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Radiolabeling and biological characterization of TPGS-based nanomicelles by means of small animal imaging

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ABSTRACT

Introduction: In recent years, nanomedicines have raised as a powerful tool to improve prevention, diagnosis and treatment of different pathologies. Among the most well investigated biomaterials, D-α-tocopheryl polyethylene glycol succinate (also known as TPGS) has been on the spot for the last decade. We therefore designed a method to biologically characterize TPGS-based nanomicelles by labeling them with ^{99m}Tc.
Methods: Labeling process was performed by a direct method. The average hydrodynamic diameter of TPGS nanomicelles was measured by dynamic light scattering and radiochemical purity was assessed by thin layer chromatography. Imaging: a dynamic study was performed during the first hour post radioactive micelles administration in a gamma camera (TcO_4^- was also administered for comparative purposes). Then two static images were acquired in ventral position: 1 h and 12 h post injection. Blood pharmacokinetics of ^{99m}Tc-TPGS during 24 h was performed.
Results: Images revealed whole body biodistribution at an early and delayed time and semiquantification was performed in organs of interest (%Total counts: soft tissue 6.1 ± 0.5; 3.9 ± 0.1, Bone 1.2 ± 0.2; 1 ± 0.1, Heart 1.5 ± 0.6; 0.7 ± 0.3, Kidneys 16.6 ± 1.3; 26.5 ± 1.7, Liver 8.6 ± 1.1; 11.1 ± 0.1 for 1 and 12 h post injection respectively).
Conclusion: This work demonstrated that TPGS based nanomicelles are susceptible to be radiolabeled with ^{99m}Tc thus they can be used to perform imaging studies in animal models. Moreover radiolabeling of these delivery nano systems reveals their possibility to be used as diagnostic agents in the near future.

1. Introduction

In recent years, nanomedicines have raised as a powerful tool to improve prevention, diagnosis and treatment of different pathologies. Their nano-sized range along with their high surface-to-volume ratio and their favorable physico-chemical characteristics makes them suitable for modulation of the pharmacokinetic and pharmacodynamic drug profiles. In this context nanotechnology offers a variety of strategies to develop novel drug delivery systems with not only an improved drug aqueous solubility and chemical stability, but also with controlled drug release and preferential accumulation in certain tissues or in solid tumors (passive or active targeting) [1,2].

Among the most well investigated biomaterials, D-α-tocopheryl polyethylene glycol succinate (also known as TPGS) has been on the spot for the last decade. It is the water-soluble form of vitamin E, resulting from the esterification of vitamin E succinate with polyethylene glycol 1000. It exhibits an average molecular weight of 1513 Da and a hydrophile–lipophile balance value of 13.2 (amphiphilic nature). TPGS is a generally regarded as safe (GRAS)-listed oral supplement which has been approved by the FDA as a safe pharmaceutical adjuvant used in drug formulation [3].

Due to TPGS properties as an absorption/permeation enhancer, emulsifier, solubilizer and stabilizer agent, it has been investigated for the development of a wide variety of drug delivery systems including micelles, TPGS-based nanoparticles (NPs), liposomes, nanosuspensions, solid dispersions and TPGS-based pro-drugs. For instance, TPGS-based block copolymers NPs have been studied to antineoplastic drugs delivery [4]. Also TPGS surface-decorated NPs have been employed for paclitaxel delivery [5]. Due to TPGS amphiphilic nature, it has been explored as a micelle-forming biomaterial, especially for oral and parenteral administration in antineoplastic therapy [6–10]. In this context, it has been reported that TPGS could serve as a pharmaceutical additive for overcoming multidrug resistance and as an inhibitor of P-glycoprotein for increasing the cytotoxicity and bioavailability of anticancer drugs [5,11,12]. It has also been investigated for the treatment of other pathologies including the drug delivery of antiretrovirals and calcium channel blockers [13,14].

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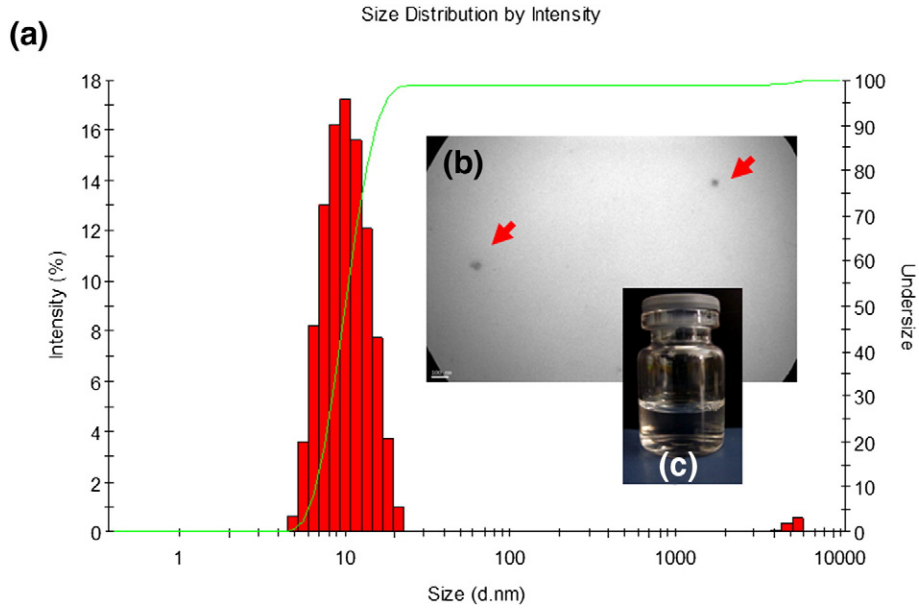

Fig. 1. Size distribution (a) and TEM micrographs (b) of TPGS nanomicelles (10% w/v), scale bar: 100 nm. (c) Macroscopic aspect of a TPGS micellar dispersion in distilled water.

