Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 281–282

Mendeleev Communications

Enzymatic hydroxyapatite as a carrier for yttrium-90 and copper and ruthenium radionuclides

Varvara K. Dolgova,[a] Aleksander V. Gopin,[a] Aleksander L. Nikolaev,[a] Alexey P. Orlov,[a] Tatiana P. Trofimova[a,b] and Marina A. Orlova*[a,c]

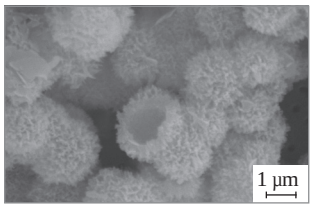
[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: orlova.radiochem@mail.ru*

[b] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation*

[c] *N. I. Pirogov Russian National Research Medical University, 117997 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2022.03.043

The use of hydroxyapatite obtained by enzymatic synthesis (HAP_E) as a carrier of radionuclides (yttrium-90, copper(II) as a prototype of ^{64}Cu and ^{67}Cu and ruthenium-103 as a prototype of ^{97}Ru) is considered. The processes of sorption and desorption of ions in different solutions are compared. The sorption of copper and yttrium on HAP_E is almost irreversible, in contrast to the sorption of ruthenium, for which the reverse process depends on the medium.



Enzymatic hydroxyapatite

Keywords: hydroxyapatite, alkaline phosphatase, ^{103}Ru, ^{90}Y, copper ions, sorption, desorption, sorption isotherms.

The development of cancer treatment methods is of considerable current importance. Among them is radioembolization, which consists of introducing large particles of a solid carrier containing a therapeutic radionuclide into a blood vessel feeding the tumor.[1] As a result, the tumor dies both from irradiation and from lack of nutrition.[2,3] Enzymatic hydroxyapatite (HAP_E)[4–6] can be used as an embolizer system component due to its suitable particle sizes and sorption properties. The second component of the system is a radionuclide that is actively absorbed by HAP_E and has a therapeutic effect on the tumor. Yttrium-90 and copper-67 can be used as therapeutic radionuclides due to their nuclear-physical parameters.[7,8] The production and use of ruthenium complexes in medicine have been of increasing interest in the last years. Among the ruthenium radionuclides, ruthenium-97 is the most promising due to its relatively long half-life (2.9 days), applicability as a therapeutic agent and selectivity for metastatic cancer cells.[9,10] Comparative data on the sorption and desorption parameters of radionuclides used in radioembolization are necessary for their direct application in nuclear medicine. Desorption is an important process due to the possible radionuclide losses in the body, which can increase the dose load on critical organs. In this work, we obtained these parameters for yttrium (with ^{90}Y) and ruthenium (with ^{103}Ru as a long-lived analog of ^{97}Ru)[11] using the radioactive tracer method. Copper(II) ions, as a prototype of ^{67}Cu, were determined analytically.

Enzymatic hydroxyapatite was prepared by hydrolysis of calcium glycerophosphate in the presence of alkaline phosphatase, as described previously[6] (for details, see Online Supplementary Materials). The maxima of the differential particle size distribution functions varied from 0.5 to 2.7 μm depending on the reaction time and enzyme concentration. At reaction times of 1 and 7 days, the pore sizes were 9 and 10 nm with the corresponding specific surface area of 100 and 130 $m^2\ g^{-1}$, respectively. The particles had a spherical shape and a developed surface relief.

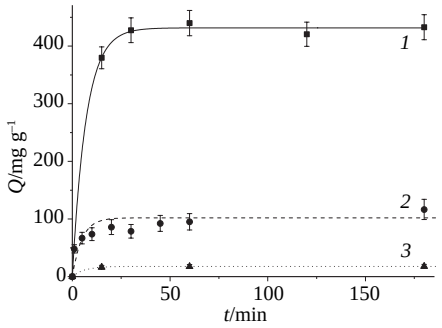


Figure 1 Sorption kinetics of (*1*) yttrium, (*2*) copper and (*3*) ruthenium.

The sorption of yttrium was determined using $^{90}Y^{III}$ with the addition of yttrium(III) nitrate as a carrier (Figure 1). The sorption was almost irreversible and reached a maximum after 15 min. The sorption of copper ions on hydroxyapatite obtained by non-enzymatic methods has been described previously.[12,13] The binding of copper with hydroxyapatite was also irreversible, and no desorption was observed. The sorption was fast, and saturation occurred after 1 h (see Figure 1).

