DOUBLE LABELLED ^{99}TC/^{14}C[HIDA] RADIOPHARMACEUTICAL FOR PROTEIN BINDING STUDIES

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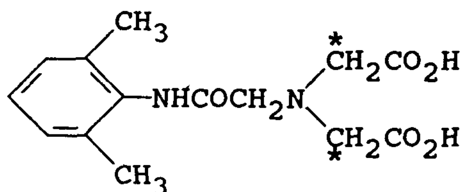
^{99m}Tc-labelled radiopharmaceuticals for γ-scintigraphy are in widespread clinical use for organ imaging. In the majority of studies on the biodistribution of these complexes, it has been assumed that the complex remains intact, and only ^{99m}Tc-activity is measured. Consequently there is little information on the metabolic fate and protein-binding of the intact complex, and on whether dissociation occurs. Initially we sythesised ^{14}C-labelled N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid (HIDA) to prepare the doubly labelled complex- ^{99}Tc/^{14}C[HIDA].



HIDA

During the course of this work it was observed that neither the melting point of the synthesised nor that of the commercial HIDA was always in agreement with reported values (Callery et al 1976; Graham et al 1982). Elemental analysis of all the HIDA samples was however consistent with the molecular formula $C_{14}H_{18}N_2O_5$. Interestingly, differential thermal analysis (DTA) of synthesised and commercial HIDA samples sometimes showed two peaks, one at 182°-192°C and the other at 213°-218°C. Other samples had one peak at 213°-218°C. It was possible to eliminate the first peak by pre-heating the sample to about 196°C. Although this treatment altered the DTA properties, there was no chemical modification of the sample due to heating since elemental analysis and spectral analysis (mass spectrometry and NMR spectroscopy) indicated no structural change. Pre-heating the sample did however induce significant changes in the infra-red spectrum both in the 'fundamental' and 'fingerprint' regions. The existence of two HIDA polymorphs would account for these observations, each having different crystal structures due to possible differences in their intra- and inter-molecular hydrogen-bonding.

Singly (^{99}Tc/HIDA) and doubly (^{99}Tc/^{14}C[HIDA]) radiolabelled complexes were prepared for protein binding studies by reducing a solution of ammonium pertechnetate ($^{99}TcO_4^-$) with $SnCl_2$ to which was added either HIDA or ^{14}C[HIDA]. Radiochemical purity of the complexes was confirmed by TLC. Whilst both complexes were weakly bound (ca 25%) to bovine serum albumin (1x10^{-4}M) and negligible binding was observed for $^{99}TcO_4^-$ and HIDA, the other common impurity in ^{99}Tc-radiopharmaceuticals, ^{99}Tc-reduced-hydrolysed was strongly bound (95%). Similar protein-binding results have been obtained for singly and doubly radiolabelled DTPA complexes.

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Callery, P.S. et al (1976). J. Med. Chem 19: 962-964
Graham, B.W. et al (1982). J. Pharm. Sci. 71: 362-364