Optimization of a Synthetic Step Using a Design of Experiments Approach: Application to a Late-Stage Radiolabeling Method by Aluminium-[18F]Fluoride Coordination

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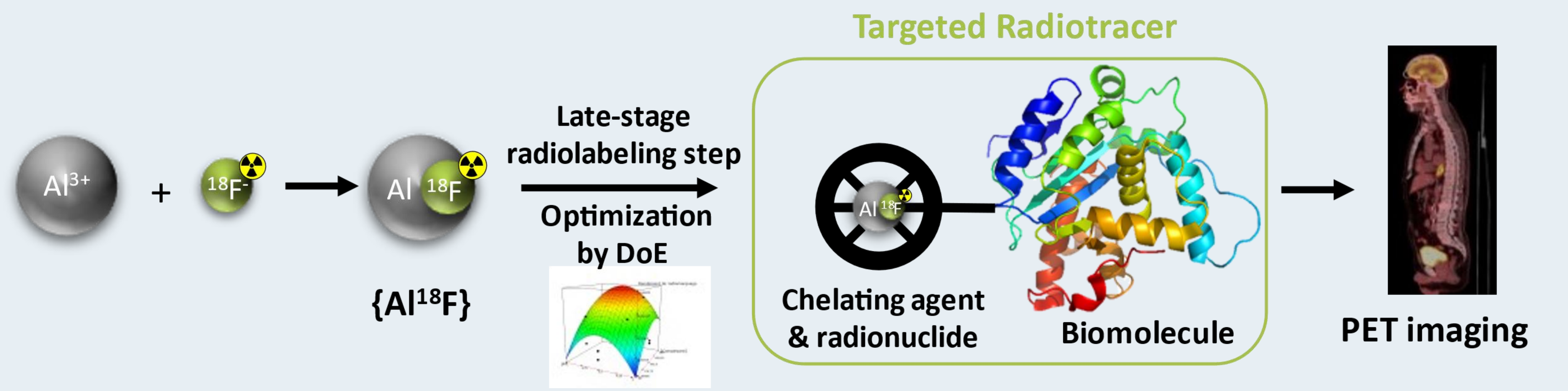
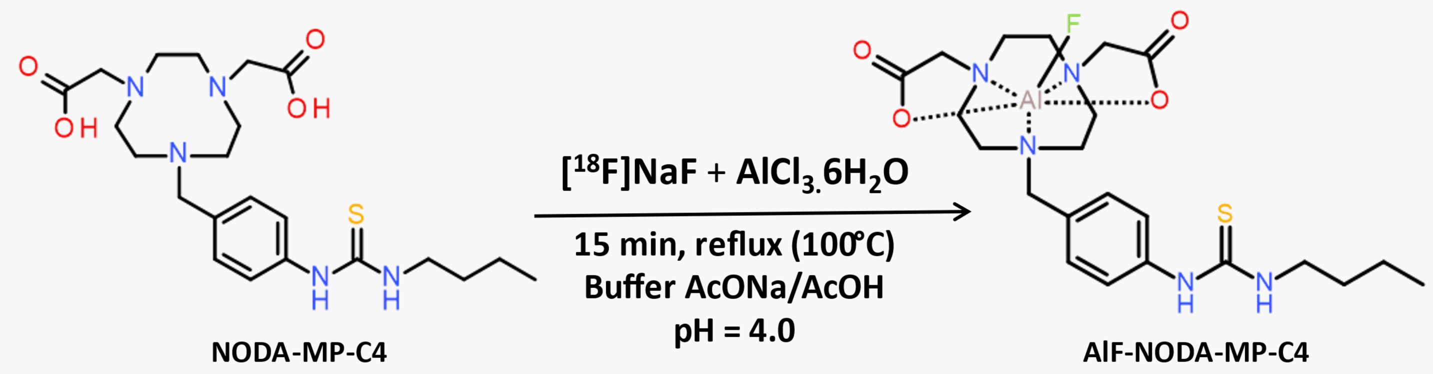
Introduction

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 {Al^{18}F} at 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 worker radioprotection

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 (100°C)
- Duration: 15 min
- Volume: 110 µL
- No 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

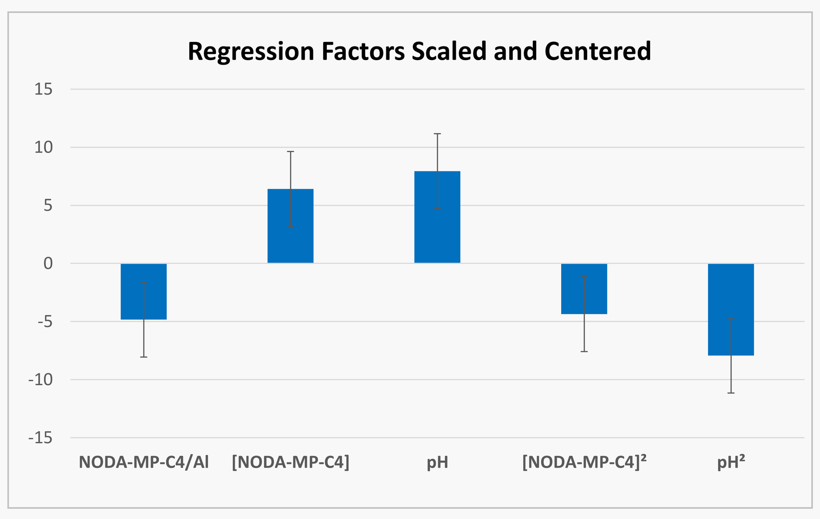
N°	NODA-MP-C4/Al ratio	[NODA-MP-C4] (µM)	pH	Radiolabeling yield (%)**	
1	1.4:1	156	4.2	26.6	53.8
2	1.4:1	156	4.8	45.2	51.8
3	1.4:1	450	4.2	75.6	74.8
4	1.4:1	450	4.8	75.0	72.3
5	2.6:1	156	4.2	21.8	26.4
6	2.6:1	156	4.8	12.5	19.7
7	2.6:1	450	4.2	30.0	67.9
8	2.6:1	450	4.8	41.7	68.9
9	2:1	303	4.5	70.8	66.7
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

