



## Review Article

## Nano drug delivery strategy of 5-fluorouracil for the treatment of colorectal cancer

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## ARTICLE INFO

## Article history:

Received 11 October 2016

Accepted 16 February 2017

Available online 17 February 2017

## Keywords:

Colorectal cancer

5-fluorouracil

Nano drug delivery

Nanoparticles

Silica nanoparticles

## ABSTRACT

Colorectal cancer (CRC) is the leading cause of cancer-related mortality, annually responsible for around 655,000 deaths worldwide. CRC usually develops very slowly, over a period of 10 to 20 years and typically begin as a non-cancerous polyp that develops on the inner layer of the colon or rectum. However, CRC is curable if detected at an early stage. The current treatment of colorectal cancer primarily depends on surgery, chemotherapy, radiotherapy and targeted therapy. A combination of two or more treatments is often recommended to achieve the best outcome, depending on the stage of cancer development. In this review, we summarized the challenges of using 5-Fluorouracil as chemotherapy to treat colorectal cancer, and discussed the implications of nano drug delivery system for improved therapeutic outcome of 5-Fluorouracil.

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## 1. Introduction

## 1.1. Colorectal cancer

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality, with around 655,000 deaths worldwide every year.<sup>1,2</sup> The majority of the cancer-related deaths could be prevented by applying existing knowledge about cancer prevention, increasing the use of recommended screening tests, and ensuring that all patients timely receive standard treatment.<sup>3</sup> In the past decade, there has been unprecedented progress in reducing both the incidence and mortality rates of colorectal cancer in the United States, largely due to the prevention and early detection of CRC through screening.<sup>4</sup> CRC usually develops very slowly, over a period of 10 to 20 years, with most beginning as non-cancerous growths that develop on the inner layer of the colon or rectum. The most common kind of polyp is called an adenomatous polyp or adenoma these adenomas arise from glandular cells, which secrete mucus to lubricate the colorectum. An estimated one-third of patients will

eventually develop one or more adenomas progressing to invasive cancer. As the adenoma becomes larger, there is an increasing likelihood it will evolve into cancer.<sup>5,6</sup>

## 1.2. Current treatment option for colorectal cancer

If found early colorectal cancer can be successfully treated. The current treatment of colorectal cancer mainly depends on surgery, chemotherapy, radiotherapy and targeted therapy.<sup>7</sup> Depending on the stage of cancer development, combinations of two or more treatments are often recommended to achieve the best outcome. Surgery is the main treatment option for CRC wherein the tumor surrounding healthy tissue and adjacent lymph nodes is removed. The five-year relative survival rate of patients with CRC metastasis to distant organs is much lower than CRC patients at earlier stages.<sup>8</sup> The current pharmacotherapy, such as chemotherapy, and targeted therapy act on cancer cells principally through cell apoptosis, cell senescence and autophagy.<sup>9</sup>

## 1.3. Chemotherapy for colorectal cancer

The existing therapeutic compounds for the treatment of colorectal cancer are diverse. They include cytotoxic agents (5-fluorouracil, oxaliplatin, capecitabine and irinotecan), targeted

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Peer review under responsibility of The Chinese Oncology Society.

therapies (anti-vascular endothelial growth factor-A antibody [bevacizumab], and anti-epidermal growth factor receptor antibodies [cetuximab, and panitumumab]). Many scientists began testing drug combinations with 5-FU as early as the 1980s, and, in the mid-1990s, the combination of 5-FU and leucovorin became standard adjuvant therapy for patients with stage III colon cancer. The addition of oxaliplatin to 5-FU and leucovorin was soon found to improve survival compared with 5-FU and leucovorin alone. A latest drug, capecitabine, is an alternative to 5-FU and leucovorin. Capecitabine is sometimes combined with oxaliplatin as well. Capecitabine is administered by mouth, whereas 5-FU must be given I.V route. For some patients whose cancer has metastasized, the drug irinotecan may also be part of chemotherapy.

