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Review article

Colorectal cancer: Current treatments and its novel drug delivery systems

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ABSTRACT

Nowadays, one of the most common tumors in the world is colorectal cancer (CRC) which is increasing day by day and attributes to the mortality of many lives around the globe. It is also the second most lethal and third most widespread cancer diagnosis for both males and females. However, numerous inventive treatments had been developed for both primary and advanced colorectal cancer which include surgery, chemotherapy, immunotherapy, and utilizing some of the novel drug delivery systems. In the present review, we have attempted to address several innovative, novel treatment methods, procedures, and targeting strategies employing different polymers and drugs to deliver at colonic region. Also, the present review highlighted the applications of nanocarriers such as carbon nanotubes, gold nanoparticles, dendrimers, liposomes, hydrogels, and phytotomies for the effective treatment of CRC.

Keywords: Colorectal cancer, novel treatment methods, polymers, approaches in colon drug targeting, nanocarriers in CRC treatment

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INTRODUCTION

It is reported that more than 600,000 deaths across the world are attributed to CRC each year, making it one of the main causes of cancer-related mortality. CRC serves as the third most common cancer identified in both males and worldwide females. Only a small percentage of CRC cases are linked to underlying genetic diseases and the majority are caused by lifestyle factors and advancing age [1]. Essentially, the CRC begins in the intestine's lining and, if left untreated, can spread into the muscle layers that lie beneath the gut wall. CRCs begin in the colon epithelium move forward to polyp-adenoma, then cancer [2]. In colonic epithelial cells, these tumors are referred to as adenocarcinomas. Recent advances in molecular biology have established conclusively that stable changes in the structure or sequence of DNA (mutations) are the first step in the development of tumors, which are then followed by the unchecked growth of the neoplastic tissue clones that identify tumor growth. Most colorectal cancers are caused by adenomas that already exist**.** Colon cancer mainly occurs in the right colon, left colon, and rectum [3]. Even though many treatment options for colorectal cancer have been extensively reported over the past ten years, the disease's poor prognosis following lymphatic metastasis or distant organs continues to be the main factor contributing to high mortality and a low overall 5-year survival rate. There are numerous treatment options for colon cancer, including chemotherapy, X-rays, and surgery. The most common kind of treatment for many individuals is surgery, which is frequently referred to as surgical removal [4]. The most common medications used for standard therapies, other than surgery, are first-line chemotherapeutic medicines for CRC like 5-Flououracil, Irinotecan, and Oxaliplatin [5].

National and international status of colon cancer

The only place in the world where colorectal cancer incidence and mortality rates are said to be significantly down while yet showing persistent health disparities in cancer screening, treatment, and survival is the United States. In the US and around the world, colorectal cancer is a substantial cause of death and morbidity. Every country is affected by colorectal cancer, which also significantly affects public health in many nations. Because of the disparities in data accessibility, comparing the epidemiology of different nations can be challenging. But these comparisons might give individual nations perspectives as they appreciate their particular illness load and create effective cancer prevention and treatment plans [6]. In 2020, CRC cancer cases were reported to 73,157 in India and followed in the United States 147,950 [7, 8].

Incidence rate

The Republic of Korea has the highest CRC incidence rates in 2012 (AGR = 45). The countries with the lowest incidence rates were Singapore (AGR = 33.7), Spain (33.1), Costa Rica (32.9), Serbia (32.6), and Japan (32.2 per 100,000) (ASR= Age Standardized Rates). Eastern Europe and Western Asia, particularly Israel and

Kuwait, saw the largest increases (Czech Republic, Slovakia, and Slovenia).

Mortality rate

Central and Eastern Europe had the highest death rates for both sexes (ASR = 20.3 for men and 12.1 for women, per 100,000). The Middle Division of Africa has the lowest death rates (ASR = 3.5 and 2.7 per 100,000 for men and women, respectively). In terms of gender, men have a mortality rate that is 30-40% greater than women [9].

Figure 1: Stages of Colorectal Cancer [10].

