Enteric-Coated Strategies in Colorectal Cancer Nanoparticle Drug Delivery System

Abstract: Colorectal cancer is one of the most common cancer diseases with the increase of cases prevalence >5% every year. Multidrug resistance mechanisms and non-localized therapy become primary problems of chemotherapy drugs for curing colorectal cancer disease. Therefore, the enteric-coated nanoparticle system has been studied and proved to be able to resolve those problems with good performance for colorectal cancer. The highlight of our review aims to summarize and discuss the enteric-coated nanoparticle drug delivery system specific for colorectal cancer disease. The main and supporting literatures were collected from published research articles of journals indexed in Scopus and PubMed databases. In the oral route of administration, Eudragit pH-sensitive copolymer as a coating agent prevents the degradation of the nanoparticle system from the gastric fluid and releases drug to intestinal-colon track. Therefore, it provides a colon-specific targeting ability. Impressively, enteric-coated nanoparticles having a sustained release profile significantly increase the cytotoxic effect of chemotherapeutic drugs and achieve cell-specific target delivery. The enteric-coated nanoparticle drug delivery system represents an excellent modification to improve the effectiveness and performance of anticancer drugs for colorectal cancer disease in terms of the oral route of administration.

Keywords: drug delivery system, oral route, cytotoxic, anticancer drugs

Introduction

Colorectal cancer is one of the most common cancers in the world with about 1.9 million new colorectal cancer (CRC) cases reported in 2018 and 900,000 deaths, making it the third most commonly diagnosed cancer worldwide. In 2020, around 147,950 individuals will be predicted with CRC, 53,200 might die from these diseases. Even though the prognosis of CRC patients has improved over the last few decades in many developed countries, mostly due to improved prevention and treatment, the incidence and mortality in low-and middle-income countries are rising rapidly, in part due to adaptation of western-lifestyle.

Conventional colon cancer treatment depending on the tumor stage consists mainly of surgery, chemotherapy, and radiation. However, these methods bear several risks. Besides, the usual risks of surgery such as major blood loss and infections, colectomy might lead to serious tissue damage causing leakage of the anastomosis. It is also worth mentioning that the risk of fecal and urinary incontinence after radiation therapy is high. Another problem associated with radiotherapy and chemotherapy is tissue toxicity as both cancerous and healthy cells are affected.
In addition, the application of chemotherapeutics is greatly limited, ascribable to multi-drug resistance caused by efflux mechanisms, enhancement of drug inactivation, or mutations of the drug target.\(^{28-31}\) Besides that, common chemotherapeutics like 5-Fluorouracil have a poor site-specificity leading to the fact that a growing dose size of anti-cancer drugs is required, which increases toxic side effects.\(^{32}\) For example, the overall response rate for 5-Fluorouracil regarding colorectal cancer alone is only 10% to 15%.\(^{29}\) Furthermore, researchers are challenged to overcome the limitations of conventional cancer therapy with new approaches.

Targeted anti-cancer agents such as Bevacizumab and Cetuximab have been developed. Both are monoclonal antibodies specific for molecular targets, which block transduction pathways or cancer proteins. These targeted monoclonal agents are able to reach the tumor site specifically.\(^{12,33,34}\) Currently, first-line treatments combine targeted therapy and fluoropyrimidine-based chemotherapy.\(^{35,36}\)

In order to increase anti-tumor efficacy, current therapeutic methods involve the combination of different chemotherapeutic drugs in a series of cycles.\(^{3,12,31}\) However, the emergence of drug-resistant tumor cells reduces the efficacy of chemotherapeutics and endure a crucial problem in colon cancer chemotherapy.\(^{37}\)

One promising approach to improve the efficacy and to reduce the systemic side effects of anti-cancer agents is nanoparticle drug delivery systems. They are biodegradable, nano to submicron colloidal systems with a diameters range between 3 and 200 nm, able to effectively carry the anti-cancer agents to the tumor site,\(^{30,34,38}\) attaining a high local drug concentration by site-specific targeting, enhanced permeability, and greater retention.\(^{39,44}\) Thus, the use of nanocarriers can reduce the unwanted systemic side effects and drug resistance.\(^{27,45}\)

However, nanoparticles for colon-targeted oral drug delivery systems have to overcome pH-sensitivity and transit time in the stomach. For oral administration, the formulation must be protected in order to prevent degradation, premature drug release and absorption before reaching the colon.\(^{46,47}\) These problems can be overcome by enteric coating of the nanoparticle delivery system. The enteric coating acts as a barrier protecting the loaded drug against the stomach acidic environment and controlling its release to reach sites in the lower gastrointestinal tract.\(^{32,48-52}\)

In recent years more and more nanoparticles for various purposes have been developed. Previous review articles discussed the application of polymers in delivering cancer drugs to colorectal cancer individually.\(^{53-55}\) This review article summarizes and discusses the enteric-coated nanoparticles as oral drug delivery systems for treating colorectal cancer. In this review, the comparison of different applied formulations and polymers for enteric-coated nanoparticles in colorectal cancer drug delivery system were discussed.

### Methodology

This review is focused on published articles indexed in Scopus and PubMed database using the keyword “enteric-coated nanoparticle colorectal cancer,” “enteric-coated nanoparticle cancer,” and “enteric-coated nanoparticles.” Opinions, assessments, and unrelated subjects such as pharmacological characteristics and bioactivities have been utilized for exclusion criteria. The flowchart of the methodology can be seen in Figure 1. The distribution of articles based on the year of publication can be seen in Figure 2.

In this review, we examined the studies on nano-sized cancer drugs with a macroporous sponge and multilayer dispersion system from macro to nano-sized. This system serves as a protection, targeted delivery to cancer cells, modification of release, and enhancing cell uptake in cancer drugs. Therefore, we also discussed the enteric-coated nanoparticle drug system for non-colorectal cancer and its development in targeted delivery to colorectal cancer.

### Colorectal Cancer

Colorectal cancer is a type of cancer that grows in the large intestine (colon), or at the very end of the large intestine that is connected to the rectum. The term colorectal cancer refers to cancer that develops slowly. Its development starts from tumor or tissue growth in the inner lining of large intestine or rectum.\(^{56}\) In general, colorectal cancer originates from the inner wall of colorectal epithelial layer as a polyp, which then invades the lymph node and muscles surrounding it. In the next stage, colorectal cancer will spread to other organs, especially the liver. Recurrence and widespread cancer (metastatic) distribution are the two main factors that are affecting the survival of patients with colorectal cancer. The chance of survival of colorectal cancer patients can reach up to around 90% for 5 years if colorectal cancer did not metastasize. But the survival rate is reduced to around 12% in
patients with metastatic colorectal cancer. Several factors are influencing the incidence of colorectal cancer including age, gender and genetic factors. Concomitant chronic diseases such as ulcerative colitis, diabetes, and obesity can increase the risk of developing colorectal cancer. At this time, patients with colorectal cancer are being treated by surgical removal of the tumor, chemotherapy as well as radiation therapy.

**Nanoparticle Drug Delivery System**

Nanoparticles are defined as size structures ranging from 1 to 100 nm in at least one dimension. However, the “nano” prefix refers to nanostructured particles, is usually used for particles up to several hundred nanometers in secondary size contained nano-sized primary particles. Nanocarriers have certain physicochemical and biological characteristics, which makes it easier to enter cells in comparison to larger molecules, so they can successfully deliver active substances intracellularly, and have the ability to carry cancer drugs having small or large molecular weights including genes or proteins. Thus, nanocarriers can be used for targeted anticancer delivery approaches for better accumulation in cancer cells. In addition, nanocarriers can increase the solubility of hydrophobic drugs, protect drugs from degradation, reduce renal clearance, increase the half-life, and can be used for controlled systemic release.

Nanotechnology has been widely developed as a new strategy for drug delivery and cancer treatment. When compared to conventional drug delivery systems, nanotechnology-based drug delivery systems have superior potential in several aspects, for example, targeting specific organs, increased circulation times and controlled systemic release. The application of nanotechnology has the potential to overcome drug resistance especially through reversing Multi-Drug Resistance (MDR). Thus, allowing sufficient drugs to accumulate in the cytoplasm resulting in remarkable improvement in chemotherapy efficiency.

