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Micelle mixtures for coadministration of Gemcitabine and GDC-0449 to treat pancreatic cancer

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Hedgehog (Hh) signaling plays an important role in the development and metastasis of pancreatic ductal adenocarcinoma (PDAC). Although gemcitabine (GEM) has been used as a first-line therapy for PDAC, its rapid metabolism and short plasma half-life restrict its use as a single chemotherapy. Combination therapy with more than one drug is a promising approach for treating cancer. Herein, we report the use of methoxy poly(ethylene glycol)-block-poly(2-methyl-2-carboxyl propylene carbonate)-graft-dodecanol (mPEG-b-PCC-g-DC) copolymer for conjugating GEM and encapsulating a Hh inhibitor, vismodegib (GDC-0449), into its hydrophobic core for treating PDAC. Our objective was to determine whether the micelle mixtures of these two drugs could show better response in inhibiting Hh signaling pathway and restraining the proliferation and metastasis of pancreatic cancer. The *in vivo* stability of GEM significantly increased after conjugation, which resulted in its increased antitumor efficacy. Almost 80% of encapsulated GDC-0449 and 19% conjugated GEM were released *in vitro* at pH 5.5 in 48 h in a sustained manner. The invasion, migration, and colony forming features of MIA PaCa-2 cells were significantly inhibited by micelle mixture carrying GEM and GDC-0449. Remarkable increase in PARP cleavage and Bax proved increased apoptosis by this combination formulation compared to individual micelles. This combination therapy efficiently inhibited tumor growth, increased apoptosis, reduced Hh ligands PTCH-1 and Gli-1, and lowered EMT-activator ZEB-1 when injected to athymic nude mice bearing subcutaneous tumor generated using MIA PaCa-2 cells compared to monotherapy as observed from immunohistochemical analysis. In conclusion, micelle mixtures carrying GEM and GDC-0449 have the potential to treat pancreatic cancer.

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Development of semisolid preparations containing Nifedipine for anorectal application and in vitro evaluation

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Anal fissure is the tear localized in the distal anal canal and it is one of the commonly observed painful pathology of this region. It is common in middle age or young adults, and if the disease is not cured it disturbs the patients in further periods. The disease considerably decreases quality of life and diminishes their physical-mental health. Although surgical operation is considered as the only option for the treatment of chronic anal fissures, the recent researches revealed that nonsurgical techniques have efficacy on the disease cure. This focused the interests on drug treatment. For this purpose there is a glyceryl nitrate ointment in Turkish drug market. But the severe headache that comes out as a side effect with a 40% incidence upon the usage of this ointment reduces the patient compliance and cause patients to quit the therapy. According to researches nifedipine came out to be an alternative to other therapeutic agents used in anal fissure treatment due to its high healing efficacy and reduced side effects. In this study, semisolid preparations containing nifedipine were developed for anorectal application. Semisolid preparations in the form of lipophilic gel and hydrophilic gel were prepared by different methods. These formulations were characterized in terms of organoleptic control, pH, viscosity, texture analysis, nifedipine assay, *in vitro* drug release and microbiological respect. By considering the patient comfort and ease of drug application and as the result of characterization studies a hydrophilic gel formulation containing Carbopol® 974P was selected as the most appropriate formulations.

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