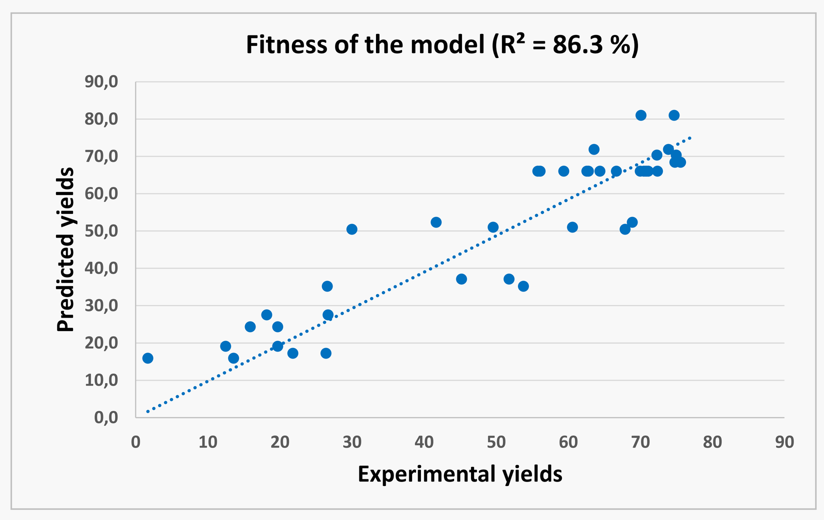
DoE generated with Ellistat software v.6.8

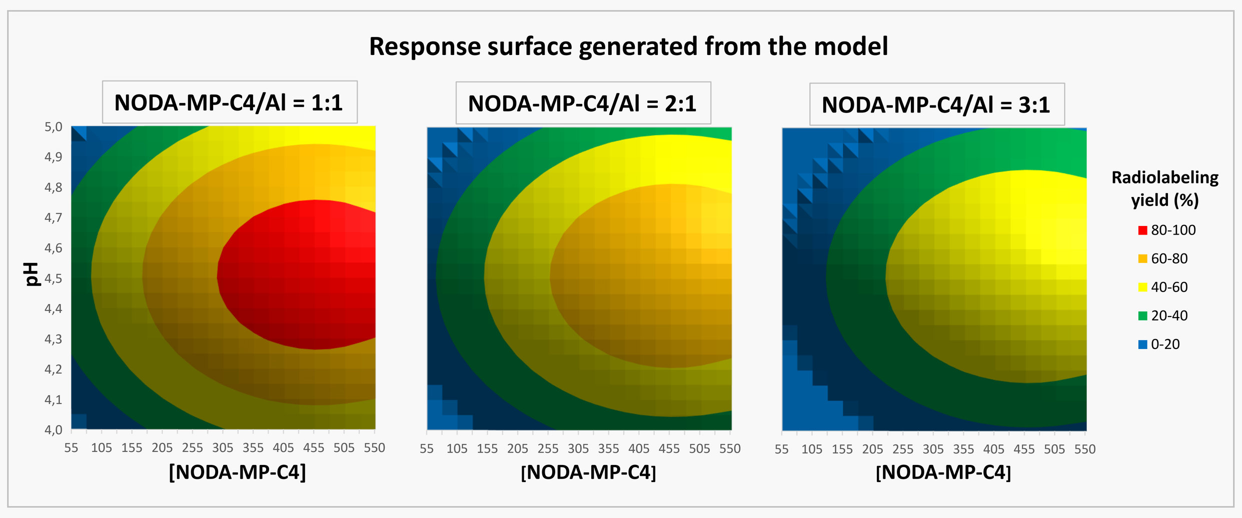
** Determined by radio-HPLC

4. Obtain the model

Radiolabeling yield =
− 3234 − 14,99 x **NODA-MP-C4/Al** + 0,3316 x **[NODA-MP-C4]** + 1477 x **pH** – 0,0003614 x **[NODA-MP-C4]²** - 160,4 x **pH²**







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 ± 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** = **78 ± 2 % (n = 3)**

Conclusion

Optimization was performed in **45 tests** representing **7 days** of experimentation. With the optimized parameters, the radiolabeled complex was obtained with high and reproducible radiolabeling yield **(78 ± 2 %, n = 3).**

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