

Poster 4

Improving the Drug Release of Clofazimine by Developing Amorphous Solid Dispersions via Hot-melt Extrusion using Acid-Base Supersolubilization

Authors: Mufaddal H Kathawala, Hari-Priya Kandagatla, Tatyana Verbic, Alex Avdeef and Abu Serajuddin.

Presenting Author: Mufaddal H Kathawala

Affiliation: (1) St. John's University and (2) University of Belgrade

Corresponding Author's email: mufaddal.kathawala17@stjohns.edu

Purpose

Acid-base supersolubilization (ABS) is a novel approach for enhancing aqueous solubility of basic drugs by interaction with weak acids that would not form salts but convert to amorphous solid dispersion (ASD) upon drying. The ASD can also be prepared in dry state by hot melt extrusion (HME) of mixtures. In this study, ABS was applied to develop ASDs for clofazimine (CFZ), which is a poorly water-soluble drug having intrinsic solubility of <11 ng/ml in the gastrointestinal pH range. It is recognized as an essential drug by WHO for use against leprosy and tuberculosis. Despite its importance and therapeutic efficacy, no commercial CFZ products are currently available; one previously marketed lipid-based product was later withdrawn due to variability in bioavailability. This presentation describes the development of an ASD of CFZ by HME using glutaric acid (GA) to enhance drug solubility and dissolution rate.

Methods

Miscibility of CFZ with GA was studied using hot-stage microscopy. Then melt-viscosity was measured to optimize the processing conditions. Finally, mixture containing CFZ, GA, poloxamer-407 (surfactant) and Kollidon VA64 (polymer) were extruded. In-vitro dissolution testing was conducted using USP-II apparatus at 50 RPM and 37°C, using 50 mg and 5 mg drug equivalents in 250 mL of pH-2, pH-6.8, FaSSGF and FeSSIF-V2.

Results

The melting point of CFZ is 224°C, and, therefore, at least 170°C was required to extrude drug-polymer mixtures. However, with the addition of GA, the melting point of CFZ was reduced to <100°C and the formulation containing 10% CFZ, 11.16% GA, 10% Poloxamer-407 and 68.84% VA64 could be extruded at 120°C. The formation of ASDs was confirmed via DSC and PXRD. The in-vitro dissolution studies using 50 mg drug equivalent in 250 ml of FeSSIF-V2 produced 32% drug release while 48% drug release was achieved in 500 ml of media. This was much higher than the drug release observed in absences of GA and P407 (<10%). Further using 5mg drug equivalents, complete drug release was achieved in 250 mL of FeSSIF-V2.

Conclusion

By reducing CFZ's melting temperature with GA, HME could be performed at lower temperature, and we developed an ASDs that improved the dissolution profile of CFZ.

Keywords: Clofazimine, Amorphous solid dispersion, Hot-melt extrusion and Acid-base supersolubilization