#### 1.4. 5-Fluorouracil

For the last 70 years, the fluoropyrimidine 5-fluorouracil (5-FU) has been positioned as a first line chemotherapy in the treatment of various cancers including colorectal, head, neck and breast cancers.<sup>10,11</sup> This combination has multiple mechanisms of cytotoxicity including the inhibition of thymidylate synthase, which improves overall and disease-free survival of patients with resected stage III colorectal cancer.<sup>12</sup> It is soluble in water, and also upon intravenous administration. However, the response rates of 5-FU for advanced colorectal cancer is less than 15%, and the bioavailability is also limited.<sup>14</sup> Furthermore, 5-FU causes severe toxic effects on the gastrointestinal tract, hematological, neural, cardiac and dermatological reactions.<sup>13–16</sup> Hence, there is a need to identify a potential drug delivery system for 5-FU to achieve better therapeutic efficacy with fewer side effects.

#### 1.5. Strategies to improve CRC chemotherapy

Use of a nanodrug delivery system has been explored for transporting anti-cancer drugs to colorectal cancer cells, while reducing undesired drug distribution in healthy tissues.<sup>17,18</sup> Compared to conventional drug delivery, nanoparticles (NPs) may be changing to protect cancer drugs from first-pass metabolism, enzymatic degradation in the stomach and small intestine, which leads to an increase in the amount of drug available for localized delivery within the colon.<sup>19</sup> Currently, most of the drug-loaded NPs have been designed for IV administration, gathering and accumulating in the blood vessels and subsequently eradicating cancer cells.<sup>20</sup> This delivery of therapeutic NPs to the colorectal region may overcome the barriers to achieve successful CRC chemotherapy. Herewith, we have summarized the nanodrug delivery of 5-FU for the treatment of colorectal cancer.

##### 1.5.1. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) have gained an increasing importance as an alternative colloidal carrier system. This delivery system has certain specific advantages which include inexpensive, feasible, ease to scale up,<sup>21,22</sup> high dispersibility in an aqueous medium, higher entrapment in case of hydrophobic drugs and extended release behavior.<sup>23</sup> In her research Alaa Eldeen and her colleagues prepared SLNs using a simple double-emulsion method that offers a superior flexibility and reduced process-related stress on the encapsulated drug. The SLNs system has a high potential to improve the uptake of anticancer drugs inside colon tumors.<sup>24</sup> Patel et al. prepared 5-FU loaded SLN by temperature-modulated solidification method. The anticancer activity of 5-FU loaded SLNs was investigated with Caco-2 cell line, revealing that it produced a concentration-dependent decrease in cell viability in Caco-2 cell line. From this study they concluded that a 5-FU loaded SLNs delivery system can produce superior anticancer activity than pure

5-FU.<sup>20</sup>

##### 1.5.2. Chitosan-based nanoparticles

Chitosan-based nanoparticles have attracted increasing attention for their wide therapeutic applications including proteins, genes, and anti-cancers, and administered through various routes including oral, nasal, intravenous, and ocular delivery.<sup>25–27</sup> In 2015, researchers Shashank Tummala and associates developed chitosan-loaded 5-FU nanoparticles to minimize the toxic effects of these powerful pharmaceuticals on healthy cells and localize drug delivery to the colon region. They concluded that the formulated chitosan nanoparticles improved localization of the drug at the colon region, which was followed by a sustained release mechanism over a prolonged period of 24 h. This can lead to a decrease in drug-induced toxicity to healthy cells as a greater volume of the drug is localized in the colorectal cancer. These changes also benefit the patient because dose frequency and drug administration can be reduced.<sup>28</sup> In another study, Tan et al. developed the 5-FU loaded chitosan nanoparticles to achieve better targeting efficiency and localization of drug to the tumor cells. Their *in vitro* release studies indicated a controlled and sustained release of 5-FU from chitosan nanoparticles with the release amount of 29–60% due to varied pH environment after a 48 h incubation period. Finally, the authors suggested that 5-FU encapsulated chitosan nanoparticles should be explored as a pH-responsive smart drug delivery for cancer treatments.<sup>29</sup>

