

Effects of excipients of filgrastim products on the structure and dynamics of the drug substance

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Filgrastim is the generic name for recombinant methionyl human granulocyte colony-stimulating factor. Filgrastim products are formulated as a low ionic strength solution containing cryoprotectant such as sorbitol, non-denaturing detergents, usually polysorbate-80, in a buffer at an unusually low pH of 4.0, or 5.0 in some case. It is well documented that the low pH stabilizes the protein fold and we have proposed the presence of a cation- π (π) interaction as a major stabilizing interaction. In addition, there is a significant body of literature suggesting that interactions of excipient molecules with the API may provide benefits from a conformational stability aspect. In order to shed some light in this area, we have used NMR spectroscopy to probe the effects on the structure, via chemical shifts, and dynamics using relaxation measurements of filgrastim when subjected to various excipient conditions. The NMR results are analyzed in parallel with thermal unfolding studies using circular dichroism.