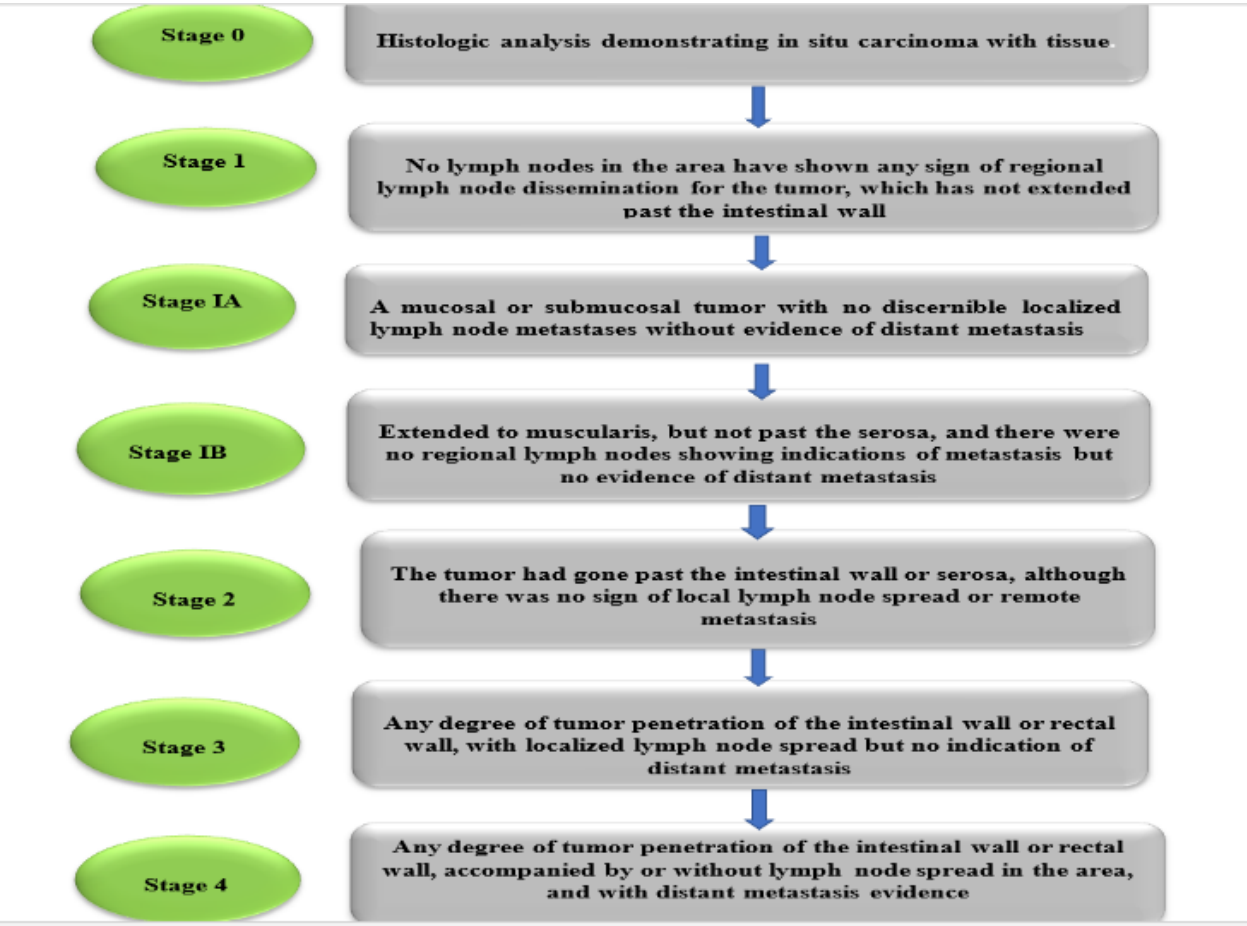
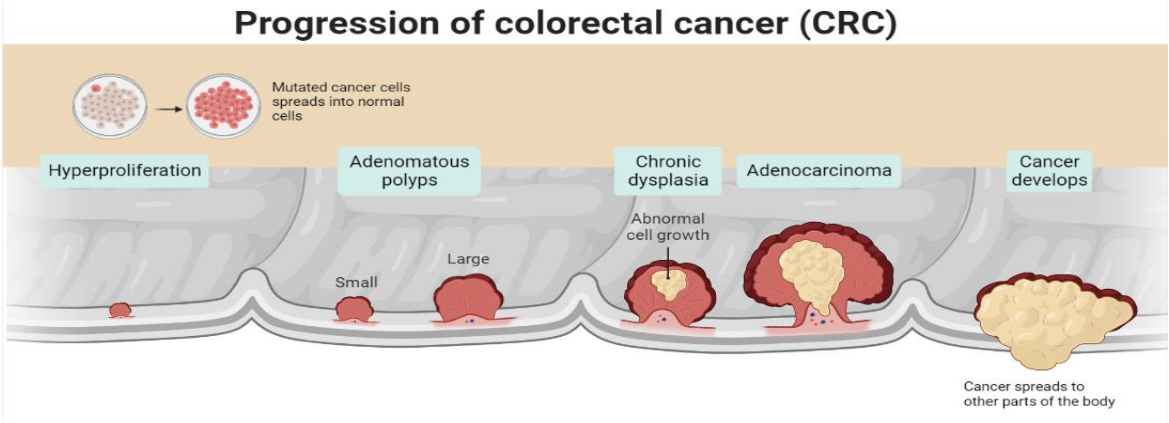


