Towards Greener Solid-Phase Peptide Synthesis: Combining a Novel Support with Eco-Friendly Solvents

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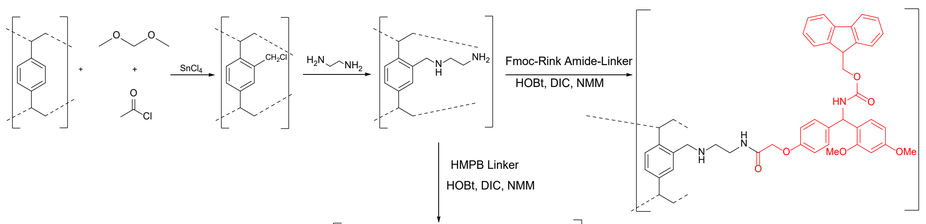
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Introduction

Peptides are attracting increasing investment across multiple sectors, particularly in the pharmaceutical industry, where they represent a highly important class of active pharmaceutical ingredients (APIs). Over the past decade, a growing number of peptide-based therapeutics have received regulatory approval, further highlighting their clinical and commercial relevance.
Peptide synthesis is predominantly performed using solid-phase peptide synthesis (SPPS). Despite significant advances in protecting group strategies, coupling reagents, and optimized reaction protocols, SPPS remains a costly process. This is largely due to the substantial excess of amino acids and coupling reagents required to drive reactions to completion, which necessitate the use of large volumes of solvents to remove the excess materials and washing steps. Additionally, downstream purification significantly contributes to overall waste generation, representing a major concern from both economic and industrial sustainability perspectives.
A further challenge is associated with the toxicity and environmental impact of commonly used solvents in peptide synthesis, such as N,N-dimethylformamide (DMF), dichloromethane (DCM), and N-methyl-2-pyrrolidone (NMP).[1]
To address these limitations, we recently introduced a novel mesoporous polymeric support for SPPS based on poly(divinylbenzene) (pDVB).[2] Owing to its unique morphology, this material exhibits minimal solvent-dependent swelling behavior, making it largely unaffected by the nature of the solvents employed during synthesis. Using this support, we successfully synthesized model peptides in alternative solvent systems, including acetonitrile (ACN) and isopropanol/dimethyl sulfoxide (IPA/DMSO) mixture. Here, we extend our evaluation to the synthesis of APIs., Degarelix and fragment (1-14) of Tirzepatide.

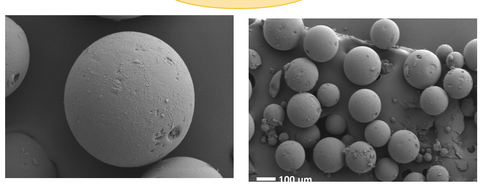
New solid support

The novel **polymeric mesoporous support** (pDVB) was modified with the two different linkers and used for SPPS

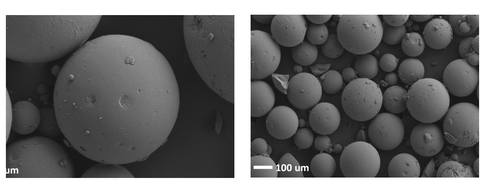


An important feature of this new support is the **reduced dependence** on swelling capacity, which allows the use of a **wider range of solvents**.

pDVB-Cl resin



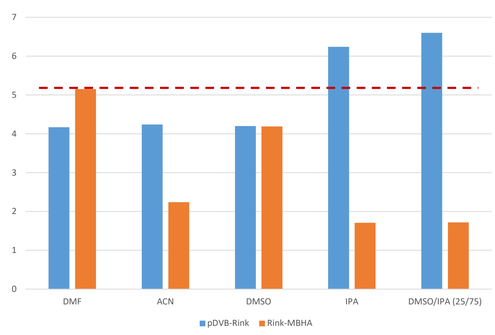
pDVB-Rink resin

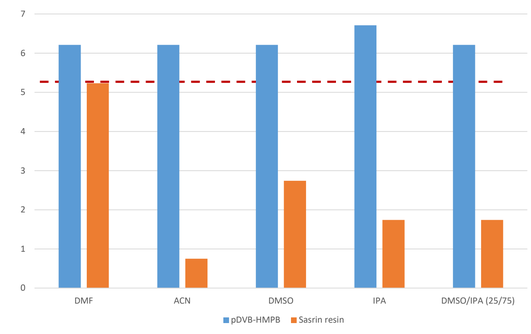


SEM performed with a Zeiss Sigma HD microscope. The samples were deposited on carbon tape and sputter coated with 15 nm of gold.

Swelling Test

The degree of swelling in pure and mixed solvents of pDVB supports was evaluated in comparison with the corresponding commercial resins.



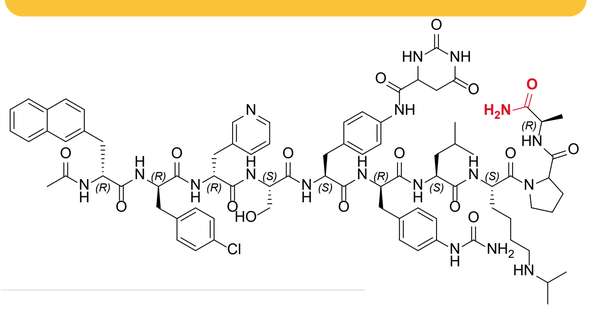


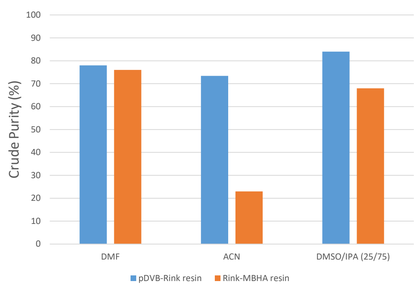
While the swelling properties for gel-type resins are highly dependent on the solvent used, the swelling degree values for the pDVB resins are almost the same in most solvents.

