

# Future of 5-fluorouracil in cancer therapeutics, current pharmacokinetics issues and a way forward

Iqbal, SZ., Jubeen, F. & Sher, F.

Published PDF deposited in Coventry University's Repository

**Original citation:**

Iqbal, SZ, Jubeen, F & Sher, F 2019, 'Future of 5-fluorouracil in cancer therapeutics, current pharmacokinetics issues and a way forward' Journal of Cancer Research and Practice, vol. 6, no. 4, pp. 155-161.

[https://dx.doi.org/10.4103/JCRP.JCRP\\_10\\_19](https://dx.doi.org/10.4103/JCRP.JCRP_10_19)

DOI 10.4103/JCRP.JCRP\_10\_19

ISSN 2311-3006

ESSN 2589-0425

Publisher: Wolters Kluwer - Medknow

**This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.**

**Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.**

Print ISSN: 2311-3006  
Online ISSN: 2589-0425



# Journal of Cancer Research and Practice

**JCRP**

October-December 2019  
VOL. 6, NO. 4



## Review Article

# Future of 5-Fluorouracil in Cancer Therapeutics, Current Pharmacokinetics Issues and a Way Forward

Sania Zafar Iqbal<sup>1,2</sup>, Farhat Jubeen<sup>1,2</sup>, Farooq Sher<sup>1,3\*</sup>

<sup>1</sup>Department of Chemical and Environmental Engineering, University of Nottingham, Nottingham, UK

<sup>2</sup>Department of Chemistry, Government College Women University, Faisalabad, Pakistan

<sup>3</sup>School of Mechanical, Aerospace and Automotive Engineering, Faculty of Engineering, Environment and Computing, Coventry University, Coventry, UK

## Abstract

**Background:** In addition to exhibiting antitumor potential, antitumor drugs exhibit toxicity due to a poor pharmacokinetic profile. An enormous amount of research has been carried out and is still ongoing to obtain more targeted, potent, and safe drugs to treat cancer, and pharmacokinetic evaluations of anticancer drugs are needed. **Objectives:** The present review examined different delivery systems and methodologies designed in recent years to investigate the pharmacokinetics of the anticancer drug, 5-fluorouracil (5-FU). These methodologies highlight how the issues of bioavailability, absorption, half-life, targeted neoplastic cell potential, and high therapeutic index of 5-FU are resolved. **Results:** A number of naturally occurring macromolecules such as modified starch, porphyrin, peptides, and folic acids have been found to be successful *in vitro* to improve the permeability and retention effect of 5-FU against solid tumors. A promising approach for targeted 5-FU delivery to oncoproteins has resulted in a number of potentially sound anticancer nanocomposites. Chitosan nanoparticles loaded with 5-FU have been shown to exhibit cytotoxicity equivalent to 5-FU injections against gastric carcinoma. At the level of inter- and intra-molecular interactions, the co-crystal approach has been found to be successful against colorectal cancer proteins. Because of the 5-FU ligand-like nature and its metal-binding potential, researchers have shifted attention toward the synergistic co-administration of gold complexes with this drug. **Conclusions:** This study highlighted the techniques used to improve the pharmacokinetics of 5-FU and that “nanocarriers” are a promising approach in this field. The conclusion is supported by solid evidence.

**Keywords:** Delivery systems, nanocomposites, pharmacokinetic targeted potentials, prodrug

## INTRODUCTION

Cancer is a leading cause of mortality worldwide. In 2012, 8.2 million deaths and 14.1 million new cases of cancer were reported, among which 57% occurred in Asia, Africa, and Central America. It is estimated that the number of new cancer cases

per year will increase to 23.6 million by 2030.<sup>[1,2]</sup> According to the GLOBOCAN estimates, the third-most common cancer worldwide and the second-most common cancer in Europe is

**Address for correspondence:** Dr. Farooq Sher,  
Faculty of Engineering, Environment and Computing, Coventry University,  
Coventry CV1 2JH, UK.  
E-mail: [farooq.sher@coventry.ac.uk](mailto:farooq.sher@coventry.ac.uk)

Received: 16-Feb-2019 Revised: 22-Apr-2019

Accepted: 03-May-2019 Published: 23-Sep-2019

### Access this article online

Quick Response Code:



Website:  
[www.ejcrp.org](http://www.ejcrp.org)

DOI:  
10.4103/JCRP.JCRP\_10\_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** [reprints@medknow.com](mailto:reprints@medknow.com)

**How to cite this article:** Iqbal SZ, Jubeen F, Sher F. Future of 5-fluorouracil in cancer therapeutics, current pharmacokinetics issues and a way forward. *J Cancer Res Pract* 2019;6:155-61.

colorectal cancer (CRC).<sup>[3]</sup> Types of cancer treatments available include surgery, chemotherapy, radiotherapy, hormone therapy, gene therapy, and others. In chemotherapy, anticancer drugs are used to destroy cancer cells.<sup>[3]</sup>

