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Review

Determination of impurities in detonation nanodiamonds by gamma activation analysis method ☆

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ABSTRACT

This paper describes the use of gamma activation analysis methods for determining impurities in detonation nanodiamonds (DNDs) from different manufacturers, in different probes of the same batch from the same manufacturer, in chemically modified DNDs, and in DND–glycine conjugate. Twelve impurity elements were detected and quantified in DND samples: Cl, Ti, Cr, Fe, Ni, Zr, Mo, Sb, Sr, Mn, U and Eu. The content of impurity elements in DND samples varies from 0.1 to 3 wt.%. Considering possible medical applications of DND, compliance with approved maximum permissible concentrations of heavy metals in medicinal agents is required.

Contents

1. Introduction

Today, the development of nanoparticle-based drug delivery systems is mainstream in nanomedicine and pharmaceutical nanotechnology [1,2]. Such systems enhance local drug concentration within the target organ which increases the drug's therapeutic action while reducing its toxicity and adverse effects. Over 400 types of nanoparticles

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used as drug carriers have already been described, and each of them has its own advantages and disadvantages [2,3]. Carbon nanoparticles such as fullerenes, nanotubes, graphene and nanodiamonds are being studied intensively in this capacity [4–7]. As a result of numerous experiments, it has become apparent that the most promising material for biomedical applications is detonation nanodiamonds (DNDs) [6]. This is attributed to a unique set of their physicochemical and biopharmaceutical properties such as: the size of their primary particles of about 5 nm, therefore an extremely specific area (up to 250–400 m^2/g); availability of a wide range of functional groups making it possible to use chemical modification and immobilization of various drug substances with different chemical structures; and their biocompatibility and nontoxicity.

The effectiveness of DNDs has been demonstrated in anticancer drug delivery systems [8–10], in analytical diagnostics [11], as material for nanosurgery [11], as a photoluminescent biomarker [12], as a biosensor [13] and as a biochip [14]. There have also been suggestions to use them in cosmetology as a protector from solar UV radiation [15].

DNDs are fabricated by oxygen-deficient detonation of carbonaceous explosives in a special blasting chamber followed by extracting DNDs from the detonation products and then purifying them in oxidation processing [16]. At each stage of the process, there is a possibility of DNDs being contaminated with process-related impurities containing both nonmetals and metals. However, quality certificates and accompanying documentation for commercially available DNDs hardly ever include information on the impurity concentration since such information is not required by the DND production specifications. Nevertheless, the presence of some impurities in DNDs – especially heavy metals and some other elements – is strictly regulated when used for biomedical purposes. Therefore, in the production of DNDs for medical use it is extremely important to find a way to analytically determine the impurities and, when necessary, to additionally purify DNDs to get a product standardized by impurity content [17]. The medical use of DNDs requires strict inspection of their impurity composition in accordance with medicinal agents' standards. Purity tests of pharmaceutical substances and drugs based on them involve the assessment of chemical impurities and microbial contamination.

Inorganic-anion contamination control of DNDs is done to assess their purity level, since the most commonly encountered anions (chlorides, sulfates and phosphates) are usually nontoxic. The measurement of DND heavy-metal contamination levels is an obligatory procedure due to their possible high toxicity. To control their concentration, the “heavy metal” index is added to the pharmacopeia requirements [18]. The index is aimed at restricting the permissible concentration of such elements as Pb, Hg, Bi, Sb, Sn, Cd, Ag, Cu, Mo, V, Ru, Pt, and Pd. As a rule, the concentration of heavy metals must not exceed 0.001 [19] or 0.002 wt.% [20].

Usually, the examination of DND metal contamination is done with the use of atomic-absorption spectroscopy (AAS) and atomic-emission spectral analysis (AES) [21,22]. The limitation of AAS is that detection of every element has to be done separately, while the limitation of AES is its high detection level. As a result, it is impossible by both of these methods to detect elements of low atomic numbers (below 20 amu). Even the inductively coupled plasma atomic emission spectroscopy (ICP-AES), which has a lower detection level compared to AES, will by no means always yield information on DND impurity content [23].

