Biopharmaceutical Assessment of an Anti-viral Compound (AVI). Clinical Formulation Efforts

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Purpose. Preclinical biopharmaceutic assessment of formulations to define a solid dosage form that gives good exposure of a highly water-insoluble anti-viral compound, AVI. **Methods.** Beagle dogs were given a 10 mg/kg oral dose of A) AVI free base as a solution in acidified propylene glycol; B) capsules filled with AVI dissolved in semi-solid PEG1000; C) AVI embedded on an ion-exchange resin support in capsules; D) ion-exchange resin supported AVI capsules in pentagastrin pre-treated dogs; E) AVI besylate salt suspension with Pluronic surfactant and F) AVI lyophilized, amorphous wafer. Blood samples were drawn at the appropriate times. Plasma samples were extracted and analyzed by LC/MS/MS. **Results.** AVI has low aqueous solubility, 70 ng/mL at neutral pH. The solubility is highly pH dependent, 8.9 mg/mL at pH 1.2. The ranking and relative AUC values from the dogs studies were: E (31) > B (21) > D (17) > A (14) > C (3.0) > F (1.0). PEG 1000 is a semi-solid at room temperature, but melts at physiological temperatures and thus this formulation should perform similarly to solution. Bioavailability was poor when the ion-exchange resin capsules were given to dogs without pentagastrin pre-treatment. Lowering the stomach pH to 2 with pentagastrin increased the bioavailability from this formulation 5-fold. A suspension of the besylate salt, formulated with a 1:8 ratio of Pluronic surfactant to AVI, gave the best exposure. An attempt to enhance dissolution of AVI from amorphous form in a rapid dissolving wafer did not translate into enhanced bioavailability. **Conclusions.** Results of these formulation comparisons indicate AVI free base is minimally bioavailable from the solid state and under achlorhydric conditions. Semi-solid filled capsules or solid dosage forms using an appropriate AVI salt may be viable approaches for clinical development.