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Novel drug delivery systems for actinides (uranium and plutonium) decontamination agents☆

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ABSTRACT

The possibility of accidents in the nuclear industry or of nuclear terrorist attacks makes the development of new decontamination strategies crucial. Among radionuclides, actinides such as uranium and plutonium and their different isotopes are considered as the most dangerous contaminants, plutonium displaying mostly a radiological toxicity whereas uranium exhibits mainly a chemical toxicity. Contamination occurs through ingestion, skin or lung exposure with subsequent absorption and distribution of the radionuclides to different tissues where they induce damaging effects. Different chelating agents have been synthesized but their efficacy is limited by their low tissue specificity and high toxicity. For these reasons, several groups have developed smart delivery systems to increase the local concentration of the chelating agent or to improve its biodistribution. The aim of this review is to highlight these strategies.

Contents

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1. Introduction

The safety of the nuclear industry is generally considered good, but accidents do still happen worldwide. The threat of a nuclear terrorist event involving the release of radionuclides should also be considered. Accidental exposure to radionuclides can occur by inhalation or ingestion or via wounds during industrial application, waste disposal, and warfare [1]. Among actinides, highly active isotopes of plutonium (Pu), americium (Am) and to a lesser extent uranium (U), are considered as dangerous. In this review, we focused on U and Pu mainly, because of their widespread use in the nuclear industry which has led to many studies in drug design and delivery. Nevertheless, one should not forget the danger of other radionuclides such as Strontium-90, Iodine-131, Cesium-134, Cesium-137, Ruthenium-103 or Ruthenium-106 which are the other principal harmful radionuclides following a nuclear reactor accident.

Natural U is composed of three isotopes existing in different proportions in mass: U-234 (0.0054%), U-235 (0.7110%) and U-238 (99.2836%). The two most abundant isotopes on earth are U-238 and U-235. U-234 is produced by α decay of U-238 (emission of a helium nucleus) and represents a small part of the total mass of U. However, it is the most radioactive isotope of U. U-235 is the only natural and readily fissile isotope which releases energy under neutrons particles bombardment. This nuclear property explains the use of the U-235 isotope for energy production in nuclear reactors. Different forms of enriched, depleted or reprocessed U exist depending on the proportions of the three isotopes mentioned. For example, enriched U comprises 3–5% U-235 for civilian applications, and more than 90% for military applications. This highly enriched U might induce radiological toxicity. Conversely, depleted U comprises a lower amount of this isotope than natural U, and is consequently less radioactive. The major industrial applications of enriched U are the production of energy in nuclear power plants while depleted U is mainly used for the manufacture of armor and ammunition. Owing to the low specific activity and long half-life of its main radioisotope U-238, natural or depleted U is not considered to be a radiological hazard but can induce a non-negligible chemical toxicity.

Pu is almost entirely of artificial origin but can be found in trace amounts in U ores (Pu-239) or rare earth (Pu-244). The 15 isotopes of Pu from Pu-232 to Pu-246 are all radioactive. The most frequently encountered in the nuclear industry are the isotopes Pu-238, Pu-239, Pu-240 and Pu-241. The different isotopes of Pu are produced from U in nuclear reactors. Two main industrial applications are developed from the isotopes Pu-238 and Pu-239. Pu-238 is used as a source of thermoelectric energy and is a component of pacemaker batteries, satellites and spacecraft. Pu-239 is mainly used as fissile material in some nuclear power reactors for electricity production. In France and in Europe, it is used along with U as a mixture of oxides (MOX) resulting from processing operations of spent U fuel. In pessimistic scenarios, civilians could be exposed to radioactive aerosols in case of nuclear accidents.

