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https://doi.org/10.17952/38EPS.2026.P426

ADMET of peptides: Are we there yet?

C. Yildiz, N. Köhler, A. Park, T. Kühl, D. Imhof

Department of Pharmaceutical Biochemistry and Bioanalytics, Pharmaceutical Institute, University of Bonn, 53121 Bonn, Germany

Introduction and Objectives

The **development of new pharmaceuticals** requires a preliminary evaluation of efficacy and safety, in which ***in-vitro*** **ADMET-studies** play a central role**. Peptide-based therapeutics** have emerged as a rapidly expanding drug class. However, the establishment of predictive, and standardized ADMET-assessment strategies for peptides remain an ongoing challenge.

This raises a critical question for the field: are current ADMET methodologies sufficient to support the **development of peptide-based drugs**?

Investigate

1. solubility
2. lipophilicity
3. plasma stability (PS)
4. plasma protein binding (PPB)
5. hepatic microsomal stability (HLM)
6. cytotoxicity

Identify

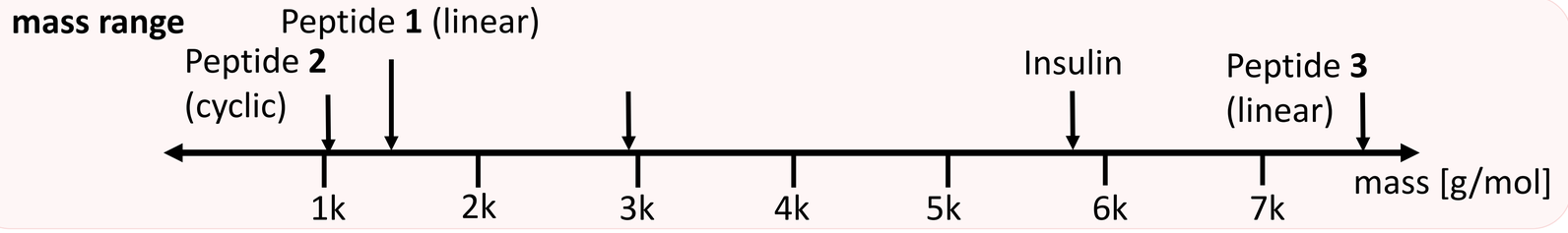
methodological challenges

peptide-specific limitations

Establish

adaptations

standardized *in-vitro* workflow

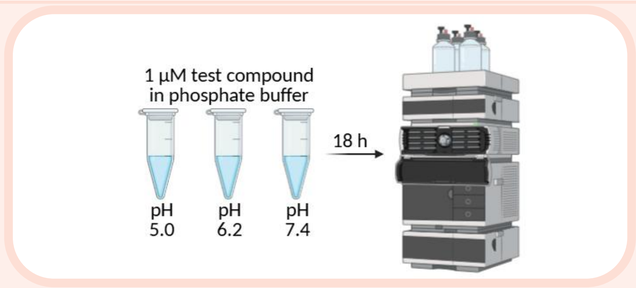


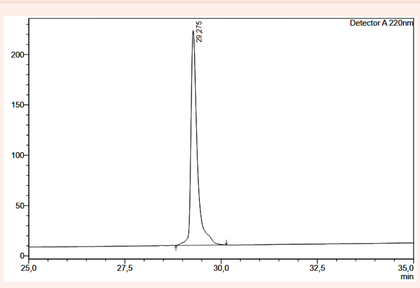
Methods

Results

Modifications

1 solubility



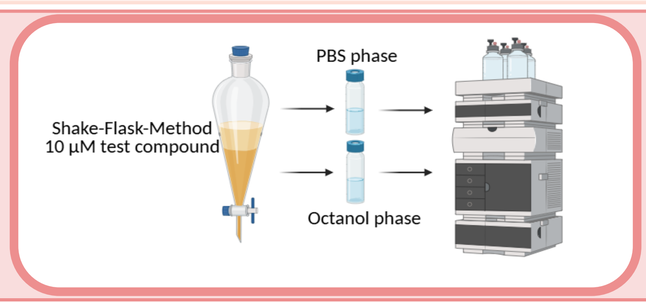


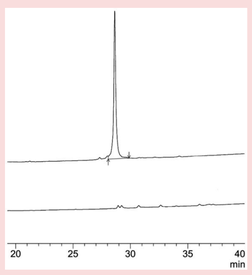
P	pH 5.0	pH 6.2	pH 7.4
Insulin	0	0	72.9
1	91.1	87.7	91.8
2	>100	>100	87.7
3	90.4	93.3	89.5

- HPLC-based peptide quantification

☑ Confirms previously published values for insulin

2 lipophilicity



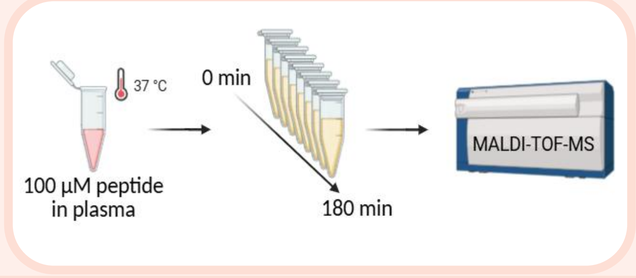


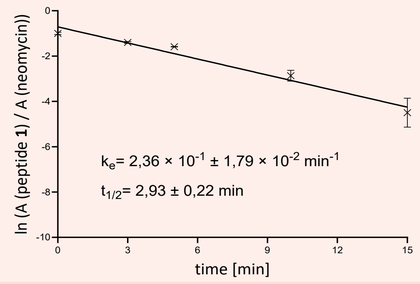
P	$logD_{7.4}$
Insulin	-2.08 ± 0.07
1	< 0
2	-2.20 ± 0.03
3	-2.10 ± 0.05

