THE POTENTIAL OF NANO- AND MICROPARTICLES FOR THE SELECTIVE COMPLEXATION AND SEPARATION OF METAL IONS/RADIONUCLIDES

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Abstract

Nano- and microparticles for the selective complexation of metal ions and especially radionuclides on their surface are presented. Beside several applications of such magnetic and non-magnetic particles in the fields of biomedicine, diagnostics, molecular biology, bioinorganic chemistry and catalysis a high potential exists for the complexation of radionuclides from nuclear wastewater on particle surfaces. The magnetic properties of nano- and microparticles allow the fast magnetic separation of radionuclides from the radioactive liquid waste stream, for example. The removal of radionuclides from strongly acidic wastes requires a high stability of the particles in combination with the protection of the incorporated iron oxide. The covalent binding of selective chelators allows the fractionation of different types of radionuclides regarding the special needs of nuclear waste treatment.
1. Introduction

Nano- and microparticles are widely used for the immobilisation of metal ions [1] and radionuclides [2,3] in the fields of biomedicine [4], molecular biology [5], medical diagnostics [6], bioinorganic chemistry and catalysis [7]. In general there are two possibilities for the binding of metal ions on particle surfaces. One method is based on the simple physical adsorption of chelators [8] or metal ions on particle surfaces by inclusion into pores of the particles, adhesion processes or electrostatic interactions. The second more specific method consists of the complexation of metal ions by selective chelators which are covalently attached to the particle surface. Nearly all applications of the metal ion immobilisation on particle surfaces require an efficient complexation of the metal ions to prevent traces of free metal ions in the special medium. Therefore the effective chemical binding of metal ions on particle surfaces is our method of choice.

Here we report our results on the selective binding of metal ions and radionuclides on the surface of magnetic and non-magnetic particles for the application in the magnetic field assisted radionuclide therapy, for the selective binding of histidine-tagged proteins via the formation of a nickel(II) protein complex, and for the complexation of palladium ions by sulfur-rich macrocyclic ligands on the surface of silica particles.

These experiences resulting from the immobilisation of metal ions and especially radionuclides for life sciences applications initiated our first attempts of the selective complexation of lanthanides and actinides on the surface of magnetic silica beads. Current approaches for the recovery of lanthanides and actinides from high level nuclear waste are based on the TRUEX process which utilises the highly efficient, neutral, organophosphorous ligand octyl-phenyl-N,N-diisobutyl-carbamoylmethyl-phosphine oxide (CMPO) [9]. Previously, calix[4]arene based extractants which incorporate CMPO moieties at either the wide [10,11] or narrow rim have been reported [12]. Such pre-organisation of the chelating ligands leads to a 100-fold (or even more) increase [10] in extraction efficiency combined with an enhanced selectivity for actinides and lighter lanthanides [13]. Derivatives with single CMPO groups and CMPO-substituted calixarenes were covalently attached to the surface of magnetic silica particles allowing controlled ligand loading with defined orientation [14].

First solid-liquid extraction experiments were performed under conditions that simulate European nuclear waste streams (4M NaNO₃, 1M HNO₃). Separation of europium, cerium or americium, as representatives of the early lanthanides and actinides, was evaluated. ICP-MS measurements of the initial nuclide activity in the aqueous phase and the activity after shaking with the particles were used to calculate the percentage extraction [14].

2. Selective complexation of the radionuclides ⁹⁹mTc/¹⁸⁸Re and ¹¹¹In/⁹⁰Y on the surface of microparticles for therapeutical purposes

The magnetic field assisted radionuclide therapy aims the targeting of diagnostically and therapeutically important radionuclides like ⁹⁹mTc or ¹¹¹In and ¹⁸⁸Re or ¹⁹⁰Y, respectively, to the tumour. Therefore the radionuclides are efficiently complexed on the surface of biocompatible magnetic nanoparticles. These nanoparticles are injected in the near of the tumor region and kept in the target area by means of external magnetic fields. This leads to a high concentration of radioactivity at the tumor and prevents side effects on the healthy tissue [15]. Another strategy for successful tumour treatment is the intracavitary radionuclide therapy: The radioactive labelled microspheres are immobilised in the tumour because of their size, and irradiate the tumour cells. After the radioactivity is faded away the microspheres are biotransformed into harmless metabolites [16]. Both strategies ideally require magnetic or non-magnetic biodegradable particles able to complex radionuclides...
efficiently and stable. This can be reached by reacting one of the best known chelators for technetium and rhenium, \( \text{MAG}_3 \) [1], or for indium and yttrium, \( \text{DOTA} \) [2], with a functionality, e.g. an amino group, on the surface of the microsphere (Schemes 1 and 2).

