In-vivo study of self-assembled glycol chitosan nano-radiopharmaceutical for liver imaging

98

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Purpose:

To develop biocompatible and stable radiolabeled polymeric nanoparticles that are taken-up by the liver and to explore their utility as a liver imaging agent by studying their biodistribution and pharmacokinetic parameters

Methods:

Modified glycol chitosan nanoparticles (GCPQ NP) were formulated using a probe sonicator. GCPQ NP's were radiolabeled using stannous chloride as reducing agent, Fig. 1.

In-vitro stability studies were carried out for the prepared radiopharmaceutical (^{99m}Tc GCPQ NP) in normal saline and human serum for up to 6 hrs. Variation in the size, zeta potential and labeling efficiency were determined.

For bio-distribution studies five rabbits were injected with labeled GCPQ NP at a dose of 80 MBq/5mg/ml/kg through marginal ear vein. Dynamic anterior and posterior images of whole body were acquired for 35 minutes using 165 frames followed by 1500 k-count spot views of the whole body at 0.5, 1, 2, 3, 4 and 24 hours. Kinetic modeling was performed using 2-Tissue compartmental analysis (2T model) and Logan graphical analysis to estimate the volume of distribution (VT) in liver, where atrial input function was image derived (ROI in left ventricle).

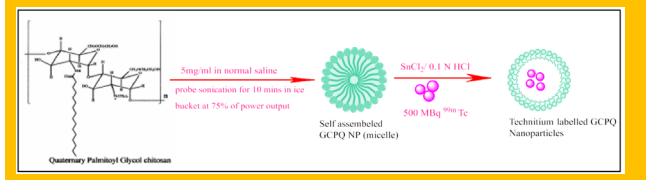

Fig 1: Schematic illustration of the formation of micelles by probe sonication of GCPQ and subsequent radio-labelling with technetium-99m using stannous-chloride based reduction method.

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RESULTS

Preparation and optimization of formulation

GCPQ NP and ^{99m}Tc GCPQ NP prepared by probe sonication have mean diameters of 60.0 nm and 65.0 nm respectively, Table 1. Radio-labeling yield of GCPQ NP with ^{99m}Tc was more than 99 %, as determined by ITLC-SG strips, Fig 2.

	DLS (nm)	PDI
GCPQ NP	60.00nm	0.361
Tc 99-m GCPQ NP	65.00 nm	0.231

Table 1 DLS data for the self-assembled GCPQ nanoparticles and technetium labelled GCPQ nanoparticles

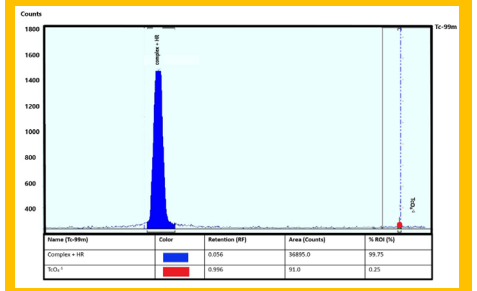

Fig 2. Chromatogram of radiochemical analysis showing labeling efficiency of Tc^{99m} GCPQ NP; ITLC-SG Chromatogram of Tc^{99m} GCPQ NP at R.F = 0 and Free TcO_4^{-1} at Rf= 1