Figure 2: Progression of Colorectal Cancer.



Current treatments for CRC

Surgery of localized disease

Surgery aims to completely remove the affected intestine segment and its lymphatic drainage. The location of the local lymph nodes and blood supply dictate how much of the colon is removed. Although broader margins are frequently included due to the mandatory closure of the arterial blood supply, the resection should encompass a segment of the colon measuring at least 5 cm on either side of the tumor. There is no survival benefit to extensive "super radical" colonic and lymph node excision over segmental resection [11].

Adjuvants in Chemotherapy

With only a limited percentage of isolated local failure, CRC typically fails in the peritoneal cavity, the liver, or in distant

regions. The best adjuvant is therefore systemic chemotherapy or immunotherapy. Clinical trials are necessary to find more active medicines because the best adjuvant therapy for colon cancer in stages II and III has not yet been developed [12]. Adjuvant chemotherapy to enhance colorectal cancer survival rates following resection has increased and attracted a great deal of attention recently [13]. One of the first significant randomized trials to demonstrate the benefit of adjuvant surgery was the National Surgical Adjuvant Breast and Bowel Program (NSABP) trial C-01. Adjuvant chemotherapy is not anticipated to be beneficial for patients with Stage I CRC because they can be cured by surgery alone, with survival rates of 85% to 95%. Adjuvant therapy with high-risk stage II cancer patients with colon cancer has a 75% to 80% 5-year survival rate. The most contentious region in colon cancer treatment is now 80% following surgery alone [14].

Current Adjuvant Therapy

5-Fluorouracil/Leucovorin(5-FU/LV) continues to be the foundation of adjuvant therapy in CRC. In stage III of the disease, 5-FU/LV results in 3-year disease-free survival rates of 61% to 67%, according to several phase III trials. The oral fluoropyrimidine capecitabine was linked to a 3-year disease-free survival rate of 64% in the X-ACT study (Xeloda in Adjuvant Colon Cancer Therapy). Infusion 5-FU/LV and oral capecitabine are less toxic and at least as effective as bolus 5-FU/LV. Bevacizumab and cetuximab are now undergoing trials for determining their beneficial role for CRC as first-line chemotherapy [15].

Targeted Therapy

Targeted medicines can directly affect cancer cells and prevent migration, differentiation, and cell division. The local blood vessels and the tumor microenvironment are altered Targeted medications may also change immune cells to inhibit better immune attack and surveillance, and slow tumor growth. The key participants are small compounds like monoclonal antibodies in targeted treatments. The first CRC-specific agent authorized by the Food and Drug Cetuximab was approved by the Food and Drug Administration (FDA) in 2004 and in the same year, the FDA-approved bevacizumab and various targeted CRC medications have been introduced to the market. Even though focused therapy is linked to longer survival, several negatives exist, but the cost-benefit ratio is the key one. Questionable given how much less expensive modern chemotherapy is than more specialized regimens, particularly for those who may require several targeted agents [16].

Adjuvant Radiation Therapy

Radiotherapy has developed into a crucial component of the multidisciplinary approach in the last twenty years for colorectal cancer patients in medical care. But, the combination of minimal radiation exposure and the outcome of surgery is questionable.

