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Aluminum- ^{18}F Fluoride Radiolabeling Optimization by Design of Experiments Approach

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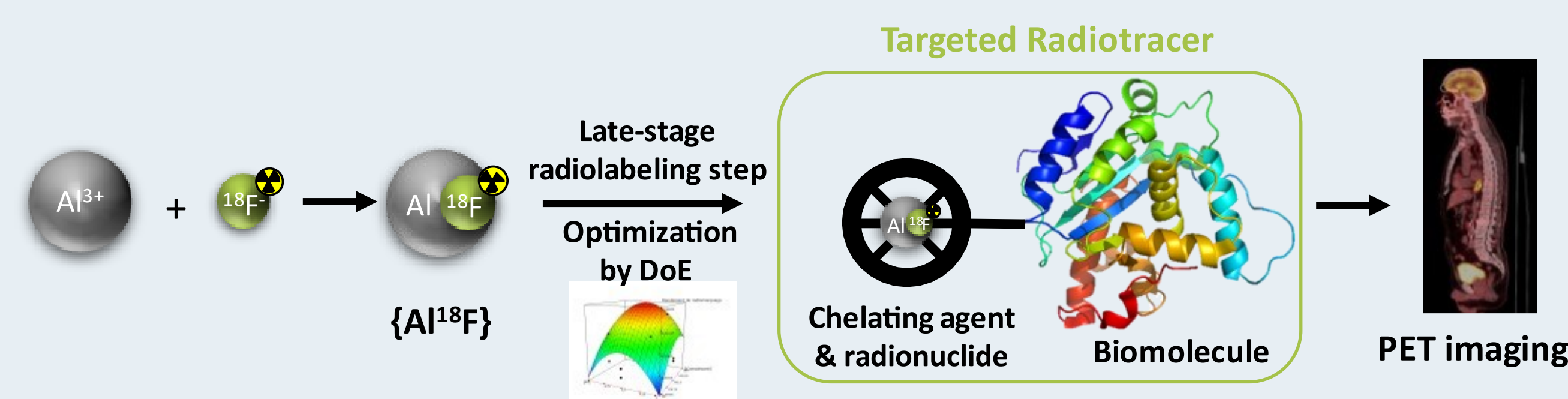
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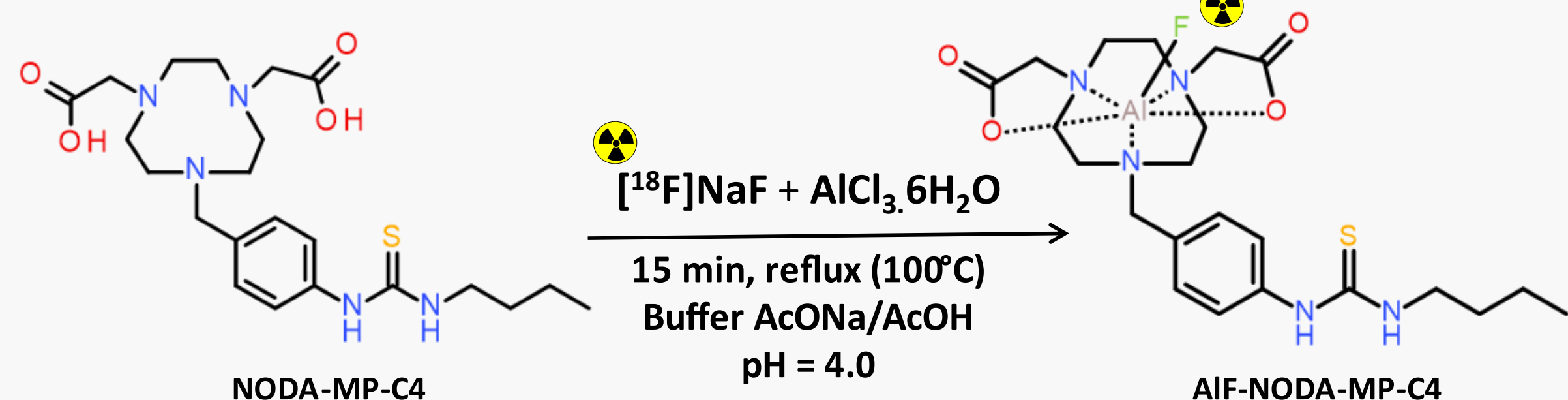
Introduction