**Enteric Nanoparticle Development**

In 1930, the first ingredient used in the enteric coating system was shellac. The enteric coating technique was first introduced by Unna in 1984 in the form of keratin-coated pills. Micro- to nano-encapsulated forms were then developed due to various needs in improving the quality and stability of drugs such as controlling drug release, reducing gastrointestinal irritation, and preventing drug interactions. This delivery system was first developed by Bodmeier et al (1989) using chitosan and alginate as coatings. Furthermore, the development of nano-sized enteric coating systems has been developed to date with various coating modifications and the addition of cell targeting or magnetic labeling agents (see Figure 3).

**Enteric-Coated Nanoparticle Formulations for Non-Colorectal Cancer**

Each part of the digestive tract has a different pH. The stomach has an acidic pH environment (1–3) while the small intestine has a slightly acidic to neutral environment pH (5.9 –7.8). The colon has a pH ranging from 5 to 8. Based on physiological conditions of the gastrointestinal tract, targeted drug delivery systems that are suitable for certain parts of the gastrointestinal release the active compounds triggered by pH. pH-dependent coating technology is usually applied to protect active substances from degradation by gastric acid and as targeted delivery in certain parts of the digestive tract. Enteric-coated drug delivery systems are designed to be able to survive in the acidic environment and disintegrate at a higher pH environment, preventing the degradation of active compounds by gastric fluid components. Some examples of enteric-coated drug formulas for non-colorectal cancer are summarized in Table 1.

The application of enteric-coated in several studies has successfully delivered drugs through the gastric channel (low pH) by maintaining the stability of active substances, even those in the form of peptides and proteins such as vaccines, insulin to be absorbed via lymphatic or bile pathways. These formulas can be used as innovators in the development of targeted delivery systems to colon cancer cells.

Natural or synthetic polymers are used in the enteric-coated system. However, in the colorectal drug delivery system, the polymers used need to be modified in order to deliver drugs to the targeted cells and increase its bioavailability. Therefore, mediators such as receptors, peptides, and other compounds are needed to be linked to the surface of the carrier. The mediators facilitate the attachment of the drug to the cell and increase its uptake.

**Enteric-Coated Nanoparticle Formulations for Colorectal Cancer**

Enteric-coated nanoparticles are one of the drug delivery technologies that can improve the bioavailability of drugs by oral administration, increase intracellular penetration and retention time, control the release of
encapsulated drugs and targeted delivery in specific parts of the gastrointestinal tract such as in the treatment of colorectal cancer. Cellular uptake and efficacy of nanoparticle drug delivery systems for colorectal cancer therapy are influenced by several factors, namely, size, shape, and surface chemistry. The size of the drug delivery carrier plays an important role in colorectal cancer therapy. Nanoparticles sizes around 100–200 nm have better cancer-targeting properties than larger particles. This can increase selective accumulation in the colon tissue due to the epithelial-enhanced permeability and retention effect. This can increase selective accumulation in the colon tissue. In order to be absorbed into the cells, the particle size of the drug should not exceed $10^4$ nm. With a particle size of $10^2$ nm, nanoparticle drugs are generally absorbed via the clathrin pathway. The illustration of anticancer
drug delivery and its release in the colon can be seen in Figure 4.

Materials used for enteric coating are usually water-resistant or pH-sensitive (Table 2). Enteric-coated systems use polymer coatings that do not dissolve in a gastric fluid consequently prevent or slowing down the release of drug compounds in stomach.\textsuperscript{39} Eudragit is a pH-dependent enteric-coated polymer, dissolves in a pH>5.5 medium,\textsuperscript{142} and has the highest entrapment ability compared to other polymers.\textsuperscript{143,144} It protects the active ingredient from gastric fluid, improves drug effectiveness, and enables targeting specific areas at intestine. Eudragit polymers are versatile polyacrylate polymers with various degrees of solubility, which make it suitable for sustained release formulation. Eudragit S100 has solubility characteristics above pH 7, making it suitable for use in colonic release targeting. Therefore, it is often used as an enteric coating in the drug delivery system for colorectal cancer.

**Chitosan Nanoparticle**

In 2017, Sun et al tried to develop a nanoparticle system for 5-Fluorouracil as drug payload by using ionic gelation. In this study, they used chitosan as the main carrier. The observed mean particle size was around 283.9 nm, with 44.28% of entrapment efficiency and 20.12% loading capacity. The highest entrapment efficiency and drug-loading could be achieved by using a 1:1 mass ratio of 5-FU and Chitosan. The PDI was around 0.252, indicating that the distribution is relatively homogeneous. In addition, the nanoparticle system showed good stability with a zeta-potential of about 45.3 mV. Impressively, the in vitro and in vivo drug release study implies that compared to the normally used 5-FU solution, a notably sustained and extended drug release by 5-FU Chitosan nanoparticles can be observed. Regarding the bioavailability in rats, the AUC value of 5-FU Chitosan nanoparticles showed more than 2-fold increase to the solution. Furthermore, the nanoparticles show the same in vitro cytotoxic efficacy on gastric cancer SGC-7901 as conventional 5-FU injections.\textsuperscript{145}

Another study from Tummala et al in 2015 demonstrated that nanoparticle formulations with enteric coating become an excellent modification of the previously mentioned nanoparticles. In this study, the solvent emulsification evaporation technique was used to prepare the same type of nanoparticles, which were additionally coated with an enteric coating (Eudragit S100) to protect the nanoparticles from degradation in gastric fluid and to achieve drug release when the carrier reaches the intestine. Comparing the 1:1 mass ratio formulations of S. Tummala and L. Sun, the particle size with about 192 nm which is much smaller, even though having an extra enteric coating. Moreover, the average particle size of the formulation prepared using a 1:3 mass ratio was about 138 nm, which is even smaller.

In addition, the study revealed a significantly higher entrapment efficiency (69.18%) and drug loading (28.14%), using a drug: polymer ratio of 1:3. In contrast to the study of Sun et al the drug loading did not increase with the increase of 5-FU. Other than that, the other particle characteristics regarding stability and distribution showed similar results.

In in vitro study, non-enteric-coated 5-FU chitosan nanoparticles released up to 70% of 5-FU before reaching the colonic fluid. Due to the Eudragit S100 coating, which contains acidic functional groups, dissolving only in alkaline colonic medium, the enteric-coated nanoparticles remain stable in gastric fluids and reach the tumor sites in the colon. Drug release of enteric-coated nanoparticles started only after 4h in simulated intestinal fluid and showed a sustained release profile over 24h of a time period, whereas non-enteric-coated nanoparticles released about 50% of 5-FU after 2 to 3 hours and up to 70% before reaching colonic fluid.\textsuperscript{32}

Continuing the previous study, Tummala et al focused on improving 5-FU anti-cancer activity of 5-FU loaded enteric-coated chitosan nanoparticles, they have evaluated
| No | Polymer                                      | Active Ingredient                                                                 | Application                              | Ref |
|----|---------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------|-----|
| 1. | Propylene glycol alginate sodium sulfate    | —                                                                                 | Potential enteric delivery system        | 90  |
| 2. | Copper-substituted mesoporous silica        | 16-Hydroxy-cleroda-3,13-dien-16,15-olide (HCD)                                    | Controlled anti-glioma drug delivery     | 91  |
| 3. | Starch and chitosan                         | Withania coagulans extract                                                        | Enteric extract delivery system          | 92  |
| 4. | Polylactic acid (PLA), polyvinyl alcohol, poloxamer 188 | β-galactosidase                                                                   | Protection on enzymatic degradation      | 93  |
| 5. | PLGA, lipid, PEG                            | Insulin                                                                           | Oral insulin delivery system             | 94  |
| 6. | Polymethylacrylic resin II (PRII) and solid lipid (polyvinyl alcohol and octadecanoic acid) | Enrofloxacin (ENR)                                                                | Enteric delivery and light protector system | 95  |
| 7. | Deoxycholic acid-conjugated chitosan        | Insulin                                                                           | Oral insulin delivery system             | 96  |
| 8. | Hydroxypropyl methylcellulose and Eudragit® L100 | Darunavir                                                                         | Enteric antivirus delivery system        | 97  |
| 9. | (methoxy-polyethylene glycol)-b-poly(DL-lactide-co-glycolide)-b-poly(L-lysine) | Peptide Val-Leu-Pro-Val-Pro-Arg                                                   | Enteric peptide delivery system          | 98  |
| 10.| Hyaluronic acid, chitosan, and Eudragit® L-100 | Insulin                                                                           | Oral insulin delivery system             | 99  |
| 11.| Chitosan and Eudragit® L-100                | Bovine serum albumin (BSA)                                                        | Oral protein vaccine delivery system     | 100 |
| 12.| Deoxycholic acid conjugated PEGylated polyhydroxybutyrate | Insulin                                                                           | Oral insulin delivery system             | 101 |
| 13.| Hyaluronic acid (HA)                        | Insulin                                                                           | Oral insulin delivery system             | 102 |
| 14.| Guar gum and Eudragit® L30D                 | Amphotericin B                                                                    | Antileishmanial drug delivery system     | 103 |
| 15.| Compritol 888 ATO, cetyl palmitate, stearic acid, Dynasan® 114, Dynasan® 116, Dynasan® 118, Gelucire® 50/13, Softisan® 154, lauric acid, glyceril monostearate, glyceril trioleat, Labrafil® M-2151 CS, Labrafac® WL 1349, corn oil, sesame oil, steryl oleat, oleic acid, Eudragit® S1000 | Budesonide                             | Inflammatory Bowel Disease          | 104 |
| 16.| Gelatin, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), monophosphoryl lipid A, glycerol tripalmitate, and cholesterol | HBsAg                                                                               | Oral vaccine delivery system             | 105 |
| 17.| Eudragit® S-100 and Eudragit® L-100         | Sulfasalazine                                                                     | Oral-specific delivery                   | 106 |
| 18.| Glyceril monooleate and Eudragit® L100-55   | Pravastatin sodium (PVS)                                                           | Duodenal-triggered delivery              | 107 |
| 19.| Eudragit® L100-55 and polyvinyl alcohol     | Nifedipine                                                                        | Oral pH-sensitive delivery               | 108 |
| 20.| N-(2-hydroxy)-propyl-3-trimethylammonium chloride modified chitosan (HTCC) and sodium tripolyphosphate (TPP) | Insulin                                                                           | Oral insulin delivery system             | 109 |

