International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-8, Issue-5; May, 2021
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.85.29

Strategies to improve bioavailability of the existing Drugs for Colorectal Cancer

Pratik Chatterjee

Department of Biotechnology, Vellore Institute of Technology, Vellore, India

Received: 27 Jan 2021;

Received in revised form:

06 Apr 2021;

Accepted: 01 May 2021;

Available online: 18 May 2021

***Keywords*— Colorectal cancer, Bioavailability, pharmacokinetics, Antitumor growth, Anticancer treatment, Drug absorption.**

***Abstract*—** *Colorectal cancer has many drugs which are available and approved by the FDA with anti-tumorigenesis property and in this study very few drugs are chosen in terms of pharmacological activity and bioavailability of the drugs. Colorectal cancer is cancer that starts in either colon or the rectum. Based on the location from where cancer starts it can either be known as colon cancer or rectal cancer. The colon and rectum are a part of the large intestine and are a part of the human digestive system. Among all the drugs which have been deployed to reduce tumor formation in case of colorectal cancer or to reduce metastasis, show pharmacokinetic and pharmacodynamic properties. The drugs which are less soluble in an aqueous solution even though they have good permeability, dissolution rate becomes the limiting factor for absorption. The saturation solubility could be increased by changing the physical state of the drug along with the addition of co-solvents or it can be improved by reducing the particle size with the increase in surface area. The solid dispersion form of the drug in a dissolved form can improve the efficacy and bioavailability of that particular drug. the drugs available for colorectal cancer patients for enhancing the bioavailability by pharmacokinetic parameter. The existing drugs have some unmet conditions which have reduced clinical efficacy against the anticancer treatment and the limitations and inhibition are pointed out for which a hypothetical theory could be drawn to achieve maximum bioavailability. The lower bioavailability of a drug could be increased by adding another drug or by the method of nano-emulsion and solid dispersion method or by adding natural compounds. Few drugs are not approved yet but have undergone clinical trials, cannot act effectively until and unless they are bound to some other drugs. The combined effect of two drugs can moderate the bioavailability of the drug used before.*

I. INTRODUCTION

Colorectal cancer is cancer that starts in either colon or the rectum. Based on the location from where cancer starts it can either be known as colon cancer or rectal cancer. The colon and rectum are a part of the large intestine and are a part of the human digestive system. The colon consists of four segments: the ascending, transverse, descending, and sigmoid colon. The common symptoms of colorectal cancer are constipation, diarrhea, change in stool color and shape, blood in stool, bleeding from the rectum, excessive gas, and abdominal cramps. In the advanced stages of cancer, the symptoms are excessive

fatigue and weakness, sudden weight loss, vomiting, a feeling that the bowels won't completely empty. If cancer spreads to other parts of the body one can also experience jaundice, difficulty in breathing, bone fractures, blurry visions, headaches. A sub-group of the patients is formed due to a specific hereditary colorectal cancer syndrome known as the 'Lynch syndrome' caused due to the mutation in any one of the DNA mismatch repair genes: MLH1, MSH2, MSH6, PMS2, or EPCAM which results in the accumulation of the mutation. The second most common cancer syndrome is caused due to the mutation in the adenomatous polyposis (APC) gene which regulates the occurrence of the "Wnt" pathway. The patients develop colorectal adenomas which may lead to the formation of colorectal cancer. Several environmental factors also affect the incidence of colorectal cancer in an individual. Smoking, drinking, and obesity increase the risk for colorectal cancer. Excessive smoking and drinking can increase the risk by about 50%. Intake of too much processed and red meat can increase the risk of cancer whereas intake of milk, fibers, vitamins can decrease the risk of cancer occurrence.

II. LIST OF DRUGS AVAILABLE FOR COLORECTAL CANCER TREATMENT

Drugs available for colon cancer based on the similar model of action we have refined the following drugs:

