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Unlocking the Scale in a Cyclic Labyrinth:

Manufacturing of API-grade 2-Hydroxypropyl-β-Cyclodextrins and Their In-depth Characterization

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Since the first patent applications on the use of 2-Hydroxypropyl-β-Cyclodextrin (HPBCD) as a solubilizing agent was filed almost forty years ago, this multipurpose class of molecules slowly gained attention as an active pharmaceutical ingredient. HPBCD achieved orphan drug status in 2015 for Niemann-Pick type C disease treatment, catalyzing further research into its therapeutic potential for various disorders. However, broader acceptance is impeded by the complex nature of HPBCD mixtures. Current Pharmacopeial methods are limited to describing purity and the average degree of substitution (DS), but lack guidance around determining assay, pattern of substitution (PS) analysis, extent of oligomerization (EO) analysis, and impurity profiling.[3,4] Analogous to the analytical challenges, current synthetic processes enable the large-scale preparation of HPBCDs with well-defined and symmetrical distribution of DS. Controlling the PS or EO at the lab-scale, however, is a challenging task. Earlier works of Pitha and Barcza pointed out that selective substitutions on the secondary hydroxyls, which surround the larger opening of the cavity, may improve host-guest interaction and molecular recognition.[1,2] Despite these, industries still lack robust processes an analytical method that would provide the desired control over selectivity at a large scale. The importance of controlled HPBCD manufacturing and characterization is emphasized by the fact that properties of HPBCD may differ based on their DS, PS, EO and impurity profile in our presentation, we aim to fill this gap by comparing commercially available HPBCDs from different sources with our *de novo* synthesized, proprietary HPBCDs. We will address the challenges faced upon the various stages of the scale-up, from the gram to the metric ton scale. Lastly, we will discuss how various process parameters impact product profiles and subsequently, leading to the rise of new analytical methods that allowed successful production of multiple campaigns.[5]

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