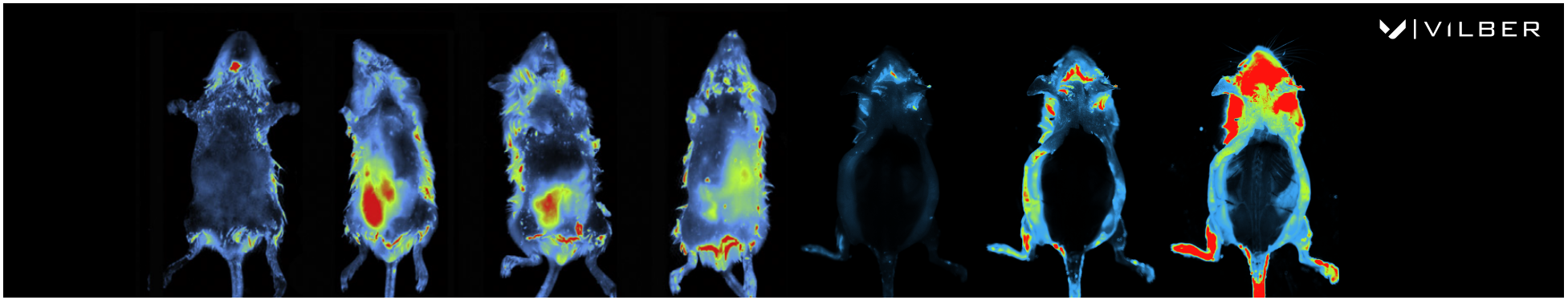

DEVELOPMENT OF ORALLY APPLICABLE NANOPARTICLE DRUG DELIVERY SYSTEM FOR LOCAL TREATMENT OF COLORECTAL CANCERS

AUTHORS

Sedat ÜNAL, Doctoral Thesis (2020)

Hacettepe University - Institute of Health Sciences Pharmaceutical Technology Program, Turkey

INTRODUCTION

Colorectal cancers start in the colon or rectum where they begin as a polyp and turn into cancer over time. Drugs used in the treatment of colorectal cancer have to be administered mostly parenterally due to limitations of their physicochemical properties. Since oral administration is not possible during treatment, parenteral administration implies low patient compliance, high cost of treatment, frequency of side effects and difficulty of repeated administration specific to chemotherapy. Those inconveniences have created the necessity to work on alternative routes of administration to the parenteral route. The oral pathway stands out as the most promising route in chronic treatments in terms of ease of administration, thus reducing the burden on health economics and patient compliance. Camptothecin (CPT), which is known to have strong anticancer activity against colon cancer cells, remains limited in clinical practice due to solubility and stability problems in physiological conditions. This situation requires a different formulation approach such as the use of an oral nanoparticle drug delivery system (NPs DDS). NPs DDS can reduce or prevent side effects due to chemotherapy and increase the stability of CPT and thus provide better quality of life to patients.

OBJECTIVE

This study aims to develop an oral anticancer drug model using Amphiphilic cyclodextrin (CD)- based nanoparticles (Poly-β-CD-C6) carrying CPT, with specific physico-chemical attributes chosen to favor structure integrity down to the colon, accumulation to the target site and degradation by the colon microflora.

MATERIAL & METHODS

A colon tumor mice model was created. For this purpose, 6-8 weeks old male Balb/c orthotopic mice model were anesthetized, laparotomized, caecum scratched, surgically stitched and inoculated with CT-26cells (100µL of $2x10^6$) into the cecum submucosa. The surgically created syngeneic mice model of the colorectal cancer cell line CT-26 were divided into 4 groups: Group1.Poly-β-CD-C6 nanoparticles (blank); Group 2. Poly-β-CD-C6 nanoparticles (drug loaded) (containing 5 mg / kg CPT); Group 3. Suspension of anticancer drug CPT in saline solution (1% DMSO) (5 mg / kg CPT) and Group 4. Negative control (tumor induced and untreated group). In order to monitor the localization and thus the extent of the anti-tumor activity of the drug loaded amphiphilic CD nanoparticle *in vivo*, Nil Red (NR) fluorescent dye, was encapsulated in Poly-β-CD-C6 nanoparticle. The presence of tumors in the colon and cecum region was surgically confirmed in one mouse sacrificed for each group. The prepared NR loaded amphiphilic CD nanoparticles and NR solution were then administered to mice by oral gavage and the mice left for 24 hours. The mice were then euthanized with high dose anesthesia. Following this procedure, the GI tract were rapidly surgically removed as a whole and the segments of the organ were used for *ex vivo* visualization in the Newton 7.0 (Vilber Lourmat, France).

RESULTS

Figure 1. Gastrointestinal distribution of Nile red (NR) encapsulated Poly-β-CD-C6 nanoparticles. *Ex vivo* image of undisrupted GI tract 24hrs after oral gavage of mice bearing colorectal tumors. A low fluorescence in the stomach and intestines has been detected, and no significant fluorescence was observed in the colon area after the cecum.

Figure 2. Gastrointestinal distribution of NR solution and NR encapsulated Poly-β-CD-C6 nanoparticles. *Ex vivo* imaging of the gastrointestinal tract tissues removed from mice 24hrs following oral administration of NR solution and NR encapsulated nanoparticles in mice bearing colorectal tumors. (NR çözeltisi =NR solution, NR yüklü NP = NR loaded particles, Tumor odagi = tumor focus). As a result of surgical opening of the abdominal region of sacrified mice, it was confirmed that specific and localized tumors were formed in the intestinal region, especially in the colon where a high fluorescence is observed, starting from the cecum, which is the tumor inoculation site. The primary tumor, represented with high fluorescence in the cecum region, was due to the inoculation area and was considered an expected and desired result. As a function of time after inoculation of CT-26 cells, primary and secondary tumors were observed. The amphiphilic CD nanoparticle formulation designed to target the column proved to be effective in delivering the active substance to the cecum and down to the colon.

CONCLUSION

Camptothecin (CPT) loaded (Poly-β-CD-C6) nanoparticles orally administered to mice bearing colorectal cancer revealed to be effective in the course of this study. Imaging the extent to which the amphiphilic CD nanoparticle formulation could carry the encapsulated drug 24hours post injection in the gastrointestinal tract segments was made possible with the Newton 7.0 (Vilber Lourmat, France).

Figure 1.

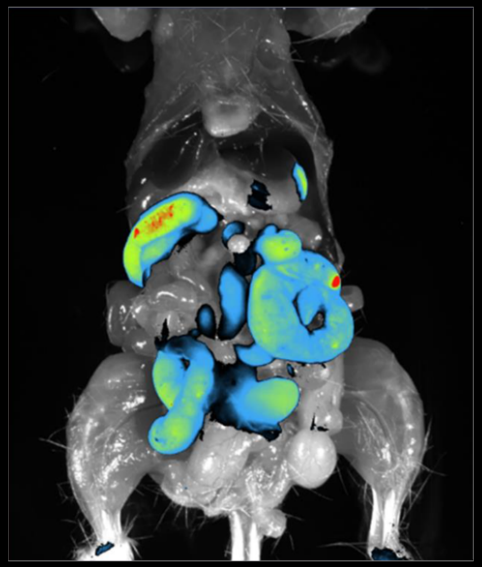

Figure 2.