Fluorine-18 (^{18}F) is the most favorable positron emitter for tumor imaging. However, direct ^{18}F -labeling of biomolecules is challenging as it involves multiple steps and stringent conditions that are generally not suitable for biomolecules whose integrity may be altered. Over the past decade, an elegant new approach has been developed by coordination of aluminum fluoride $\{\text{Al}^{18}\text{F}\}$ in water medium and at the late stage of synthetic process.

This work presents an optimization of the radiolabeling step by using a Design of Experiments (DoE) approach.



1. Define the objectives



- Optimize the radiolabeling yield
- Minimize the number of experiments and the costs
- Improve the radioprotection of workers

2. Identify the influencing parameters to study*

Parameters	Min	Max
pH	4	5
[NODA-MP-C4]	50	550
NODA-MP-C4/Al ratio	1:1	3:1

Fixed parameters:

- Temperature: reflux
- Duration: 15 min
- Volume: 110 μL
- No organic co-solvent

*Based on literature and our previous work:
 • McBride et al, J. Nucl. Med. 2009, 50 (6), 991–998.
 • Fersing, C. et al, Molecules 2019, 24 (16), 2866.
 • Shetty, D. et al, Bioorg. Med. Chem. 2012, 20 (19), 5941–5947.
 • San, C. et al, 28th Young Research Fellows Meeting; Paris, 2021

3. Plan the DoE and collect experimental data

N°	NODA-MP-C4/Al ratio	[NODA-MP-C4] (μM)	pH	Radiolabeling yield (%)**	
1	1.4:1	156	4.2	26.6	53.8
2	1.4:1	156	4.8	45.2	51.8
3	1.4:1	450	4.2	75.6	74.8
4	1.4:1	450	4.8	75.0	72.3
5	2.6:1	156	4.2	21.8	26.4
6	2.6:1	156	4.8	12.5	19.7
7	2.6:1	450	4.2	30.0	67.9
8	2.6:1	450	4.8	41.7	68.9
9	2:1	303	4.5	70.8	66.7
10	2:1	303	4.5	56.1	62.8
11	2:1	303	4.5	55.8	62.6
12	2:1	303	4.5	70.0	64.4
13	2:1	303	4.5	72.4	59.4
14	2:1	303	4.5	70.5	71.1
15	1:1	303	4.5	70.1	74.7
16	3:1	303	4.5	49.6	60.6
17	2:1	55	4.5	1.7	13.6
18	2:1	550	4.5	63.6	73.9
19	2:1	303	4	15.9	19.7
20	2:1	303	5	18.2	26.7

