Satish Shilpi et al., Pharmaceut Anal Acta 2014, 5:3
http://dx.doi.org/10.4172/2153-2435.S1.022

OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference and Exhibition on
Pharmaceutics & Novel Drug Delivery Systems
March 24-26, 2014 Hilton San Antonio Airport, San Antonio, USA

Transferrin conjugated nanoparticles for intracellular delivery of anticancer drug

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Objectives: The objective is to develop transferrin coupled biodegradable nanoparticles (NPs) contaning pH sensitive fusogenic endosomolytic peptide added to enhance the endosomal lysis that will further potentiate the delivery of anticancer drug inside tumor cell as well as prevent loss of drug via endosomes.

Materials and Methods: Nanoarticles were prepared in two steps. Firstly biodegradable amphiphilic polymer i.e., poly (H2NPEGCA-co-HDCA) was synthesized which is having high encapsulation efficiency. In second step, doxorubicin and peptide encapsulated NPs of synthesized polymer was prepared using double emulsification method reported by Stella (2000) which was further conjugated with transferrin as reported by Minghuang (2010). The optimized NPs formulations such as Npf-Dox, Npf-Dox-Tf, Npf-Dox-Tf-Ga respectively were used for further studies. Size and size distribution of NPs were determined using a Zetasizer (Malvern Instruments, UK). Shape and surface morphology of NPs were studied using TEM and SEM. *In vitro* drug release was carried using dialysis bag (MW 1200 da). *Ex vivo* antitumor studies such as MTT cell cytotoxicity and cell uptake study were carried out on MCF-7 human breast cancer cell line.

Results and Discussion: Prepared NPs were found in spherical shape with average size 192.86±2.03 nm with small polydispersity index (0.196) with 67.74±2.14% encapsulation efficiency. NPs showed a matrix diffusion controlled first order release with 60-75% release in 24 h. Npf-Tf-Dox-Ga exhibiting highest percent cell growth inhibition and higher cell uptake (flouroscence microscopy) compared to other formulations. It is possible due to the formulation containing peptide which has endosomolytic properties and receptor specific targeting of NPs due to surface conjugation with Transferrin respectively. As expected, Dox loaded, Npf-Dox-Tf, Npf-Dox-Tf-Ga NPs are showing greater activity in tumor as compared to plain Dox and Npf-Dox. It is possible due to the transferrin which was conjugated in NPs. Npf-Dox-Tf-Ga is exhibits higher anti tumor activity due to the presence of peptide because it prevents escaping of drug loaded NPs from cells as well as preventing lysosomal drug degradation which results in more concentration of drug in cytosol and higher anti cancer activity.

Conclusion: The surface modified NPs were found to protect entrapped drug and showed a release profile that was suitable for systemic delivery. *Ex vivo* and *in vivo* results shows considerable promise in complimenting the therapy of cancer and it is further synergism with the help of peptide which help in increasing drug concentration in cytosol by lysing the endosomal layer.

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