Pre- and Post-operative Radiotherapy for CRC

In both preoperative and postoperative contexts, adjuvant radiation has been used. Pre-operative radiation may have the ability to destroy tumor cells more effectively because of enhanced oxygenation when contrast to the condition following surgery when vascular changes are expected. It may also cause cellular injury that may be distributed locally or far during resection. As an option, postoperative radiation has the potential to reduce delays in treatment through careful patient selection. With tumors in the bottom or middle portion of the rectum, better staging procedures, such as pre-operative radiology, could enhance patient screening for pre-operative research [17]. Unlike rectal cancer, where radiation therapy combined with chemotherapy is the conventional adjuvant treatment, the use of radiation in colon cancer is still under examination (either local/regional or the whole of the stomach) [18].

Immunotherapy for CRC

Immune modulators coupled with chemotherapy are another strategy to improve the chemotherapy's effects in individuals with severe colorectal cancer. A significant target for therapeutic intervention, the Immunological Tumor Microenvironment (TME) of colorectal cancer (CRC) plays a vital role in the biology of the disease. It has been discovered that immune profiling of the TME has both prognostic and predictive benefits for patients as a result of the variety of immune cell populations within different subgroups of CRC. Clinical care has changed dramatically as a result of the merging of greater molecular and cellular characterization of CRC and the extensive use of immunotherapy in tumor cells. In microsatellite instability-high (MSI-H) CRCs, monoclonal antibodies (mAbs) that directly target key immunological checkpoints, such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), have several recent therapeutic efficacies [19].

Colorectal cancer has a well-defined mutator mechanism called microsatellite instability (MSI) (CRC). It has been demonstrated that CRCs with high levels of microsatellite instability (MSI-H) and concomitant peritumoral lymphocytic infiltration (TILs) respond more effectively to the anti-tumor immune system. TILs are closely attributed to antitumor responses and patients whose histological samples of CRC contain TILs likely to have a survival benefit. Five immune checkpoint molecules, including lymphocyte-activation gene (LAG-3) and indoleamine 2,3-dioxygenase (IDO), have recently been recognized as potential immuno-oncology targets. These molecules are programmed cell death-1 (PD-1), a part of the family of a cluster of differentiation (CD28) T-cell regulators, PD ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLAP4) [20].

Nanocarriers for CRC treatment

Carbon Nanotubes

Alkenes of carbon that are usually cylindrical, carbon nanotubes (CNTs), have wrapped graphite with a diameter of less than 1 micrometer and a few nanometers in diameter. Due to CNT's chemical characteristics, including its large area, thread framework, temperature resistance, and chemical inertness, it has the potential to be used in a variety of applications, which include genetic engineering, immunotherapeutic, diagnosis, and as a system for drug delivery carriers. Numerous studies revealed that various methods for using CNTs to transport anticancer medicines have been devised. Single-walled carbon nanotubes coupled with an artificial polyampholyte were employed to deliver paclitaxel to Caco-2 cells. Caco-2 and HT-29 cells treated with paclitaxel-SWCNT demonstrated enhanced antitumor effects in CRC.

Gold Nanoparticles

Recent technological advancements have enabled precise surface coating of gold nanoparticles with a predetermined size and shape parameters. Because of these characteristics, gold nanoparticles are a more effective and safer chemotherapeutic and drug carrier vehicle. For targeted therapy applications, gold nanospheres can also be easily coupled with a variety of optical sensors and used to transport genes, medicine loads, and other anti-cancer agents. Normally, gold nanoparticles collect passively in tumors and work in conjunction with active targeting ligands like epitopes, antibodies, and proteins to obtain precise pharmacological activities [21].

Dendrimers

In the group of polymer nanoparticles are dendrimers. However, they are distinct from conventional polymers in that they have a fundamentally different structure. The most prevalent class of dendrimers is PAMAM. After alteration, these special "polymeric compounds" can develop into intelligent species that deliver medications to key sites and can also be used to track the condition of organs being attacked by cancer cells as well as the progression of the healing process. Nanotechnology is now a desirable strategy for developing cutting-edge healthcare solutions for CRC attributable to recent advancements in the field. In the latest report, PAMAM dendrimer nanoparticles were used to wrap gold nanoparticles. This study's goal was to look into the novel therapeutic potential of dendrimer-gold heterocycles loaded with curcumin [22].

Liposomes

Liposomes are spherical, lipid-containing particles that range in size from nanometers to microns. They have a shape like that of cells, with an exterior phospholipid bilayer envelope entrapping an inner aqueous interior. Due to their distinctive structure, liposomes may enclose and transfer both hydrophilic and lipophilic drugs. These nanocarriers are used as effective DDS for CRC [23].

