Designing Targeted PLGA Nanoparticles with a Peptide Antagonist of VLA-4 as a Smart Drug Delivery System for Dysfunctional Endothelial Cells

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INTRODUCTION: Dysfunctional endothelium is the initial and critical step of atherosclerosis. Rapid regeneration of damaged endothelial cells is expected to have a very important role in preventing of the disease. Discovery of smart drug delivery systems, directed against endothelium is essential due to its low access to imaging and pharmacological agents in the blood stream.

METHODS: Fluorescein isothiocyanate-loaded poly (DL-lactic-co-glycolic acid, PLGA) nanoparticles (NPs) were fabricated using double-nozzle electrospraying (at flow rate, DTAB salt concentration and polymer concentration values of 0.08 ml/h, 0.8 mM, and 0.7 w/v%, respectively). NPs were targeted directed against VCAM-1 with a peptide antagonist of VLA-4 (mZD7349 with sequence (cyclo(MePhe-Leu-Asp-Val-D-Arg-D-Lys)). Size, polydispersity index (PDI), zeta potential, and encapsulation efficiency (EE) of NPs and mZD7349-NPs were determined by Zetasizer. Rate of binding and internalization of mZD7349-NPs and NPs to activated human umbilical vein endothelial cells (HUVECs) by TNF-α (10 ng/ml, for 6h) were compared using fluorometry at 4ºC and 37ºC for incubation times of 30, 60, and 120 min.

RESULTS: Characteristics of NPs and mZD7349-NPs are shown in Table 1. The rate and the extent of binding of mZD7349-NPs were greater than NPs in all the three incubation times (Figure 1). Internalization of NPs and mZD7349-NPs decreased at 4ºC than to 37ºC.

Table 1. *Characteristics of NPs (n=3, mean± SD).*

Type	Size (nm)	PDI	Zeta potential (mV)	EE (%)
NPs	225± 14	0.47± 0.06	-11.7± 0.8	86.3± 6.5
mZD7349-NPs	229± 12	0.46± 0.07	-11.6± 1.1	69.6± 7.6

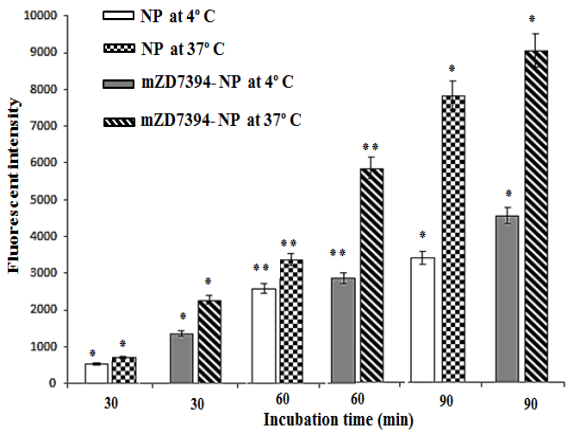

Figure 1. *Rate of binding and internalization of mZD7349-NPs and NPs to activated HUVECs at 4ºC and 37ºC for times 30, 60, 120 min. mZD7349-NPs interacted faster and more with HUVECs compared with NPs at all time-points. Data are presented as mean ± S.D. (n=3), *, ** indicate p < 0.05, p <0.01, respectively.*

DISCUSSION & CONCLUSIONS: Encapsulation efficiency in electrospraying is high and in this technic separation procedure of particles from the solvent is not required. Take up of ligand conjugated- NPs occurs by receptor-mediated endocytosis that occurs faster than the unconjugated NPs endocytosis. Internalization reduction of NPs and mZD7349-NPs at low temperature suggested energy dependent endocytosis of NPs. To conclude, mZD7394- NPs directed against VCAM-1 is suggested as a suitable carrier for atherosclerotic lesions upregulating VCAM-1.

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