##### 1.5.3. PLGA nanoparticles

Poly (lactic-co-glycolic acid) (PLGA), is one of the most successfully developed polymers to produce polymeric nanoparticles, due to its attractive properties including biodegradability and biocompatibility.<sup>30</sup> Sutar et al. used PLGA and Eudragit S-100 to fabricate the 5-FU nanoparticles to treat CRC through a target delivery mechanism. They prepared the nanoparticles by use of the emulsion droplet coalescence method, utilizing pH sensitive polymer and PLGA. The *in-vitro* anticancer efficacy of formulated 5-FU nanoparticles was investigated on HT-29 cell lines using MTT assay method. The results revealed that the rate of cell lysis was about 80%, and that the nanoformulation prominently exhibited an effect on the target colon cancer cells. Based on this data, they have concluded, that 5-FU loaded nanoparticles might be a potential delivery system for targeting colorectal cancer.<sup>31</sup>

##### 1.5.4. Folic acid and PLGA conjugates

Folic acid (FA) has been widely employed as a targeting moiety for various anticancer drugs.<sup>32–34</sup> It can specifically attach with folate receptors, which are widely found in most cancer cells.<sup>35</sup> Moreover, the folate receptor density also appears to increase at the stage of cancer progression.<sup>36</sup> Therefore, FA can be used as a targeting agent for the treatment of metastatic cancers, particularly at the advanced stage. Based on this hypothesis, FA has been conjugated with many anticancer agents for selective targeting against cancer cells.<sup>37,38</sup> 5-FU loaded PLGA nanoparticles were fabricated by a modified W/O/W multiple emulsion and solvent evaporation technique. The high FA conjugation ratio contributes significantly to the cytotoxicity of nanoparticles. *In vitro* cell viability for drug loaded nanoparticles was investigated by MTT assay and the prepared nanoparticles have shown enhanced anticancer activity. The *in vitro* cells viability study showed the lowest cell viability when treated with PLGA and FA conjugates compared to pure 5-FU.<sup>39</sup>

##### 1.5.5. Eudragit S100 coated citrus pectin nanoparticles

Pectin is a natural polymer suitable as a colon-specific drug delivery vehicle in the treatment of colorectal cancer and other colonic diseases.<sup>40</sup> 5-FU citrus pectin nanoparticles (CPNs) were

**Table 1**  
The importance of various drug delivery systems for 5-Fluorouracil for CRC therapy.

Delivery system for 5-Fluorouracil	Advantages	Reference
Solid lipid nanoparticles	Enhanced cytotoxic effect	Eldeen et al., 2010 <sup>24</sup> Patel et al., 2014 <sup>25</sup>
Chitosan nanoparticles	Achieved better targeting efficiency Ability to localized drug to tumor cells	Tan et al., 2012 <sup>29</sup>
PLGA nanoparticles	Maximum cell-lysis effect Better targeting efficiency	Sutar et al., 2013 <sup>31</sup>
Folic acid and PLGA conjugates	Enhanced anticancer activity with less cell viability	Yichao et al., 2015 <sup>39</sup>
Eudragit S100 coated citrus pectin nanoparticles	Better targeting efficiency and prolonged drug release	Subudhi et al., 2015 <sup>2</sup>
Silica nanoparticles	Enhanced cellular uptake Improved cytotoxic effect	Liu et al., 2015 <sup>43</sup>

fabricated and coated with Eudragit S100 (E-CPNs) for targeted delivery of colon cancer. *In vitro* cytotoxicity assay was performed against HT-29 cancer cells and exhibited a 1.5-fold greater cytotoxicity potential of nanoparticles compared to a 5-FU solution. *In vivo* data clearly depicted that Eudragit S100 successfully protected nanoparticles, enabling them to reach the colonic region. There, the nanoparticles were taken up and exhibited drug release for a prolonged period of time.<sup>2</sup>

