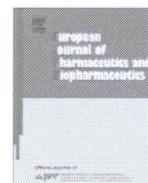




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Research paper

Design and evaluation of cyclodextrin-based delivery systems to incorporate poorly soluble curcumin analogs for the treatment of melanoma

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ABSTRACT

Various analogs of curcumin show high *in vitro* cytotoxic activity and are potential candidates for treating a deadly skin disease, melanoma. Due to the low solubility of the drugs, a new delivery agent, namely a cationic gemini surfactant-conjugated β -cyclodextrin, was designed to incorporate novel drug candidates of the 1,5-diaryl-3-oxo-1,4-pentadienyl family. Based on physicochemical parameters, such as particle size and zeta potential, a schematic model for the potential interaction of the drug with the delivery agent was developed. The drug formulations were highly efficient in inhibiting the growth of melanoma cells, with IC₅₀ values significantly lower than melphalan, the drug currently used for the treatment of in-transit melanoma. CDgemini formulations showed excellent cellular selectivity, triggering apoptosis in the A375 cell line while showing no cytotoxicity to healthy human epidermal keratinocytes. The goal is to develop this novel nanoparticle approach into a non-invasive therapy for in-transit melanoma metastasis that lacks adequate treatment to date.

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1. Introduction

Cancer therapy, despite formidable efforts in oncology research, remains largely ineffective. In addition to limited specificity and high overall toxicity of the anticancer agents [1], chemoresistance is a major contributor to this inefficiency [2]. One of the cancer types that urgently needs efficient therapy is melanoma [3]. It is a malignant skin disease primarily caused by damaging UV rays from the sunlight on the genetic material in melanocytes. The number of melanoma cases has been increasing in Canada; 5300 new cases are expected to be reported for 2010 of which more than 900 patients die every year (www.cancer.ca). Melanoma is considered the most dangerous of the skin diseases due to its high propensity for metastasis. Currently, there is a lack of efficient and specific non-invasive treatment for melanoma, especially for the in-transit metastatic melanoma that develops between the primary lesion and the regional lymph nodes. The prognosis for this stage is as poor as for multiple nodal metastases. The possibility of surgical resection is limited and systemic treatment is not beneficial. Isolated limb perfusion or infusion with melphalan is the

only viable therapy [3]. The aim of this study was to find chemical entities, selected from a large library of potential anticancer agents, with high toxicity for melanotic cells and little effect on normal tissue. In addition, by combining the antineoplastic agents with novel delivery systems, there is an opportunity to eliminate the invasive nature of certain routes of drug administration and improve the efficiency of the treatment. We have demonstrated that Gemini surfactants are efficient topical drug delivery agents [4–6]. Based on these results, we undertook the design and synthesis of a new cyclodextrin-gemini (CDgemini) surfactant that could be applied topically and has the ability to deliver the drug into the cancer cells, efficiently.

Some analogs of curcumin, the active ingredient of turmeric rhizome, demonstrate high potency toward a number of human cancer cell lines [7]. These molecules contain the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore that is mounted on a piperidine ring. In addition, incorporating an N-acyl group into the design of the molecules, which is thought to interact at an auxiliary binding site, enhances potency [7]. Compounds containing a conjugated styryl ketone moiety have a marked affinity for thiols [8,9] rather than hydroxyl and amino groups. These latter groups are found in nucleic acids and represent the target for many of the currently available anticancer drugs. Hence, the genotoxic effects associated with chemotherapy may be avoided by using curcumin analogs. As well, some of these drugs have selective tumor toxicity,

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