5-fluorouracil (5-FU) is a US Food and Drug Administration (FDA)-approved anticancer drug that is used for the treatment of various types of solid tumors. However, it has a poor pharmacokinetics profile<sup>[4]</sup>, and therefore, it was not the most recommended or best-selling anticancer drug from 2014 to 2017.<sup>[5]</sup> Nevertheless, 5-FU has been studied extensively in parallel with the following top four recommended and best-selling anticancer drugs: revlimid, rituximab, trastuzumab, and bevacizumab. Even though 5-FU is not the most recommended anticancer drug,<sup>[6]</sup> it has been shown to have a promising anticancer effect, and improving its pharmacokinetics behavior may increase its use.<sup>[7]</sup>

In addition to poor pharmacokinetics, some chemotherapeutics have severe side effects. Designing economical, novel, and effective chemotherapies is an important topic in anticancer research, in which 5-FU is an excellent example. After approval from the FDA in 1962, cancer-causing malignancies have been widely treated by fluoropyrimidines, particularly 5-FU.<sup>[8]</sup> After insertion into deoxyribonucleic acid and ribonucleic acid,<sup>[9]</sup> the pyrimidine nucleus induces apoptosis by inhibiting thymidylate synthase. Poor tumor cell selectivity and irregular distribution in healthy tissues limit the application of 5-FU. Using a typical dose of 600 mg/m<sup>2</sup>/day, tumor cells are exposed to rate-limited active metabolites only for a short time. 5-FU is cleared quickly after administration due to a short half-life of 20 min.<sup>[9]</sup>

Due to its narrow therapeutic window, it causes severe health complications. Therefore, targeted 5-FU therapy in oncologic tissues is an important issue to improve its pharmacokinetic profile and facilitate its specific accumulation in tumor cells with long exposure.<sup>[10]</sup> A number of clinical trials using different strategies have been conducted and shown promising results, and some are ongoing to improve the pharmacokinetics of 5-FU through plasma level dose adjustment,<sup>[11]</sup> administration through the hepatic artery,<sup>[12]</sup> synergistic formulation,<sup>[13]</sup> and the use of commercial My-5FU PCM™ kits.<sup>[14]</sup>

To tackle the issues related to 5-FU as discussed above, different approaches have been used in recent years including: (1) delivery systems (macromolecular carriers and polymeric nanocarriers),<sup>[15]</sup> (2) solid states of 5-FU,<sup>[16]</sup> and (3) a synergistic approach with 5-FU and active anticancer metals.<sup>[17]</sup> Figure 1 shows the number of studies conducted from 2009 to 2019 to develop techniques which are useful in assessing the problems and side effects that hinder the widespread application of 5-FU.<sup>[7]</sup> Data from the ISI Web of Science indicated that the use of nanocarriers for improving the efficacy of 5-FU is a popular choice [Figure 1], and that the synergistic effect of 5-FU with metals to form complexes is a popular technique to evaluate the pharmacokinetics of 5-FU.<sup>[7]</sup>

This study aimed to briefly review all the techniques that have recently been shown to be effective in improving the pharmacokinetics of 5-FU, including absorption, sustained release, retention time, sorption, dissolution rate, solubility, and stability. The findings of this study may be helpful for further research on 5-FU.

## MACROMOLECULE CARRIERS OF 5-FLUOROURACIL

The aforementioned problems have led to the use of conjugates of 5-FU with larger molecules to enhance the absorption and retention of macromolecular prodrugs.<sup>[15]</sup> Macromolecular prodrugs formed by combining small drug molecules (e.g., 5-FU) with polymeric carriers can help in the sustained release of the therapeutic drugs *in vivo*, which results in an improved half-life.<sup>[17]</sup> In addition, researchers have designed and prepared a prodrug-based conjugate of 5-FU substituted with acetic acid at N<sub>1</sub> (FUAC), with hydroxyethyl-substituted starch (HES) through an ester linkage. Hydrolysis experiments of these prodrugs have shown the stability and slow release of FUAC at pH 5.8. The FUAC/HES conjugates were tarnished to active drug in human and mouse plasma with 20.4 h and 24.6 h half-lives, respectively. The *in vitro* and *in vivo* drug release results showed that HES is a promising carrier for the controlled release of 5-FU and its derivatives.<sup>[18]</sup> Other studies have shown associations between 5-FU and many macromolecules, including pectin,<sup>[19]</sup> porphyrin, porphyrin,<sup>[19]</sup> and folic acid.<sup>[20]</sup> Another prodrug was recently reported, 5-FU-1-acetic acid-polyethylene glycol-allyl glycidyl ether-mercaptoproethanol (5-FA-PAE),<sup>[21]</sup> and 5-FA, a derivative of 5-FU, was used with conjugation of the derivative with macromolecules to synthesize 5-FA-PAE. The newly designed prodrug evaluated *in vitro* and *in vivo* for pharmacokinetics and antitumor effects, the results were promising. *In vivo* antitumor experimental results of drug (5-FU), derivative (5-FA), saline solution, and prodrug (5-FA-PAE) revealed that this prodrug could transport the drug to malignant cells with higher antitumor potential [Figure 2].