The main exposure routes to U and Pu are oral, lungs and intact or injured skin. In all cases, the radionuclides can reach the blood and damage several tissues. Although many chelating agents have been synthesized in the recent years, little is known about their biopharmaceutical properties and toxicity. Well-known old chelating agents are poised with a low tissue specificity together with a high toxicity, slowing down their clinical development. For these reasons, most of these active molecules have been reformulated in the light of the progress achieved in the field of local and systemic delivery to increase their efficacy and reduce their toxicity. These approaches will be discussed in the present review.

2. Exposure to uranium and plutonium and consequences

2.1. Modes of exposure

Exposure to radionuclides can occur either by an external exposure when the radionuclide remains outside or at the surface of the body, or by an internal exposure when the radionuclide is incorporated or absorbed into the body either by inhalation, ingestion, through intact skin or through wounds. Following external exposure, the radionuclide can induce tissue irradiation which can be damaging depending on the nature of the emitted radiation. The risk is higher if the radiation is penetrating, which is the case of gamma or X radiations, and to a lesser extent, beta radiation. The risk of external exposure can be easily lowered or minimized by shielding the individual or by removing the radiation source. Following internal exposure, the radionuclide is incorporated into the body and the damage induced by irradiation of cells or tissues at the vicinity of the element can be of concern, whatever the radiation type, and especially in the case of highly ionizing alpha particles which transfer their energy more rapidly and at shorter range than gamma radiation for instance. Hence, since the major isotopes of the actinides U and Pu are mostly alpha emitters, the toxicological consequences related to the incorporation of these elements can be quite concerning. This mode of exposure to both actinides mainly depends on the industrial or military uses of the different compounds.

Inhalation is considered as the most frequent mode of contamination in the industry. It can occur after an explosion or a fire, causing atmospheric dispersion of radionuclides in case of containment disruptions. The second most frequent mode of contamination after inhalation is skin exposure. This can occur especially on injured skin, after an explosion or improper handling of contaminated tools or sharps inside a glove-box. The skin can also be contaminated by contact with aerosols or by contact with surfaces contaminated with radionuclides. Ingestion is unlikely to be a frequent mode of contamination among workers in the nuclear industry because it is minimized by health and safety instructions. However, it may be more critical for civilians in the case of an accidental release of radioactivity into the environment [2] occurring after an accident such as the one that took place in Chernobyl or more recently in the Fukushima Dai-ichi Nuclear Power Plant [3–5].

For illustration purpose, the frequencies of contamination that can occur in French nuclear plants or research centers were published in two different reports in 2004 and 2007 [6,7]. The first report on the management of individuals potentially contaminated after internal exposure during incidents occurring between 1996 and 2002, shows that 88% of the 1,529 incidents treated during this period were recorded as suspected inhalation and 11% as suspected contamination through wounds [6]. The second report in which 548 cases of exposure to actinides were recorded between 1970 and 2003, shows that dermal contamination in the presence or absence of injury is significant since it is the first route of contamination, with 53.8% of cases, followed closely by inhalation with 39.5% of cases [7] (Fig. 1).

2.2. Biodistribution

As shown in Fig. 2, whatever the exposure route, the actinides will follow a particular pathway that will affect several particular tissues. This section deals with the biodistribution of two actinides: U and Pu.

2.2.1. Uranium

Occupational activities involving the handling of U in different forms entail possible contamination of exposed workers. To better predict and prevent the toxic effects of U, it is necessary to understand the mechanisms of its absorption. The absorption of U depends on its physicochemical form, the solubility of the compounds and the mode of contamination. The more soluble forms such as uranyl nitrate $UO_2(NO_3)_2$ or ammonium uranyl tricarbonate $(NH_4)_4UO_2(CO_3)_3$ are more diffusible. Ammonium diuranate $(NH_4)_2U_2O_7$ or uranyl acetate $UO_2(CH_3COO)_2$ are less soluble and therefore less diffusible. Finally, U dioxide UO_2 is less soluble [8]. Soluble forms, such as nitrate, can release uranyl ions which will be distributed to target organs such as the kidneys and bones. The least soluble forms have the tendency to be retained in organs and then to express their toxicity locally.