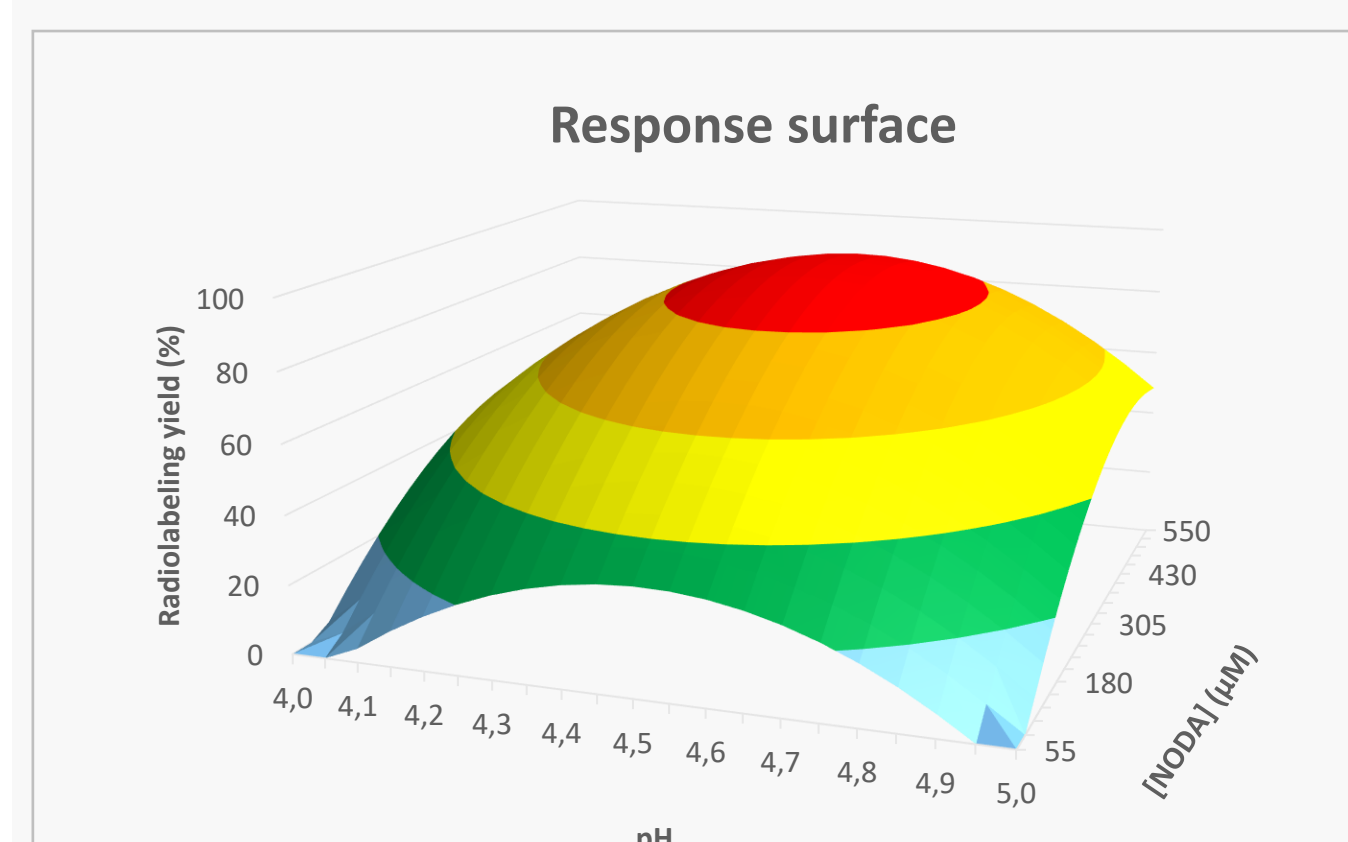
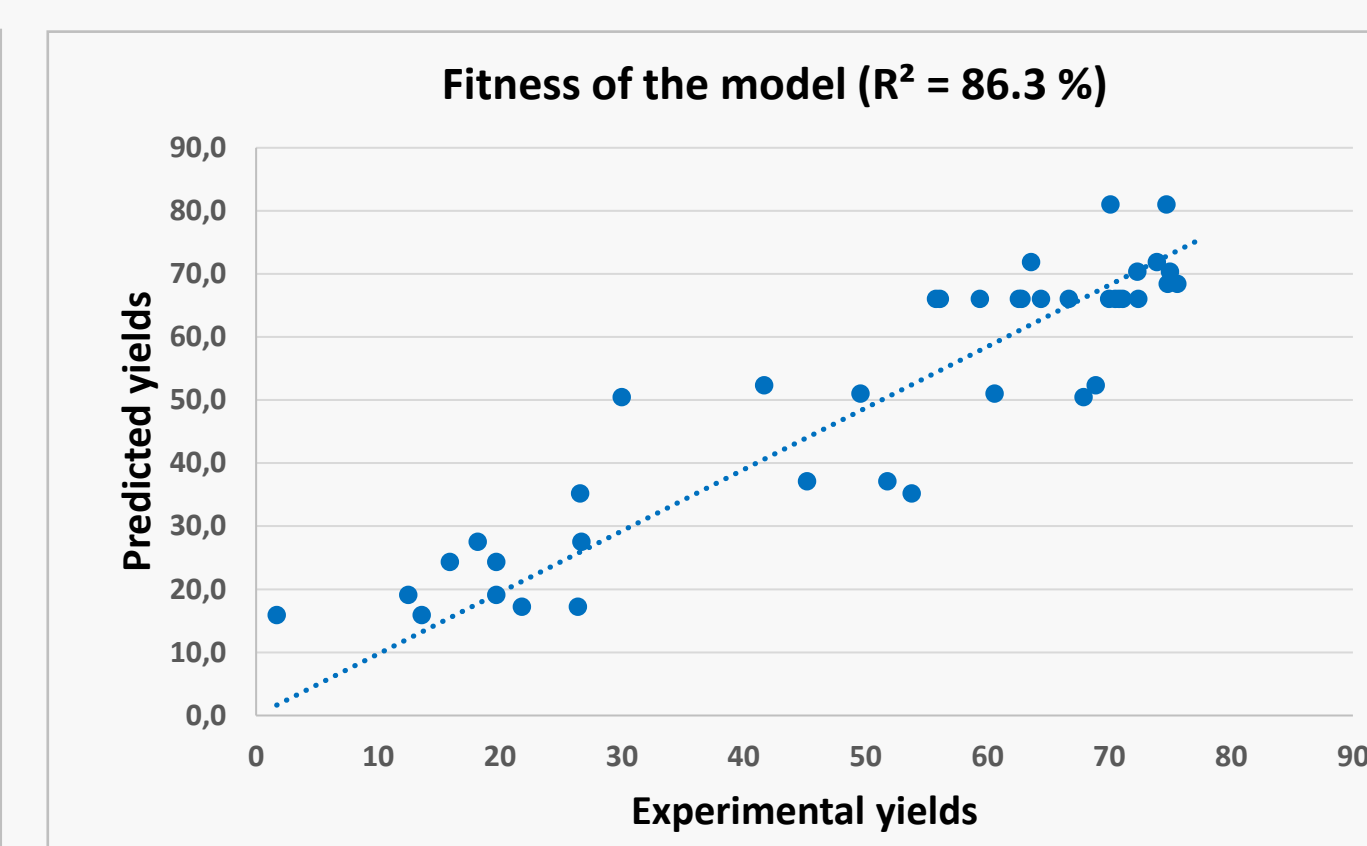
