Wolfe Laboratories

Hit to Lead | Lead Optimization | Candidate Selection | Early Clinical Development

Formulation Development: Enabling Formulations for BCS Class II Compounds

Purpose

Wolfe Laboratories was hired to develop an oral dosing formulation for a poorly soluble non-ionizable compound that would increase exposure and enable execution of a preclinical 14-day toxicology study.

Experimental Design

Wolfe Laboratories designed the formulation strategy based on evaluation of physicochemical properties of the active pharmaceutical ingredient (API), which had a high melting point and no ionizable groups. Oral bioavailability of the API was expected to be limited by dissolution rate and/or solubility in the intestinal lumen.

In theory, preparation of an amorphous solid dispersion (ASD) can accomplish the removal of the lattice energy and achieve the maximum possible particle size reduction. Administration of an ASD may, in turn, improve the oral bioavailability of the compound by creating a supersaturated solution in the intestinal lumen.

Results

Wolfe Laboratories scientists prepared ASD formulations with various excipients and drug load. Two prototype formulations, ASD A and ASD B, were selected based on their *in vitro* performance in fasted-state simulated gastric and intestinal fluids (FaSSGF and FaSSIF, respectively), shown in Figure 2. One additional formulation, ASD C, was then generated using the same components as ASD B but with an increased drug load. The physical stability of the three final formulations was demonstrated over a period of 14 days, as shown in Figure 3. The PK data obtained from the 14-day toxicity study indicate a 10- to 20-fold increase in bioavailability for the ASD formulations compared to control, summarized in Figure 4.

Conclusions

Wolfe Laboratories' rational, hypothesis-driven formulation development strategy, based on the physicochemical properties of the API and *in vitro* screening, yielded significant improvement in bioavailability of a non-ionizable BCS Class II compound. The formulations had good *in vitro-in vivo* correlation and showed physical stability sufficient for the course of study.

Figure 1: *XRD diffractograms for API show the amorphous character of selected ASDs*

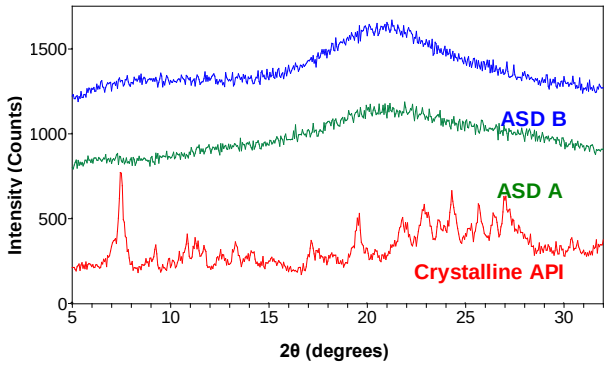
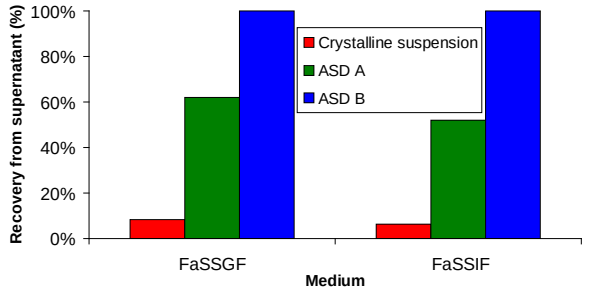


Figure 2: *In vitro performance of selected formulations*



Note: Recoveries normalized to highest value in each medium

Figure 3: *XRD diffractograms demonstrating physical stability of selected formulations over 14 days*

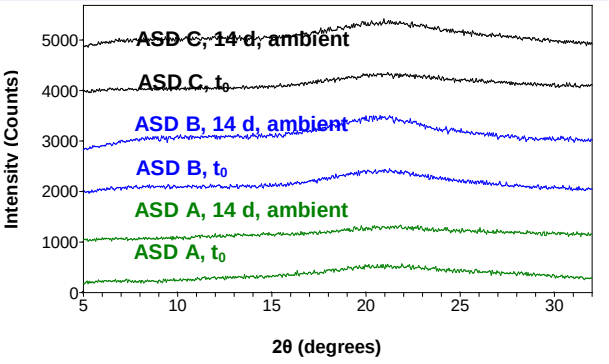
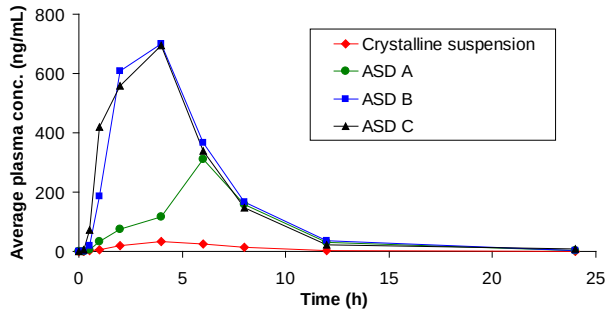


Figure 4: *In vivo performance of selected formulations*



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