

Co-amorphous Formation of Clofazimine with Organic Acids to Improve Solubility and Dissolution rate

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SUMMARY. The objective of this study was to improve solution and dissolution rate of clofazimine (CFZ) by co-amorphous technology, since CFZ is a Biopharmaceutics Classification System (BCS) class II drug and virtually insoluble in water. Co-amorphous mixtures of CFZ with 2,4-dihydroxybenzoic acid (2,4-HDBA), 2,5-dihydroxybenzoic acid (2,5-HDBA), 3-dihydroxybenzoic acid (3-HDBA), and 4-aminobenzoic acid (4-AMBA) at a 1:1 mol ratio were prepared respectively by solvent assisted grinding. The co-amorphous CFZ-organic acid systems showed 3 to 60-fold solubility increase both in water and in 60% ethanol, and exhibited significant increase in dissolution rate. The X-ray powder diffraction (XRPD) proved that the co-amorphous CFZ-organic acid systems are amorphous and homogeneous. Elevated glass transition temperature (T_g) of different co-amorphous mixture was observed by differential scanning calorimetry (DSC) compared with the CFZ alone. The intermolecular interactions between CFZ and each organic acid in the co-amorphous system were measured by IR spectra. The co-amorphous sample remained in the amorphous state for over 90 days at 25 °C under 60% RH, whereas the amorphous CFZ showed rapid crystallization. This co-amorphous system provides a feasible way to promote the solution and dissolution rate of insoluble drugs.

RESUMEN. El objetivo de este estudio fue mejorar la solubilidad y la velocidad de disolución de clofazimina (CFZ) mediante tecnología co-amorfa, ya que CFZ es un fármaco de clase II del Sistema de Clasificación Biofarmacéutica (BCS) y prácticamente insoluble en agua. Mezclas co-amorfas de CFZ con ácido 2,4-dihidroxibenzoico (2,4-HDBA), ácido 2,5-dihidroxibenzoico (2,5-HDBA), ácido 3-dihidroxibenzoico (3-HDBA) y ácido 4-aminobenzoico (4-AMBA) a una relación molar 1:1 se prepararon mediante molienda asistida por disolvente. Los sistemas de ácido orgánico CFZ co-amorfo mostraron un aumento de solubilidad de 3 a 60 veces tanto en agua como en etanol al 60% y exhibieron un aumento significativo en la velocidad de disolución. La difracción de rayos X en polvo (XRPD) demostró que los sistemas de ácidos orgánicos CFZ co-amorfos son amorfos y homogéneos. Se observó una temperatura elevada de transición vítrea (T_g) de diferentes mezclas co-amorfas por calorimetría diferencial de barrido (DSC) en comparación con la CFZ sola. Los espectros IR midieron las interacciones intermoleculares entre CFZ y cada ácido orgánico en el sistema co-amorfo. La muestra co-amorfa permaneció en estado amorfo durante más de 90 días a 25 °C por debajo del 60% de HR, mientras que la CFZ amorfa mostró una cristalización rápida. Este sistema co-amorfo proporciona una forma factible de promover la solución y la velocidad de disolución de los medicamentos insolubles.

KEY WORDS: co-amorphous, clofazimine, dissolution, organic acid, solution.

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