(Continued)
Table 1 (Continued).

| No | Polymer                                                                 | Active Ingredient       | Application                          | Ref  |
|----|-------------------------------------------------------------------------|-------------------------|---------------------------------------|------|
| 21 | Mesoporous silica                                                      | Safranin O              | Colonic targeted delivery system       | 109  |
| 22 | Monomethoxyl poly(ethylene glycol)-b-poly(L-lactide-co-glycolide)     | Growth factor           | Enteric protein delivery system        | 110  |
| 23 | Hydroxypropyl methylcellulose phthalate (HPMCP)                        | Omeprazole              | Enteric drug delivery system           | 111  |
| 24 | Hydroxypropyl methylcellulose phthalate (HP55), poly(lactic-co-glycolic acid) (PLGA), and Eudragit® RS | Insulin                 | Oral insulin delivery system           | 112  |
| 25 | Polyacrylic acid                                                       | Papain                  | Small intestine targeted delivery system | 113  |
| 26 | Polyethylene imine                                                     | Insulin                 | Oral insulin delivery system           | 114  |
| 27 | Mesoporous silica and polyacrylic acid                                 | Metoprolol tartrate     | Enteric delivery and sustained release system | 115  |
| 28 | Eudragit® RS100 and poly(lactic-co-glycolic acid) (PLGA)               | Lansoprazole            | Enteric delivery and sustained release system | 116  |
| 29 | Eudragit® L100                                                         | Darunavir               | Enteric antiviral delivery system      | 117  |
| 30 | Methacrylic acid-methyl methacrylate and chitosan                      | Recombinant human keratinocyte growth factor (rHuKGF) | Enteric protein delivery system      | 118  |
| 31 | Phospholipon® 90H, Arlacel® 1689, Crodamol® CP-PA-(SG), and Eudragit® S100 | Lipo-endomorphin-1     | Enteric peptide delivery system         | 119  |
| 32 | Compritol 888 ATO (COMP) and Poloxamer 188 (P-188)                     | Carvedilol              | Lymphatic absorption                   | 120  |
| 33 | poly(g-glutamic acid) and chitosan                                     | Exendin-4               | Enteric peptide delivery system        | 121  |
| 34 | Poly(methacrylic acid)-polysorbate 80-grafted-starch terpolymer and ethylcellulose | Diltiazem               | Enteric delivery and controlled release system | 122  |
| 35 | Pluronic                                                               | Efavirenz               | Microfold cells (M-cells) targeted delivery system | 123  |
| 36 | Poly(DL-lactide-co-glycolide) and Eudragit S100                        | Eluxadoline             | Enteric delivery and sustained release system | 124  |
| 37 | Alginate and chitosan                                                 | Goat anti-mouse IgG peroxidise conjugate | Oral vaccine delivery system | 125  |
| 38 | Hydroxypropyl methylcellulose phthalate (HP55)                         | Insulin                 | Oral insulin delivery system           | 126  |

(Continued)
their apoptotic activity in vitro using HCT 116 colorectal cancer cells. A decrease in the IC50 value of 5.5 folds compared to pure drugs was shown, whereas plain nanoparticles showed no toxicity indicating the safety of nanoparticles. Furthermore, the research demonstrated the ability in localizing the drug at the colon and releasing the majority of the payload once it arrives at the ascending colon after 4 h. Moreover, the improved apoptotic activity

Table 1 (Continued).

| No | Polymer                                                                 | Active Ingredient           | Application                                       | Ref |
|----|-------------------------------------------------------------------------|----------------------------|---------------------------------------------------|-----|
| 39 | Diethylene triamine pentaacetic acid and poly(γ-glutamic acid)         | Insulin                    | Oral insulin delivery system                      | 127 |
| 40 | Folate-chitosan                                                          | 5-fluourouracil (5-FU) and leucovorin (LV) | Multiple drug and targeted delivery system        | 128 |
| 41 | Poly(lactic-co-glycolic acid)                                           | Docetaxel                  | Lymphatic absorption                              | 129 |
| 42 | Chitosan and Eudragit L-100                                             | Insulin                    | Oral insulin delivery system                      | 130 |
| 43 | Acrylic acid and methacrylic                                            | Rifampicin                 | Sustained release and mucoadhesive delivery       | 131 |
| 44 | Poloxamer 188, polyvinyl alcohol, and polyacryl resin II                | Tilmicosin                 | Prevent gastrointestinal degradation               | 132 |

Figure 4 The illustration of nanosized drug entrapped in polymeric matrix (A) and its mechanism in release and delivery at colon (B).
of enteric-coated nanoparticles was determined compared with free nanoparticles and pure 5-FU.\textsuperscript{133}

In conclusion, an enteric-coated nanoparticle system with a significant sustained and localized release and enhanced anticancer activity for colorectal cancer treatment was successfully developed.

As for various cancer diseases including colorectal cancer hyaluronic acid (HA) receptors in tumor cells are overexpressed, making it a suitable target for anticancer drugs, which seems to be a promising approach to improve orally targeted drug delivery systems for colorectal cancer.

In a study from Jain et al in 2010 hyaluronic-acid coupled Oxaliplatin (L-OHP) loaded nanoparticles with Chitosan as the main carrier were prepared using ionotropic gelation as an attempt to develop an optimal targeted delivery system for colorectal cancer. Afterward, the nanoparticles were processed into pellets, which were then coated with Eudragit S100.

Characterization studies showed that HA-coupled chitosan nanoparticles had similar characteristics as the previously mentioned nanoparticles. However, compared to uncoupled nanoparticles, the entrapment efficiency of HA-coupled nanoparticles was significantly less.

Other than that, zeta potentials of uncoupled chitosan nanoparticles (CTNPOP) and HA-coupled chitosan nanoparticles (HACTNPOP) formulations were observed to be around 40.3 and 10.0 mV, which mean that the stability differs significantly. It was also concluded that the optimal total weight gain regarding the film thickness is 10%. In this range, the coat is stable enough to pass gastric fluids in the upper gastrointestinal tract without degradation but is still able to ensure an optimum drug release in the colon. In terms of the in vitro drug release, non-coupled nanoparticles had a higher drug release profile than the HAcoupled ones. HA coupling might act as an additional barrier for drug diffusion, which has to be overcome. Furthermore, the mural study could confirm, that coated nanoparticles mainly started to release the drug in the ascending colon after 4 to 5 hours, which implies, that colon-specific delivery of L-OHP was achieved after oral administration of enteric-coated nanoparticles and, that the enteric coating process was successful.

