World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:15, No:09, 2021

Calcein Release from Liposomes Mediated by Phospholipase A_2 Activity: Effect of Cholesterol and Amphipathic Di and Tri Blocks Copolymers

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Abstract : Background: Liposomes have been widely used as a model of lipid bilayer to study the physicochemical properties of biological membrane, encapsulation, transport and release of different molecules. Furthermore, extensive research has focused on improving the efficiency in the transport of drugs, developing tools that improve the release of the encapsulated drug from liposomes. In this context, the enzymatic activity of PLA_2, despite having been shown to be an effective tool to promote the release of drugs from liposomes, is still an open field of research. Aim: The aim of the present study is to explore the effect of cholesterol (Cho) and amphipathic di- and tri-block copolymers, on calcein release mediated by enzymatic activity of PLA2 in Dipalmitoylphosphatidylcholine (DPPC) liposomes under physiological conditions. Methods: Different dispersions of DPPC, cholesterol, di-block POE_{45}-PCL_{52} or tri-block PCL_{12}-POE_{45}-PCL_{12} were prepared by the extrusion method after five freezing/thawing cycles; in Phosphate buffer 10mM pH 7.4 in presence of calcein. DPPC liposomes/Calcein were centrifuged at 15000rpm 10 min to separate free calcein. Enzymatic activity assays of PLA_2 were performed at 37°C using the TBS buffer pH 7.4. The size distribution, polydispersity, Z-potential and Calcein encapsulation of DPPC liposomes was monitored. Results: PLA_2 activity showed a slower kinetic of calcein release up to 20 mol% of cholesterol, evidencing a minimum at 10 mol% and then a maximum at 18 mol%. Regardless of the percentage of cholesterol, up to 18 mol% a one-hundred percentage release of calcein was observed. At higher cholesterol concentrations, PLA_2 showed to be inefficient or not to be involved in calcein release. In assays where copolymers were added in a concentration lower than their cmc, a similar behavior to those showed in the presence of Cho was observed, that is a slower kinetic in calcein release. In both experimental approaches, a one-hundred percentage of calcein release was observed. PLA_2 was shown to be sensitive to the 4-(4-Octadecylphenyl)-4-oxobutenoic acid inhibitor and calcium, reducing the release of calcein to 0%. Cell viability of HeLa cells decreased 7% in the presence of DPPC liposomes after 3 hours of incubation and 17% and 23% at 5 and 15 hours, respectively. Conclusion: Calcein release from DPPC liposomes, mediated by PLA_2 activity, depends on the percentage of cholesterol and the presence of copolymers. Both, cholesterol up to 20 mol% and copolymers below it cmc could be applied to the regulation of the kinetics of antitumoral drugs release without inducing cell toxicity per se.

Keywords : amphipathic copolymers, calcein release, cholesterol, DPPC liposome, phospholipase A_2
Conference Title : ICTDDS 2021 : International Conference on Targeted Drug Delivery System
Conference Location : Paris, France
Conference Dates : September 20-21, 2021

Open Science Index, Biomedical and Biological Engineering Vol:15, No:09, 2021 publications.waset.org/abstracts/138744.pdf