Other properties explored for TPGS are: i) its ability to act as an adjuvant in vaccine systems for intranasal administration [15] and ii) its use as a nutrition supplement [16].

Recently, a new generation of multifunctional nanocarriers for simultaneous diagnosis and therapy, known as "theranostics" nanoformulations, has risen representing a new platform for personalized nanomedicines. These nanoformulations allow the assessment of drugs biodistribution and accumulation in a certain target along with the possibility of reaching therapeutic efficacy [17,18]. Labeling TPGS or any of the TPGS-based nanostructures stands as a real challenge and the first rational step toward building a true theranostic agent. This first step is evaluated in this work and further research is needed to test loading (with a therapeutic drug) and labeling of TPGS-based nanostructures altogether. In addition, small animal imaging represents a powerful tool to follow up labeled probes and could help with characterization of nanosystems as it can show *in vivo* kinetics and organ biodistribution [19,20]. These techniques can also provide information about *in vivo* stability of labeled compounds or structures. We therefore designed a method to biologically characterize TPGS-based nanomicelles by labeling them with ^{99m}Tc, a widely known and used radionuclide with diagnostic purposes in nuclear medicine [21]. Radiolabeling TPGS-based nanomicelles has an enormous potential for multiple purposes: first it can easily enlighten the pharmacokinetic and pharmacodynamic of this nanosystem by using noninvasive techniques, second it could also constitute a tumor diagnostic agent for nuclear medicine and finally and even more significant it could, potentially and with further research needed, constitute itself a theranostic agent if it is susceptible to carry a therapeutic drug and to stay labeled.

2. Materials and methods

2.1. Micelles preparation

For the TPGS nanomicelles preparation, 10 g of commercial TPGS was weighted and dissolved in 100 mL of distilled water with continuous agitation and temperature (30 °C) until a homogeneous dispersion

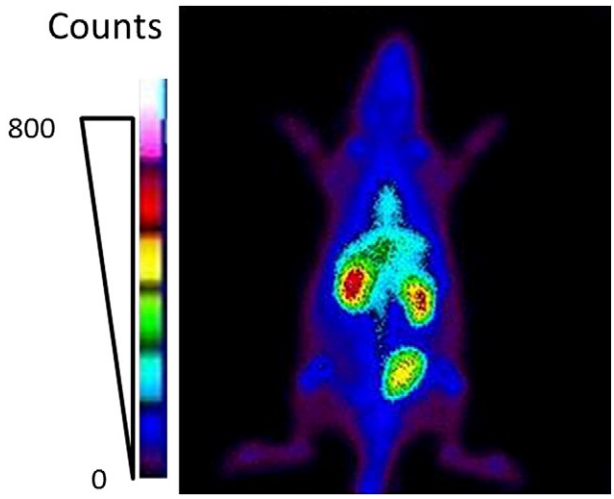

Fig. 2. Biodistribution of ^{99m}Tc radiolabelled TPGS-based nanomicelles (74 MBq). Static image was acquired 1 h post administration in ventral view (256 × 256 matrix, 1.5 zoom, ≥1.5 million counts, 20 min scan). Anesthesia: ketamine/xilazine. Color Band scale is shown.

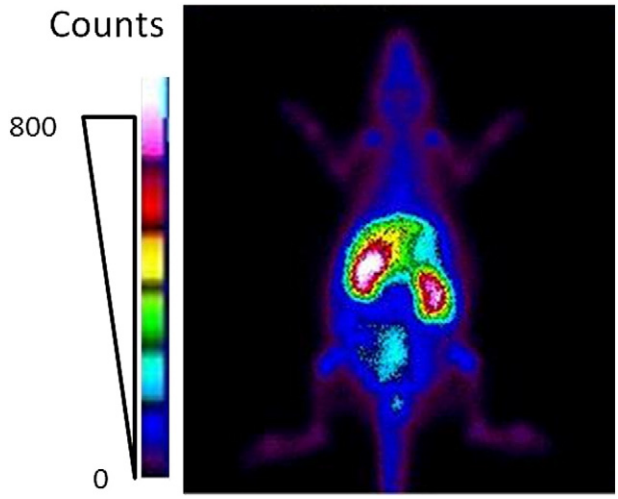

Fig. 3. Biodistribution of ^{99m}Tc radiolabelled TPGS-based nanomicelles (74 MBq). Static image was acquired 12 h post administration in ventral view (256 × 256 matrix, 1.5 zoom, ≥1.5 million counts, 35 min scan). Anesthesia: ketamine/xilazine. Color Band scale is shown.