Porphyrin, a sulfated galactan isolated from *Porphyra haitanensis* (red algae), has shown numerous potent biological actions along with anticancer potential. A water-soluble macromolecular prodrug was prepared by fixing 5-FU at the 6<sup>th</sup> position of porphyrin, and the pharmacokinetics showed a slow release with reduced toxicity of 5-FU. The antineoplastic and immunomodulation actions on transplanted S180 tumor mice with low-molecular-weight porphyrin conjugated with 5-FU showed enhanced antitumor activity and immunocompetence that were impaired by 5-FU.<sup>[22]</sup>

In 2017, a novel conjugate of 5-FU with poly (amidoamine) (PAMAM)<sup>[4]</sup> was used to deliver drugs to targeted cervical cancer oncoproteins. The interactions between E6/E7 oncoproteins and the PAMAM/5-FU conjugate were investigated through molecular docking, and higher affinity was seen for the oncoprotein than for 5-FU. The authors also confirmed that this material was less toxic by hematological

analysis in female mice with cervical cancer. These results provide evidence that the newly designed PAMAM/5-FU macromolecular conjugate is a latent entrant against cervical cancer [Table 1a].

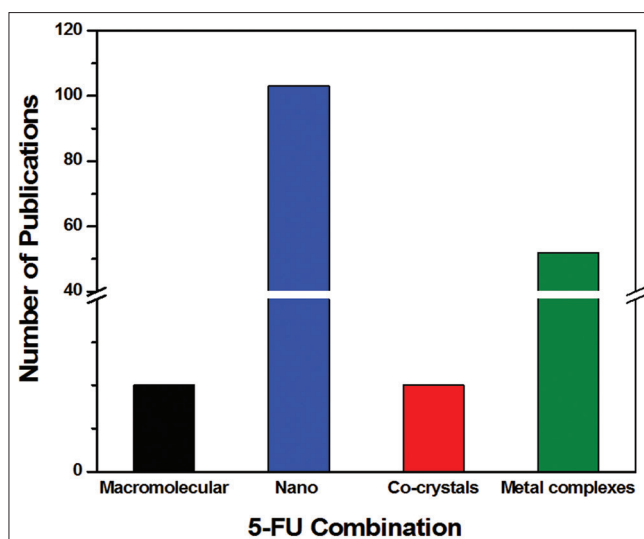
## POLYMERIC NANOCARRIERS OF 5-FLUOROURACIL

There is currently great interest in the development of innovative treatments for drug delivery to the site of action. Polymeric nanoparticles (NPs) are emerging carriers in this regard. These nanocarriers are synthesized by loading 5-FU on nanoparticles for the selective delivery of the drug to cancerous cells.<sup>[23]</sup> Another study also showed promising results of loading 5-FU conjugates on nanoparticles.<sup>[24]</sup> The mechanism used for 5-FU conjugate-loaded nanocarrier synthesis is explained in Figure 3. The mechanism consists of two steps namely (1) synthesis of nanoparticles (2) and loading of drug conjugate on the nanoparticles. This new approach is used to improve drug absorption and to protect from fast metabolism and degradation in the small intestine and stomach. In 2014, Tummala *et al.*<sup>[25]</sup> prepared enteric-coated chitosan polymeric nanoparticles (138–149 nm) loaded with 5-FU (48%–69%) and delivered them directly to the large bowel to prevent degradation by gastric pH. These particles were synthesized using a solvent evaporation emulsification method, which displayed better drug emancipation and *in vitro* 82% emancipation in a controlled manner from 4 to 24 h.

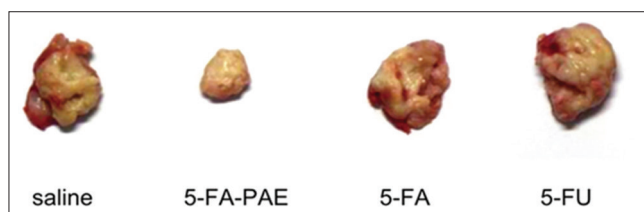
Using an ionic gelation method in 2016, Shaima *et al.*<sup>[26]</sup> prepared 5-FU-loaded chitosan nanoparticles (CNPs) and determined their antineoplastic potentials against liver cancer cell lines. These particles exhibited cytotoxicity with an  $IC_{50}$  value of 49.50  $\mu\text{g/mL}$ . The sustained release drug properties of biodegradable nano drug-transporting methodologies are used to enhance the chemotherapeutic agent's retention time in the body. CNP-based drug-transporting systems can carry the drug to the site of action with improved bioavailability, plasma half-life, and anticancer potentials [Table 1b].

Similar to Shaima's group, another study<sup>[30]</sup> was conducted in which CNPs loaded with 5-FU (5-FU-CNPs) were prepared using an ionic gelation method in a 1:1 mass ratio. The nanoparticles (280 nm) possessed the highest drug loading. *In vitro* experiments/studies showed the controlled release of the drug, and its cytotoxicity against gastric cancer cells was comparable to that of 5-FU injections.