Scheme 1. \textbf{Chemical structures of mercaptoacetyl-triglycine (MAG\(_3\)) [17] 1 and 1,4,7,10-tetraazacyclododecane-N,N',N''',N''''-tetraacetic acid (DOTA) [18] 2}

![Chemical structures](image)

Then these microspheres can either be labelled with the radioactive isotopes \(^{99m}\text{Tc}\) or \(^{111}\text{In}\), which are gamma emitters, or with the beta emitters \(^{188}\text{Re}\) or \(^{90}\text{Y}\) for therapeutic applications. In the case of \(^{99m}\text{Tc}\) we obtained first results for non-magnetic microspheres with a labeling efficiency (particle-bound activity) of 39\% and an \textit{in-vitro} stability of the particle bound \(\text{MAG}_3\)-technetium complex of 79\%. A relatively high labelling efficiency of non-magnetic microspheres of 72\% and an \textit{in-vitro} stability of more than 90\% could be reached with the gamma emitter \(^{111}\text{In}\).

In future we want to optimise the labelling procedure, develop new chelators for technetium, rhenium, indium and yttrium and investigate a combination of the intracavitary radionuclide therapy with the strategy of the magnetic drug targeting.
3. **Selective removal of histidine-tagged proteins from fermentation solutions by nickel(II)-protein complex formation on the surface of magnetic silica particles (sicastar®-M)**

The covalent binding of backbone-modified nitrilotriacetic acid (NTA) on the surface of magnetic silica particles is the basis for the formation of a nickel(II) complex with a high complex stability. The backbone-modification allows the interaction of four chelating sites of the modified NTA with nickel(II) ions, which results in a more tightly binding of nickel(II) ions in comparison to systems with only three sites available for the nickel(II) complexation (Scheme 3).

**Scheme 3.**

* a) Interaction of four donor atoms of backbone modified NTA with nickel(II) ions,
* b) Interaction of only three donor atoms of non-modified NTA with nickel(II) ions. One carboxylic acid group of the NTA is necessary for the covalent binding on the particle surface.

The high selectivity of this Ni(II)-NTA complex for proteins with an affinity tag of six consecutive histidine residues allows a one-step purification of almost any protein from any expression system under native or denaturing conditions (Scheme 4).

**Scheme 4.** Principle of the selective binding of his-tagged proteins on the surface of particles containing chelated metal ions (nickel(II) ions) on the surface.

Electrokinetic measurements of the surface potential of magnetic silica beads have been carried out to determine the optimal density of NTA on the surface of the particles. Therefore the density of NTA was increased stepwise until a saturation of the surface with NTA was achieved. This saturation range was detected by the comparison of the Zetapotential values of the particles at a constant pH-value of 8.0 (Figure 1a). In addition streaming potential measurements were carried out to determine the corresponding particle charge density values by polyelectrolyte titration against 0.001 N poly(diallyldimethylammonium chloride) (Figure 1b). An optimal surface was realised by reacting 250-500 µmol NTA-chelator with one g of functionalized particles. The binding capacity of the optimized NTA-modified particles lies in the range of 2.5-3.0 nmol nickel(II) ions per g of magnetic silica particles. The magnetic silica-NTA beads (sicastar® -M) can be used to purify 6xHis-tagged proteins from any expression system including baculovirus, mammalian cells, yeast, and bacteria.
4. Complexation of palladium ions by sulfur-rich macrocycles on the surface of silica particles

1,2-Dithioethenes are weak chelate-forming ligands [19]. In the case of bis(methylthio)maleonitrile [20] the donor power of the sulphur atoms is further decreased by the electron withdrawing effect of the cyano groups. Crowned dithiomaleonitriles are macrocyclic chelate ligands which extract Pd(II) at sufficient rate in a very good yield. The reason for that extraction behaviour is the fact that Pd(II) favours the square planar coordination geometry in opposite to the 3d-metals and thiophilic d^{10} ions like Ag(I) and Hg(II).

For the synthesis of the immobilised ligands the 2-allyloxy-1,2-propanediol is transformed into the dichloro compound, which is reacted with a dithiolate ((Z)1,2-disodium-1,2-dicyanethene-1,2-dithiolate, 1,2-disodium-4-methylbenzene-1,2-dithiolate [21]) at high dilution conditions yielding the macrocycle. Than the allylsubstituted crown ether is silylated and the resulting alkoxy silane is immobilized on activated silica beads (Scheme 5).

