

# Flow – SPPS towards greener and more efficient peptide manufacturing



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<https://doi.org/10.17952/37EPS.2024.P1029>

## Collaboration with PeptiSystems



PeptiPilot: 0.1–12 mmol for development

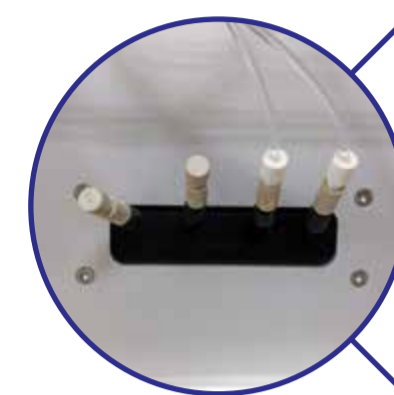
### Process development

- Reactions by flow through column (**re-circulation mode**)
- No calibration due to use of HPLC pumps
- Fully automated process
- Online monitoring implemented (**UV-Vis**)
- No visual inspection of resin due to steel column



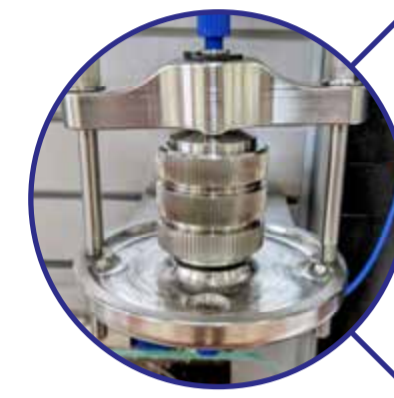
### UV-Detector

- Live in-line monitoring of coupling and washing steps



### Heater

- Optional
- Efficient heat transfer



### Column

- Interchangeable columns
- Up to 5 columns parallel



### Preactivation vessel

- Volume adjustment
- Mixing of components

### Ready for production

- Process transferable from mmols to several mols
- Additional detection modes installable (**RI**)
- Custom made based on individual requirements



PeptiPro – up to 5 mol for production

## Case study – GLP-1 agonist Exenatide

- 39 amino acid linear peptide found in venom of „Gila lizard“



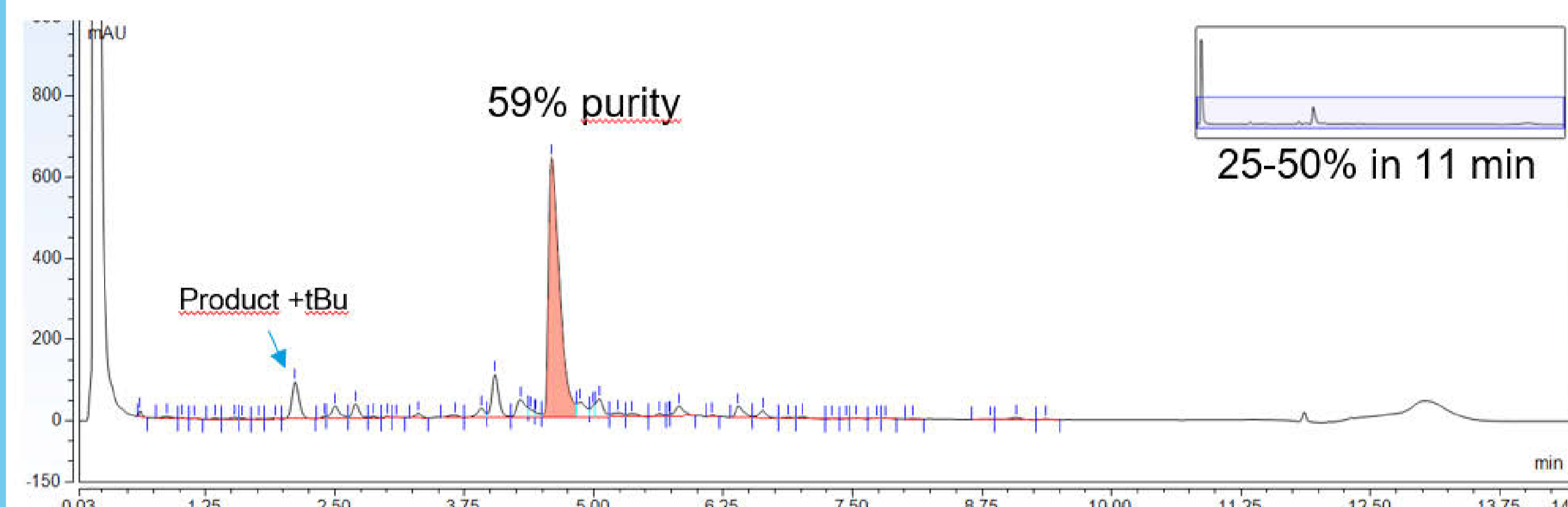
HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH<sub>2</sub>

