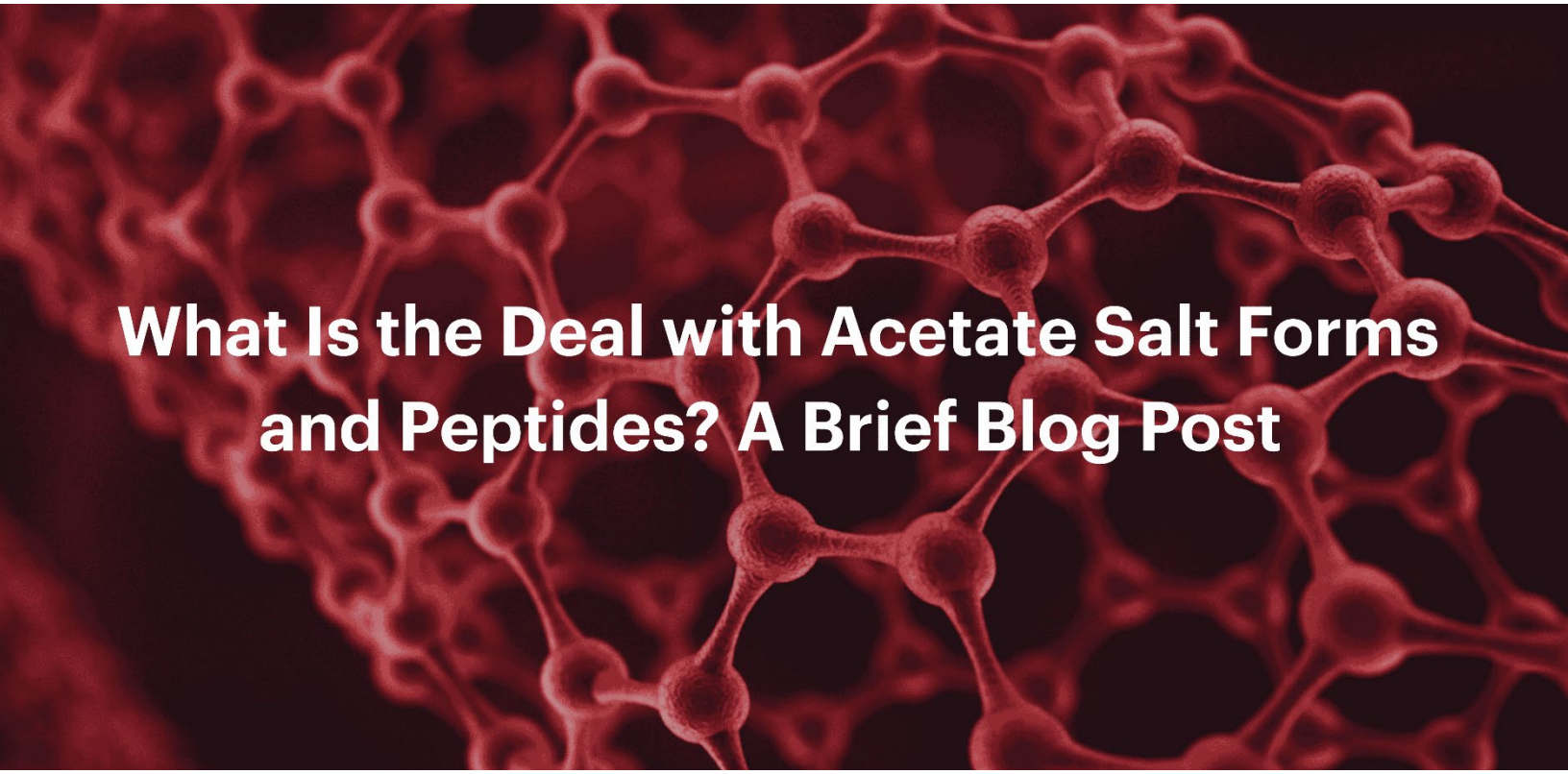

What Is the Deal with Acetate Salt Forms and Peptides? A Brief Blog Post

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If you listened in at the most recent PCAC meeting, you may have heard a lot about “free base” vs “acetate” forms of various peptides. Many of the peptide drugs discussed at the meeting come with a certain amount of acetic acid content. Understanding why acetic acid is commonly found in peptide drugs, it’s role in solubilization, and what makes something an “acetate” salt is key to a better understanding of working with peptides.

