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Nucleolipid nanoparticles properties application and toxicity

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Introduction: Development of molecular probes involves search for specific bioactive molecules that can target selectively and have desirable pharmacokinetics. A novel field of nanotheranostics has emerged as a tri-union of therapy, imaging and nanotechnology. Nucleosides analogs have emerged as small molecule probes and have potential anti-cancer and anti-viral properties. Nucleolipids are hybrid molecules having nucleoside (recognition unit) and lipid (signalling unit). Lipidization of nucleolipids has been one of the approaches, to improve the cellular internalization and brain delivery due to the lipid moiety which mediates diffusion and flip-flop mechanism thereby accelerating the absorption of nucleolipids across cellular membranes. Nucleolipids are a gateway for nano based drug delivery systems. The nucleolipids have been used as drug delivery vehicles in the form of liposomes. Single photon emission computed tomography (SPECT) imaging of radiolabeled NL-liposome can also assist in tracking the drug in vivo. The materials and methods applied in the work ranges from varied organic chemical reactions for chemical synthesis, pharmacokinetic behavior and validation using nuclear imaging-SPECT.

Materials and Methods: The methodologies used for characterization of liposomes includes DLS, SEM, Zeta potential biological studies include cell culture assay, animal model development in mice and several in vitro and in vivo assays. The scintigraphic studies were done using micro SPECT imaging modality. In-vitro assessment relies on SRB based cytotoxicity assays on HEK cell lines. The pharmacokinetic behavior focuses on in-vivo blood kinetics, stability, and detailed biodistribution studies. SPECT studies were performed using 99m-technetium.The drug delivery application has been validated using anticancer drug methotraxate for nucleolipid based liposomes (NLNP). The nucleolipid nanoparticles (NLNP) e characterized and studies for their formation and stability with the help of DLS, SEM, Radius plot analysis and Zeta sizer.

Results: The nucleolipid nanoparticles (NLNP) were prepared through nanoprecipitation in aqueous environment with slight modification. Briefly, 10 mg of nucleolipid was solubilised in 1 mL of dichloromethane at room temperature. 100 µL of this solution was added drop wise to 10 mL of distilled water under constant magnetic stirring. The suspension was then placed in ultrasonic water bath for briefly 20 min at 40 °C, characterized by SEM, DLS and Zeta Sizer for their size shape, morphology and stability at various temperature and different period of time point varying from hours to days. Nl-Lps were quite stable at room temp for 30 days and have been found to have spherical morphology. Technetium loaded liposomes (99mTc-Nl-Lps) have been tested as imaging agent using SPECT on mice models. Nl-Lps have been used as a drug delivery system with anti-cancer drug methotraxate in in vitro drug release studies. The karpluas-pappas and Higushi models for release kinetics have shown R2 = 0.864, 0.88 respectively. The nucleolipid nanoparticles (NLNP) have been utilized further in animal models to target brain (BBB model) and also in tumor bearing mice model and were found to have better accumulation and specificity in the brain than the standalone nucleolipid (I.D/gm in NL-DTPA-DPU= 0.8, NL-DPU-Lps 1.3). This work represents capability of Nl-Lps as multi-functional probe for targeting and drug delivery applications.

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