As expected, the biodistribution studies show, that HAcoupled nanoparticle increased the drug concentration at the tumor site more effectively than the uncoupled nanoparticles or the free drug, which means that the researchers were able to achieve a more specific targeted approach to the colorectal cancer site by using hyaluronic acid as targeting ligand. Impressively, tumor regression studies on C57 Balb/c mice could successfully confirm HAcoupled nanoparticles being able to stop tumor proliferation more effectively than free L-OHP and CTNPOEPs. It could be observed that the growth of tumor cells could be delayed for about 8 days, which is twice as long as non-coupled nanoparticles. These results imply that nanoparticles coupled with targeting ligand like hyaluronic acid have a significant effect.\textsuperscript{39} Five years later in 2015, Jain et al used 5-FU instead of Oxaliplatin and attempted to optimize the chitosan nanoparticles. The preparation method was comparable to the study from 2010 and very similar results regarding the characterization could be observed.\textsuperscript{155}

**Pectin-Eudragit Nanoparticle**

Subudhi et al attempted to prepare Eudragit S100-coated nanoparticles, which are loaded with 5-FU for colon targeting in cancer therapy. Instead of using Chitosan like in the previously mentioned articles, citrus pectin was used. Conveniently, citrus pectin also acts as a target mediator at the same time since it additionally functions as a ligand for galectin-3 receptors. Like hyaluronic acid receptors, Galectin-3 receptors are also overexpressed in colorectal cancer, making it a promising and specific target for anticancer medication. With a mean particle size of about 218.12 nm the enteric-coated nanoparticles are slightly bigger than coated nanoparticles consisting of Chitosan.

Surprisingly the zeta potential of the coated citrus pectin nanoparticles could be found around the value of about -27.5 mV. Compared to the same non-coated nanoparticles with -18.4 mV, an enormous improvement could be found, but the optimal stability could not be achieved as the zeta potential should be >30 mV to provide good stability of colloidal dispersions. In contrast to chitosan nanoparticles of previously mentioned articles, citrus pectin nanoparticles showed less entrapment efficacy of only around 35.15%. That being said, regarding particle size and entrapment efficacy, citrus pectin nanoparticles seem to be less optimal for colon targeted delivery systems than chitosan nanoparticles.

Thus, the effective drug delivery depends on the size, stability of the suspension and provide well-dispersed nanoparticles. The morphology of the nanoparticles also plays an important role on the hydrodynamic of the drug delivery and consequently affect the kinetic reactivity of the colloidal systems.
Table 2 Enteric-Coated Nanoparticle Formulations for Colorectal Cancer

| No | Type of Nanoparticle       | Main Carrier | Enteric Polymer          | Active Ingredients                  | Target Mediator | Ref  |
|----|----------------------------|--------------|--------------------------|-------------------------------------|-----------------|-----|
| 1  | Chitosan Nanoparticle      | Chitosan     | -                        | 5-FU                                | -               | 145 |
|    |                            | Chitosan     | Eudragit S100            | 5-FU                                | -               | 32, 133 |
|    |                            | Chitosan     | Eudragit S100            | Oxaliplatin                          | Hyaluronic Acid | 39  |
|    |                            | Chitosan     | Eudragit S100            | 5-FU - Leucovorin                    | Folate          | 127 |
|    |                            | Chitosan     | Eudragit S100            | Curcumin                             | -               | 146 |
|    |                            | Chitosan     | Eudragit S100            | Doxorubicin                          | -               | 147 |
|    |                            | Chitosan     | Eudragit S100            | 7-Hydroxy staurosporine              | -               | 148 |
| 2  | Pectin-Eudragit Nanoparticle | Citrus Pectin  | Eudragit S100            | 5-FU                                | Citrus Pectin   | 149 |
| 3  | PMMA-Eudragit Nanoparticle | PMMA         | Eudragit RS PO + Eudragit S100 | -                                  | -               | 150 |
| 4  | PLGA- udragit Nanoparticle | PLGA         | Eudragit S100            | Aspirin – Folic Acid                | -               | 151 |
| 5  | Sodium alginate-Eudragit Nanoparticle | Sodium Alginate | Eudragit S100            | Indomethacin                         | -               | 152 |
|    |                            | Sodium Alginate | Eudragit S100            | Irinotecan hydrochloride trihydrate (I) | Folic acid     | 153 |
|    |                            | Sodium Alginate | Eudragit S100            | -                                   | -               |     |
| 6  | Albumin Nanoparticle       | BSA          | Eudragit S100            | Indomethacin                         | -               | 154 |
|    |                            | BSA          | Eudragit L100            | Indomethacin                         | -               |     |

The in vitro drug release study in simulated gastrointestinal fluid mediums at different pH values showed that the enteric-coated nanoparticles did not release a significant amount of 5-FU within the first 4 hours in simulated intestinal fluid, which is similar to the result of S. Tummala et al, whereas the release rate from nanoparticles starts to increase with the increasing pH values of the release medium. Therefore, as expected, the amount of drug release of non-coated and coated nanoparticles differs significantly. Eudragit S100 coating was able to reduce the drug release by about 19% after 24 hours. In medium containing 2% rat cecal content, it could be stated that the drug release of both coated and non-coated nanoparticles was drastically increased by the numerous anaerobic bacteria, which could digest pectin, leading to 5-FU being released.

All in all, it can be concluded, that the prepared coated citrus nanoparticles have a controlled and sustained release profile. Based on sulforhodamine B assay, it was successfully proven that the cytotoxicity could be increased by using citrus pectin nanoparticles as dosage form (LC50 = 94.2 μg/mL) showed less cytotoxicity than the free 5-FU (LC50 = 56.7 μg/mL), which is probably due to the Eudragit S100 coating, that remains mostly stable in acidic pH of the medium used in the cell cytotoxicity study.

As expected, it was verified that the nanoparticles covered with Eudragit S100 released the least amount of drug in the upper GIT compared to the non-coated nanoparticles and free drug solution. In addition, there was a significant increase in colon 5-FU concentration in the case of Eudragit-coated citrus pectin nanoparticles due to facilitated microflora degradation in the colonic region.

The plasma drug concentration was analyzed to evaluate drug absorption. The maximum drug plasma level of non-coated nanoparticles was reached after 8 h, mainly released in the small intestine, also showing a prolonged and delayed-release profile due to low permeability. On the other hand, enteric-coated nanoparticles reached their maximum plasma level after 12h, slowly releasing the drug in the colon within 12 hours, achieving a higher drug concentration and prolonged effect in the colon site compared to the non-coated nanoparticle and the free.
solution. In addition, Eudragit-coated nanoparticles showed a relatively low drug plasma level at all time points, and as a result, the risk of severe systematical side effects is reduced and the exposure time to the tumor site in the colon is prolonged.\textsuperscript{149}

**PMMA-Eudragit Nanoparticle**

In 2015 another approach on developing nanoparticles as a colon targeted delivery system was attempted. Ma et al first prepared Cy5-labelled PMMA-Eudragit RS PO nanoparticles (Cy5 NPs). Subsequently, they were incorporated in IR750-dyed-chitosan-Hypromellose microcapsules using ionotropic gelation. The microcapsules were then coated with Eudragit S100 eventually. Other than the previously mentioned studies, the nanoparticles were not loaded with an anti-cancer agent. Thus, the nanoparticles were not coupled with a specific target mediator for tumor cells in the colon site. In the study, they tried to compare site-specificity of free nanoparticles and nanoparticles in a microcapsule-system and evaluated their potential for colon-targeting.

After 2 hours of in vitro incubation in simulated gastric fluid and 6 hours in intestinal fluid, only less than 4% of nanoparticles from Eudragit S100-coated IR750 MCs were released. Another 9% were released in the following 6 hours in simulated colonic fluid, which not only demonstrates an overall relatively slow release rate but also showing that Cy5 nanoparticles could be at least successfully released from Chitosan-HPMC microcapsules in colonic fluids. Moreover, a significant number of nanoparticles have been already released in the small intestine before reaching the colon. Therefore, the aim of colon-specificity could not be achieved.

To have a significant therapeutic effect, the NP must not only be released but also penetrate into the tumor tissue. In order to investigate the cellular uptake of Cy5 nanoparticles, human colon adenocarcinoma (HT29) and embryonic fibroblast (NIH/3T3) cells were used. Altogether it could be noted that the general NP from Eudragit S100-coated IR750 MCs uptake increased with the increase of NP concentration and time of exposure. Due to the higher proliferation rate of cancerous cells, the NP uptake in HT29 was higher than the uptake in NIH/3T3 cells.

Surprisingly, in contrast to the in vitro study, all of the drug was released in vivo in the lower small intestine. Altogether it could be concluded that there is an efficient, but non-specific uptake of nanoparticles in both normal and cancerous cells. After oral administration in mice, the biodistribution of free Cy5 NPs and Eudragit S100-coated Cy5 NP-in-IR750 microcapsules was examined by using fluorophore-based animal imaging. It could be stated that free Cy5 NPs and Eudragit S100-coated Cy5 NP-in-IR750 MCs, showed stomach retention over 24 hours, owing to adhesion to the gastric mucosal surface.