Hydrogels

Essentially, hydrogels are three-dimensional cross-linked aqueous structures made of hydrophilic polymers. For p^H-responsive and controlled release colon-specific drug delivery, two azo hydrogels (a single network hydrogel and an interfacial network hydrogel) have been created. *In vitro* delivery of 5-fluorouracil (5-FU) bound azo hydrogels in rat intestinal fluid (RCF). The results of the investigation revealed that azo hydrogels might be a potential medication delivery system for colon-targeted delivery.

Phytosomes

To cure a variety of ailments, phytotomies distribute diverse medications and phytoconstituents at either active or passive targeting. The therapeutic effects of 5-fluorouracil and phytosomal curcumin were investigated in a mouse colitis model to limit the growth and proliferation of cancer cells [24].

Colonic-specific drug delivery systems

Colon-specific medication delivery methods have long been understood to be necessary and advantageous. Colon-specific delivery has the potential to address significant unmet therapeutic needs in addition to improving therapies for colon-related disorders such as irritable bowel syndrome, including peptic ulcer and gastrointestinal disorders. Because of the colon's comparatively low proteolytic enzyme activity, the colon is also thought to be the optimum absorption location for oral delivery of protein and peptide medicines. According to reports, approximately one million Americans are thought to have inflammatory bowel syndrome, with 15,000–30,000 incidences being identified each year. However, effective treatment for this serious condition may depend on specific drug delivery with a suitable sustained release [25]. Additionally, some data suggest the colonic mucosa's proteolytic activity may be considerably lower than that of the small intestine. The effectiveness of drug administration in the large intestine of mammals has been examined using a variety of animals. The rodent has been crucial in the study of colonic delivery systems, as may be assumed. Dogs are frequently used to test oral controlled release delivery mechanisms [26]. Both the oral and rectal routes can be used to deliver medications to the colon. Rectal medication delivery is usually acknowledged as being less desirable than oral colonic drug delivery, despite minimizing many of the problems associated with oral colonic drug delivery [27].

Recent advances in colon-specific drug delivery systems

The effectiveness of a colon-specific drug delivery system (CDDS) depends on the drug's physiochemical parameters, the kind of delivery platform, any other variables that may affect the GI transport duration, and the level of drug-GI tract contact. As a result, some procedures used in the development of a CDDS have shown to be more effective than others in postponing the drug release until the system reaches the colon [28].

Prodrug Approach

Prodrug is a pharmacologically inert byproduct of a primary drug molecule that needs to undergo a random enzymatic change in living tissue to release the active medication. In this approach, the prodrugs are made to absorb very little water and exhibit little hydrolysis in the upper gastrointestinal tract and acid hydrolysis in the colon, unleashing the pharmaceutical active portion from the vehicle [29].

Microflora Activated System

More than 400 different strains of bacteria make the gastrointestinal tract home and each occupies a specific segment there. A wide range of gram-negative microflora lives in the colon, which is the furthest portion of the gut. Numerous enzymes produced by this flora are used in the development of colon-specific medication delivery systems. These bacteria may simply be passing through the environment or they may fill in a space that the native species have left empty for whatever reason. There are several microbially triggered technologies being tested for colon-specific medication delivery. Prodrugs and delivery methods based on synthetic or natural polymers are examples of these [30].

Time-Dependent systems

A lag period of a preset amount of time in which no release occurs is followed by a quick and complete release of the loaded pharmaceuticals in pulsatile release systems. The strategy is based on the idea that drug release should be postponed until the colon has been reached in the digestive system. Since the small intestine transit takes about 3-4 hours and is generally consistent and not greatly impacted by the type of formulation taken, a lag time of 5 hours is typically regarded as adequate. This technique has many benefits over traditional oral drug delivery methods, including improved patient compliance, decreased dosage and frequency, fewer side effects, a practically constant drug level at the target site, and the avoidance of peak and valley fluctuations [31]. Water seeps into the capsule or tablet and causes the polymer to swell when this sort of system enters the colon, which forces the capsule to break and release the medication [32].

