Comparative study of ^{68}Ga-NOTA-radiolabelling in water, citrate and HEPES-buffer as reaction media

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Introduction: The radiosynthesis of ^{68}Ga-labelled NOTA complexes is strongly dependent on the pH-value of the reaction medium. The final pH-value obtained from ion-exchanger purified n.c.a. ^{68}Ga thus is strongly dependent on the volume of the N2-solution [1] For this reason, a buffer system, capable of tolerating different amounts of ion-exchanger purified ^{68}Ga solution without affecting the radiochemical yield would be beneficial for optimisation studies. In the present study, the adequacy of citrate and HEPES-buffer as reaction media is examined.

Materials and Methods: A 1 mg/ml stock solution of NOTA was prepared in Millipore water. This solution was used in all experiments. Experiments were carried out adding the 400 µ*l* elution from the generator to 5 *mL* of reaction buffer (pH=3,7) or water. After preheating the sample for 10 minutes, a defined volume of NOTA stock solution was added subsequently. The volumes used were 1, 5 and 20 µ*l* at 60 °C of temperature. Samples were taken at 1, 2 5 10 minutes of reaction, placed on a silica TLC and run in two different solvents: NaCl 5% and Citrate buffer (pH=4). Every experiment was made triplicate.

Results and Discussion: Labeling yields are very variable in water and HEPES (up to 30 % variability). It is supposed that the NOTA labeling should go well in HEPES buffer because it has the right labeling pH value and it is used commonly to chelate DOTA and DOTA-X pharmaceuticals. Nevertheless, at this reaction temperature it seams like the HEPES buffer interfere in the labeling reaction depending on the heating time. It was found, that HEPES buffer forms a complex with ^{68}Ga. Although it is a slow reaction, the vessels in the previous experiments were prepared with HEPES + ^{68}Ga and then preheated for 10 minutes before adding NOTA. It is important also to consider concentrations, HEPES is very concentrated while NOTA is only a few *µg*. The 0.5 *mL* HEPES system shows better results, but once the elution is added to the solution pH goes to 2.22. This is not the right labeling pH, so the decision was continue with HEPES buffer to obtain the complete data labeling for NOTA in 60 and 75 °C using 1, 5 and 20 *µg* of NOTA but changing experiments a little bit to reduce HEPES effect.

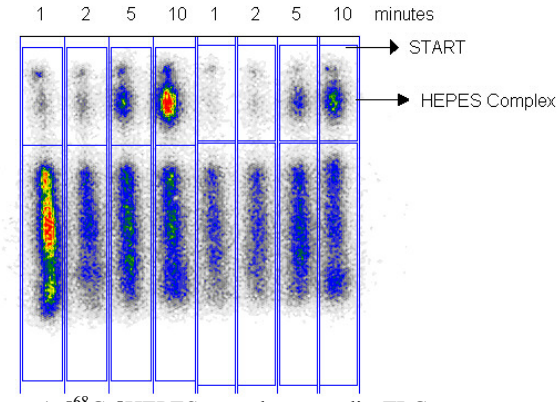

Figure 1: [^{68}Ga]HEPES-complex on radio-TLC

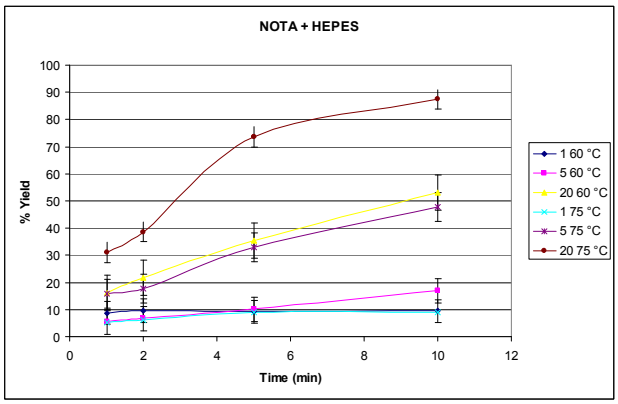

Figure 2: Data set for NOTA chelating in HEPES buffer at 60 and 75 °C for 1, 5 and 20 NOTA *µg*

Better results are achieved with these experiments up to 90 % labeling using 20 *µg* at 75 °C temperature. Nevertheless are lower that those reported for the NOTA + water system.

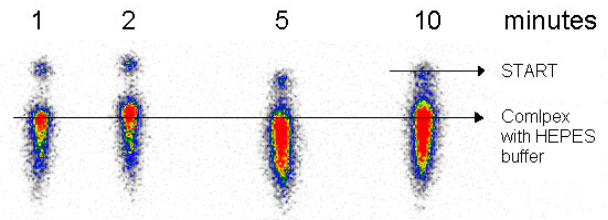

Figure 3. HEPES buffer interference for 1 *µg* NOTA at 60 °C in NaCl 5%

Conclusion: Even when precautions are taken to reduce the HEPES influence, its concentration in solution is very large and competes with NOTA in the labeling process. It is important so say that its influence can only be demonstrate using the NaCl 5% chamber.

References:

[1] Zhernosekov, K.P. , Rösch, F. et al. J Nucl Med., 48(10): 1741-8, 2007