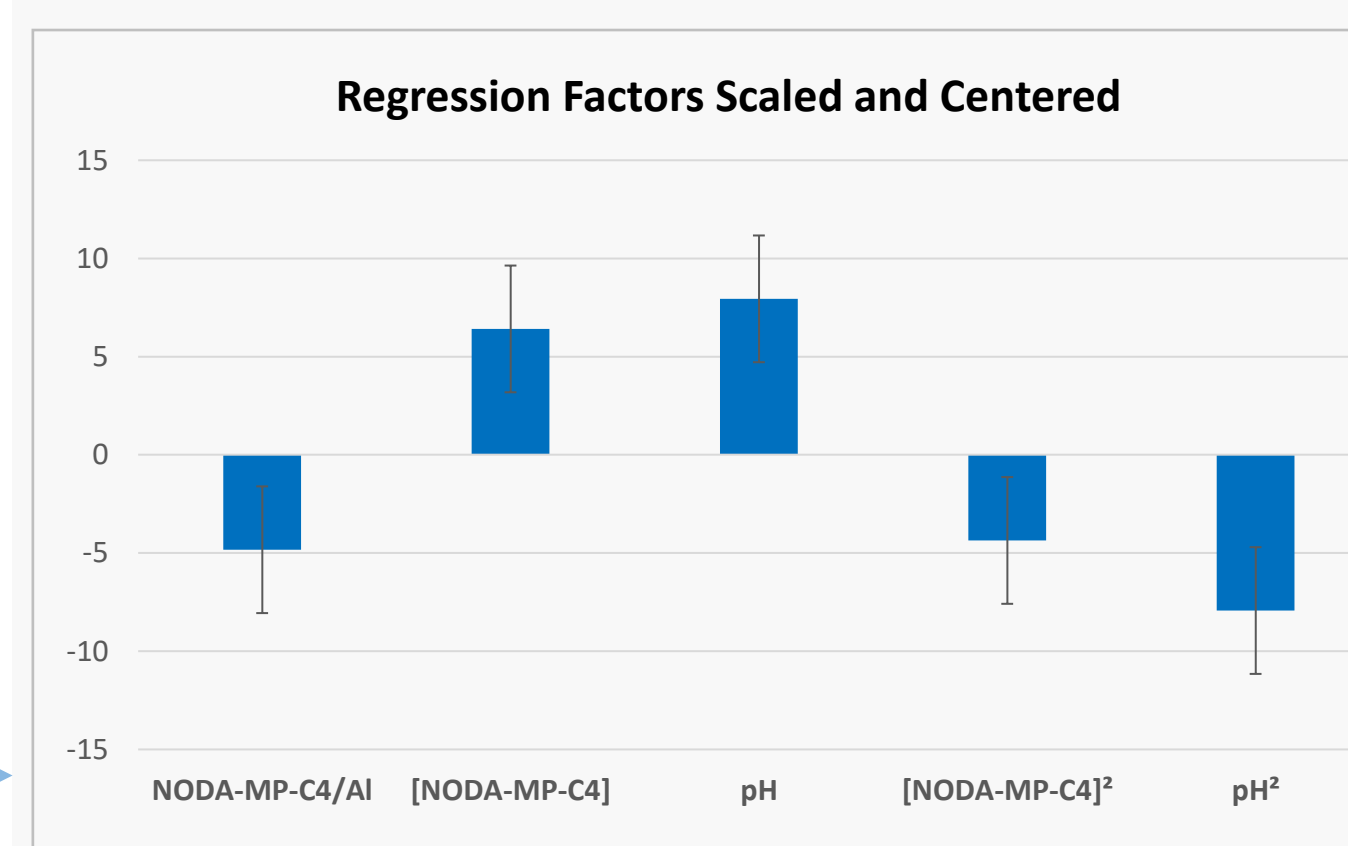
DoE generated with Ellistat software v.6.8