Invitro stability study

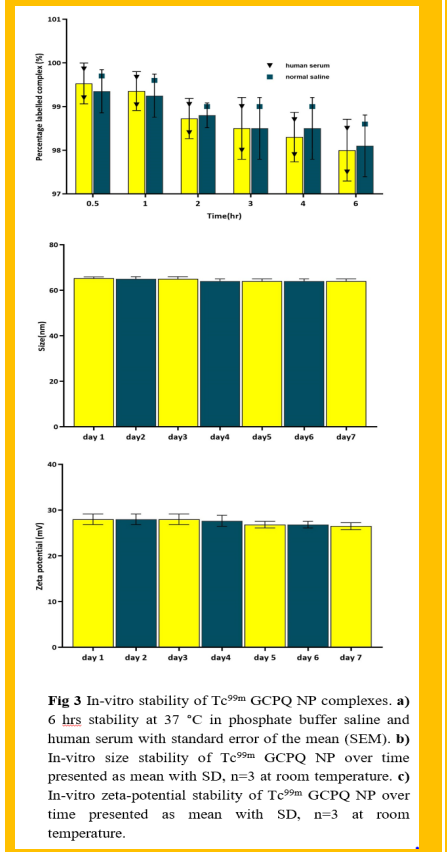

Fig 3 In-vitro stability of Tc^{99m} GCPQ NP complexes. **a)** 6 hrs stability at 37 °C in phosphate buffer saline and human serum with standard error of the mean (SEM). **b)** In-vitro size stability of Tc^{99m} GCPQ NP over time presented as mean with SD, n=3 at room temperature. **c)** In-vitro zeta-potential stability of Tc^{99m} GCPQ NP over time presented as mean with SD, n=3 at room temperature.

In vivo Imaging and biodistribution study

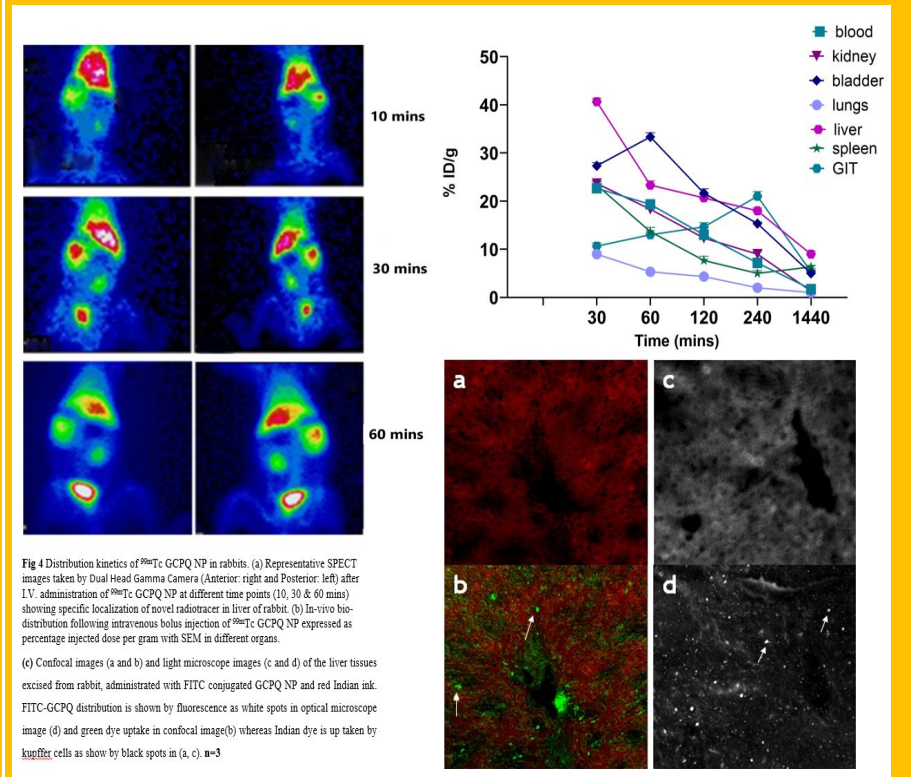

Fig 4 Distribution kinetics of ^{99m}Tc GCPQ NP in rabbits. (a) Representative SPECT images taken by Dual Head Gamma Camera (Anterior: right and Posterior: left) after I.V. administration of ^{99m}Tc GCPQ NP at different time points (10, 30 & 60 mins) showing specific localization of novel radiotracer in liver of rabbit. (b) In-vivo bio-distribution following intravenous bolus injection of ^{99m}Tc GCPQ NP expressed as percentage injected dose per gram with SEM in different organs.

(c) Confocal images (a and b) and light microscope images (c and d) of the liver tissues excised from rabbit, administrated with FITC conjugated GCPQ NP and red Indian ink. FITC-GCPQ distribution is shown by fluorescence as white spots in optical microscope image (d) and green dye uptake in confocal image(b) whereas Indian dye is up taken by kupffer cells as show by black spots in (a, c). n=3

Conclusion: The prepared radionuclide ^{99m}Tc GCPQ NP showed very good characteristics in terms of ease of preparation, high labelling yield, high in-vitro/in-vivo stability and optimum biodistribution