

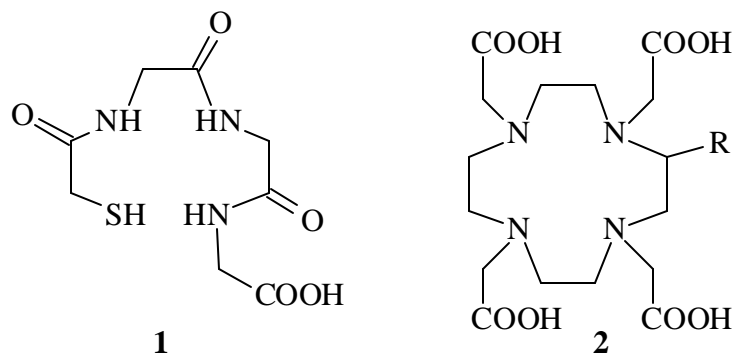
NOVEL CHELATOR CONTAINING PARTICLES SPECIFIC FOR CONTROLLED RADIOISOTOPE DELIVERY

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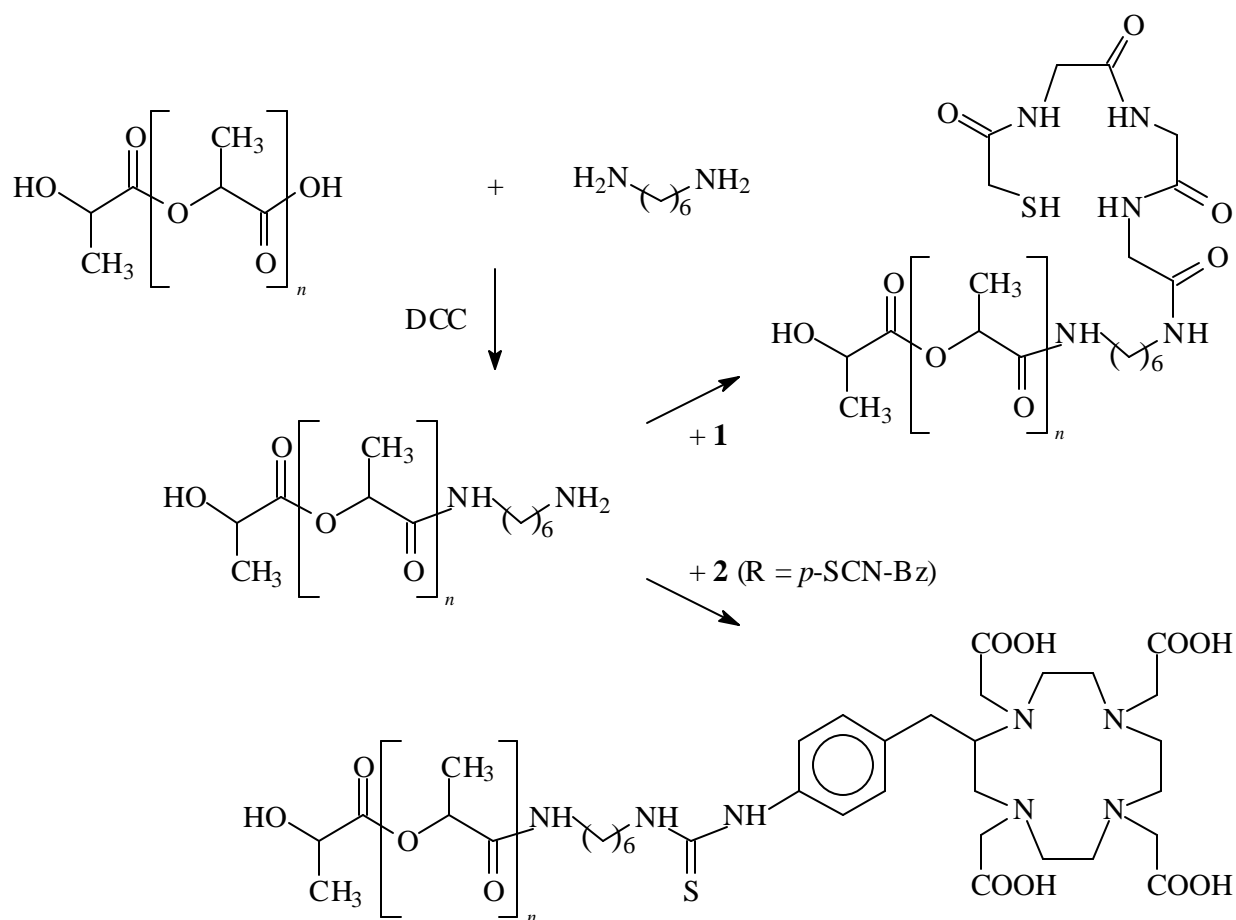
Polymeric polyesters such as the polylactides are well-suited for use as radiopharmaceuticals since they are biocompatible, non-toxic, and biodegrade in a controlled manner, according to their molecular weight and structure (1). They can be formed into nanospheres, microspheres, magnetic microspheres, polymeric sheets, and even into a gel that solidifies on contact with tissue (2). We synthesized new chelator-containing derivatives of poly(lactic acid) which have very similar physical properties to the unaltered polymer. Thus microspheres, capable of binding diagnostic and therapeutic radioisotopes in a fast and reliable fashion with high binding stability, can be formed out of these modified polylactides. Immediate applications for these microspheres radiolabeled with ^{99m}Tc or ¹¹¹In are in diagnostic imaging. They can also be used as carriers of therapeutic radioisotopes, such as ¹⁸⁶Re, ¹⁸⁸Re, ⁹⁰Y, ¹⁶⁵Dy, ¹⁵³Sm, and ¹⁶⁶Ho to treat small amounts of residual solid tumor after maximal surgery of, for example, pancreatic carcinomas and glioblastomas.



