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Synthesis, Characterization and Radiolabeling of Iminodiacetic Acid Derivative with Technetium-99m

Background/goal/objective of the study

This study aimed to synthesize and characterize of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA) and then radiolabel it with technetium-99m by direct technique using sodium didithionite as reducing agent. The labeling parameters including TMIDA concentration, sodium didithionite concentration, pH of the reaction mixture, reaction temperature and reaction time were optimized.

Methodology

Synthesis

N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA) was prepared in two steps. The first one involves the synthesis of ω-chloro-2,4,6-trimethylacetanilide and the second step involves the synthesis of TMIDA by reaction of ω-chloro-2,4,6-trimethylacetanilide (10 mmol) and iminodiacetic acid (10 mmol) in 50% aqueous ethanol was refluxed for 5 h at 85℃ and adjusted to pH 11-12 with 10% NaOH every hour. The mixture was cooled to room temperature and the ethanol was removed using rotary evaporated. The mixture was extracted three times with diethyl ether. The aqueous layer was then adjusted to pH 2-3 with HCl and the precipitate was formed on cooling. The pecipitate was filtered off, dried and recrystallized with ethanol to give TMIDA (Yield: 23.5 % and Mp: 218-221 ℃).

Labeling procedure study

TMIDA was labeled with technetium-99m by the direct technique using sodium dithionite ($Na_2S_2O_4$) as a reducing agent as shown in scheme 2. To 100 µl of freshly eluted $^{99m}TcO_4^-$ (400 MBq), the required concentration of solid sodium dithionite was added directly with continuous stirring followed by immediate addition of the required TMIDA concentration, which dissolved in 0.1 M NaOH. The pH of the preparation was adjusted followed by incubation at room temperature at specific reaction time. TMIDA concentration, $Na_2S_2O_4$ concentration pH, reaction time and temperature were studied as factors affecting labeling efficiency. Each factor studying experiment was repeated three times.

Results and discussion

Synthesis of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA)

Synthesis of TMIDA was accomplished according to the reaction sequence in two steps. The first one involves the reaction between 2,4,6-trimethylaniline derivative and chloroacetyl chloride to give ω-chloro-2,4,6-trimethylacetanilide.

The second step involves condensation reaction between ω-chloro-2,4,6-trimethylacetanilide and iminodiacetic acid at alkaline pH in ethanol for 5 h to give TMIDA.

Characterization of TMIDA

The synthesized compound, TMIDA, was confirmed by IR, mass and 1H-NMR spectra

Figure 1: enter image description here

IR spectrum of TMIDA

Radiolabeling of TMIDA

Factors affecting the percent radiochemical yield of ^{99m}Tc–TMIDA complex

Figure 2: enter image description here

Biodistribution of 99mTc–TMIDA complex
Table 1. In-vivo biodistribution study of 99mTc-TMIDA complex in mice at different time intervals p.i., (% ID/g organ ± S.E., n = 3)

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Conclusion
TMIDA can be synthesized and radiolabeled using an easy and cheap method, considering the biodistribution data results, 99mTc-TMIDA can be used as a hepatobiliary imaging agent for an evaluation of the functional status of the hepatocytes and the patency of the biliary duct.

Primary authors: Prof. A. MOTALEB, Mohamed (Atomic Energy Authority); Prof. EL-TAWOOSY, Mahmoud (AEA); Mr HAMOUDA, Walid (Atomic Energy Authority); Prof. ABDALLAH, Mohamed (Zagazig University, Egypt); Prof. HASSAN, Abdallah (Zagazig University, Egypt)

Presenter: Mr HAMOUDA, Walid (Atomic Energy Authority)

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