SL	Name of the drug	Function	Drawback	Reference
1.	*Camptothecin	Effective anti-cancer agent for treating tumor growth in colon cancer by DNA synthesis and cell apoptosis.	Less soluble in an aqueous solution readily becomes inactive form by lactone ring hydrolysis.	https://pubchem.ncbi.nlm.nih.gov/compound/Camptothecine#section=Pharmacology
2.	*5-Fluorouracil	antineoplastic anti-metabolite blocks the enzymatic changes of cytidine to deoxy derivative.	Lower absorption in the GI tract, inhibition by Eniluracil and thus lesser antitumor activity	https://pubchem.ncbi.nlm.nih.gov/compound/5-Fluorouracil
3.	Topotecan	Used in metastatic colon cancer, inhibit metastasis of cancer.	Hydrolysis of topotecan lactone in the gut, cyclosporin acts as the inhibitor molecule. Cannot be effective without irinotecan.	Holcombe RF, Kong KM, Wimmer D. Combined topoisomerase I inhibition for the treatment of metastatic colon cancer. Anticancer Drugs. 2004 Jul;15(6):569-74. doi: 10.1097/01.cad.0000132232.28888.21. PMID: 15205598.
4.	Capecitabine	An active drug that reduces tumor proliferation.	Not effective, combination with oxaliplatin gives improved efficacy	Koukourakis, Georgios V et al. "Capecitabine for locally advanced and metastatic colorectal cancer: A review." World journal of gastrointestinal oncology vol. 2,8 (2010): 311-21. doi:10.4251/wjgo. v2. i8.311

III. UNMET NEED IN DRUG DEVELOPMENT (Pharmaceutics & Biopharmaceutics)

Few drugs are approved by the Food and Drug Administration for colon and rectal cancer, among which paclitaxel (PTX) together with BEZ235 shows a synergetic inhibition effect on metastatic growth in case of colon cancer. One of the important drugs Camptothecin (CPT), a potential anticancer drug, shows the antitumor effects by site-specific inhibition of eukaryotic DNA topoisomerase-I (topo-I), enzyme playing major roles in DNA replication, transcription, recombination, and repair. It exerts its cellular toxicity by breaking DNA with a covalently trapped topo-I-DNA cleavable complex. Another drug fluorouracil is been used to treat colorectal cancer in the form of commercial name Adrucil with antineoplastic activity and classified as an antimetabolite. Even though

the drugs are useful for anticancer therapeutic purposes but certain limitations are related to the pharmaceutical approach. The bioavailability of a drug depends upon how they act on the body and their efficacy, a comparatively lower uptake may indicate in lesser efficacy, whereby a relatively high uptake can lead to acute toxicities. In the development phase of a drug formulation, the exclusive bioavailability must be determined to submit a full new drug application to the authorities as well as the degree of exposure varies. Most of the anticancer drugs are absorbed in the epithelial cell linings of the small intestine and due to the large surface area, the drugs are absorbed to a good extent. But as due to the secretion in the gut and small intestine the pH of that varies from low to high. Some drugs show lower bioavailability and it varies with the change in the difference of pH and other physicochemical factors. There are few studies in patients with impaired hepatic function which are significant for characterizing the pharmacokinetics. If safety is concerned then the substantial portion of that particular drug should be eliminated to start with the initial dosage. The drug Camptothecin has lower bioavailability as it is less soluble in an aqueous solution and very fast conversion from the pharmacologically active lactone form to pharmacologically inactive carboxylate form at physiological pH which causes hydrolysis of the lactone ring. On the other hand, 5-fluorouracil (5-FU) is used to give anticancer treatment by suppressing the tumor progression and in that drug, Eniluracil acts as an inhibitor that inhibits the drug and it shows lesser antitumor activity. Eniluracil is a potential inhibitor that catabolizes and inactivates the 5-fluorouracil group. Few drugs are not approved yet but have undergone clinical trials, cannot act effectively until and unless they are bound to some other drugs. The combined effect of two drugs can moderate the bioavailability of the drug used before.

IV. RESEARCH PROBLEM

Among all the drugs which have been deployed to reduce tumor formation in case of colorectal cancer or to reduce metastasis, show pharmacokinetic and pharmacodynamic properties. It has been observed that several drugs are not effective because of less solubility and absorption. So, the focus will remain on the hypothetical mechanism by which the bioavailability of the drug could be increased to become the drug more effective.

Working Hypothesis:

The lower bioavailability of a drug could be increased by adding another drug or by the method of nanoemulsion and solid dispersion method or by adding natural compounds. In the case of Camptothecin, the less solubility in aqueous solution drives into lower bioavailability and fast conversion into inactivate carboxylate form. This problem can be achieved by the solid dispersion method by solubilizing in a copolymeric solution. On the other hand, the drug used as chemotherapy in colorectal cancer 5-FU can reduce its functionality when eniluracil binds to it. The bioavailability can be increased by removing eniluracil in a good amount. Most anticancer drugs have a highly variable bioavailability, but a narrow therapeutic range. Many studies have been performed to reduce the pharmacokinetic variability

Mechanistic Hypothesis:

The drugs which are less soluble in an aqueous solution even though they have good permeability, dissolution rate becomes the limiting factor for absorption. The saturation solubility could be increased by changing the physical state of the drug along with the addition of co-solvents or it can be improved by reducing the particle size with the increase in surface area. In another case, the solid dispersion form of the drug in a dissolved form can improve the efficacy and bioavailability of that particular drug. The drugs are enlisted above, CPT is one of the major drugs which have been used in the anticancer treatment and to reduce the side effects of that drug bioavailability should be increased in terms of increasing solubility and stability. Solid dispersion of CPT in Solupus copolymer has been made which helps to disperse the drug in the matrix and thus enhancing the solubility of the drug in an aqueous solution. The targeted drug delivery system of the solid dispersion helps to achieve a high concentration which eventually reduces the dose and side effects. Development of the combinational drug therapy can also increase the pharmacokinetics and reduce the absorption of the drug in the human gut which helps to increase the bioavailability. The drug topotecan when used as a single dose it lacks efficacy which can be again increased by adding Irinotecan and thus the inhibition by Elacridar and Cyclosporin could be avoided. Similarly in the case of the drug Capecitabine, when Oxaliplatin is added, bioavailability could be increased when applied intravenously. The preventive use of the skimmed milk could be a helpful approach to reduce the adverse effect of antimetabolite like 5-FU in patients who have undergone cancer chemotherapy. By adding the skimmed milk with the 5-FU, not only results in good clinical benefits but also great bioavailability by increasing absorption in the GI tract. The skimmed milk reacts positively with 5-FU in a higher-order at its absorption by improving the physical condition of the patients. According to another study, an excess amount of Eniluracil can impact the metabolic activation of 5-FU by inhibiting the main target which is

uridine phosphorylase. This inhibitory effect converts 5-FU into 5 fluorouridine and uracil into uridine. Even though eniluracil does not impair orotate phosphoribosyltransferase which is another activating enzyme for 5-FU. An anabolic of eniluracil could be a cause of deactivation of active 5-FU and thus to maximize the antitumor activity of 5-FU, the presence of an excess amount of eniluracil should be avoided to active 5-FU. It is to be mentioned that eniluracil is a major activator of dihydropyrimidine dehydrogenase (DPD) hence it may be administered before 5-FU. Once the eniluracil has been eliminated, new DPD appears shortly and it is very important to engage an adequate amount of eniluracil that will eventually inactive DPD synthesized during the exposure to 5-FU. It is also to be noticed that the formation of the neurotoxic 5-FU catabolites should be prevented in the central nervous system by engaging an ample amount of eniluracil. So, DPD will be inactivated by eniluracil and it can be partially cleared before 5-FU is administered, thus the clinical efficacy will be increased.

V. AIMS & OBJECTIVES

In this study, we aim to find out the drugs available for colorectal cancer patients for enhancing the bioavailability by pharmacokinetic parameter. The existing drugs have some unmet conditions which have reduced clinical efficacy against the anticancer treatment and we need to find those limitations and inhibition for which a hypothetical theory could be drawn to achieve maximum bioavailability. For this purpose, we have studied few research articles to find all the possible methods to achieve the potential clinical efficacy and thus we can brief a hypothetical overview on the principle behind the pharmacokinetic parameter.

VI. PROPOSED METHOD

In 2007 Crowley et al. have studied the method to increase the stability and the solubility of CPT by developing an oral formulation targeted to a colon cancer cell in the intact form which would reduce the side effects. The study showed that a solid dispersion of CPT in a grafted copolymer made up of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol or namely Solupus solution was dispersed in a matrix which potentially increasing the solubility of the drug in an aqueous solution. The undue side effects of the drug can be reduced by applying the high concentrated targeted drug delivery system of the solid dispersed drug to the colon. As per the method described by Warner et al. in 1997, a method was obtained to analyze CPT by HPLC methodology. An acidic microenvironment is produced after the release of the drug and the system is managed in this way that the lactone ring of CPT can be hydrolyzed. At pH of 7.4 in 100 ml of phosphate buffer, the coated capsule having solid dispersion of CPT as bulk is mixed with or without citric acid. The withdrawn sample at regular intervals is replaced with an equal volume of fresh medium followed by the filtration through the 0.45-μm filter for analysis by the HPLC method.

The MTT test study on Caco-2 cells described by Anderberg et al. in 1993 was used to evaluate the cellular cytotoxicity of CPT in its solid dispersion to assess the antitumor activity of the drug in acidic pH of 6.0 and mildly alkaline pH of 7.4. The principle of the assay states that the enzyme dehydrogenase in the mitochondria of living cells transforms the yellow MTT [3-(4,5-dimethylthiazol-2yl) 2,5-diphenyltetrazolium bromide] into a blue-purple formazan crystal.

