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Optimization of anti-restenosis liposomal formulation for local vascular delivery: Effect of size, lipid composition, surface charge and PEG shielding

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Background and Aims: Local vascular delivery of anti-restenosis drugs through nanoparticulate systems offers a potential therapeutic approach to reduce restenosis following coronary angioplasty. The aim of this study was to achieve an ameliorated nanoliposomal formulation for local vascular delivery of anti-restenosis drugs.
Methods: Nanoliposomes with different phospholipid compositions, various lipid to drug molar ratio and mol% cholesterol content, different charge and various size (60 and 100 nm) were prepared and loaded with sirolimus (SIR), a lipophilic antiproliferative/immunosuppressive drug. Effect of PEGylation was also studied. Vesicles were prepared using remote film loading method and were fully characterized. For in-vivo studies carotid arteries of male Sprague-Dawley rats were balloon injured and treated with different liposomal formulations. Rats treated with various empty liposomes served as control groups. Two weeks later, the injured arteries were fixed and subjected to morphometric analysis, which included hematoxylin-eosin and Masson trichrome stain, for evaluation of the degree of neointimal area (NA mm2) and percentage of restenosis.
Results: Typical morphological lesions were observed in the control rat groups (average %stenosis varied from 51% to 63%). Although local delivery of formulations with various main lipid composition, Chol:EPC:DSPG 1:8:1 and Chol:EPC:DSPC:DSPG 1:5:3:1, showed a significant reduction in the NA and %stenosis, $P < 0.01$ as compared to the controls, there were not any significant difference between histomorphometric measurements of these two groups. It was also observed that the efficacy of SIR entrapped in various charged liposomes was significantly dependent on the surface charge of carriers. PEG coating reduced anti-restenosis effect of the carriers possibly due to the steric barrier effect of the surface PEG polymer and neutralization the effect of any charged component.
Conclusions: Results revealed that 100 nm conventional cationic liposomes with lipid composition of Chol:EPC:DOTAP 1:8:1 was the optimum liposomal carrier for local vascular delivery.

Keywords: Restenosis; Nanoliposomes; Local delivery; Lipid composition; Surface charge; PEGylation