Over 24 hours after oral administration, the non-encapsulated nanoparticles had a restricted allocation in the colon. On the other hand, the enteric-coated MCs increased the delivery of nanoparticles to the colon due to prolonged nanoparticle residence in the gastrointestinal tract of the mouse and reduced nanoparticle excretion in feces, although the MCs had poor colon specificity.\textsuperscript{150}

**PLGA-Eudragit Nanoparticle**

In 2011, Nassar was able to prepare nanocapsules loaded with Doctaxel using PLGA [poly(lactic-co-glycolic acid)] as the main carrier, which was then embedded in microparticles coated with Eudragit L. The average diameter and zeta potential values of the NCs formed were around 300 nm and −60.1 mV to −37.7 mV, which is the prevalent size for PLGA nanoparticles, and also demonstrates that the solution is stable. Interestingly, the nanoparticle-microparticle system showed a significant better oral absorption and higher bioavailability compared to both, the doctaxel solution and the free doctaxel NC formulation.

Cell viability assay, MTT, on Walker 256 cells could demonstrate, those blank microparticles alone have a certain toxic effect due to the cytotoxicity of Eudragit L. A higher intrinsic cytotoxic activity can be seen when testing free doctaxel nanoparticles.

Interestingly, there were even more pronounced cytotoxic impacts of nanocapsulated doctaxel microparticles than blank microparticles and Doctaxel in solution. At a Doctaxel concentration around 5 μg/mL, it could be observed that cytotoxicity increased significantly compared with the free solution and blank nanocapsules. These results could be found for an incubation time of 72 hours in a cell growth medium. When incubating only for 3 hours, we can surprisingly see that the doctaxel solution has a significantly higher cytotoxic effect than the microparticle system. Comparable results could be observed in the studies of M. Subudhi, where coated nanoparticles had less cytotoxicity effect than free nanoparticles and free drug solution. It can be assumed that the enteric coating could be the reason for this result. Only 3
hours of incubation may not be enough time for the polymer to degrade, which might show a delayed-release profile because Eudragit L is only soluble at pH level above 6.\(^6\)\(^,\)\(^156\) Furthermore, the microcapsules showed promising stability for one hour in a solution with a pH of 1.2, whereas a complete degradation of the enteric coating could be observed at pH value of 7.5.

The study was also able to show, that an enormous improvement in docetaxel oral absorption was achieved by this nanoparticle system. A higher bioavailability and lower clearance could be observed compared to both the docetaxel solution and the docetaxel NCs injected intravenously.\(^157\)

**Sodium Alginate-Eudragit Nanoparticle**

Research conducted by Ma (2013) shows a double coating of indomethacin-complexed Eudragit RS nanoparticles that are incorporated into alginate microcapsules successfully delivering indomethacin to the colon with 60% drug loading. The nanoparticles’ size ranges from 116 nm with a drug loading of 5%. The entrapment efficiency increases when the nanoparticle-microcapsule system was drained (0.7% alginate). The nanoparticles also release the drug immediately in the gastric and intestinal tract by 90%. But, the double coating using alginate as the outer layer can maintain the drug entrapment up to the colon and reduce systemic toxicity from indomethacin.\(^152\) Meanwhile, research conducted by Rajpoot and Jain (2020) resulted in targeted cancer drug delivery to colon cancer cells using radio labelling and the addition of folic acid to solid lipid nanoparticles as ligand cell targeting. The solid lipid nanoparticles (SLN) that have been labeled and given the ligand were then encapsulated into the S-100 eudragit polymer and alginate. The results showed that the maximum drug accumulation was achieved to the cancerous tissue in the colon in the alb/c mouse model.\(^153\)

**Albumin Nanoparticle**

The delivery system of indomethacin to the colon has also been studied by Cerchiara et al by using a multi-coating system. The increased solubility of Indomethacin was significant with increasing cyclodextrin concentrations. However, the swelling index of the indomethacin-cyclodextrin complex was smaller than that of indomethacin-albumin. The swelling index of Indomethacin-cyclodextrin-albumin was greater in an alkaline atmosphere with the release rate following zero order. However, this system still releases some drugs in an acidic atmosphere. With a multi-coating system using Eudragit as the outer layer, the release of drugs in an acidic atmosphere can be reduced.\(^154\)

**Size and Mechanism Comparison**

Some of the encapsulation forms described in the previous sections vary in size and shape of the system used. This difference will lead to different deliveries and endocytosis mechanisms. The comparison of size and coating system can be seen in Figure 5.

Figure 5 describes that the enteric-coated nanoparticle drug formulations for colorectal cancer system can be in the form of a single drug coating or in the form of a matrix. The single form of coating generally aims to prevent drug aggregation and targeted delivery while the matrix form aims to increase solubility and controlled release.\(^150,\)\(^154\) For anionic charged drugs that reach target cells in the 10\(^2\) nm size will be uptaken via the clathrin pathway. Whereas those with cationic and neutral charges with a larger size (not to exceed 104 nm) will be uptaken via other channels besides clathrin.\(^141\)

As enteric-coated polymer, eudragit releases nearly 90% drug in a zero-order pattern at 10 h time at small intestinal pH. Meanwhile, ethylcellulose and cellulose acetate phthalate released 90% of the drug at 20 hours. When compared with these polymers, shellac has a more sensitive response to intestinal pH where drug release reaches 100% at 10 hours.\(^158\) However, when compared to natural polymers, eudragit is more reproducible and is not absorbed, so they do not give systemic side effects.\(^159\)

**The Perspective of the Author**

In the last decades, researchers have been developing and using nanoparticle systems with controlled drug release profiles. It was possible to elaborate nanoparticles for sustained and delayed drug release, which prolongs release and extends the drug effect, leading to a significant increase of bioavailability.

Chitosan polymer is often used in nanoparticle technology, as studies prove that it shows low toxicity. Besides, it is biodegradable and biocompatible.\(^160\)

In order to improve the delivery efficiency of oral nanoparticle systems even more, the enteric coating seems to be a promising approach, but every dosage form taken orally has to face the problem of degradation, resulting in reduced oral availability. This can be prevented by enteric coating. So far enteric-coated nanoparticles for various purposes have been developed. For instance, oral delivery of insulin,\(^94,\)\(^111,\)\(^161,\)\(^162\)
antihypertensive agents, anti-glioma therapeutics, and cancer therapeutics for colorectal cancer.

As for nanoparticle system in colorectal cancer treatment, Eudragit has been used commonly as an enteric coating. These copolymers are perfectly suitable for colon-specific targeting as their dissolution is pH-dependent, which is necessary since there are several milieus of different pH levels throughout the gastrointestinal tract, making it a perfect option as an enteric coating of oral nanoparticle systems. In the previously mentioned articles, Eudragit S100 was commonly used taking advantage of the fact that it dissolves above a pH level of 7, which makes it perfectly suitable for colon-specific release.

As a summary, the reviewed articles discussed the enteric coating of the nanoparticles significantly improves the delayed and prolonged drug release in the colon. Also, the sustained drug release profile can be enhanced. Thus, a more localized release at the tumor site could be achieved leading to a significantly enhanced antitumor activity.

Moreover, nanoparticles modified with ligand seem to be a promising attempt to improve specific active colorectal tumor targeting, although they did not show optimal characteristics compared to non-modified nanoparticles. Therefore, more research has to be conducted to optimize these modified nanoparticles, but other than that, combining enteric coating with modified nanoparticles could enhance the colon-specific targeting and release, which is essential for antitumor agents in colorectal cancer therapy.

As for the anticancer activity, in vitro studies should consider the characteristics of enteric coating. Cell toxicity assays should be tested in a medium similar to the colonic fluids instead of acidic cell medium. Only then, studies can be informative and comparable.

Further, more in vivo studies should be taken into consideration that optimal colon-targeted drug release depends on many various factors, which can hardly be simulated fully in vitro.

**Conclusion**

In recent years the field of nanotechnology in cancer treatment has been expanding rapidly. Nanoparticles used as oral drug delivery systems seem to be one of the most promising approaches in colorectal cancer therapy these days. The development of different formulations and technologies has been carried out to improve colon-specific drug delivery by controlled drug release. The overall research, which has been conducted so far, showed that enteric-coated nanoparticles were able to enhance the controlled drug release. An improved delayed, prolonged, and sustained drug release profile in the colonic area could be confirmed, leading to an enhanced antitumor activity on tumor cells. Enteric-coated nanoparticles showed a great potential to increase the effect of anticancer agents like 5-FU significantly, which could be a big next step in colorectal cancer therapy.