The kinetics of ruthenium sorption was obtained using ^{103}Ru with $T_{1/2}$ = 39.8 days. In the case of ruthenium sorption with a carrier, the concentration of $RuCl_3$ was 5 g dm^{-3} (Figure 1, curve *3*). Earlier, Tõnsuaadu *et al.*[14] assumed that an intrinsic phase containing ruthenium could be formed if the macro concentration of ruthenium was used, but we failed to confirm this in our experiments. The maximum sorption of 18 mg g^{-1} was reached in 60 min, and it was significantly lower than that of yttrium. Figure 2 illustrates the sorption kinetics of carrier-free ^{103}Ru (see also Online Supplementary Materials). Partial desorption is clearly present here (the sorption also reached a maximum in 60 min); however, this may be due to the dissolution

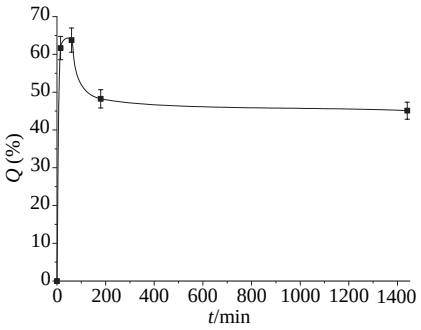


Figure 2 Sorption of carrier-free ^{103}Ru. Precipitation of the intrinsic ruthenium-containing phase under the experimental conditions was impossible.

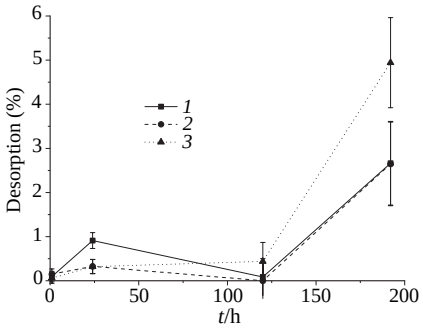


Figure 4 Desorption of yttrium in (*1*) saline, (*2*) BSA and (*3*) acetate buffer (pH 5.0) solutions.

of HAP_E in an acidic medium (because the neutral and alkaline solutions of ruthenium cannot be used).

Figure 3 shows sorption isotherms of yttrium and copper ions on HAP_E (see also Online Supplementary Materials). The sorption reached maximum values of 470 mg g^{-1} for yttrium and 220 mg g^{-1} for copper. The Langmuir-type model can satisfactorily describe the sorption isotherm of copper ions. Table 1 compares the parameters of copper sorption isotherms on HAP_E and nanohydroxyapatite[13] (synthesized by a precipitation method) obtained by approximation using this model. The best fit was observed for HAP_E, which had a significantly higher specific surface area and maximum sorption.

The sorption isotherm of yttrium (see Figure 3) cannot be described by simple Langmuir and Freundlich models and is characterized by a significantly higher maximum equilibrium sorption. The sorption isotherms of ruthenium, both using ^{103}Ru without a carrier and with a carrier of ruthenium(III) chloride solution, cannot be correctly characterized by the radioactive tracer method because of the low pH of the solutions.

Figure 4 illustrates the desorption of yttrium in saline, bovine serum albumin (BSA) (C = 48 mg ml^{-1}) and acetate buffer (pH 5.0) solutions. In all systems, desorption did not exceed 5% of the total sorbed yttrium and reached a maximum (5%) in the buffer solution. Thus, the sorption of yttrium was almost irreversible. In conclusion, we note that the kinetics of sorption cannot be described by relatively simple pseudo-first or pseudo-second order models.

Enzymatic hydroxyapatite is a promising material for tumor embolization because it has a high sorption capacity and low desorption (or its absence). For this goal, ^{90}Y and copper radionuclides (in particular, therapeutic ^{67}Cu) are the most promising. Ruthenium is also of interest in radiopharmaceutical chemistry.

Table 1 Approximation parameters for sorption isotherms of copper ions on hydroxyapatite according to the Langmuir model (K_L is the adsorption equilibrium constant, and R^2 is the linearization factor).