#### 1.5.6. Silica nanoparticles (HMSNs)

Silica nanoparticles (SiNP) possess unique advantages as a drug delivery carrier, including excellent biocompatibility, hydrophobicity, systemic stability, and resistance to pH changes.<sup>41</sup> To improve the chemotherapeutic efficacy of 5-FU in colon cancers, 5-FU loaded hyaluronic acid (HA) was conjugated with silica nanoparticles (SiNPs), and prepared to target colon cancer cells.<sup>42</sup> In fact, the researchers investigated the cytotoxic potential of targeted nanoparticles against colo-205 cancer cells. The result clearly revealed that HA-conjugated NP was more effective in inducing apoptosis in cancer cells than non-targeted NP (see Table 1). Overall, they revealed that conjugation of HA to SiNPs could result in enhanced uptake of 5-FU through CD44-mediated endocytosis uptake and could result in significant anticancer efficacy.<sup>43,44</sup>

#### 1.6. Alternative for 5-FU nanoformulations

ONIVYDE, also known as MM-398 or PEP02, has been formulated as a nanoliposomal formulation of irinotecan, which enhances the pharmacokinetics of the drug by increasing drug encapsulation and loading efficiency, protecting the drug in the active lactone configuration, prolonging circulation time, providing sustained drug release, rerouting the drug from sites of toxicity such as the gastrointestinal tract, improving tumor accumulation through the EPR effect, and reducing host toxicity. In this clinical trial, ONIVYDE+5-FU/LV demonstrated an improvement in median overall survival (OS). Since, the improvement in median OS means patients receiving ONIVYDE+5-FU/LV had a greater chance of living longer when compared with the 5-FU/LV alone group. And also, the researchers suggested that the liposomal formulation of ONIVYDE may not work for every patient. The outcome may vary from patient to patient. However, based on the promising preclinical and clinical report available for the treatment of several solid tumors, Onivyde was recently approved by the US Food and Drug Administration in 2015 as a combination regimen for patients with gemcitabine-based chemotherapy-resistant metastatic pancreatic cancer. In addition, it is also currently undergoing Phase II/III clinical trials for the treatment of many cancers, including pancreatic cancer, esophago-gastric cancer, and colorectal cancer.<sup>47</sup>

## 2. Future challenges and conclusion

In recent decades several anticancer drugs have been approved for the management and treatment of colorectal cancer. These drugs do not represent a revolution in the treatment of CRC. However, 5-FU has continued to be used for the treatment of tumors, and widely employed in clinical chemotherapy for the treatment of carcinomas of the colorectal region. Nevertheless, its clinical benefits are greatly limited due to drug resistance, which could result from various causes, including alteration of drug influx and efflux mechanism, enhancement of drug inactivation and mutations of the drug target.<sup>45,46</sup> Certainly there could be many mechanisms of 5-FU anticancer potential and drug resistance, which have yet to be demonstrated. The nano drug delivery technologies might one day enable practitioners to fabricate 5-FU and investigate the molecular mechanisms more specifically. Therefore, the urge to seek the better therapeutic strategies to increase 5-FU cytotoxicity, sensitivity and reverse resistance to drug are the key tasks in the near future.

### Conflict of interest

The authors declare no conflicts of interest in this study

### Acknowledgement

The author Satheesh Babu N, gratefully acknowledges the financial assistance provided by MOHE- Malaysia, in the form of Fundamental Research Grant Scheme (Ref No: FRGS/1/2014/SKK02/LINCOLN/03/1) and is also thankful to Prof. Dr. Wong Tin Wui (Non Destructive Biomed Pharmaceutical Research Centre, UiTM, Malaysia) for providing his technical and instrumentation facility. The author extends his gratitude to Kotra Pharma for providing Papain enzyme as a gift sample.

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