$_{P}^{H}$ Dependent Systems

The $_{P}^{H}$-dependent delivery systems make use of raise in the GI tract's $_{P}^{H}$. Enteric-soluble polymers are frequently employed as coating materials to stop the medication from dissolving and escaping from the upper intestine [33]. They are classified as:

a. Enteric Coated System

Solid oral dosage forms are generally shielded by enteric coatings from the gut's extreme $_{P}^{H}$. They disintegrate quickly in the intestinal tract lumen, where the pH of the membrane and the decomposition $_{P}^{H}$ of the polymers determine how quickly drugs from extended-release formulations are released. To further control the drug release, the coating thickness must be increased if the proximal jejunum or the colon is the intended target organ for the medication. This will enable a $_{P}^{H}$ and time-controlled polymer dissolving and drug dissolution process [34].

b. $_{P}^{H}$ Sensitive Hydrogels

When taken orally, the $_{P}^{H}$-sensitive hydrogel ensures the drug stays whole in the stomach and small intestine. However, this medication is likely to be absorbed or broken down in the stomach and small intestine before reaching the colon areas. 5-Aminosalicylic acid (5-ASA) is beneficial for targeted treatments of colitis. It is well known that the colon functions as a reductive medium where azo groups can be split, resulting in the creation of the corresponding amines. Azo compound metabolism is regarded as a significant detoxifying pathway. PEG has been authorized for a variety of biological uses and has good biocompatibility [35].

Magnetically Driven System

A very effective way to deliver medicine to a specific disease location is using magnetic drug delivery by particle vehicles to the desired location with the aid of the magnetic field. These carriers involve magnetic liposomes, magnetic microspheres, magnetic nanoparticles, magnetic resealed erythrocytes, magnetic neutrophils, biomodulators, and magnetic emulsion [36]. The use of magnetic nanoparticles as next-generation medication carriers is very appealing. External magnetic fields have the power to remotely impact the endogenous bio-distribution of Magnetic nanoparticles by directing and focusing them on the desired pathogenic region. This ability of Magnetic nanoparticles to ultimately function as target medication delivery systems depends greatly on these magnetic fields [37].

Polysaccharides-Based Delivery Systems

Simple sugars can be combined to form polysaccharides (sugars). They are affordable, highly accessible, widespread, and obtainable in a variety of forms with a wide range of attributes. Natural polysaccharides are currently widely used in the creation of solid dosage forms for colon drug delivery. The existence of significant amounts of polysaccharides in the human colon is the justification for the creation of a polysaccharide-based delivery system for colorectal. Numerous polysaccharides, including chitosan, pectin, glucosamine sulfate, cyclodextrins, dextran, xanthan gum, casein, corn starch, locust bean gum, and mannose, have already been tested for their potential as colon-specific drug carrier systems. Pectin, chondroitin sulfate, Carbopol, and HPMC films have also been studied for their potential as colon-specific drug delivery applications [38, 39].

New approaches for colon-specific drug delivery systems

CODES^{TM} Technology

The CODES™ system is based on the observation that some specific polysaccharides can only be broken down by bacteria in the colon. The enteric coating keeps the system together in the stomach as it travels through the digestive system, but once it reaches the small intestine, where the p^H is above 6.0, the colonic and impermeable coating erodes. The polysaccharide is biochemically broken down by intestinal bacteria into organic substances. As a result, the pH in the system's microclimate is adequately decreased to cause the alkaline coating to erode, releasing the drug. The thickness of the coating membrane determines the rate of release of the drug. According to recent studies, colonic microbial enzymes break down the lactulose in the tablet core into organic acids, creating an acidic milieu that facilitates the breakdown of Eudragit E. Enteric polymer Eudragit L makes up the outermost coating of the CODES™ formulation. Eudragit L dissolves as the fluid enters the duodenum, exposing the undercoating, which is made of Eudragit E. CODES™ will continue to enable fresh applications in medication delivery and addresses issues related to inadequately delivered pharmaceuticals.

COLAL™ Technology

It is a microbe-triggering mechanism in which the avoidance of major issues associated with acidity or time-dependent systems can be solved. Degradable polymer enables the prevention of drug release in the stomach and intestine but facilitates release in the colon. The large bacteria in the colon release enzymes that break down the tablet's polysaccharide covering and release the drug. The amount of coating used has a significant impact on the system's ability to release drugs under controlled circumstances. The medication is currently being tested in phase III clinical trials for the treatment of severe Crohn's disease after a successful Phase II study trial [40].