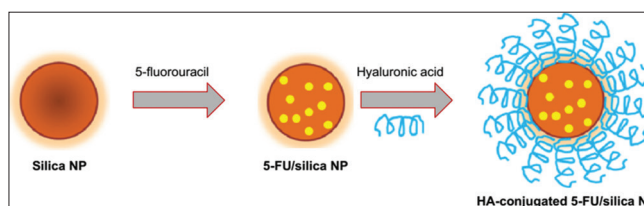
Pectin-based nanoparticles (PNPs) were synthesized in one study to deliver 5-FU specifically to hepatocellular carcinoma, due to galactose residues present in the polymer assembly.<sup>[31]</sup> These residues showed selectivity for cancer cells due to their targeting ligand abilities. The particles had a diameter of 300 nm and were synthesized in an aqueous medium comprising  $\text{Ca}^{2+}$  and  $\text{CO}_3^{2-}$  ions, with the drug-loading content of 24.8%. Cytotoxicity analysis of 5-FU-PNPs performed against cell lines of HepG2 and A549 indicated better potency in killing cancer cells with the overexpression of asialoglycoprotein receptors compared to the free drug.



**Figure 1:** Comparisons between the methodologies opted for pharmacokinetic improvement of 5-FU from 2009 to 2019<sup>[7]</sup>



**Figure 2:** Antitumor effects of saline, 5-fluorouracil prodrug, 5-fluorouracil derivative, and drug on tumor-bearing mice<sup>[21]</sup>



**Figure 3:** Assembly of 5-fluorouracil loaded nanoparticle and 5-fluorouracil conjugate-loaded nanoparticle<sup>[24]</sup>

Furthermore, an *in vivo* study of pharmacokinetics in rats confirmed that 5-FU-PNPs in circulatory fluids have a longer half-life than the free drug. In summary, pectin-based drug delivery systems may be promising platform against hepatocellular carcinoma. To improve the nonspecificity of 5-FU, Liu *et al.*<sup>[24]</sup> prepared 5-FU-loaded hyaluronic acid (HA)-conjugated silica nanoparticles (HSNPs). These particles were approximately 130 nm and showed sustained release of 5-FU for 120 h. Cytotoxic studies against colon cancer cells revealed that, after 1 day of incubation, the  $IC_{50}$  values of 5-FU/HSNPs and 5-FU/SNP were 0.65 and 2.80  $\mu\text{g/mL}$ , respectively. Hence, HA-conjugated nanoparticles may be more effective as an apoptosis inducer in cancer cells. Furthermore, 5-FU/HSNPs exhibited cell apoptosis of 45% compared to only 20% for 5-FU/silica nanoparticles (SNP). Therefore, 5-FU/HSNPs may be an active drug delivery system for colon cancer treatment.



**Table 1a: Delivery systems of 5-fluorouracil and 5-fluorouracil conjugate: Macromolecule carriers**

Macromolecule carrier	Methodology	Significance	Study ID (reference)
FUAC/HES <sup>a</sup>	Prodrug	Stable and slow release of drug at pH 5.8	[17]
5-FU/PAMAM <sup>b</sup>	Prodrug	Selective delivery of drug to cervical oncoproteins	[4]
5-FA-PAE <sup>c</sup>	Prodrug	Improved loading of drug, half-life, bioavailability, and <i>in vivo</i> antitumor potentials	[21]

5-FU: 5-fluorouracil, FUAC/HES<sup>a</sup>: 5-FU-1-acetic acid/hydroxyethyl substituted starch, 5-FU/PAMAM<sup>b</sup>: 5-FU/polyamidoamine, 5-FA-PAE<sup>c</sup>: 5-FU-1-acetic acid-polyethylene glycol-allyl glycidyl ether-mercaptoethanol

**Table 1b: Delivery systems of 5-fluorouracil and 5-fluorouracil conjugate: Chitosan-based nanocarriers**

Nanocarrier	Methodology	Significance	Study ID (reference)
5-FU/curcumin thiolated CSNPs <sup>d</sup>	Ionic cross-linking	Improved bioavailability, plasma half-life, and anticancer potentials	[28]
5-FU magnetic CSNPs	Reverse microemulsion method	Slow release of drug with significant anticancer actions	[29]
5-FU loaded CS/Ag/MWCNT <sup>e</sup>	Chemical method	Prolonged and sustained release of drug with IC <sub>50</sub> 50 µg/mL	[30]
5-FU-CSNPs	Ionic gelation	Inhibitory effect against SGC-7901 cancer cell was similar to 5-FU injection	[27]

5-FU: 5-fluorouracil, CSNPs<sup>d</sup>: Chitosan nanoparticles, MWCNT<sup>e</sup>: Multiwalled carbon nanotube

In recent years, conventional chemotherapy has not been very effective in CRC treatment because the drug does not get into the tumor site in effective therapeutic concentrations. Therefore, researchers have developed site-specific carriers/transporters to selectively deliver the drug in the colon region. Eudragit S100-coated citrus pectin nanoparticles (E-CPNPs) were formulated for colon-specific routing of 5-FU.<sup>[32]</sup> Citrus pectin plays the role of a ligand for galectin-3 receptors overexpressed in colon cancer cells. Selective drug release was observed in *in vitro* studies for E-CPNPs in the colonic region, which showed >70% after 1 day. The cytotoxicity assay against HT-29 cells demonstrated a 1.5-fold increase in the cytotoxic potential of NPs compared to 5-FU solution. Therefore, it is a complex methodology in terms of receptor-mediated uptake using E-CPNPs for effective chemotherapy against CRC with improved safety. In 2016, Sağır *et al.*<sup>[33]</sup> prepared super paramagnetic magnetite zeolite nanocomposites (MZNCs) and further loaded them with 5-FU. These nanocomposites showed a sustained release without bursts and evaluated their cytotoxic effects against human gastric carcinoma (AGS) cells. Apoptosis studies indicated the loss of cell membrane integrity, and the authors concluded that 5-FU-loaded MZNCs displayed concentration-dependent cell proliferation inhibition against AGS cells.