Scheme 5. Derivatization of the macrocycle for the immobilization on silica beads

The substituent forms simultaneously a spacer which can be modified in the future. The selectivity of the ligand should be applied by immobilisation at an inactive matrix for the accumulation of Pd(II) from diluted solutions. The extraction of Pd(II) was performed from nitric acid solution with a yield of 93% into a ligand solution (chloroform, kerosene). The extraction equilibrium is reached after 10 min. By AAS the metal concentration in the aqueous phase was determined to calculate the extraction rate.
Scheme 6. **Formation of the macrocycle-Pd(II) complex**

The extraction rate increases from the acyclic compound through maleonitrile-dithio-21-crown-7, maleonitrile-dithio-15-crown-5 and maleonitrile-dithio-18-crown-6 by modification of the cavity of the macrocycle. The best results can be observed for the maleonitrile-dithio-12-crown-4. The rise of the function $\lg D = f(\lg c_L)$ gives the composition of the extracted compounds as 1:1. Summarising, a very good separation of Pd(II) can be specified from 3d-metals and other thiophilic metal ions. In addition to the extraction experiments and the crystal structures the formation constants of selected chelates were determined by UV spectroscopy. The observed order corresponds to that found by the extraction of palladium in the system water/chloroform.

5. **Extraction of lanthanides and actinides by magnetically assisted chemical separation technique**

The removal of radionuclides from strongly acidic wastes requires a high stability of the particles in combination with the protection of the incorporated iron oxide. Therefore magnetic silica particles were additionally coated with functionalized alkoxysilanes to encapsulate the iron oxide and to introduce functional groups for the covalent binding of chelators on the particle surface.

Carboxylic acid modified sicastar$^\text{®}$-M (I) were used as the basis for the attachment of simple CMPO ligands directly onto the particle surface (II). The CMPO-modified particles (II) enable extraction of $^{152}$Eu, $^{241}$Am and $^{139}$Ce albeit at a very low level only slightly higher than with I (Scheme 7, Table 1). However, the calix[4]arene based particles (III), with a roughly identical concentration of ligating functions, show a significantly higher level of extraction (Scheme 7, Table 1). This demonstrates the importance of pre-organization of the chelating ligands on a suitable macrocyclic scaffold, prior to their attachment at the particle surface [14].

<table>
<thead>
<tr>
<th>Magnetic silica particles</th>
<th>$^{152}$Eu</th>
<th>$^{241}$Am</th>
<th>$^{139}$Ce</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.7%</td>
<td>&lt;1%</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>1.5%</td>
<td>0.4%</td>
<td>7.5%</td>
</tr>
<tr>
<td>III</td>
<td>77.6%</td>
<td>81.7%</td>
<td>91.6%</td>
</tr>
</tbody>
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Scheme 7. Magnetic silica particles (sicastar®-M) with carboxylic acid groups (I), CMPO-derivatives (II), and calix[4]arenes with pre-organised CMPO-derivative units (III) on the particle surface

Partition coefficients comparable to those seen for the systems with adsorbed ligands [8] are obtained for europium extraction. However, in contrast, larger $K_D$ values per mass of ligating function are found for americium. Thus the covalent systems show considerably enhanced extraction of americium over europium and offer the potential of selective separation. This reinforces the importance of initial pre-organisation in imparting selectivity. CMPO extractants, such as octyl phenyl $N,N$-diisobutyl carbamoylmethyl phosphine oxide are unable to discriminate greatly between actinides and lanthanides showing only a slight preference for the heavier lanthanides. In contrast, it has previously been shown, with non-particulate systems [10,11], that incorporation onto a calix[4]arene allows differentiation between the actinides and lanthanides based on their cationic radii; the actinides and lighter lanthanides with larger radii being extracted more efficiently. The ease of separation of magnetic particles from the waste stream using magnetic fluidised bed techniques makes this system more attractive for future industrial development.

6. Conclusion

Nano- and microparticles have a high potential for the selective binding of metal ions on their surface. Thus the particles can be applied in different fields by variation of the particle matrix, the particle size and chelators, which are covalently bound on the particle surface. Beside the established particle use in the life sciences and chemistry the special application of magnetic nano- and microparticles increases for the removal of heavy metal ions and radionuclides from wastewater.
REFERENCES


