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Infectious Diseases 2015 : Lipid-based nanoformulations of antimicrobial peptides to treat bacterial infectious diseases - Matougui Nada - University of Angers

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The rapid increase in drug-resistant infections presents an acute problem that continues to challenge the healthcare sector, generating interest in novel antimicrobial strategies. Antimicrobial peptides (AMPs) have a high potential as new therapeutics against infectious diseases as they are less prone to induce resistance due to their fast and non-specific mechanism of action. The new peptides included in the study are well-defined AMPs, established to have an antimicrobial effect and an acceptable safety profile. The aim of this work is to explore the potential of lipid nanocapsules (LNCs) for AMP delivery, and especially its ability to protect the peptide against degradation while at the same time maintain proper drug activity. The LNCs are described as an oily core composed of medium chain triglycerides, and surrounded by a surfactant shell made of lecithin and PEGylated surfactants. Their lipidic cores are not favourable as they stand to encapsulate hydrophilic molecules. To promote the peptide loading, the incorporation of the cationic peptides in the shell of the LNCs was envisaged. Two strategies are tested: adsorption of the AMPs on the surface of LNCs by incubation under magnetic stirring or incorporation of charged linkers to the formulation of LNCs. The incubation performed at different conditions shows a good association of the peptides to the surface of the LNCs. The minimal inhibitory concentrations (MIC) of the LNC-AMPs were determined for the sensitive strains. The results show a preservation of the antibacterial activity of the native peptide and in some cases a decrease of the MIC.The lipid components of lipid-based nanoformulations (LNFs) are generally phospholipids, cholesterol and triglycerides (Copland et al., 2005, Rawat et al., 2008), but also bile salts and free fatty acids (Liu et al., 2007a). These excipients are relatively innocuous, biocompatible and biodegradable in vivo. Nanoformulations have attracted tons of attention due to their size-dependent properties. Among the array of nanoformulations, lipid nanoformulations (LNFs) have evoked increasing interest due to the benefits of their high degree of biocompatibility and flexibility. The performance of lipid nanoformulations is greatly influenced by their composition and structure. Therapeutic peptides represent a growing share of the pharmaceutical market. However, the most challenge for his or her development into commercial products is their inherent physicochemical and biological instability. Important peptides like insulin, calcitonin and cyclosporin anincorporated into LNFs. The association or encapsulation of peptides within lipid-based carriers has shown to guard the labile molecules against enzymatic degradation. This review describes strategies used for the formulation of peptides and a few methods used for the assessment of association efficiency. The benefits and disadvantages of such carriers also are described. Lithium biocompatible microemulsion supported Peceol®, lecithin, ethanol and water was studied in plan to identify the optimal compositions in term of drug content, physicochemical properties and stability. Lithium solubilization in microemulsion was found to be compatible with a drug-surfactant binding model. Lithium ions were predominantly solubilized within lecithin head group altering significantly the interfacial properties of the system. Pseudo-ternary phase diagrams of drug free and drug loaded microemulsions were built at constant ethanol/lecithin weight ratio (40/60). Lithium loaded microemulsion has totally disappeared within the Peceol® rich a part of phase diagram; critical fractions of lecithin and ethanol were required for the formation of stable microemulsion. The effect of lithium concentration on the properties and physical stability of microemulsions were studied using microscopy, Karl Fischer titrations, rheology analyses, conductivity measurements and centrifugation tests. The investigated microemulsions were found to be stable under accelerated storage conditions. The systems exhibited low viscosity and behaved as Newtonian fluid and no structural transition was shown. Low chemical reactivity of carbon nanotubes is one among the main obstacles in their functionalization via chemical reactions. As a non-destructive method,

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Friedel-Crafts acylation was suggested among the explored reactions that only a couple of methods are reported under harsh reaction conditions, e.g., heat all resulting in low yields. During this study, we propose a completely unique method for the acylation of multi-walled carbon nanotubes (MWCNTs) at a coffee temperature (i.e., 42 °C), using SiO2-Al2O3 as a catalyst and 6-bromohexanoic acid because the acylating agent to supply high yield functionalized MWCNTs. After acylation, MWCNTs are conjugated with polyethylenimines (PEIs) with three molecular weights (1.8, 10 and 25 kDa). Three different MWCNT-PEI conjugates are synthesized and evaluated for his or her condensation ability, viability, size and zeta potential properties. The transfection efficiency of the functionalized MWCNTs is evaluated using luciferase assay and flow cytometry during a Neuroblastoma cell line. MWCNT-PEI (10 kDa) conjugate shows the very best transfection efficacy compared to others. For this carrier transfection efficacy exceeds the quantity of PEI 25 kDa at similar carrier to plasmid weight ratio (C/P) and is around 3 times higher compared to PEI 25 kDa at C/P = 0.8 as positive control regarding its high transfection efficiency and low cytotoxicity. Cationic lipid nanoparticles (LNs) are tested for sustained release and site-specific targeting of epigallocatechingallate (EGCG), a possible polyphenol with improved pharmacological profile for the treatment of ocular pathologies, like age-related macular edema, diabetic retinopathy, and inflammatory disorders. Cationic EGCG-LNs were produced by double-emulsion technique; the in vitro release study was performed during a dialysis bag, followed by the drug assay employing a previously validated RP-HPLC method. In vitro HET-CAM study was administered using chicken embryos to work out the potential risk of irritation of the developed formulations. The pharmacokinetic study of the corneal permeation showed a primary order kinetics for both cationic formulations, while EGCG-cetyltrimethylammonium bromide (CTAB) LNs followed a Boltzmann sigmoidal profile and EGCG-dimethyldioctadecylammonium bromide (DDAB) LNs a primary order profile. Our studies also proved the security and non-irritant nature of the developed LNs. Thus, loading EGCG in cationic LNs is recognised as a promising strategy for the treatment of ocular diseases associated with anti-oxidant and anti-inflammatory pathways.

Biography

Matougui Nada is a second year PhD student in biology and health doctorate school at the University of Angers working under the supervision of the professor Patrick Saulnier. Her research is focused on the development of a Lipid-based nanoformulations of antimicrobial peptides to treat bacterial infectious diseases. She is pharmacy graduate from the Medicine University of Algiers, followed by a Master degree in “Technologies Innovantes en Formulation” at University of Angers. She worked as an intern at the “MINT” laboratory on the development of a nanomedicine for glioblastoma therapy.

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