Summary of the original work

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Radiopharmaceuticals are preparations of adequately constant composition, radiochemical and radionuclidic purity and uniformity of physiological action for use in nuclear medicine as diagnostic agents or therapeutic agents. Nearly about 80% of all radiopharmaceuticals used in nuclear medicine are ^{99m}Tc – labelled compounds. The reason for such a permanent position of the technetium –99m in clinic use is its extremely favorable physical and radiation characteristics. The six hours physical half-life and the absence of beta particles permit the administration of millcurie amounts of ^{99m}Tc- radioactivity without significant radiation dose to the patient. In addition the monochromatic 140 KeV photons are readily collimated to give images of superior spatial resolution. Technetium–99m is readily available in a sterile, pyrogen free state from ^{99m} Mo- ^{99m}Tc generator.

The goal of this study is the organic synthesis of two iminodiacetic acid derivatives and their labelling with technetium–99m. The factors affecting the labelling yield were studied and the labelled complexes were evaluated radiochemically and biologically.

This thesis is divided into three chapters. Chapter one, includes the general introduction. Chapter two includes the organic synthesis of two iminodiacetic acid (IDA) derivatives and the characterization of the synthesized compounds, besides the labelling of the three IDA derivatives with technetium-99m and their biological distribution. Chapter three includes the experimental part

The results obtained from this study can be summarized as follows:

Chapter I

General introduction

This chapter includes detailed discussion about nuclear medicine and radioactivity,chemistry of technetium, nuclear and radiochemistry of technetium, source of technetium-99m, ^{99m}Tc–radiopharmaceuticals, groups of ^{99m}Tc–radiopharmaceuticals, kit preparation and quality control of radiopharmaceuticals.

Chapter II

Results and Discussion

Several iminodiacetic acid derivatives had gained much popularity in the recent years as an important class of ligands for technetium –99m labelling to be used as hepatobiliary imaging agents . A number of studies have been performed to evaluate their chemical properties and also to improve their biological characterization.Because IDA derivatives are not available commercially , it is necessary to synthesize them in our laboratory . The following IDA derivatives were synthesized:

1) 2-N,N (dicarboxyaminoacetyl) aminopyridine (DCAA-AP)

2) 2-N,N (dicarboxyaminoacetyl) aminothiazole .(DCAA-AT)

The structure of the synthesized compounds was confirmed using analytical techniques (Elemental Analysis, IR, NMR and Mass spectroscopy).

Technetium-99m iminodiacetic acid derivatives were found to be better suited for hepatobiliary tract studies. These complexes are taken up by the polygonal cells of the liver and cleared rapidly through the biliary system. To elucidate the reaction route and to determine the optimum conditions to produce high radiochemical yield, high purity and stability of ^{99m}Tc - IDA derivatives, the effect of many parameters were studied.

IDA-derivatives were labelled with technetium-99m using the direct technique, in which the chelate reacts with the reduced technetium-99m. The percent labelling yield for the ^{99m}Tc - DCAA-AP , ^{99m}Tc - DCAA-AT and ^{99m}Tc - Br-IDA were found equal 93.18% , 91.2 % and 97.81 % respectively.The optimum ligand amounts which were found sufficient to produce a high radiochemical yield for ^{99m}Tc - DCAA-AP , ^{99m}Tc - DCAA-AT and ^{99m}Tc - Br-IDA were equal to 10, 10 and 40 mg respectively using a minimum amount of stannous chloride required for the complete reduction of pertechnetate .The amount of stannous chloride used is 0.1, 0.1 and 0.3 mg respectively. Another important factor affecting the radio labelling yields of DCAA-AP , DCAA-AT and Br-IDA with technetium-99m is the pH of the reaction medium . The optimum radiochemical yields were obtained at pH 3, 2.8 and 7 respectively. When the pH value was increased towards the alkaline side up to 8, the degree of complex formation decreased and the reduced technetium was complexed by OH^- leading to the formation of reduced hydrolyzed ^{99m}Tc (RH-^{99m}Tc) in concentrations equal to 59.78%, 56.81% and 45.79 % for DCAA-AP , DCAA-AT and Br-IDA respectively.

Increase in the temperature is one of the important factors affecting the percent labelling yield where elevation in the temperature from 25 – 50 °c increases the percent labelling yield from 58.42 % and 52.63 % to 65.23 % and 62.13 % for ^{99m}Tc–DCAA-AP and ^{99m}Tc–DCAA-AT respectively

By increasing the temperature up to 100 °c the percent labelling y increased to a maximum values 93.18 % and 91.20%. The increase in the temperature above 100 °c leads to the decomposition of ^{99m}Tc–DCAA-AP and ^{99m}Tc–DCAA-AT. But ^{99m}Tc-Br-IDA was not affected by increasing the temperature.

The radiochemical purity of the labelled IDA derivatives was determined using thin layer–silica gel chromatography (TLC-SG) as the stationary phase with acetonitrile :H_2O (3:1) or acetone as mobile phase .This system was found suitable for the separation of the reaction species quickly and with a high efficiency . Also, ^{99m}Tc – IDA complexes were found stable all over the period sufficient for their clinical uses, 8 hours, without formation of breakdown species.

The biodistribution properties of the formulated IDA derivatives after labelling with technetium-99m were evaluated in mice .The results showed that all IDA derivatives were cleared by the hepatiliary pathway with a varying degree of renal excretion and liver retention. ^{99m}Tc – DCAA-AP complex showed high liver uptake equals to 26.1 % after 5 min post injection which is very high compared to the commercially used Br-IDA (13.20 %). Also, a very short hepatobiliary transport time was observed with ^{99m}Tc – DCAA-AP as shown from the accumulation of the activity in the intestine which is equal to 32.59 % of the injected dose after 60 min from injection. In opposite to ^{99m}Tc -DCAA-AP, ^{99m}Tc - DCAA-AT complex was found to be excreted in the urine with a high rate equals to 50.47 % of the injected dose after 3 hours post injection. Also ^{99m}Tc-DCAA-AT complex showed low liver uptake equals to 16.2 % of the injected dose after 5 min post injection and increased to 26.69 % after 60 min post injection.

The activity in the urine in case of ^{99m}Tc-DCAA-AT was found smaller than in the case of ^{99m}Tc-DCAA-AP after 3 hours post injection.

Chapter III

Experimental

This chapter contains detailed information concerning the chemicals, the solvents, the equipments, the synthesis of IDA-derivatives, and the labelling of IDA derivatives which includes the kit preparation, the factors affecting the labelling yield of ^{99m}Tc–IDA and the determination of the radiochemical purity by using TLC-SG and ITL-SG