In situ monitoring of the crystallization of amorphous solid dispersions in aqueous solution, using synchrotron radiation

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Amorphous pharmaceuticals are of interest because of their ability to enhance the dissolution rate and the bioavailability of compounds with poor aqueous solubility. However, the physical stability of amorphous drugs, denoted by their recrystallization propensity, is of major concern. We present a new material-sparing approach for rapidly evaluating the physical stability of amorphous materials, based on synchrotron powder X-ray diffractometry. A small quantity of the sample (~20 mg) in an aluminum pan is uniformly wetted with ~25 µL of water, sealed, and exposed to synchrotron radiation in transmission mode. The onset time, rate and extent of recrystallization, are then monitored periodically for up to 6 hours.

We tested the validity of this approach, by investigating the physical stability of a range of amorphous solid dispersions (ASDs) prepared with different model drugs (indomethacin, ketoconazole and nifedipine) and polymers (poly acrylic acid, polyvinylpyrrolidone, poly-ethylene-glycol and hydroxypropyl methyl cellulose acetate succinate). The strength of interaction between the drug and the polymer in the ASDs was characterized using nuclear magnetic resonance spectroscopy and infrared spectroscopy.

The onset time for crystallization of each ASD in aqueous solution, correlated with the strength of interaction between the drug and polymer. Systems with strong drug-polymer interactions in the solid state did not crystallize, or crystallized at very slow rates, with very long onset times. The converse was observed for systems with weak drug-polymer interactions, for which rapid crystallization onset times and crystallization rates, were observed. The results of the experiments were also in good agreement with dissolution tests carried out in aqueous solution, using standard United States Pharmacopoeia dissolution apparatus (II and IV). This new testing approach can serve as an effective screening tool for rapidly evaluating the physical stability of amorphous pharmaceuticals.