### Generic protocol (non-optimized)

- **Amino acid / Oxyma / DIC (1.5 / 1.5 / 3.0 eq)**
- Rink amide resin (**0.65 mmol/g**), (0.085 g resin / mL column)
- Synthesized on 25 mL column (1.38 mmol scale)
- **80 min coupling** duration for each cycle (**50 °C**)
- **6 CV washes** – 4 CV after DeFmoc, 2 CV after capping (4+2)  
(can be reduced to 2 CV and 1 CV with 100 mL column (2+1))

## Results

- **89% crude yield** over all steps
- High crude **purity 59%**
- **25% less AA/Oxyma** used
- **35–61% less solvent** consumption



## Fmoc deprotection

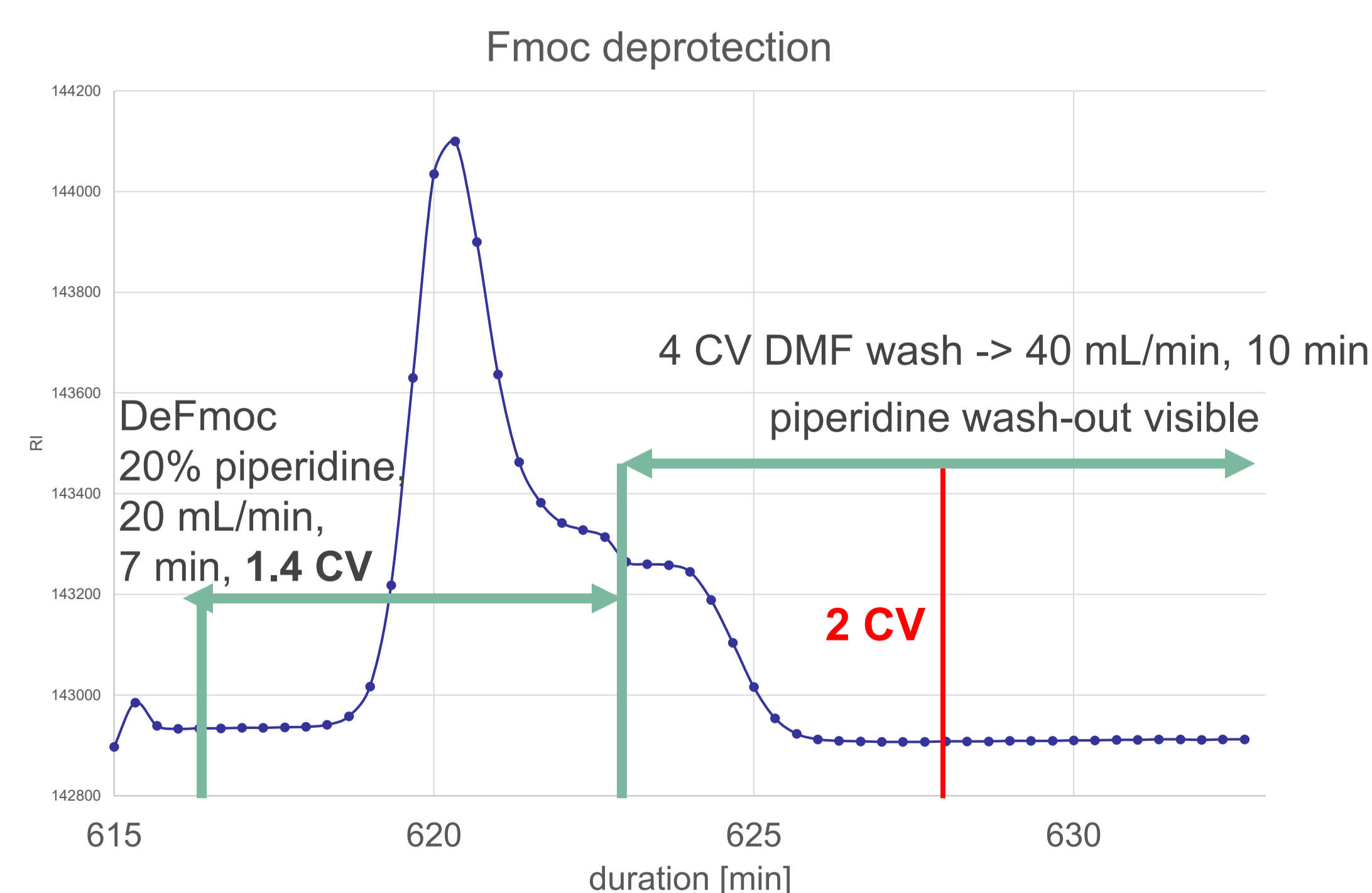
### 20% piperidine in DMF flow:

- Dibenzofulvene wash-out monitored by UV (full conversion ensured)
- **~50% less piperidine** utilized compared to batchwise SPPS

### DMF washing step

- complete washing out of piperidine monitored via **RI**
- **2 CV are sufficient**, might be further reduced

## PAT (RI) monitoring (100 mL column)



## References

- Lukas TJ, Prystowsky MB, Erickson BW (1981). *PNAS*, 78(5), 2791–2795.
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- de la Torre BG, Ramkisson S, Albericio F, Lopez J. (2021). *Org. Process Res. Dev.* 25(4), 1047-1053

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