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APPLICATION OF ASCORBIC ACID AS A RADIOLYTIC STABILIZER FOR [^{131}I]mIBG

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Abstract
In this paper the results of a stability of [^{131}I]mIBG, stored under various conditions, are presented. The stability was followed during 14 days. The most important radiochemical impurity in [^{131}I]mIBG is free [^{131}I]iodide, formed by radiolysis. The results indicate that the rate of radiolytic decomposition of [^{131}I]mIBG is much slower at higher concentration of ascorbic acid (20 mg/mCi) and at lower storage temperature (4^{0}C).

Introduction
Meta-iodobenzylguanidine (mIBG) is an analogue of the adrenergic neuron blocking guanethidine. mIBG labeled with iodine-131 is intensively used radiopharmaceutical in diagnostic scintigraphy and radionuclide therapy of neural crest derived tumors such as neuroblastoma, malignant pheochromocytoma and paraganglioma [1]. [^{131}I]mIBG undergoes radiolytic decomposition over time, resulting in the release of free [^{131}I]iodide which after intravenous application accumulates mainly in the thyroid, causing unnecessary radiation damage. Moreover, only bound radioactivity in the form of [^{131}I]mIBG will reach the targeted tumors [2]. As radiolabeled compound should stay unchanged for a period up to 2 weeks, the amount of free [^{131}I]iodide in the pharmaceutical preparation of [^{131}I]mIBG has to be reduced. In order to limit the formation of free [^{131}I]iodide, some producers keep [^{131}I]mIBG at -40°C or in lyophilized form that is inconvenient for transport and application in nuclear medicine departments. Therefore, addition of stabilizing agents such as ascorbic acid in the final kit preparation could solve the problems related to the relative instability of [^{131}I]mIBG at room temperature.

Purpose of this experiment was to investigate the effects of temperature and amount of stabilizer on the radiopharmaceutical stability of [^{131}I]mIBG.

Experimental
mIBG was synthesized according to a slightly modified version of Wieland et al [3] in the Laboratory for radioisotopes of the Vinča Institute.

The radiolabelling procedure of mIBG involved isotopic exchange reaction (160 ^{0}C, 45 min) catalyzed by Cu(I) generated *in situ* by addition of $Na_2S_2O_5$ to $CuSO_4$ [4]. Purification of radiolabelled mIBG from the excess of unbounded iodine-131 was performed by column chromatography (DEAE cellulose). To

ascertain the effect of temperature and the quantity of stabilizer on the stability of [^{131}I]mIBG, three samples of purified radiopharmaceutical were formulated with 5mg, 10mg and 20 mg of ascorbic acid per 1mCi of [^{131}I]mIBG. The stability was followed by investigation of the radiochemical purity of [^{131}I]mIBG at 22^{0}C, 15^{0}C and 4^{0}C during 14 days. Radiochemical purity of [^{131}I]mIBG was determined by thin layer chromatography (TLC) on silica gel (Merck) using the mixture of ethyl acetate and ethanol as the mobile phase. The most important radiochemical impurity in the form of free [^{131}I]iodide migrates with the solvent front (Rf=0.9-1.0), while [^{131}I]mIBG remains at the origin. The radioactivity distribution was obtained by measuring 1cm long pieces of the strips and the percentage of both fractions were calculated against the total strip radioactivity.

Results and Discussion

It was found that the stability could be affected by both – the amount of stabilizer and temperature. According to Eur.Pharmacopoeia [5] the radiochemical purity of [^{131}I]mIBG in use for nuclear medicine investigation in human, must be at least 95 %. Figure 1 shows the effect of temperature on the stability of [^{131}I]mIBG in the kit formulation with 5 mg/mCi of ascorbic acid.