Furthermore, for the future development of drug delivery systems in colorectal cancer therapy not only target pH-stimulated release but also combined with specific targeting of colorectal cancer cells. The interaction between the targeted ligands decorated on the nanoparticle surface and certain receptors that are overexpressed at the diseased site or certain cells is expected to increase the adhesion and internalization of the nanoparticles. This effect will lead to selective drug accumulation at the target site which can increase therapeutic efficacy and reduce side effects.

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References
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145–164. doi:10.3322/caac.21601
3. Brouwer NPM, Bos ACRK, Lemmens VEPP, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 2018;143(11):2758–2766. doi:10.1002/ijc.31785
4. Haggard FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22(4):191–197. doi:10.1055/s-0029-1242458
5. Hähnler MF, Debus J. Radiotherapy for colorectal cancer: current standards and future perspectives. Visc Med. 2016;32(3):172–177. doi:10.1159/000446486
6. Aiello P, Sharghi M, Mansourkhan SM, et al. Medicinal plants in the prevention and treatment of colon cancer. Oxid Med Cell Longev. 2019;2019:1–51. doi:10.1155/2019/2075614
7. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–691. doi:10.1136/gutjnl-2015-310912
8. Mishra J, Drummond J, Quazi SH, et al. Prospective of colon cancer treatment and scope for combinational approach to enhanced cancer cell apoptosis. Crit Rev Oncol Hematol. 2013;86(3):232–250. doi:10.1016/j.critrevonc.2012.09.014
9. Bertelsen CA, Neuenwander AU, Jansen JE, et al. Disease-free survival after complete mesorectal excision compared with conventional colon cancer surgery: a retrospective, population-based study. Lancet Oncol. 2015;16(2):161–168. doi:10.1016/S1470-2045(14)71168-4
10. Angenete E. The importance of surgery in colorectal cancer treatment. Lancet Oncol. 2019;20(1):6–7. doi:10.1016/S1470-2045(18)30679-X
11. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg. 2013;100(1):75–82. doi:10.1002/bjs.8945
12. Terriere L, Holvoet J, Schrijvers D. Colorectal cancer. ESMO Handb Cancer Prev. 2008;1:127–135. doi:10.1038/ndrp.2015.65
13. Tevis SE, Kennedy GD. Postoperative complications: looking forward to a safer future. Clin Colon Rectal Surg. 2016;29(3):246–252. doi:10.1055/s-0036-1584501
14. Climent M, Martin ST. Complications of laparoscopic rectal surgery. Mini-Invasive Surg. 2018;2018. doi:10.20517/2574-1225.2018.62
15. Chiu -C-C, Lin W-L, Shi H-Y, et al. Comparison of oncologic outcomes in laparoscopic versus open surgery for non-metastatic colorectal cancer: personal experience in a single institution. J Clin Med. 2019;8(6):875. doi:10.3390/jcm8060875
16. Bedirli A, Salman B, Yuksel O. Laparoscopic versus open surgery for colorectal cancer: a retrospective analysis of 163 patients in a single institution. Minim Invasive Surg. 2014:1-6. doi:10.1155/2014/530314
17. Song X-J, Liu Z-L, Zeng R, Ye W, Liu C-W. A meta-analysis of laparoscopic surgery versus conventional open surgery in the treatment of colorectal cancer. Medicine (Baltimore). 2019;98(17):e15347. doi:10.1097/MD.0000000000015347
18. Yang X-F, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation. Chin J Cancer Res. 2014;26(3):331–340. doi:10.3978/j.issn.1000-9604.2014.06.11
19. Kirchhoff P, Clavien P-A, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. Patient Saf Surg. 2010;4(1):5. doi:10.1186/1754-9493-4-5
20. Beraldo FB, Yusuf SAI, Palma RT, Kharmandayan S, Goncalves JE, Waisberg J. Urinary dysfunction after surgical treatment for rectal cancer. Arq Gastroenterol. 2015;52(3):180–185. doi:10.1590/0004-28032015000300005
21. Cicchetti A, Avuzzi B, Palorini F, et al. Predicting late fecal incontinence risk after radiation therapy for prostate cancer: new insights from external independent validation. Int J Radiat Oncol Biol Phys. 2018;102(1):127–136. doi:10.1016/j.ijrobp.2018.05.013
22. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer – a systematic overview. Acta Oncol (Madr). 2007;46(4):504–516. doi:10.1080/02841860701348670
23. Lange MM, van de Velde CJH. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol. 2011;8(1):51–57. doi:10.1038/nruro.2010.206
24. Lange MM, den Dulk M, Bossera ER, et al. Risk factors for faecal incontinence after rectal cancer treatment. Br J Surg. 2007;94(10):1278–1284. doi:10.1002/bjs.5819
25. Lange MM, van de Velde CJH. Faecal and urinary incontinence after multimodality treatment of rectal cancer. PLoS Med. 2008;5(10):e202. doi:10.1371/journal.pmed.0050202
26. Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. Radiat Oncol J. 2014;32(3):103–115. doi:10.3857/roj.2014.32.3.103
27. Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci. 2009;30(11):592–599. doi:10.1016/j.tips.2009.08.004
28. Bigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev. 2012;64(SUPPL):24–36. doi:10.1016/j.addr.2012.09.006
29. Zhang N, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: mechanisms of resistance and reversal strategies. Molecules. 2008;13(8):1551–1569. doi:10.3390/molecules13081551
30. Cho K, Wang X, Nie S, Chen Z, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res. 2008;14(5):1310–1316. doi:10.1158/1078-0432.CCR-07-1441
31. Luqmani YA. Mechanisms of drug resistance in cancer chemotherapy. Med Princ Pract. 2005;14(SUPPL. 1):35–48. doi:10.1159/000086183
32. Tummala S, Satish Kumar MN, Prakash A. Formulation and characterization of 5-Fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer. Saudi Pharm J. 2015;23(3):308–314. doi:10.1016/j.sjps.2014.11.010
Al-Gousous et al. submit

Polymer need for medicinal
coatings in the form of monodisperse alginate nanoparticles. J Biomater Sci Polym
Eng. 2015;26(13):1383–1404. doi:10.1080/09205063.2014.982805

Janet M, Eric KM, Steven SB, et al. Polymeric nanoparticles for site-specific
delivery of antithrombotic agents. J Biomed Biotechnol. 2012;2012:232651. doi:10.1155/2012/232651

Wu R, Li Y, Liu, et al. Enteric-coated capsules filled with mono-disperse micro-particles containing PLGA-lipid-PEG nanoparticles for oral delivery of insulin. Int J Pharm. 2015;484(1–2):181–191. doi:10.1016/j.ijpharm.2015.02.055

Fan W, Xia D, Zhu Q, et al. Functional nanoparticles exploit the bile acid pathway to overcome multiple barriers of the intestinal epithelium for oral insulin delivery. Biomaterials. 2018;151:13–23. doi:10.1016/j.biomaterials.2017.10.022

Nguyen DN, Palangeti L, Clase C, Van den Mooter G. One-step production of darunavir solid dispersion nanoparticles coated with enteric polymers using electrospraying. J Pharm Pharmacol. 2016;68(5):625–633. doi:10.1111/jphp.12459

Sun H, Liu D, Li Y, Tang X, Cong Y. Preparation and in vitro/in vivo characterization of enteric-coated nanoparticles loaded with the anti-hypertensive peptide VLPVFR. Int J Nanomedicine. 2014;9(1):1709–1716. doi:10.2147/IJN.S56092

Sladec S, McCarty F, Eskander M, et al. An enteric-coated poly-electrolyte nanocomplex delivers insulin in rat intestinal instillations when combined with a permeation enhancer. Pharmaceutics. 2020;12(3):259. doi:10.3390/pharmaceutics12030259

Xu B, Zhang W, Chen Y, Xu Y, Wang B, Zong L. Eudragit® L100-coated mannosylated chitosan nanoparticles for oral protein vaccine delivery. Int J Biol Macromol. 2018;113:534–542. doi:10.1016/j.ijbiomac.2018.02.016

Chaturvedi K, Ganguly K, Kulkarni AR, et al. Oral insulin delivery using deoxycholic acid conjugated PEgylated polyhydroxylate co-polymeric nanoparticles. Nanomedicine. 2015;10(10):1569–1583. doi:10.2217/nnm.15.36

