Chem Sci J 2016, 7:2(Suppl)
http://dx.doi.org/10.4172/2150-3494.C1.003

European Chemistry Congress

June 16-18, 2016 Rome, Italy

Oral delivery of gemcitabine loaded CSKSSDYQC peptide conjugated N-trimethyl chitosan nanoparticles to treat cancer: Synthesis, characterization and animal studies

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The oral delivery of anticancer drugs represents a significant challenge for global scientist. N-trimethyl chitosan (TMC) is a polymer with the potential to facilitate effective oral drug delivery. Recently, the peptide CSKSSDYQC (CSK) has been conjugated to TMC as a means of active goblet cell targeting for gastrointestinal uptake. The aim of the study is to develop and optimize a TMC-CSK modified nanoparticules for oral delivery of gemcitabine. TMC was synthesised from deacetylated chitosan using a novel two-step synthesis, then conjugated with CSK to actively target goblet cells. Gemcitabine-loaded TMC-CSK nanoparticles were prepared via ionic gelation. Characterisation studies including particle size, zeta potential, entrapment efficiency and *in vitro* drug release were then carried out. Cytotoxicity of drug solution and drug loaded formulation was tested on 4T1 breast cancer cell. Lastly, in-vivo pharmacokinetic and pharmacodynamics studies were conducted. The results showed the optimal delivery system showed particle size of 173.6±7.7 nm and zeta potential of 18.5±0.2 mV. Entrapment efficiency of 66.44±0.02%, and a sustained drug release profile was obtained. LD_{50} of 0.23 µg/mL was determined in cytotoxicity studies. Gemcitabine loaded TMC-CSK nanoparticles significantly improved the oral bioavailability, raised the plasma half-life, and AUC0-∞ of 4.5 fold higher than for gemcitabine solution in pharmacokinetic studies. Obvious tumour size reduction of 2.6 fold was observed for TMC-CSK nanoparticles compared to drug solution in pharmacodynamics studies. In conclusion, gemcitabine can be delivered using this TMC-CSK modified nanoparticulate delivery systems via oral route to elevate its oral bioavailability and therapeutic anticancer effect.

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New systems for organocatalytic asymmetric epoxidation

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The development of methods for the introduction of asymmetry into organic molecules remains a topic of great importance. Catalytic systems are particularly desirable, and the combination of a catalytic asymmetric process with an environmentally friendly reaction system and an inexpensive oxidant offers an especially attractive goal. Non-racemic chiral epoxides are important intermediates for enantioselective carbon-carbon bond formation. We are developing organocatalytic systems in which asymmetric oxidants are formed by reaction of iminium salts with simple oxidants under mild conditions. We currently formulate the reactive intermediates as oxaziridinium ions, from which the iminium salt mediators are regenerated following oxygen transfer to alkene substrates. We can accomplish epoxidation of simple alkenes with up to ca 99% ee. Catalyst loading may be as low as 0.1 mol%. The epoxidation reactions may be carried out under aqueous or non-aqueous conditions. The iminium salt mediators can be easily prepared without chromatography in many cases, and the procedures used are simple to carry out, and require no preparation of unstable reagents. This lecture will discuss the recent developments including new generations of catalyst, the first examples of kinetic resolution, the use of non-aqueous as well as the usual aqueous conditions, and alternative oxidants in place of Oxone, including hydrogen peroxide, bleach, and even electrochemical conditions by oxidant generation at boron-doped diamond electrodes.

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