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Title:

Radiation sterilization of implantable anticancer drug delivery systems

Abstract

Cancer is one of the leading cause of death worldwide. According to the World Health Organization (WHO), the most common cancer types in 2020 were breast and lung cancer, responsible for 2.26 million and 2.21 million of new cases respectively. Additionally, lung cancer was the most common cause of cancer deaths, accounting for 1.8 million deaths in 2020.

However, some of the common cancer types, such as breast cancer (685 000 deaths in 2020), have high cure probabilities when detected early. Therefore it is very important to study on the development of new active substances and new formulations of the drug substances already known.

Paclitaxel (PTX) is an active substance widely used in anticancer therapy, in the treatment of breast, ovarian, non-small cell lung cancers, and Kaposi's sarkoma. However, its low aqueous solubility is challenging in relation to the method of administration. In recent years, in order to develop safe and effective system of PTX administration, the encapsulation of PTX in nanoparticulate drug delivery systems (DDSs) is extensively studied. The most desirable are drug carriers obtained from biodegradable and biocompatible polyesters. The advantage of polyesters is their biodegradability and biocompatibility. These polymers, introduced to the organism, are metabolically decomposed into completely removable and non-toxic products. Nevertheless, polymer drug carriers administered parenterally, are required to withstand harsh conditions of the sterilization process. Considering biodegradable polyester drug carriers, the assurance of sterility is particularly demanding. Polyesters are thermally unstable, therefore, the number of potentially available sterilization methods is limited. This is therefore of great interest to establish an effective, alternative method of the sterilization process, that does not affect physicochemical properties and the structure of the sterilized material.

The main purpose of the study was to investigate the influence of ionizing radiation, by both, γ-rays and fast electrons (sterilization dose, 25 kGy), in relation to possible sterilization of new, self-developed anticancer DDSs. The properly developed drug carriers are able to reduce the side effects of cytostatics and enhance their tumor deposition with highly controlled pharmacokinetics, and thus, improved therapeutic efficacy. In this regard, the first goal of the study was to develop novel polyester drug carriers, capable of controlled release of PTX. The research involved the synthesis of aliphatic polyesters via ring-opening polymerization of L-lactide (L-LA), ε-caprolactone (CL) and glycolide (GA) in the presence of bismuth catalyst (bismuth 2-ethylheksanoate, $BiOct_3$).The use of the bismuth catalyst system allowed to obtain the polymers not cyto– nor genotoxic, that is critical in terms of medical applications.

The research is a complex study on the influence of ionizing radiation on the physicochemical properties and the structure of developed polyester carriers of PTX, as well as the kinetic of PTX release from the nanoparticles obtained. The structural and physicochemical changes in the examined polymers were evaluated in relation to potential processes (chain scission and cross-linking), participating during the irradiation of the polymers, as well as their effects on the kinetic of PTX release.

Keywords: nanoparticles, radiation sterilization, electron beam, γ-irradiation, paclitaxel, biodegradable polymers, aliphatic polyesters, drug delivery systems