He Z, Liu Z, Tian H, et al. Scalable production of core-shell nanoparticles by flash nanocasting to enhance mucosal transport for oral delivery of insulin. Nanoscale. 2018;10(7):3307–3319. doi:10.1039/C7NR08047F

Ray L, Karthik R, Srivastava V, et al. Efficient antielastosomal activity of amphotericin B and piperine entrapped in enteric coated guar gum nanoparticles. Drug Deliv Transl Res. 2020. doi:10.1007/s13346-020-00712-9

Sinhar G, Shah NN, Chokshi NV, Khatri HN, Patel MM. Process, optimization, and characterization of budesonide-loaded nanostructured lipid carriers for the treatment of inflammatory bowel disease. Drug Dev Ind Pharm. 2018;44(7):1078–1089. doi:10.1080/03639045.2018.1434194

Kankala RK, Kuthati Y, Sie H-W, et al. Multi-laminated metal hydroxide nanocoitainers for oral-specific delivery for bioavailability improvement and treatment of inflammatory paw edema in mice. J Colloid Interface Sci. 2015;458:217–228. doi:10.1016/j.jcis.2015.07.044
105. Tayel SA, El-Nabarawi MA, Tadors MI, Abd-Elsalam WH. Duodenum-triggered delivery of pravastatin sodium: II. Design, appraisal and pharmacokinetic assessments of enteric surface-decorated nanocapsule suspensions. Drug Deliv. 2016;23(9):3266–3278. doi:10.3109/10717544.2016.1172367

106. Jog R, Unachukwu K, Burgess DJ. Formulation design space for stable, pH sensitive crystalline nifedipine nanoparticles. Int J Pharm. 2016;514(1):81–92. doi:10.1016/j.ijpharm.2016.08.039

107. Sun L, Liu Z, Tian H, et al. Scalable manufacturing of enteric encapsulation systems for site-specific oral insulin delivery. Biomacromolecules. 2019;20(1):528–538. doi:10.1021/acs.biomac.8b01530

108. González-Alvarez M, Coll C, Gonzalez-Alvarez I, et al. Gated mesoporous silica nanocarriers for a “two-step” targeted system to colonic tissue. Mol Pharm. 2017;14(12):4442–4453. doi:10.1021/acs.molpharmaceut.7b00556

109. Shi Y, Li K, Tian B, et al. Oral delivery of human growth hormone: preparation, characterization, and pharmacokinetics. J Biomater Appl. 2017;31(6):851–858. doi:10.1177/0885328216674347

110. Bendas ER, Abdelbary AA. Instantaneous enteric nano-encapsulation of omeprazole: pharmaceutical and pharmacological evaluation. Int J Pharm. 2014;468(1–2):97–104. doi:10.1016/j.ijpharm.2014.04.030

111. Wu ZM, Zhou L, Guo XD, et al. HP55-coated capsule containing PLGA/RS nanoparticles for oral delivery of insulin. Int J Pharm. 2012;425(1–2):1–8. doi:10.1016/j.ijpharm.2011.12.055

112. Müller C, Perera G, König V, Berkop-Schnürch A. Development and in vivo evaluation of papain-functionalized nanoparticles. Eur J Pharm Biopharm. 2014;87(1):125–131. doi:10.1016/j.ejpb.2013.12.012

113. Salvioni L, Fiandra L, Del Curto MD, et al. Oral delivery of insulin via polyethylene imine-based nanoparticles for colonic release allows glycomic control in diabetic rats. Pharm Res. 2016;110:122–130. doi:10.1007/s11095-016-1506-9

114. Luo S, Hao J, Gao Y, Liu D, Cai Q, Yang X. Pore size effect on adsorption and release of metoprolol tartrate in mesoporous silica: experimental and molecular simulation studies. Mater Sci Eng C. 2019;100:789–797. doi:10.1016/j.msec.2019.03.050

115. Alai M, Lin WJ. Novel lansoprazole-loaded nanoparticles for the treatment of gastric acid secretion-related ulcers: in vitro and in vivo pharmacokinetic pharmacodynamic evaluation. AAPS J. 2014;16(3):361–372. doi:10.1208/s12248-014-9564-0

116. Nguyen DN, Claesen C, Van den Mooter G. Encapsulating danuvair nanocrystals within Eudragit L100 using coaxial electrospaying. Eur J Pharm Biopharm. 2017;113:50–59. doi:10.1016/j.ejpb.2016.12.002

117. Kumar PV, Maki MAA, Wei YS, et al. Rabbit as an animal model for pharmacokinetics studies of enteric capsule contains recombinant human keratinocyte growth factor loaded chitosan nanoparticles. Curr Clin Pharmacol. 2019;14(2):132–140. doi:10.2174/1574884714666181120103907

118. Eskandari S, Varamini P, Toth I. Formulation, characterization and permeability study of nano particles of lipo-endomorphin-1 for oral delivery. J Liposome Res. 2013;23(4):311–317. doi:10.3109/08922140.2013.805339

119. Shah MK, Madan P, Lin S. Preparation, in vitro evaluation and statistical optimization of carvedilol-loaded solid lipid nanoparticles for lymphatic absorption via oral administration. Pharm Dev Technol. 2019;14(4):475–485. doi:10.3109/10837450.2013.795169

120. Nguyen H-N, Wey S-P, Jiang J-H, et al. The glucose-lowering potential of exendin-4 orally delivered via a pH-sensitive nanoparticle vehicle and effects on subsequent insulin secretion in vivo. Biomaterials. 2011;32(10):2673–2682. doi:10.1016/j.biomaterials.2010.12.044

121. Chen K, Chang HHR, Shalviri A, et al. Investigation of a new pH-responsive nanoparticulate pore former for controlled release enteric coating with improved processability and stability. Eur J Pharm Biopharm. 2017;120:116–125. doi:10.1016/j.ejpb.2017.08.014

122. Roy U, Ding H, Pilakka Kanthikeel S, et al. Preparation and characterization of anti-HIV nanodrug targeted to microfold cell of gut-associated lymphoid tissue. Int J Nanomedicine. 2015;5819. doi:10.2147/INJN.S66348.

123. Warrier MK, Ali-Shفاد R, Ezzeldin E, Alshahrani SM, Alshetaiwi AS, Iqbal M. Preparation, evaluation and bioavailability studies of eudragit coated PLGA nanoparticles for sustained release of eluxadoline for the treatment of irritable bowel syndrome. Front Pharmacol. 2017;8. doi:10.3389/fphar.2017.00844.

124. Biswas S, Chattopadhyay M, Sen KK, Saha MK. Development and characterization of alginate coated low molecular weight chitosan nanoparticles as new carriers for oral vaccine delivery in mice. Carbohydr Polym. 2015;121:403–410. doi:10.1016/j.carbpol.2014.12.044

125. Zhao X, Shan C, Zu Y, et al. Preparation, characterization, and evaluation in vivo of Ins-SiO2-HP55 (insulin-loaded silica coating HP55) for oral delivery of insulin. Int J Pharm. 2013;454(1):278–284. doi:10.1016/j.ijpharm.2013.06.051

126. Su F-Y, Lin K-J, Sonaje K, et al. Protease inhibition and absorption enhancement by functional nanoparticles for effective oral insulin delivery. Biomaterials. 2012;33(9):2801–2811. doi:10.1016/j.biomaterials.2011.12.038

127. Liu P, Yang Z, Wang Y, et al. Microencapsulation of coupled folate and chitosan nanoparticles for targeted delivery of combination drugs to colon. J Microencapsul. 2015;32(1):40–49. doi:10.3109/02652048.2014.944947

128. Nassar T, Attili-Qadri S, Harush-Frenkel O, et al. High plasma levels and effective lymphatic uptake of doctelexan in an orally available nanotransporter formulation. Cancer Res. 2011;71(8):3018–3028. doi:10.1158/0008-5472.CAN-10-3118

129. Mahjub R, Najafabadi FK, Dehkhodai N, et al. Eudragit L-100 capsules/aromatize and quaternize chitosan for insulin nanoparticle oral delivery on toxic oxidative stress in rat liver and kidney. Pharm Nanotechnol. 2018;8. doi:10.2174/221173850866200628033442

130. Yus C, Irusta S, Sebastian V, Arruebo M. Controlling particle size and release kinetics in the sustained delivery of oral anti-biotics using pH-independent mucoadhesive polymers. Mol Pharm. 2020;acs.molpharmaceut.0c00408. doi:10.1021/acs.molpharmaceut.0c00408

