Improving Solubility to Drive Clinical Translation

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Potency is a key driver of therapeutic success, but even highly potent peptides often stumble at the clinic-translation step if their physicochemical properties, especially solubility and aggregation, are not adequately addressed. Low solubility limits dosing, bioavailability, and efficacy, and it also drags down manufacturing yields, complicates formulation/sterilization, and destabilizes the final products.[1] Moreover, poor physicochemical properties have been linked to increased risks of injection-site reactions and immune responses (immunogenicity). Hydrophobic or aromatic-rich sequences are particularly prone to aggregation, although such behavior can be difficult to predict.[2]

Solubility is one of the most critical developability factors as it determines whether a peptide can be reliably produced, formulated, and scaled for clinical and commercial use. A potential misstep in peptide discovery is focusing on biological activity while deferring solubility concerns to late-stage formulation. This reactive approach can compromise the original activity of the lead compound and add significant time, cost, and risk to development.

Promising fixes span both design and formulation. The most direct route is sequence engineering: for longer peptides, adjusting overall charge and isoelectric point (pI) is crucial; ideally targeting a pI<5 or >9 to enhance solubility near neutral pH. Modulating hydrophobicity, introducing cyclization, or incorporating non-canonical residues to balance physicochemical profiles are also common tactics. [3] Additional approaches have been reported in the literature, such as PEGylation, to boost aqueous behavior and exposure.[4] Increasingly, computational prediction tools; some capable of handling non-natural amino acids, allow more accurate assessment of intrinsic solubility by integrating sequence and structural features.[5]

Takeaway: solubility isn't a late-stage formulation cleanup, it's a core developability gate that should be optimized during lead optimization to de-risk translation and scale-up. The PDHC is interested in sharing knowledge on this important topic. How are you building solubility thinking into your peptide design or formulation workflows (screening rules, SAR knobs, platform excipients, or process parameters)?

References

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