Onivyde, PEP02 or MM-398, is a nano liposomal form of irinotecan, which was approved in October 2015 by the US FDA as a combination regimen for the treatment of resistant metastatic pancreatic cancer associated with gemcitabine-based chemotherapy.<sup>[34]</sup> It has recently been investigated in Phase II and Phase III clinical trials against various cancers, including pancreatic, esophago-gastric, and CRC. It has attracted attention because it can: (i) enhance drug pharmacokinetics profile, increase encapsulation of the drug, (iii) improve loading efficiency, (iv) protect the drug in the active lactone form through its nano formulation, (v) prolong circulation time, (vi) control drug release, (vii) reroute the drug from toxic

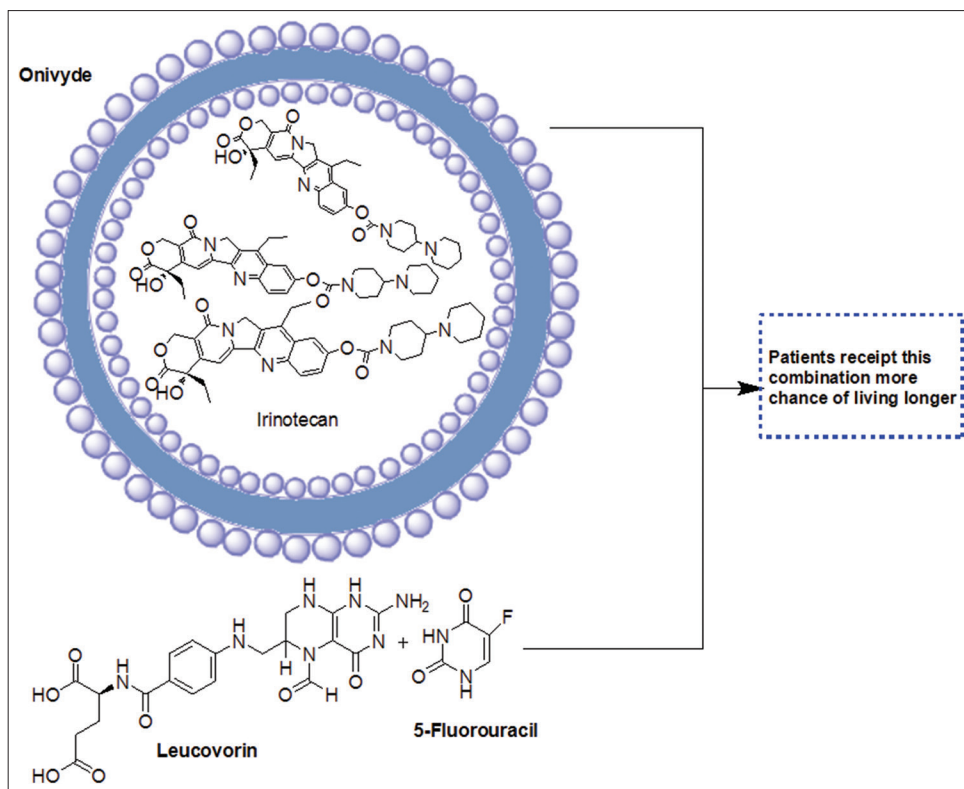
sites, gastrointestinal tract, and (viii) enhance permeability and retention effect of the drug and reduce host toxicity.<sup>[35]</sup> In a clinical trial, a combination of Onivyde with 5-FU/leucovorin (5-FU/LV) [Figure 4] confirmed an enhancement in median overall survival (OS), which means that the survival rate increased in the patients who received the regimen compared with the 5-FU/LV alone group.<sup>[36]</sup> The good results may be because of the improvement in the pharmacokinetics of 5-FU with Onivyde.<sup>[34]</sup> This combination therapy has become a standard first-line therapy in the treatment of mCRC.<sup>[37]</sup>

## ANTITUMOR SOLID STATES OF 5-FLUOROURACIL

Co-crystalline states are well-designed, synthesized structures with preferred inter- and intra-molecular interactions (hydrogen bonding). Co-crystallization is a process of formulation and elucidation of crystalline systems of active pharmaceutical ingredients (APIs) with improved sorption, dissolution rate, solubility, and stability toward degradation. A number of co-crystals containing 5-FU as the active component have been manufactured through grinding and a normal solution method. Docking studies have been used to investigate the potential of novel co-crystals against CRC target proteins, and the results have shown promising antitumor activity. Nadzri *et al.* prepared<sup>[38]</sup> solid states of 5-FU with bases, i.e., urea, thiourea, 2,2'-bipyridine, and 4,4'-bipyridine. Following this, Mohana *et al.* prepared<sup>[16]</sup> co-crystals of 5-FU with halogenated substituted thiophene carboxylic acids and substituted nitrobenzoic acid. However, they did not evaluate the synthesized solid states for their anticancer actions.