Defining peptide drugs: Peptides are complex molecules composed of two or more amino acids joined by a covalent bond. The delineation between peptide and protein is slightly more nebulous. The FDA currently defines a protein as “any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size”. Peptides have a long history of use in the pharmaceutical industry, dating back to the use of insulin as the first peptide drug.[1-3] Given the extensive role that various peptides play in regulating essential systems of the body, there has been an increasing interest in peptides as drug candidates in recent years.

Solubilization and Stabilization of Peptide Drugs: Peptide and protein drugs can be notoriously difficult to work with. Aggregation, the formation of clusters of peptide molecules stuck together, forming often insoluble masses, is a common issue. These aggregates can be amorphous or may present as fibrils. In many cases, aggregation is irreversible, making it a troublesome issue even if factors contributing to that aggregation (e.g. pH out of range) are corrected after the fact. Some factors are intrinsic to the peptide and cannot be changed, for example, peptide sequence and extended peptide length can impact risk of aggregation, with shorter peptides (like oxytocin) of course being much less prone to aggregation. Peptide sequences that include stretches of amino acids in sequence with a tendency to promote aggregates are at the highest risk.[4] Some studies regarding aggregation propensity found that highest risk corresponded with isoleucine, phenylalanine,

valine, and leucine, whereas other amino acids such as glutamine and arginine among others exhibited the lowest risk of aggregation. Higher relative amounts of hydrophobic amino acid residues (leucine, isoleucine, valine, phenylalanine, tryptophan, methionine) tend to be associated with aggregation whereas higher amounts of polar amino acids (arginine, lysine, asparagine, proline) tend to be associated with improved solubility.[5,6] Amino acid sequence can also impact the risk of a peptide being prone to "salting out", a process via which exposure to a salt reduces solubility of the given molecule. Charged and polar amino acids like the ones mentioned previously can compete with ions for water molecules leading to solubility issues as ion concentration increases.[7] For example, sermorelin has a relatively high ratio of polar amino acids, and lab tests find that higher concentrations of sermorelin can be prone to precipitation in the presence of sodium chloride, whereas tirzepatide has a lower ratio of polar amino acids and commercial injectable products do include sodium chloride for tonicity adjustment without a solubility issue.

Another important factor for solubilization is pH. Many peptide drugs have limited information available on pH stability and solubility. For peptides without robust solubility or stability data, looking at amino acid sequences can help to determine whether starting with an acid or neutral pH may be more conducive to solubilization. One common method for evaluating peptide sequence is:

1. Assign a "-1" to asparagine, glutamine, and the C-terminal COOH

2. Assign a "+1" to arginine, lysine, histidine, and the N-terminal NH_2

3. Add up the final value, if the overall charge is positive the peptide is basic and acetic acid may help with solubilization, if the overall charge is negative then the peptide is acidic and aiming for a neutral pH or adding a base to help with solubilization may be considered[8]

As an example, based on these parameters, Sermorelin would be assigned an overall positive charge, meaning it is basic and acetic acid may help with solubilization. In practice, we find that Sermorelin solubility can be highly contingent on the amount of acetic acid content in the original material or on adding acetic acid to solution prior to adding the peptide. Bremelanotide (also commonly referred to as "PT-141" also has a net positive charge, and we find that bremelanotide is generally used as an acetate salt and kept in a slightly acidic pH range to aid with solubility. Conversely, tirzepatide and semaglutide have neutral charges and therefore acetic acid isn't necessarily helpful in solubilizing these two peptides. Instead, aiming for a neutral pH confers better solubility.

Naming conventions: At the most recent PCAC meeting on July 23-24 th, 2026, there seemed to be a lot of chatter about "acetate" vs "free base". However, it should be noted that the peptides discussed have no USP monograph that would confer a standard naming convention and therefore it is not always the case that a peptide without "acetate" in the title is truly the free base form or contains no acetic acid. Even in the case of peptides with USP monographs, there can be some confusion regarding acetate salt forms vs a free base. For example, "Oxytocin, USP" contains 6-10% acetic acid content per the monograph, so the peptide in question (if there were no monograph standards) could reasonably be referred to by someone reviewing a CoA as "oxytocin acetate" in that sense. The monograph for another peptide, "Desmopressin Acetate, USP" has 3-8% acetic acid content, but that acetic acid content is clearly reflected in the monograph title whereas it is left out in the case of oxytocin. When reviewing CoAs for peptide drugs without USP drug monographs, it is important to be aware that "free base" vs "acetate" may come down to nomenclature issues and not true material difference.

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