**Quality by design approach for the development of pH-modulated carvedilol solid dispersions via hot-melt extrusion**

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**Background and aims:** This study aimed to develop a pH-modulated solid dispersion of the poorly water-soluble drug carvedilol by employing a quality by design (QbD) strategy.

**Methods:** The effects of hydrophilic polymers and acidifiers on the solubility of carvedilol were initially evaluated. Drug–polymer miscibility was further assessed using Hansen solubility parameters. Solid dispersions were subsequently prepared via hot-melt extrusion (HME) based on the screening results. A QbD approach was adopted to optimize the formulation. The Quality Target Product Profile (QTPP) was defined, and Critical Quality Attributes (CQAs) were identified through a preliminary risk assessment. Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) were established using prior knowledge and exploratory studies. Formulation optimization was conducted using a Design of Experiments (DoE) approach with a Box–Behnken design (BBD). The optimized formulation was then subjected to verification and comprehensive physicochemical characterization.

**Results:** The solubility of carvedilol was enhanced in the order of Soluplus > PVP-K30 > PVP-VA64 (Figure 1a). Among the tested acidifiers, lactic acid demonstrated greater solubility enhancement compared to succinic acid (Figure 1b). However, due to its liquid physical state, lactic acid was deemed incompatible with the HME process; thus, succinic acid was selected as a suitable alternative. Hansen solubility parameter (HSP) analysis revealed that PVP-VA64 exhibited the lowest Δδt value (2.6), indicating superior miscibility with carvedilol (Figure 1c). Based on these findings, solid dispersions containing PVP-VA64, succinic acid, and carvedilol were prepared. Critical Quality Attributes (CQAs)—defined based on the pre-established Quality Target Product Profile (QTPP) and prior risk assessment—included the drug’s solubility and its dissolution rate at 30 minutes (Table 1). The Critical Process Parameter (CPP) was identified as the extrusion temperature, and the Critical Material Attributes (CMAs) were defined as the concentrations of the acidifier and drug, based on prior knowledge and preliminary studies. Formulation optimization was performed using a BBD with 15 experimental runs (Table 2). As the study is still in progress, additional experimental results will be presented in the full conference poster presentation.

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**Figure 1.** Solubility screening and parameters. (a) Screening of various hydrophilic polymers; (b) Screening of various acidifiers; (c) Table of the Hansen solubility parameters. Each value represents the mean ± SD (n=3).

**Table 1.** Quality target product profile (QTPP) for CAV-pH-SDG.

**Table 2.** Box-Behnken optimization experimental design layout.

**Conclusion/Discussion:** The pH-modulated solid dispersion formulation developed in this study demonstrates potential for improving the solubility and oral bioavailability of carvedilol. Furthermore, the implementation of a QbD approach proved effective in guiding the systematic development of a robust and high-quality formulation.

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