$$\text{Degree of swelling } (mL \cdot g^{-1}) = \frac{(V_{swollen\ resin} - V_{filter})\ (mL)}{m_{resin}\ (g)}$$

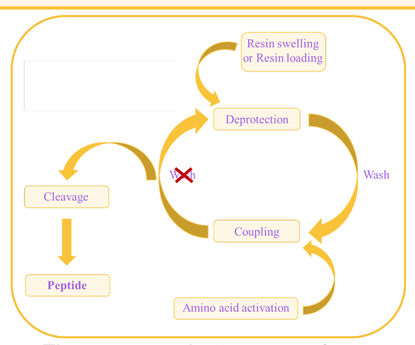
The minimal effect of solvent type on swelling, combined with the generally high swelling degrees, supports the conclusion that the pDVB resins allow for a broader range of solvents to be used in SPPS, potentially improving the environmental sustainability of the process.

Degarelix



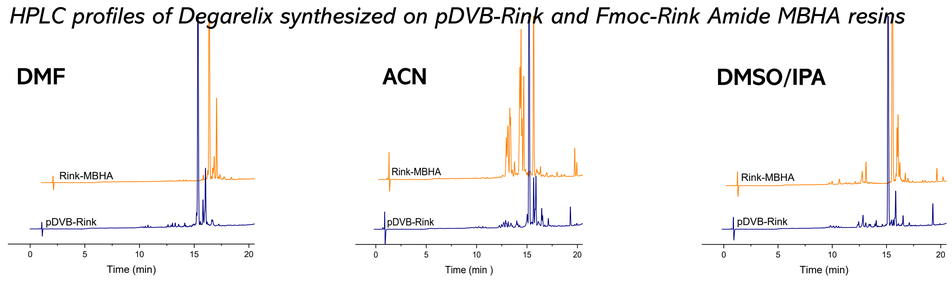


Although most of the amino acids are unconventional and have bulky side chains, **pDVB Rink outperformed the classical gel-type Rink Amide MBHA** resin in ACN and DMSO/IPA mixture

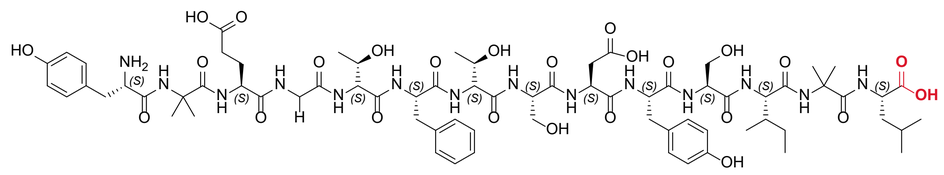


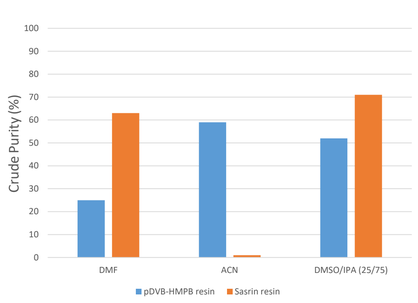
The same synthetic protocol was applied to obtain the two peptides, **no sequence-based optimization** was carried out.

HPLC profiles of Degarelix synthesized on pDVB-Rink and Fmoc-Rink Amide MBHA resins



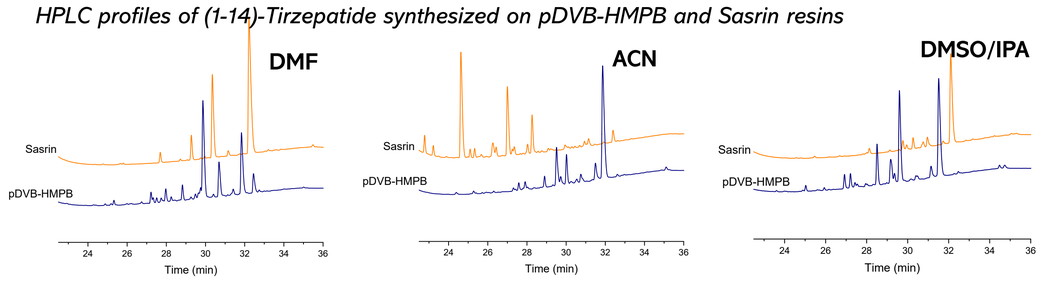
(1-14)-Tirzepatide





pDVB HMPB resin outperformed the classical gel-type Sasrin in ACN while also the conventional resin produces good results in DMSO/IPA mixture

HPLC profiles of (1-14)-Tirzepatide synthesized on pDVB-HMPB and Sasrin resins



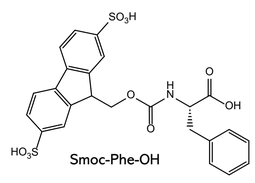
Conclusions

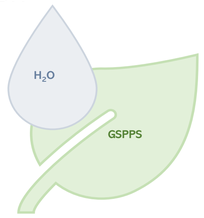
- Functionalization of pDVB support with Rink-Amide and HMPB linkers
- Identification of a support with reduced dependency on swelling properties
- Possibility of using a wider range of solvents other than DMF
- Relevant results using ACN and the promising mixture DMSO/IPA
- Synthesis of peptides of pharmaceutical interest with good results using more sustainable solvents
- Development of a greener process for peptide synthesis

Perspectives

Optimization and scale–up of the synyhetic process using pDVB resins

Development of in-water procedure using Smoc-AA-OH





References

[1] Green Chemistry 2016, 18, 3879–3890.
[2] J. Pept. Sci. 2025; 31:e70038

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