In some studies [24,25] fifteen brands of detonation and synthesized nanodiamonds were analyzed in which the following elements with concentrations over 1 mg/g have been detected: Na, K, Mg, Ca, Ba, B, Al, Mn, Zn, Fe, Cu, Pb, Ni, Cr, Si, Sn, Ti, Zr, Sb, W, V, Mo and S. In these studies the determination of impurities was done using inductively coupled plasma mass spectrometry (ICP-MS). One of the main difficulties limiting the use of this method is the obligatory requirement to recalibrate the device before or during measurement of every batch of samples. Another difficulty is the method's inability to detect some light elements, such as O, N, and Cl.

In a number of studies, X-ray fluorescence (XRF) [26,27], X-ray photoelectron spectroscopy (XPS) [21], and secondary-ion mass spectrometry (SIMS) [28] were used to determine the composition of the impurities in DNDs. However, it must be noted that XRF doesn't have a low enough detection threshold for light elements, while XPS and SIMS are useful to retrieve valuable information on the presence of impurity elements only in superficial layers of nanoparticles.

In one study [29], neutron activation analysis (NAA) was used to determine the isotopic impurity composition of the nanodiamond fraction extracted from meteorites. This study showed for the first time that instrumental gamma activation analysis (GAA) (based on the exposure of an analyzed sample to neutrons or gamma-quantum followed by measuring the characteristic gamma rays from resulting radionuclides) could become the most effective and convenient way to analyze impurity composition of nanodiamonds [30,31]. The most commonly used types of activation analysis are NAA and GAA.

With NAA it is possible to detect up to 50 elements with an accuracy of 1% to 10% at a very low detection threshold: from hundreds of ng to a few pg [32,33]. However, such high sensibility is not required and is never used for drug products.

The GAA method is based on the interaction of high-energy gamma-quantums (5 to 30 MeV) with atomic nucleus of the matter under study. The resulting reactions depend on the gamma energy. Of practical relevance are the reactions of 8 to 14 MeV interaction threshold. These are, as a rule (γ, n) and (γ, p) interactions and much more rarely (γ, 2n), and (γ, pn). The result of the main (γ, n) reaction is radionuclides of a variety of half-life periods [34]. The method is used to determine both nonmetals (C, O, N), and metals such as Zr, Ag, Ti, and Ni. The limit of detection lies within the range of 10^{-4} to 10^{-7} g [32], which is acceptable for pharmacopeia analysis.

One of the advantages of an activation method, in particular, of GAA is that it gives the possibility of non-destructive multielement determination. However, despite high productivity and rapid testing ability, GAA has some limitations connected, first of all, to irregularity of the gamma-quantum beam by volume of the activated assembly of samples [32]. Nevertheless, due to its positive features GAA compares favorably with other analytical techniques and can be effectively used both for chemical and pharmacopeia analyses of DND and DND-based products.

The purpose of this study is to examine the possibilities and viability of application of multielement gamma activation analysis for qualitative and quantitative analysis of impurities in different brands of commercial DNDs, in DNDs with chemically modified surface and in DND–drug substance conjugates for medical use.

2. Experimental

2.1. Objects of research

Four commercial brands of detonation-synthesis nanodiamonds from three manufacturers were used for the study of impurity composition. Manufacturing companies and sample codes are given in Table 1.

The impurity composition of DND brand UDA-TAN was also analyzed following the modification of its surface in various conditions:

- reductive hydrogenation in a hydrogen stream at 800 °C for 2 h (code of sample IV_B–H);
- oxidation with boiling mixture of oxidant acids (HNO_3:H_2SO_4 = 1:4) at 120 °C for 24 h (code of sample IV_B–COOH).

Apart from that, impurities were analyzed in the conjugate of the UDA-TAN brand DND with an immobilized glycine (sample IV_B–Gly) which is a promising medical delivery system for glycine and for the treatment of hemorrhagic stroke [35,36].