Scheme 1. Chemical structures of mercaptoacetyltriglycine (MAG₃) **1** and 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) **2**

A well-known chelator for the complexation of technetium and rhenium is mercaptoacetyltriglycine (MAG₃, **1** in Scheme 1). It has been extensively used in radioimmunotherapy where it is bound to antibodies and then labeled with ¹⁸⁶Re (3). 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) derivatives (**2** in Scheme 1) are able to bind In and Y with very high affinity constants (4), even *in vivo* (5). The introduction of a reactive spacer (R) in the backbone of the DOTA allows for protein conjugation via mercapto groups (6). Changing the reactive group R into an isothiocyanate allows for the coupling to a polymer via aliphatic amine groups. To avoid leakage of radioactivity from the poly(lactic acid) microspheres, it is necessary to covalently bind the respective chelator to the matrix material. For this purpose, poly(lactic acid) (PLA) was modified by reacting its carboxyl group with an amine group of a diamine (carbodiimide activation), yielding a functionalized amide (scheme

2). The carboxylic acid group of MAG₃ was activated with carbodiimide, immediately followed by coupling to the modified polymer. The backbone modified *p*-isothiocyanato-benzyl-DOTA was easily reacted with the amine group of the modified poly(lactic acid) (Scheme 2).



Scheme 2. Amine functionalization of PLA and coupling of MAG₃ and DOTA.

Chelator-modified polylactide microspheres were then prepared by a solvent evaporation method and the size distribution determined by Coulter[®] counter measurements. The microspheres had a diameter of about 2 μm .

Different conditions for the radiolabeling of the chelator containing microspheres with ¹¹¹In, ⁹⁰Y, ^{99m}Tc and ¹⁸⁸Re were investigated. Typical labeling efficiencies and stabilities after incubation at 37 °C are listed in Table 1.

The stability of the magnetic ¹¹¹In-labeled PLA-M-DOTA microspheres is excellent. Both the labeling efficiency and stability are worse in PLA-DOTA microspheres without inclusion of 40% magnetite. A possible mechanism might be the reduction of the radionuclide on the incorporated magnetite resulting in higher and more stable labeling. The conditions for radiolabeling with ⁹⁰Y require further improvements, which is also true for the PLA-MAG₃ microspheres radiolabeled with ^{99m}Tc and ¹⁸⁸Re. The stability of the ^{99m}Tc- and ¹⁸⁸Re-microspheres, however, would be sufficient for local applications, especially since these two radioisotopes are excreted rapidly and cause no myelotoxicity.

Radio-isotope	Microspheres	Conditions	Labeling Efficiency	Stability [^]
¹¹¹ In	PLA-DOTA	Acetate buffer 0.5 M pH 7, 70 °C, 1 h	73%	92%
¹¹¹ In	PLA-M-DOTA	Acetate buffer 0.5 M, pH 7, 50 °C, 1 h	94%	98%
⁹⁰ Y	PLA-DOTA	Acetate buffer 0.5 M pH 7.4, 50 °C, 1 h	50%	N/A
^{99m} Tc	PLA-MAG ₃	Carbonate buffer pH 10.5, SnCl ₂ , 70 °C, 30 min	39%	79%
¹⁸⁸ Re	sicastar [®] -MAG ₃ [*]	Citric / gentisic acid / SnCl ₂ , 99 °C, 1 h	68%	88%

Table 1. Labeling results of chelator containing microspheres. Microspheres with -M- in the name are magnetic. *Preliminary comparative studies were carried out with silica particles (sicastar[®], diameter: 500 nm). ^Stability measured after 24 h incubation in phosphate buffered saline at 37 °C.

Applications for the radiolabeled biodegradable poly(lactic acid) microspheres include their local use for the radioembolization therapy of liver tumors, radiosynovectomy of arthritic joints and local tumor therapy, e.g., brain tumor booster doses. The use of biodegradable materials with biodegradation half-lives between a few days and a few months, depending on the PLA molecular weight used, allows for the reliable delivery of radioactive isotopes, with the matrix microsphere material then degrading and being absorbed in the tissue, leaving no trace of the treatment. The labeling methods are currently being improved such that highly stable radioactive microspheres can be produced in a simple single-step radiolabeling kit. The aim is to radiolabel the chelator-microspheres without additional purification steps.

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