Biorelevant dissolution behavior of amorphous furosemide forms as determined by UV imaging and Raman spectroscopy.

Gordon, Sarah; Nielsen, Line Hagner; Pajander, Jari Pekka; Østergaard, Jesper; Rades, Thomas; Müllertz, Anette

Publication date:
2014

Document Version
Early version, also known as pre-print

Biorelevant dissolution behavior of amorphous furosemide forms as determined by UV imaging and Raman spectroscopy

Sarah Gordon[1], Line Hagner Nielsen[2], Jari Pekka Pajander[2], Jesper Østergaard[2], Thomas Rades[2], Anette Müllertz[2,3]

[1]Department of Drug Delivery, Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarland University, Saarbrücken, Germany
[2]Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3]Bioneer:FARMA, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

PURPOSE: To investigate the biorelevant dissolution behavior of amorphous furosemide sodium salt and an amorphous furosemide acid form, and obtain information regarding the solid state of these amorphous forms during dissolution.
METHODS: Amorphous furosemide sodium salt and an acid form of amorphous furosemide were prepared by spray drying. Their dissolution behavior was evaluated in a biorelevant intestinal medium at pH 6.5. Dissolution was investigated using a flow-through cell coupled to a UV imaging system, and further quantified by UV spectrophotometric analysis of flow cell effluent samples. The solid state form of amorphous furosemide compacts during dissolution was also investigated using *in situ* Raman spectroscopy, as well as off-line X-ray powder diffraction (XRPD). Furthermore, thermogravimetric analysis (TGA) and hot stage microscopy were utilized for investigation of the polymorphic form of remaining amorphous salt upon dissolution.
RESULTS: UV imaging and analysis of effluent samples showed that the amorphous furosemide salt exhibited a greater dissolution rate than the amorphous acid form, as well as crystalline acid and salt forms of furosemide. Both amorphous furosemide forms were shown to convert extremely quickly (within 1 min) to more stable crystalline forms during dissolution. Partial least squares-discriminant analysis modeling of the Raman spectroscopic data obtained during the biorelevant dissolution showed that the amorphous acid form converted to the crystalline acid form of furosemide within 20 min. This was also confirmed by XRPD of amorphous acid compacts following dissolution. TGA and hot stage microscopy investigations showed that the amorphous salt converted to a trihydrate of furosemide during biorelevant dissolution. Principal component analysis of the Raman spectral data recorded during the dissolution process indicated that this conversion started at the time of drug wetting.
CONCLUSIONS: Evaluation of the biorelevant dissolution behavior of amorphous furosemide salt and acid forms indicated a dissolution advantage of the amorphous salt form, but also showed that a rapid solid state conversion to a more stable polymorph occurred in the case of both amorphous furosemide salt and acid. Such behavior could significantly influence the *in vivo* performance of amorphous furosemide, and demonstrates the importance of biorelevant *in vitro* drug characterization.