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Formulation and evaluation of new oxazaphosphorine prodrugs-loaded lipid nanocapsules for cancer treatment

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Résumé en anglais	Oxazaphosphorines (cyclophosphamide (CPA) and ifosfamide (IFO)) represent an important group of therapeutic molecules due to their substantial antitumor and immunomodulating activities. Unfortunately, despite the benefits brought by these molecules, their clinical use shows limitations, notably in chemotherapy, due to the development of resistance, interpatients variation and toxicities (urinary toxicity, neurotoxicity and nephrotoxicity). To circumvent these problems, new oxazaphosphorine analogs have been synthetized and present an interesting anti-tumor activity alone with reduced toxicity [1]. Pentanoxy moiety has been grafted on C4 position of ifosfamide (P-IFO). Nevertheless, these new analogs are lipophilic and unstable in aqueous medium. To administer it, this paper proposes to formulate this analog into nanocarriers. Lipid nanocapsules form a new generation of nanovector that can encapsulate a number of anticancer agents [2]. In the present research, P-IFO-loaded LNCs were formulated and characterized. A new formulation based on glycerol monooleate (Peceol®) was developed, optimized and then characterized. Batches of P-IFO-LNCs were obtained with a size of 47.2±0.7nm with a narrow size distribution and a drug payload of 8.42±1.05mg/g. The suspension remained stable at 4°C for 14 days in terms of mean particle size, polydispersity index and pH. The drug payload decreased after 7 days but a high rate was still found (5.88±1.01mg/g) up to 14 days. The stealth properties of these nanoparticles were examined in vitro using the complement activation (CH50) test. This test revealed a low consumption of plasma protein in the presence of such P-IFO-LNCs. In vitro cytotoxicity of P-IFO-LNCs was determined in two human cell lines; i.e. rhabdomyosarcoma (RMS-1) and Ewing sarcoma (A673) and showed a similar activity compared to the free form. Finally, in vivo activity testing of P-IFO-LNCs is in progress in a murine model bearing a RMS-1 xenograft after intravenous administration. References [1] Skarbek C, et al., Preactivated Oxazaphosphorines Designed for Isophosphoramide Mustard Delivery as Bulk Form or Nanoassemblies: Synthesis and Proof of Concept. Journal of Medicinal Chemistry. 22;58(2):105-17, 2015. [2] Huynh NT, et al., Lipid nanocapsules: A new platform for nanomedicine. International Journal of Pharmaceutics. 379(2):201–9, 2009. Acknowledgments: The authors are very grateful to the Ligue contre le Cancer, Comité du Maine et Loire and Comité d’Ille et Vilaine which founded this work.
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