131. Zhou K, Yan Y, Chen D, et al. Solid lipid nanoparticles for duodenum targeted oral delivery of tilmicosin. Pharmaceutics. 2020;12(8):731. doi:10.3390/pharmaceutics12080731

132. Sahu KK, Kaurav M, Pandey RS. Chylomicron mimicking solid lipid nanoemulsions encapsulated enteric microparticles targeted to colon for immunization against hepatitis B. Int Immunopharmacol. 2019;66:317–329. doi:10.1016/j.intimp.2018.11.041

133. Tummala S, Kuppasamy G, Satish Kumar MN, Praveen TK, Wadhwani A. 5-Fluorouracil enterico-coated nanoparticles for improved apoptotic activity and therapeutic index in treating colorectal cancer. Drug Deliv. 2016;23(8):2902–2910. doi:10.3109/10717544.2015.1116026

134. Hosny KM. Alendronate sodium as enteric coated solid lipid nanoparticles; preparation, optimization, and in vivo evaluation to enhance its oral bioavailability. Santos HA, ed. PLoS One. 2016;11(5):e0154926. doi:10.1371/journal.pone.0154926

135. Valat MT. Mechanistic study of NVP-CGM097: A potent, selective and species specific inhibitor of p53-Mdm2. Drug Des Open Access. 2015;04.02. doi:10.4172/2169-0138.1008
136. Amini-Fazl MS, Mohammadi R, Kheiri K. 5-Fluourouracil loaded chitosan/polyacrylic acid/Fe 3 O 4 magnetic nanocomposite hydrogel as a potential anticancer drug delivery system. Int J Biol Macromol. 2019;132:506–513. doi:10.1016/j.ijbiomac.2019.04.005

137. Choi JS, Cao J, Naeem M, et al. Size-controlled biodegradable nanoparticles: preparation and size-dependent cellular uptake and tumor cell growth inhibition. Colloids Surfaces B Biointerfaces. 2014;122:545–551. doi:10.1016/j.colsurfb.2014.07.030

138. Choi YH, Han HK. Nanomedicines: current status and future perspectives in aspect of drug delivery and pharmacokinetics. J Pharm Invest. 2018;48(1):43–60. doi:10.1007/s40005-017-0370-4

139. Banerjee A, Qi J, Gogoi R, Wong J, Mitragotri S. Role of nanoparticle size, shape and surface chemistry in oral drug delivery. J Control Release. 2016;238:176–185. doi:10.1016/j.jconrel.2016.07.051

140. Xiao B, Si X, Han M, Viennois E, Zhang M, Merlin D. Codelivery of camptothecin and curcumin by cationic polymeric nanoparticles for synergistic cancer colon combination chemotherapy. J Mater Chem B. 2015;3:7724–7733. doi:10.1039/c5tb01245g

141. Akinc A, Battaglia G. Exploiting endocytosis for nanomedicines. Cold Spring Harb Perspect Biol. 2013;5(11):a016980–a016980. doi:10.1101/cshperspect.a016980

142. Chen S, Guo F, Deng T, et al. Eudragit S100-coated chitosan nanoparticles co-loading tat for enhanced oral colon absorption of insulin. AAPS Pharm Sci Tech. 2017;18(4):1277–1287. doi:10.1208/s12249-016-0594-z

143. Karr PR, Vanic Z, Pepi I, Škalko-Basnet N. Mucoadhesive liposomal delivery systems: the choice of coating material. Drug Dev Ind Pharm. 2011;37(4):482–488. doi:10.3109/03639045.2010.523425

144. Nikam V, Kotade K, Gaware V, et al. Eudragit a versatile polymer: a review. Pharmcolonline. 2011;1:152–164.

145. Sun L, Chen Y, Zhou Y, et al. Preparation of 5-fluorouracil-loaded chitosan nanoparticles and study of the sustained release in vitro and in vivo. Asian J Pharm Sci. 2017;12(5):418–423. doi:10.1016/j.ajps.2017.04.002

146. Khatik R, Mishra R, Verma A, et al. Colon-specific delivery of curcumin by exploiting Eudragit-decorated chitosan nanoparticles in vitro and in vivo. J Nanosci Nanotechnol. 2013;13:5. doi:10.1007/s11051-013-1893-x

147. Li CF, Li YC, Chen LB, Wang Y, Sun LB. Doxorubicin-loaded Eudragit-coated chitosan nanoparticles in the treatment of colon cancers. J Nanosci Nanotechnol. 2016;16(7):6773–6780. doi:10.1016/j.jnnanotech.2016.11.1374

148. Jain A, Jain S, Jain R, Kohli DV. Coated chitosan nanoparticles encapsulating caspase 3 activator for effective treatment of colorectal cancer. Drug Deliv Transl Res. 2015;5(6):596–610. doi:10.1007/s13346-015-0255-x

149. Subudhi MB, Jain A, Jain A, et al. Eudragit S100 coated citrus pectin nanoparticles for colon targeting of 5-fluorouracil. Materials (Basel). 2015;8(3):832–849. doi:10.3390/ma8030832

150. Ma Y, Fuchs AV, Boase NR, Rolfe BE, Coombs AGA, Thurecht KJ. The in vivo fate of nanoparticles and nanoparticle-loaded microparticles after oral administration in mice: evaluation of their potential for colon-specific delivery. Eur J Pharm Biopharm. 2015;94:393–403. doi:10.1016/j.ejpb.2015.06.014

151. Kanthamneni N, Chaudhary A, Wang J, Phabhu S. Nanoparticulate delivery of novel drug combination regimens for the chemoprevention of colon cancer. Int J Oncol. 2016;43:177–185. doi:10.3892/ijo

152. Ma Y, Coombes AGA. Designing colon-specific delivery systems for anticancer drug-loaded nanoparticles: an evaluation of alginate carriers. J Biomed Mater Res. 2014;102(9):3167–3176. doi:10.1002/jbm.b.34988

153. Rajpoot K, Jain SK. Oral delivery of pH-responsive alginic microbeads incorporating folic acid-grafted solid lipid nanoparticles exhibits enhanced targeting effect against colorectal cancer: a dual-targeted approach. Int J Biol Macromol. 2020;151:830–844. doi:10.1016/j.ijbiomac.2020.02.132

154. Cerchiara T, Bigucci F, Corace G, Zecchi V, Luppi B. Eudragit-coated albumin nanoparticles carrying inclusion complexes for oral administration of indomethacin. J Incl Phenom Macrocycl Chem. 2011;71(1–2):129–136. doi:10.1007/s10817-010-9396-z

155. Jain A, Jain SK. Optimization of chitosan nanoparticles for colon tumors using experimental design methodology. Artif Cells Nanomedicine Biotechnol. 2016;44(8):1917–1926. doi:10.3109/21691401.2015.1111236

156. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert Opin Drug Deliv. 2013;10(1):131–149. doi:10.1517/17425247.2013.736962

157. Nassar T, Attili-Qadri S, Harush-Frenkel O, et al. High plasma levels and effective lymphatic uptake of docetaxel in an orally available nanotransporter formulation. Cancer Res. 2011;71(8):3018–3028. doi:10.1158/0008-5472.CAN-10-3118

158. Sinha VR, Kumria R. Coating polymers for colon specific drug delivery: a comparative in vitro evaluation. Acta Pharm. 2003;53(1):41–47.

159. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert Opin Drug Deliv. 2013;10(1):131–149. doi:10.1517/17425247.2013.736962

160. Mohammed MA, Syeda JTM, Wasan KM, Wasan EK. An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics. 2017;9:4. doi:10.3390/pharmaceutics9040053

161. Sonaje K, Chen YJ, Chen HL, et al. Enteric-coated capsules filled with freeze-dried chitosan/poly(+)-glutamic acid) nanoparticles for oral insulin delivery. Biomaterials. 2010;31(12):3384–3394. doi:10.1016/j.biomaterials.2010.01.042

162. Alai MS, Lin WJ, Pingale SS. Application of polymeric nanoparticles and micelles in insulin oral delivery. J Food Drug Anal. 2015;23(3):351–358. doi:10.1016/j.jfda.2015.01.007

163. Thiyagarajan V, Lin SX, Lee CH, Weng CF. A focal adhesion kinase inhibitor 16-hydroxy-cleroda-3,13-dien-16,15-olide incorporated into enteric-coated nanoparticles for controlled anti-glioma drug delivery. Colloids Surfaces B Biointerfaces. 2016;141:120–131. doi:10.1016/j.colsurfb.2016.01.038
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