** Determined by radio-HPLC

4. Obtain the model

Radiolabeling yield =

$$-3234 - 14,99 \times \text{NODA-MP-C4/Al} + 0,3316 \times [\text{NODA-MP-C4}] + 1477 \times \text{pH} - 0,0003614 \times [\text{NODA-MP-C4}]^2 - 160,4 \times \text{pH}^2$$



- All the parameters studied have a significant impact on the radiolabeling yield
- No second order interaction is observed but quadratic effect for the following parameters: NODA-MP-C4 concentration and pH
- Good correlation between predicted and observed radiolabeling yields

5. Validate the model: quality of the prediction

1st test : conditions not tested in the DoE

- pH = 4.3
 - [NODA-MP-C4] = 223 μM
 - NODA-MP-C4/Al = 1.8:1
- Radiolabeling yield **predicted** = 51 %
 Radiolabeling yield **obtained** = $62 \pm 5 \%$ (n = 2)

2nd test : optimal conditions

- pH = 4.5
 - [NODA-MP-C4] = 464 μM
 - NODA-MP-C4/Al = 1:1
- Radiolabeling yield **predicted** = 90 %
 Radiolabeling yield **obtained** = $79 \pm 3 \%$ (n = 5)

Conclusion

Optimization was performed in **40 tests** representing **5 days** of experimentation. With the optimized parameters, the radiolabeled complex was obtained with high and reproducible radiolabeling yield ($79 \pm 3 \%$, n = 5).