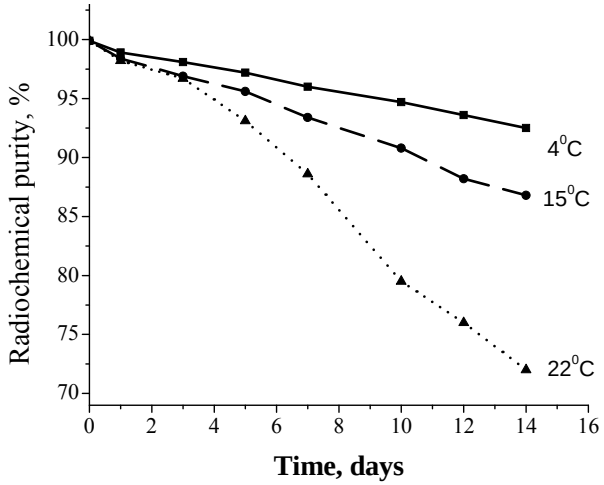

Fig. 1. The effect of temperature on the stability of [^{131}I]mIBG

From this data, it is evident that at 4^{0}C, level of [^{131}I]iodide in [^{131}I]mIBG increases from 0 % to 5 % in 10 days, while if it is stored at 15^{0}C, the [^{131}I]iodide level increased to 5% in 5 days. At room temperature (22^{0}C) the radiochemical purity was decreased 2 % within 24 hours.

The stabilization effect of ascorbic acid on [^{131}I]mIBG at room temperature (22^{0}C) during two weeks (Fig. 2) was observed in the kit formulation with increasing concentration of ascorbic acid. It is evident that radio chemical stability of [^{131}I]mIBG in the kit, at room temperature, increases with increasing concentration of the ascorbic acid.

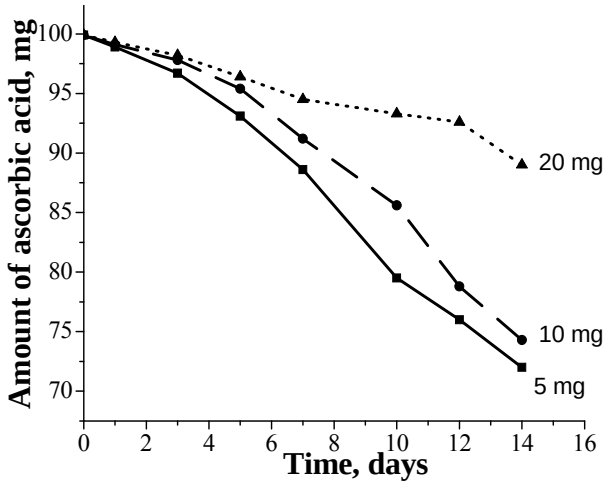

Fig.2. The effect of the concentration of ascorbic acid on the stability of [^{131}I]MIBG

Conclusion

In this study, we explored the factors influencing the stability of [^{131}I]mIBG and found that both temperature and the amount of ascorbic acid have significant impact on the stability of [^{131}I]mIBG. As results in Fig. 1 and Fig. 2 shows, the highest concentration of ascorbic acid (20 mg/mCi) as well as the lowest storage temperature (4^0C) equally affected on the reduction of radiolytic decomposition of [^{131}I]mIBG. Further, [^{131}I]mIBG kit formulation with 20 mg of ascorbic acid per 1mCi, added after labeling, will be prepared since it is particularly simple for further handling in nuclear medicine departments and radiochemically stable for a longer period.

References

[1] T. Yassine, M. A. Bakir, S. Shanan, M. Al-Asaad, J. Radioanal. Nucl. Chem., 2003, **258**, 635-637.

[2] A. R. Wafelman, C.A. Hoefnagel, R. A. A. Maes, J. H. Beijnen, Appl. Radiat. Isot., 1994, **45**, 183-189.

[3] D. M. Wieland, J. L. Wu, L.E. Brown, T. J. Mangner, D. P. Swanson, T. J. Mangwaltes, J. Nucl. Med., 1980, **21**, 349.

[4] N. S. Nikolić, M. D. Mirković, S. D. Vranješ-Đurić, D. D. Đokić, Proceedings Phys. Chem, 2006, 431-436.

[5] Eur. Pharmacopoeia (Third Edition), Council of Europe, Strasbourg, 1997.