits low oral bioavailability, significant adverse effects, and gastrointestinal distress, which restrict its clinical efficacy. The authors optimized a thermosensitive liquid suppository formulation incorporating poloxamers and surfactant polysorbate 80 to enhance gelation properties and mucoadhesion at body temperature. The formulation maintained a liquid state at room temperature but quickly transitioned to a gel upon rectal administration, facilitating targeted and sustained drug release at the tumor site. In vitro studies indicated the liquid suppository markedly enhanced drug release relative to plain drug suspension. In vivo experiments conducted on Sprague-Dawley rats revealed improved drug localization and bioavailability, accompanied by decreased systemic toxicity. The RG-loaded liquid suppository resulted in minimal rectal tissue damage, in contrast to the RG suspension, which caused significant tissue injury.

In summary, NDDs for CRC have significantly progressed, especially with pH-sensitive and enzyme-dependent drug delivery systems. However, a significant challenge for CRC treatment with NDDs is the heterogeneous pH gradient within the GIT, which can result in inconsistent drug release. Additionally, The dense mucus layer and epithelial barrier in the colon also limit drug penetration and bioavailability. To address these challenges, future research should focus on multifunctional NDDs that combine pH sensitivity, enzymatic responsiveness, and targeted drug release. NPs functionalized with targeting ligands (eg, folic acid or antibodies targeting CRC receptors) could improve tumor specificity. Additionally, microbiota-sensitive systems that leverage the unique enzymatic environment of the colon could further enhance targeted drug delivery. Lastly, combination therapies utilizing NDDs could help overcome drug resistance and improve treatment outcomes.

Colon Cancer Liver Metastasis

Metastasis presents a significant challenge in clinical treatment, and the majority of patients with metastatic CRC are incurable.[144] Hepatic metastases is the primary contributor to CRC mortality, responsible for 70% of metastatic cases due to the ease of cancer cell migration through the liver's portal venous drainage and the large intestine's lymphatic drainage.[145,146] CRC metastasis often involves a multi-step process comprising epithelial-to-mesenchymal transition (EMT), invasion, survival in circulation, extravasation, mesenchymal-to-epithelial transition, and colonization in the distant liver. This multi-step cascade not only facilitates liver metastasis but may also increase the risk of hepatocellular carcinoma (HCC), especially in cases where chronic liver damage or fibrosis occurs as a consequence of persistent metastatic growth.

The presence of HCC can mediate CRC liver metastasis through various mechanisms. Chronic liver damage or fibrosis resulting from the metastatic growth of CRC in the liver creates a microenvironment conducive to both HCC development and CRC metastasis progression.[147] The crosstalk between CRC cells and HCC within the liver microenvironment promotes EMT, enabling CRC cells to invade and colonize liver tissue. This interaction significantly worsens prognosis, as the coexistence of both tumors increases therapy resistance and the risk of recurrence.

To mitigate liver metastases, targeting EMT with nanomedicine has emerged as a promising strategy.[148] However, addressing the liver's altered microenvironment, including alleviating hypoxia, regulating inflammation, and controlling tumor-associated fibrosis, is equally important.[149] These interventions disrupt processes that facilitate both HCC progression and CRC metastasis. Combining EMT-targeting nanomedicine with approaches to modulate the tumor microenvironment can more effectively prevent CRC spread and recurrence, particularly in patients with chronic liver pathology.

While the primary focus of treatment is on CRC, liver metastasis is often the most significant factor in prognosis and treatment resistance. Nanomaterials targeting HCC can directly address this metastatic process, improving the targeting of liver lesions and enhancing treatment outcomes in patients with CRC liver metastasis. There are various approaches to target the liver, including the use of liver-specific ligands to improve the precision of therapy.[150,151]

Diagnostic Applications of Nano-Drug Delivery Systems

Despite the availability of diverse imaging techniques, including locoregional imaging, magnetic resonance imaging, and positron emission tomography, the late detection of GI cancers remains a potential reason for the high mortality rates of GI cancers. To get around such an issue, more specific delivery systems with a high residence time are required to be developed. As mentioned above, NDDs have the potential to achieve these criteria by providing a targeted delivery with a high maintenance time. Consequently, Many studies have combined standard approaches with nanotechnology to image GI cancers, greatly boosting the accuracy of staging and early detection. Table 5 summarizes the different diagnostic applications of NDDs that have been developed.

Table 5 Overview of the Diagnostic Applications of Nanomaterials for Gastrointestinal Cancer Detection

Cancer Type	Nanomaterial	Detection Method	References
Oral cancer	Gold nanorods	NIR-absorption imaging	[152]
	Folate-chitosan-SPIONS	MRI	[153]
	EGFR mAb- silver NPs	OCT	[154]
Esophageal cancer	Gold NPs	SERS	[155]
	SPIONS	MRI	[156]
	HB-modified gold NPs	CT and PAT	[157]

(*Continued*)

Table 5 (Continued).

Cancer Type	Nanomaterial	Detection Method	References
Gastric cancer	mAb-conjugated gold NPs	PAT	[158]
	Liposomal SPIONS	CT	[159]
	CuS micellar NPs	MRI	[160]
Colorectal cancer	Quantum dots	OCT	[161]
	Paramagnetic quantum dots	MRI	[162]
	PLLA NPs	NIR-absorption imaging	[163]

Abbreviations: NIR; near infra-red, SPIONS; superparamagnetic iron oxide NPs, MRI; magnetic resonance imaging, EGFR-mAb; epidermal growth factor monoclonal antibodies, OCT; optical coherence tomography, SERS; Surface-enhanced Raman scattering, HB; hetero bivalent, CT; computed tomography, PAT; photoacoustic imaging, PLLA NPs; poly(L-lactic acid) NPs.

