Abstract

Development, safety and efficacy evaluation of smart nano-carriers for the treatment of breast carcinomas

Introduction: Breast cancer is the second leading cancer-related disease as the most common non-cutaneous malignancy among women. Curative options for breast cancer are limited, therapeutically substantial and associated with toxicities). Emerging nanotechnologies exhibited the possibility to treat or target breast cancer. Among the nanoparticles, various lipid nanoparticles namely, liposomes, solid lipid nanoparticles, nanostructured lipid carriers and lipid polymer hybrid nanoparticles have been developed over the years for the breast cancer therapy and evidences are documented.

Objective: Potential of Diallyl disulfide (DADS) as a powerful anti-oxidant and anti-cancer agent is very well documented. Significant efficacy evidences gets hindered by some limitation. Prime most is oral bioavailability is very low and the oral administration is not suitable. Another important limitation of DADS is shorter biological half-life. So, these drawbacks turn as rationale to develop drug delivery system. In our present work, we have developed a targeted delivery system using folic acid as a targeting agent for the delivery of DADS-SLNs. We used in vitro model to test the efficacy of folic acid conjugated DADS-SLNs (FA-DADS-SLNs). In vitro model, the cytotoxic effect of DADS-SLNs and FA-DADS-SLNs was tested on folate receptor positive MCF-7 breast cancer cells.

Methodology: Utilizing the principles of quality by design approach, optimization of solid lipid nanoparticles (SLNs) formulation of Diallyl disulfide (DADS) through systematic statistical study was carried out. And further conjugation of Folic acid was carried out by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) for the active targeting of breast cancers. In vitro cytotoxicity studies, reactive oxygen species estimation study were performed. Internalization of FA-DADS-SLNs was evaluated by triple fluorescence staining method. Apoptosis determination was carried out by Annexin V-Propidium iodide assay and western blot analysis.

Results: FA-DADS-SLN exhibited the particle size 167± 1.72 nm, zeta potential 3.6 mv, entrapment efficiency was 69.76 ± 0.11%, and drug loading 29.75± 0.44%. Significant elevated cytotoxicity was observed with FA-DADS-SLNs in comparison to free DADS or DADS-SLNs. High intracellular uptake and higher apoptosis of DADS was observed by the delivery through FA-DADS-SLNs compared to DADS-SLN and
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free-DADS. Western blot analysis confirmed the intrinsic or mitochondrial mediated signalling pathway is the underlying mechanism for the apoptosis of FA-DADS-SLNs.

**Conclusion:** In this study SLNs were employed for delivery of the DADS and to protect this short-lived bioactive substance. Folic acid conjugation made the lipid nanoparticles to target breast cancer cell lines. The important outcome of study was FA-DADS-SLNs which exhibited superior activity over DADS-SLNs which might be due to folate-receptor mediated endocytosis. FA-DADS-SLNs might be a suitable drug delivery system for targeting breast cancer and other folate receptor overexpressing cancers by achieving sustained release inside the tumor cells and enhancing the cytotoxicity of the DADS.

**Keywords:** Diallyl disulfide, Folic acid, Solid lipid nanoparticles, Breast cancer, Active targeting, folate-receptor mediated endocytosis.