With 5-FU treatment the excess amount of eniluracil should not be present as it is the potent inactivator of DPD and thus it can be administered before 5-FU treatment. It is important to take a limited amount of eniluracil when new DPD are formed after the elimination of eniluracil, which will eventually inactivate any DPD synthesis. As per the studied information from rats, it is observed that eniluracil dose to inactivate DPD is 6-fold higher in the brain than in non-nervous tissues. In urine samples, the limited amount of DPD inhibition could be encountered by determining total alpha-fluoro-beta-alanine. The half-life of eniluracil is 10 minutes in mice and 34 minutes in rats, respectively. Therefore, according to the study by Thomas et al. in 2010, when the rats were pre-treated with eniluracil one hour before receiving 5-FU, only low levels of eniluracil were present by the time 5-FU was administered. The half-life of eniluracil is approximately 3.5 hours in human patients. If excess eniluracil also decreases 5-FU antitumor activity in cancer patients, care must be taken to ensure that the levels of eniluracil are not more than 5-FU when 5-FU is administered. Patients treated in the phase III study received eniluracil 10 mg/m2 simultaneously with 5-FU 1 mg/m2 every 12 hours. This high ratio of eniluracil to 5-FU can be easily avoided. If 30mg to 40 mg eniluracil were dosed 12-16 hours before 5-FU, it would adequately inactivate DPD in both nervous and non-nervous tissues, and its concentration would be greatly decreased before the administration of 5-FU. This approach should be amenable to the 5-day or weekly eniluracil/5-FU dosing regimens that use 20-30 mg/m2 5-FU. Thus, the antagonism of 5-FU by excess eniluracil would be avoided. 5-FU when treated with skimmed milk according to Ahmed et al.,2008, also increases the bioavailability of the drug and lowers the side effects. The analysis will be followed by HPLC methodology.

VII. RESULTS

The dosage of 5-FU when given via oral administration with skimmed milk, it showed the stabilized weights in cancer patients after chemotherapy. It was hypothesized that oral administration of 5-FU with skimmed milk may improve absorption of 5-FU from the GI tract. 5-FU when given with skimmed is reasonably absorbed from the GI tract. This indicates that skimmed milk has some positive interaction with 5-FU at its absorption. 5-FU has achieved the plasma concentration that reasonably gave clinical benefits to colorectal cancer patients. The weights of patients can be stabilized during study and their physical conditions may also be improved. Oral 5-FU administration with skimmed milk is safe enough and showed no grade 3 toxicity in this study. It can be concluded that 5-FU can safely be given to colorectal cancer patients with skimmed milk on a long-term basis. Skimmed milk protects colorectal cancer patients from life-threatening toxicity such as Septicaemia. On other hand, when an excess amount of eniluracil is avoided in 5-FU then it can increase the bioavailability, and the absorption of the drug can be increased. Oral administration is better preferred rather than the intravenous injection of the drug. And for CPT, the solubility of CPT could be increased almost 40 times in the presence of Soluplus, indicating excellent affinity between CPT and Soluplus to form a molecular dispersion. Soluplus is a polymeric solubilizer with an amphiphilic chemical structure, having a large number of hydroxyl groups which make it a good solubilizer for poorly soluble drugs in aqueous media. So, Soluplus has been found to have a substantial impact on the solubility of CPT. The results suggest that the Eudragit S100 coated capsules containing solid dispersion of CPT and citric acid, on oral ingestion, will disintegrate in the colon where the pH is between 7.0 and 8.0 because Eudragit S100 dissolves at pH>7.0. On disruption of capsule shell, citric acid present in the capsule would lower the colonic fluid pH to 6.0 where solid dispersion of CPT would dissolve to release CPT in lactone form which would be subsequently available for uptake by tumor cells. Direct targeting of the drug in its absorbable form to the colon would reduce the dose as well as systemic side effects.

VIII. CONCLUSION

The drawbacks present in the drugs available for treating colorectal cancer can be overcome by achieving the unmet conditions of the drugs by some hypothetical strategies. By deploying few methods to increase the clinical efficacy, drugs can be acted efficiently the patients with cancer. The bioavailability of the drugs can be increased by increasing the solubility and absorption of the drug in the liver and gut. The solid dispersion method is one of the most used techniques in literature to enhance the bioavailability of the drug hence CPT can work efficiently the cancer patients suffering from colorectal cancer. 5-FU can work in an improved manner when skimmed milk is added into and the oral administration is less toxic than intravenous administration. By inhibiting eniluracil, it can be enhanced with increased bioavailability for 5-FU to act. So, the strategies obtained for improving the clinical efficacy and bioavailability by pharmacokinetic parameters would result in a better cure for therapeutics of colorectal cancer.

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