Table 6 Summary of Patents for Nanomaterial Drug Delivery Systems Targeting Gastrointestinal Cancer

Patent No.	Nanomaterial	Type of Cancer	Inventor/Year	Reference
US11071726	Liposomes	Gastric cancer	Fitzgerald et al /2021	[164]
US20230301931	Cholesterol-modified polyamidoamine-G3 NPs	Oral cancer	Leong et al /2023	[165]
US20210346518	Telodendrimer-based Photothermal NPs	Oral cancer	Lam et al/2021	[166]
US10781446	Nanoprobes	Gastric cancer	Guo et al/2020	[167]
US11603566	Exosomes	Esophageal cancer	Goel et al / 2023	[168]
WO2017172678	Liposomes	Colon cancer	Fitzgerald et al /2017	[169]
US20180125976	Quantum points of porphyrinic carbon	Colon cancer	Xunjin et al / 2018	[170]
US8673358	Gold metallic NPs	Colon cancer	Shieh et al / 2014	[171]
CN108543074	Exosomes	Esophageal cancer	Gan et al / 2018	[172]

Patents

A multitude of patents exists for NDDs applications in the treatment of cancer, encompassing GI cancers as a potential indication despite their initial development for other tumor types. Data on these patents has been acquired using internet patent databases, including the World Intellectual Property Organization (WIPO) and Google Patents. Table 6 delineates the principal patents about GI malignancies, with select entries emphasized for their significance as innovative therapy approaches.

Conclusion and Future Prospectives

Different types of cancer can affect the human GIT, starting from the oral cavity to the colon. These cancers pose significant challenges for drug delivery, as each GIT segment has its own challenges despite being within the same tract. This involves the intricate GIT environment, which varies in pH, surface area, membrane thickness, transit time, and microbiota density among its various segments. Furthermore, the tumor microenvironment and the poor pharmacokinetic characteristics of chemotherapeutic drugs add another layer of challenges.

The current treatment modalities, including surgery, chemotherapy, radiotherapy, and immunotherapy, face many limitations, calling for innovations for the targeted delivery of drugs within GIT. Despite the extensive research for targeting GI cancers, most of them focus on systemic administration, which may not be effective for localized tumors within the GIT.

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This review focuses on the localized treatment of GI cancers via NDDs. These systems can be fine-tuned in different ways, exploiting the specific physiological and anatomical features of the targeted segment within GIT, resulting in a specific localized release within this target. Consequently, they enhanced local drug concentration within the tumor and effectively decreased undesired side effects. The benefits of NDDs are not limited to these features; they also offer additional advantages, making them a potential delivery system for GI cancers. These advantages include the ability to be co-loaded with different agents to enhance cancer outcomes, a controlled, sustained manner of release, increasing the residence time for the drug, enhancing pharmacokinetic profiles, and the therapeutic efficacy of the entrapped drugs.

To confirm the potential of these systems, the review comprehensively discusses in detail various applications of NDDs, including mucoadhesive, in situ gelling, active targeting, floating gastro-retentive, expandable gastro-retentive, and stimuli-sensitive approaches, that have been employed for localized treatment of GI cancers with an outstanding in vitro and in vivo outcomes, highlighting the holding promise of NDDs for overcoming existing challenges and improving outcomes for patients with GI cancers.

NDDs present significant potential for the localized treatment of gastrointestinal tumors; however, various challenges impede their broader clinical implementation. The scalability of nanoparticle production is a primary concern. Lab-scale synthesis typically yields high-quality NPs; however, scaling these processes to fulfil clinical demand may result in challenges, including batch-to-batch variability, elevated manufacturing costs, and constraints in material sourcing. The intricate nature of nanoparticle synthesis and the necessity for rigorous quality control pose challenges for producing these systems at a commercially feasible scale. Advancements in continuous-flow manufacturing, microfluidics, and automated nanoparticle synthesis are essential to enhance scalability, maintain quality, and reduce costs in overcoming these challenges.

A significant challenge pertains to the regulatory and clinical translation of NDDs. Nanomedicines must undergo thorough regulatory evaluation, with organizations like the FDA and EMA mandating comprehensive preclinical toxicology studies and clinical trials to confirm their safety and effectiveness. The process is frequently protracted, complicated by the necessity for specialized trial protocols and extended safety monitoring. Toxicity concerns, including off-target accumulation of NPs in non-target organs and immune responses that could result in systemic side effects, impede the clinical adoption of NPs. To address these issues, prioritizing safer formulations that utilize biocompatible materials is essential. Additionally, employing adaptive clinical trial designs and real-time imaging technologies, including MRI and PET, can enhance the monitoring of nanoparticle behavior and improve the efficiency of clinical trials.

Finally, the biocompatibility and biodistribution of NPs are also critical concerns in the clinical translation of NDDs. NPs must not only effectively target tumor cells but also avoid accumulation in vital organs such as the liver, kidneys, and spleen, which could lead to severe toxicity. While targeted delivery techniques, including ligand-based targeting and stimuli-responsive systems, show promise for improving tumor-specific drug delivery, the long-term effects of NPs accumulation and clearance are not well understood. To mitigate these risks, long-term safety studies and the development of biodegradable NPs made from natural materials (eg, chitosan, albumin) are essential for reducing potential toxicity and improving the overall safety profile of NDDs.

Data Availability Statement

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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