MMX™ Technology

The multi-matrix (MMX®) delivery system is a recent innovation in delivery technology. The MMX delivery system ensures that active drugs perform their therapeutic potential on the bowel epithelial cells and reduces systemic drug absorption by coating drugs that are then administered orally and allowing them to pass through the digestive enzyme protective layer without dissolving and releasing them in the damaged pathway of the colon. A hydrophilic and insensitive polymeric matrix is present in the outer gastroprotective ionic strength layer that mediates this action [41].

PHLORAL™Technology

It is a unique coating technology, which unites two separate release mechanisms: a pH trigger and a microbiota trigger mechanism [42].

OPTICORE™Technology

This technology consists of two layers: an outside layer made of a combination of resistant starch and Eudragit® S, and an interior layer of partially neutralized enteric polymer with a buffering agent. A new colon-targeting drug delivery system called OPTICORE™ has a dual-trigger outer layer (Phloral™) and an appropriate alkaline inner layer that can speed up drug release when the pH trigger is engaged or, conversely, whenever the starch in the outer surface is degraded by proteolytic cells in the colon [43].

Intestinal Pressure controlled drug delivery system

The colon experiences greater pressures than the small intestine as a function of peristaltic movement. Due to pressure in the colon's lumen, drug release happens in these systems after a water-insoluble polymer shell has disintegrated. The colon's luminal material has a greater density than the small intestine's due to the colon's retention of water. Hence, it has been determined that colon-specific oral drug delivery systems may have issues with drug disintegration in the colon. When pressure-controlled capsules were given to individuals delay durations of 3 to 5 hours in terms of drug absorption were observed.

Osmotic Controlled Drug Delivery (OROS-CT) Systems

The OROS-CT system can include a single osmotic entity or up to 5 or 6 push-pull units, each measuring 4 mm in diameter and sealed inside a rigid gelatin capsule. An osmotic push film and a drug coating are both present in every bilayer push-pull unit, and each is encircled by a process of osmosis. The coating disintegrates as the device enters the small intestine due to the greater pH environment, water entry, swelling of the osmotic push compartment, and subsequent formation of a flowable gel in the drug compartment. Drug material is forced out of the perforation by enlargement of the osmotic push section at a pace that is properly regulated by the pace of water transport across the semipermeable membrane. When the unit enters the colon, the drug promotes the release. The colon can receive drug delivery through OROS-CT devices for up to 24 hours at a regular speed, or for as little as 4 hours. Transitional phase systems have recently emerged, and they look to be a helpful tool for colon-targeted therapy [44].

Combination therapy for CRC

A recent study demonstrated that combination chemotherapy can reduce the occurrence, and spreading of tumors in patients who have had curative surgery. A recent finding demonstrated that the combination of Oxaliplatin/5-Fluorouracil/ Leucovorin has given assured results in the second and third-stage treatments of colon cancer [45]. Moreover, postoperative therapy has played an important role in the case of a geriatric population, although the most appropriate regimen is required to be established. However, improved surgical and radiotherapy techniques also play an important role in attaining better results.

Table 1: Drugs and polymers used in the colon-specific drug delivery systems [46,47,48,49]

Drug	Polymer employed	Research outcomes
Mebendazole	Guar gum	The drug did not release in stomach p^H but was delivered to the colon and available for local action.
Mesalazine	Locust bean gum	Formulation established better release behavior with an increase in bioavailability.
Hydrocortisone	Pectin (Theobroma cocoa)	The optimized tablets exhibited a lag phase of 6 h followed by accelerated drug release in the colonic region.
Diclofenac sodium	Pectin succinate	Reduced drug release behavior was observed in acidic $_p{}^H$ and improved dissolution rate was observed in alkaline $_p{}^H$.
Indomethacin	Eudragit S 100	An increase in coating thickness showed a reduced dissolution rate of the drug in the *in vitro* release studies.

CONCLUSIONS

Nanoscience is increasingly gaining more importance as a versatile tool for cancer diagnosis and treatment. Due to the present therapeutic processes, which are based on several dosage stages, as well as the fact that standard cancer agents for CRC have certain adverse effects, this article reviews recent reports on the delivery of medications to colon tumor cells using nanocarriers. Nanoparticles are extremely exciting in terms of future drug development and therapeutic qualities, and new drug delivery systems have promising advantages over conventional therapies.

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