Sample	Q_m/mg g^{-1}	K_L/dm^3 g^{-1}	R^2
Nanohydroxyapatite[13]	83	15.8	0.931
Enzymatic hydroxyapatite (HAP_E)	230	26.6	0.967

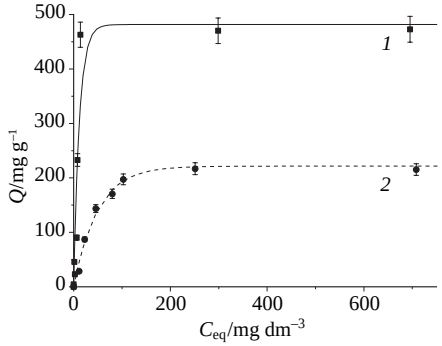


Figure 3 Sorption isotherms of (*1*) yttrium and (*2*) copper.

This work was supported by the Russian Foundation for Basic Research (grant no. 19-08-00055).

Online Supplementary Materials

Supplementary data assosiated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.043.

References

1 T. Miyazaki, T. Tanaka, Y. Shirosaki and M. Kawashita, *Ceram. Int.*, 2014, **40**, 15259.
2 G. Vesselle, I. Petit, S. Boucebci, T. Rocher, S. Velasco and J.-P. Tasu, *Diagnostic and Interventional Imaging*, 2015, **96**, 547.
3 N. Watanabe, N. Oriuchi, K. Endo, T. Inoue, S. Tanada, H. Murata and Y. Sasaki, *Nucl. Med. Biol*., 1999, **26**, 847.
4 E. Colaço, D. Brouri, C. Méthivier, L. Valentin, F. Oudet, K. Kirat, C. Guibert and J. Landoulsi, *J. Colloid Interface Sci.*, 2020, **565**, 43.
5 F. Fernane, M. O. Mecherri, P. Sharrock. M. Hadioui, H. Lounici and M. Fedoroff, *Mater. Charact.*, 2008, **59**, 554.
6 M. A. Orlova, A. L. Nikolaev, T. P. Trofimova, A. P. Orlov, A. V. Severin and S. N. Kalmykov, *Bulletin of Russian State Medical University*, 2018, **6**, 86 (*Vestnik Rossiiskogo Gosudarstvennogo Meditsinskogo Universiteta*, 2018, **6**, 94).
7 D. P. Al-Adra, R. S. Gill, S. J. Axford, X. Shi, N. Kneteman and S.-S. Liau, *European Journal of Surgical Oncology*, 2015, **41**, 120.
8 R. A. Aliev, S. S. Belyshev, A. A. Kuznetsov, L. Z. Dzhilavyan, V. V. Khankin, G. Yu. Aleshin, A. G. Kazakov, A. B. Priselkova, S. N. Kalmykov and B. S. Ishkhanov. *J. Radioanal. Nucl. Chem.*, 2019, **321**, 125.
9 G. Sava, F. Frausin, M. Cocchietto, F. Vita, E. Podda, P. Spessotto, A. Furlani, V. Scarcia and G. Zabucchi, *Eur. J. Cancer*, 2004, **40**, 1383.
10 N. E. Borisova, M. A. Orlova, V. A. Knizhnikov, V. K. Dolgova, M. D. Reshetova and A. P. Orlov, *Mendeleev Commun.*, 2021, **31**, 207.
11 V. Ostapenko, A. Vasiliev, E. Lapshina, S. Ermolaev, R. Aliev, Yu. Totskiy, B. Zhuikov and S. Kalmykov, *J. Radioanal. Nucl. Chem.*, 2015, **306**, 707.
12 A. I. Ivanets, N. V. Kitikova, I. L. Sheshkova, M. Yu. Roshchina, V. Srivastava and M. Sillenpaa, *Journal of Water Process Engineering*, 2019, **32**, 100963.
13 M. A. Orlova, A. L. Nikolaev, T. P. Trofimova, A. V. Severin, A. V. Gopin, N. S. Zolotova, V. K. Dolgova and A. P. Orlov, *Russ. Chem. Bull.*, 2019, **68**, 1102.
14 K. Tõnsuaadu, M. Gruselle, F. Villain, R. Thouvenot, M. Peld, V. Mikli, R. Traksmaa, P. Gredin, X. Carrier and L. Salles, *J. Colloid Interface Sci.*, 2006, **304**, 283.

Received: 16th September 2021; Com. 21/6695