## SYNERGISM OF 5-FLUOROURACIL WITH METAL COMPLEXES

Metal complexes have been of great interest to oncologists since the 1970s, after the development/application of cisplatin



**Figure 4:** A combination regimen of Onivyde + 5-fluorouracil/leucovorin

(platinum-based) as an anticancer agent. Researchers have subsequently studied the antiproliferative actions of other metals including silver and shown their potential for treatment. Coordination chemistry can explain the ligand-like nature of the 5-FU pyrimidine ring that helps binding to metal ions. Based on this ligand metal binding and the respective anticancer potential, recent research has investigated the binding of silver (I) metal ions<sup>[39]</sup> with 5-FU to study the enhanced anticancer and pharmacokinetic potentials. The synthesized complex, characterized by spectroscopy techniques, was evaluated for its antiproliferative activity and was shown to be active. Estimation of the antiproliferative activity of 5-FU and 5-FU/Ag (I) ion complex against ovarian multidrug-resistant and colon cancer cell lines was also performed. The complex showed 50% growth inhibition values ( $GI_{50}$ ) of 0.34  $\mu\text{g/mL}$  for colon cells and 0.36  $\mu\text{g/mL}$  for multidrug-resistant ovarian cells. The 50% growth inhibition values of free 5-FU and cisplatin against multidrug-resistant ovarian cells were 2.3 and 2.49  $\mu\text{g/mL}$ , respectively, compared to 0.42  $\mu\text{g/mL}$  and 5.11  $\mu\text{g/mL}$  for colon cells, respectively. Moreover, various studies<sup>[40-42]</sup> have shown that a wide range of gold complexes display antiproliferative properties against a range of tumor cells. Blasco *et al.*<sup>[3]</sup> prepared novel gold (I) thiolate complexes and investigated the synergistic effect of the co-administration of these gold complexes, and the results showed good cytotoxic effects with 5-FU. They also confirmed a reduction in 5-FU dose of up to forty times to achieve an equivalent effect as with 5-FU alone [Table 1c].

In addition to 5-FU metal complexes, other researchers<sup>[43]</sup> have synthesized 5-FU-loaded copper (I)-thiourea and iron (III)-fumaric acid metal organic gels (MOGs). The authors reported that the drug release for the synthesized MOGs was higher at pH 5 than at pH 7.4. Therefore, 5-FU in combination with a metal in the form of complexes or MOGs appears to be an encouraging technique to improve pharmacokinetics.

## FUTURE PERSPECTIVES

Currently, 5-FU is used for the treatment of solid malignant tumors of the stomach, pancreas, colon, breast, neck, head, cervix, urinary bladder, ovarian, prostate, and oropharynx, with a response rate of 10%–30%. 5-FU has been extensively studied over the last decade. However, due to the pharmacokinetic issues explained above, the main challenge is to make 5-FU a highly recommended anticancer drug. This study showed the side effects that must be addressed to enhance 5-FU cancer therapeutics. The results confirm that the development of pharmacokinetics of 5-FU is crucial and has become an important part of anticancer drug research because more potent and safer drugs are needed for cancer chemotherapy. This study evaluated and compared different options for successfully transporting 5-FU to cancerous cells as shown in various studies conducted in the last decade [Figure 1]. The most successful approach was the design of 5-FU-loaded nanocarriers. In summary, this study could be helpful for future research conducted to evaluate how to increase the anticancer potential of 5-FU and minimize the side effects and related issues.

**Table 1c: Delivery systems of 5-fluorouracil and 5-fluorouracil conjugate: Synergism with metal complexes**

Complex	Cancer cells	Significance	Study ID (reference)
5-FU/Ag (I) ion complex	Ovarian and colon	GI <sub>50</sub> value of 0.36 mL <sup>-1</sup> and 0.34 mL <sup>-1</sup> , respectively	[39]
5-FU/gold (I) thiolate complexes	Caco-2/PD7 and TC7	IC <sub>50</sub> , 0.74–9.25 μM, co-administration lowered effective therapeutic dose	[3]
5-FU loaded Copper (I)-thiourea and Iron (III)-fumaric acid MOGs	NM <sup>f</sup>	Drug release of MOGs is high at pH 5	[43]

MOGs: Metal organic gels, 5-FU: 5-fluorouracil, NM<sup>f</sup>: Not mentioned

## CONCLUSIONS

This study focused on the currently available methodologies designed to overcome the pharmacokinetic issues with 5-FU, which limit its therapeutic efficiency. Low bioavailability, absorption, half-life, targeted neoplastic cell potential, and therapeutic index are the major pharmacokinetic flaws associated with 5-FU. The most promising approach is nanocarrier synthesis for 5-FU loading due to improved drug absorption, protection from fast metabolism, and degradation in the small intestine and stomach. Based on the results for reducing the dose of 5-FU through a metal complex synergistic approach, we suggest that this technique should be explored further to improve the safety and anticancer potential of 5-FU. The promising results associated with the reported techniques are summarized as follows:

1. Macro- and nano-particle delivery systems of 5-FU have shown very promising results in the improvement of absorption, sustained release, and retention time of the drug in targeted cells
2. Onivyde, a nanoliposomal form of irinotecan in combination with 5-FU/leucovorin, showed an improvement in median OS
3. 5-FU co-crystal API showed improved sorption, dissolution rate, solubility, and stability toward degradation
4. The synergistic effect of 5-FU with gold complexes also showed positive results.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Abd-Rabou AA, Bharali DJ, Mousa SA. Taribavirin and 5-fluorouracil-loaded pegylated-lipid nanoparticle synthesis, p38 docking, and antiproliferative effects on MCF-7 breast cancer. *Pharm Res* 2018;35:76.
2. Nisa ZU, Zafar A, Sher F. Assessment of knowledge, attitude and practice of adverse drug reaction reporting among healthcare professionals in secondary and tertiary hospitals in the capital of Pakistan. *Saudi Pharm J* 2018;26:453-61.
3. Atrián-Blasco E, Gascón S, Rodri Guez-Yoldi MJ, Laguna M, Cerrada E. Novel gold(I) thiolate derivatives synergistic with 5-fluorouracil as potential selective anticancer agents in colon cancer. *Inorg Chem* 2017;56:8562-79.
4. Rengaraj A, Subbiah B, Haldorai Y, Yesudhas D, Yun HJ, Kwon S, et al. PAMAM/5-fluorouracil drug conjugate for targeting E6 and E7 oncoproteins in cervical cancer: A combined experimental/*in silico* approach. *RSC Adv* 2017;7:5046-54.
5. Dezzani L. 10 Best Selling Drugs 2018 – Oncology; 2018. Available from: <https://www.igeahub.com/2018/05/28/10-best-selling-drugs-2018-oncology/>. [Last accessed on 2019 Feb 13].
6. Stone K. Top 20 Blockbuster Cancer Drugs; 2018. Available from: <https://www.thebalance.com/top-cancer-drugs-2663234>. [Last accessed on 2019 Feb 13].
7. C. Analytics. Web of Science; 2018. Available from: <https://webofknowledge.com>. [Last accessed on 2018 Oct 01].
8. Miura K, Kinouchi M, Ishida K, Fujibuchi W, Naitoh T, Ogawa H, et al. 5-fu metabolism in cancer and orally-administrable 5-fu drugs. *Cancers (Basel)* 2010;2:1717-30.
9. Álvarez P, Marchal JA, Boulaiz H, Carrillo E, Vélez C, Rodríguez-Serrano F, et al. 5-fluorouracil derivatives: A patent review. *Expert Opin Ther Pat* 2012;22:107-23.
10. Carrillo E, Navarro SA, Ramirez A, García MÁ, Griñán-Lisón C, Perán M, et al. 5-fluorouracil derivatives: A patent review (2012 - 2014). *Expert Opin Ther Pat* 2015;25:1131-44.
11. Esin E, Telli TA, Yuce D, Yalcin S. A correlation study of fluorouracil pharmacodynamics with clinical efficacy and toxicity. *Tumori* 2018;104:157-64.
12. Gao J, Zhen R, Liao H, Zhuang W, Guo W. Pharmacokinetics of continuous transarterial infusion of 5-fluorouracil in patients with advanced hepatocellular carcinoma. *Oncol Lett* 2018;15:7175-81.
13. Clingan PR, Ackland SP, Brungs D, de Souza P, Aghmesheh M, Garg MB, et al. First-in-human phase I study of infusional and bolus schedules of deflexifol, a novel 5-fluorouracil and leucovorin formulation, after failure of standard treatment. *Asia Pac J Clin Oncol* 2019;15:151-7.
14. Moloney M, Faulkner D, Link E, Rischin D, Solomon B, Lim AM, et al. Feasibility of 5-fluorouracil pharmacokinetic monitoring using the my-5FU PCMTM system in a quaternary oncology centre. *Cancer Chemother Pharmacol* 2018;82:865-76.
15. Arias JL. Novel strategies to improve the anticancer action of 5-fluorouracil by using drug delivery systems. *Molecules* 2008;13:2340-69.
16. Mohana M, Thomas Muthiah P, McMillen CD. Supramolecular architectures in two 1:1 cocrystals of 5-fluorouracil with 5-bromothiophene-2-carboxylic acid and thiophene-2-carboxylic acid. *Acta Crystallogr C Struct Chem* 2017;73:481-5.
17. Hoste K, De Winne K, Schacht E. Polymeric prodrugs. *Int J Pharm* 2004;277:119-31.
18. Luo Q, Wang P, Miao Y, He H, Tang X. A novel 5-fluorouracil prodrug using hydroxyethyl starch as a macromolecular carrier for sustained release. *Carbohydr Polym* 2012;87:2642-7.
19. Zhang Z, Zhang Q, Wang J, Shi X, Zhang J, Song H. Synthesis and drug release *in vitro* of porphyrin carrying 5-fluorouracil. *Carbohydr Polym* 2010;79:628-32.
20. Liu J, Kolar C, Lawson TA, Gmeiner WH. Targeted drug delivery to chemoresistant cells: Folic acid derivatization of fdUMP[10] enhances cytotoxicity toward 5-FU-resistant human colorectal tumor cells. *J Org Chem* 2001;66:5655-63.
21. Li M, Liang Z, Sun X, Gong T, Zhang Z. A polymeric prodrug of 5-fluorouracil-1-acetic acid using a multi-hydroxyl polyethylene glycol derivative as the drug carrier. *PLoS One* 2014;9:e112888.
22. Wang X, Zhang Z. The antitumor activity of a red alga polysaccharide complexes carrying 5-fluorouracil. *Int J Biol Macromol* 2014;69:542-5.
23. Chandran SP, Natarajan SB, Chandraseharan S, Shahimi MS. Nano drug delivery strategy of 5-fluorouracil for the treatment of colorectal cancer.