- HPLC-based peptide quantification

☑ Consistent with hydrophilic character of peptides

3 PS



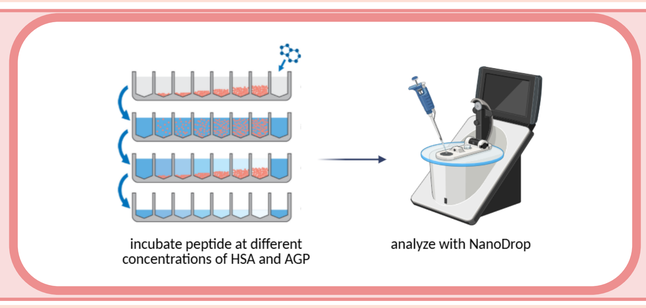


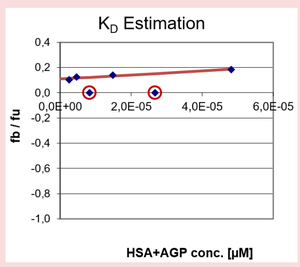
P	$t_{1/2}$ [min]
Insulin	> 180
1	2.93 ± 0.22
2	> 180
3	> 180

- 3 % TCA as precipitation solution
- Shorter incubation and centrifugation times

☑ Reliable detection of enzymatic degradation

4 PPB



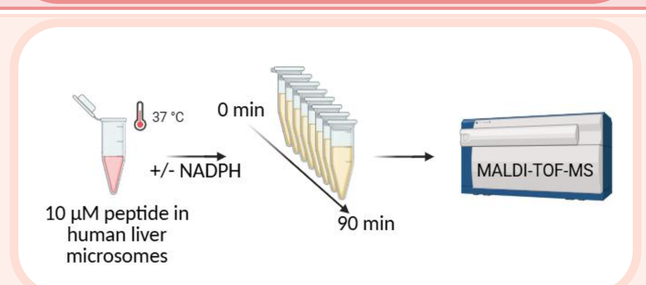


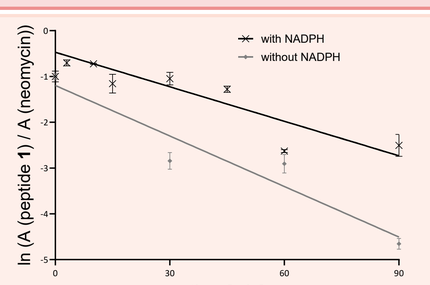
P	PPB [%]
Insulin	49.3 ± 6.11
1	82.4 ± 9.37
2	ongoing
3	ongoing

- Evaluation of a peptide-compatible PPB assay kit

☐ Validation ongoing

5 HLM



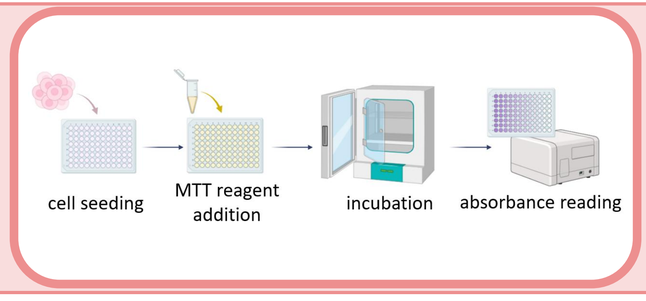


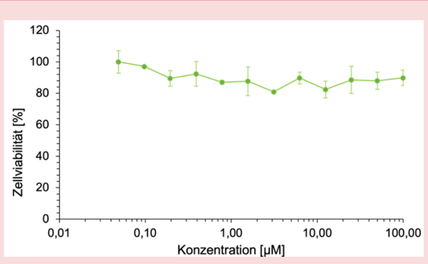
P	Cl_{int} [µl/min/mg]
Insulin	4.13 ± 1.15
1	25.11 ± 2.97
2	0
3	2.10 ± 0.26

- 3 % TCA as precipitation solution
- Shorter incubation and centrifugation times

☑ Reliable detection of metabolic stability

6 cytotoxicity





P	LD_{50} (HepG2) [µM]
Insulin	> 50
1	> 100
2	> 100
3	> 100

- No specific adaptation of the assay for peptides was required

☑ Reliable detection of cytotoxicity

Conclusion and Outlook

Established ADMET assessment strategies are designed for small molecules. We identified key methodological challenges and implemented peptide-specific adaptations. An optimized and standardized *in-vitro* workflow was successfully established for the assessment of solubility, lipophilicity, plasma stability hepatic microsome stability and cytotoxicity of peptides across a broad range of molecular weights. Further peptide-specific ADMET assays remain to be established and optimized to enable a more comprehensive assessment of peptide pharmacokinetics.

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Check Imhof lab

Acknowledgments

University of Bonn
The German Heart Research Foundation
Dr. Laura Orsatti (IRBM Science Park, Pomezia, Italy)
Prof. Dr. Marianne Engeser for access to the MALDI-TOF/TOF MS (Uni Bonn)