- J Cancer Res Pract 2017;4:45-8.
24. Liu K, Wang ZQ, Wang SJ, Liu P, Qin YH, Ma Y, *et al.* Hyaluronic acid-tagged silica nanoparticles in colon cancer therapy: Therapeutic efficacy evaluation. *Int J Nanomedicine* 2015;10:6445-54.
  25. 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;23:308-14.
  26. Shaima C, Moorthi PV, Kutty SN. *In vitro* anticancer activity of 5-fluorouracil coated chitosan nanoparticle. *Int J Curr Pharm Res* 2016;8:6-8.
  27. Sun L, Chen Y, Zhou Y, Guo D, Fan Y, Guo F, *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;12:418-23.
  28. Anitha A, Deepa N, Chennazhi KP, Lakshmanan VK, Jayakumar R. Combinatorial anticancer effects of curcumin and 5-fluorouracil loaded thiolated chitosan nanoparticles towards colon cancer treatment. *Biochim Biophys Acta* 2014;1840:2730-43.
  29. Zhu L, Ma J, Jia N, Zhao Y, Shen H. Chitosan-coated magnetic nanoparticles as carriers of 5-fluorouracil: Preparation, characterization and cytotoxicity studies. *Colloids Surf B Biointerfaces* 2009;68:1-6.
  30. Nivethaa E, Dhanavel S, Rebekah A, Narayanan V, Stephen A. A comparative study of 5-fluorouracil release from chitosan/silver and chitosan/silver/MWCNT nanocomposites and their cytotoxicity towards MCF-7. *Mater Sci Eng C Mater Biol Appl* 2016;66:244-50.
  31. Yu CY, Wang YM, Li NM, Liu GS, Yang S, Tang GT, *et al.* *In vitro* and *in vivo* evaluation of pectin-based nanoparticles for hepatocellular carcinoma drug chemotherapy. *Mol Pharm* 2014;11:638-44.
  32. Subudhi MB, Jain A, Jain A, Hurkat P, Shilpi S, Gulbake A, *et al.* Eudragit S100 coated citrus pectin nanoparticles for colon targeting of 5-fluorouracil. *Materials (Basel)* 2015;8:832-49.
  33. Sağır T, Huysal M, Durmus Z, Kurt BZ, Senel M, Isık S. Preparation and *in vitro* evaluation of 5-fluorouracil loaded magnetite-zeolite nanocomposite (5-FU-MZNC) for cancer drug delivery applications. *Biomed Pharmacother* 2016;77:182-90.
  34. DiGiulio S, DiGiulio S. FDA approves onivyde combo regimen for advanced pancreatic cancer. *Oncol Times* 2015;37:8.
  35. Shen L, Hu J, Wang H, Wang A, Lai Y, Kang Y. Synthesis and biological evaluation of novel uracil and 5-fluorouracil-1-yl acetic acid-colchicine conjugate. *Chem Res Chin Univ* 2015;31:367-71.
  36. Zhang H. Onivyde for the therapy of multiple solid tumors. *Onco Targets Ther* 2016;9:3001-7.
  37. Chibaudel B, Maindrault-Gœbel F, Bachet JB, Louvet C, Khalil A, Dupuis O, *et al.* PEPCOL: A GERCOR randomized phase II study of nanoliposomal irinotecan PEP02 (MM-398) or irinotecan with leucovorin/5-fluorouracil as second-line therapy in metastatic colorectal cancer. *Cancer Med* 2016;5:676-83.
  38. Nadzri NI, Sabri NH, Lee VS, Halim SN. 5-fluorouracil co-crystals and their potential anti-cancer activities calculated by molecular docking studies. *J Chem Crystallogr* 2016;46:144-54.
  39. Nunes JH, Bergamini FR, Lustrri WR, de Paiva PP, Ruiz AL, de Carvalho JE, *et al.* Synthesis, characterization and *in vitro* biological assays of a silver (I) complex with 5-fluorouracil: A strategy to overcome multidrug resistant tumor cells. *J Fluorine Chem* 2017;195:93-101.
  40. Berners-Price SJ, Filipovska A. Gold compounds as therapeutic agents for human diseases. *Metallomics* 2011;3:863-73.
  41. Gasser G, Metzler-Nolte N. The potential of organometallic complexes in medicinal chemistry. *Curr Opin Chem Biol* 2012;16:84-91.
  42. Bertrand B, Casini A. A golden future in medicinal inorganic chemistry: The promise of anticancer gold organometallic compounds. *Dalton Trans* 2014;43:4209-19.
  43. Rambabu D, Negi P, Dhir A, Gupta A. Fe (III) and Cu (I) based metal organic gels for *in situ* drug loading and drug delivery of 5-fluorouracil. *Inorg Chem Commun* 2018;93:6-9.