 Capsule Selection Guidance: Bioequivalence or Enhancement of Vcaps® Plus Relative to Gelatin Capsules Based on Drug Properties

Michael Grass, Ian Yates, Alex Lineweaver, Mike Morgen (Capsugel Pharmaceutical R&D Bend OR)

**PURPOSE**
Vcaps® Plus, made from hydroxypropyl methylcellulose (HPMC), are an attractive alternative to gelatin capsules. They are plant-based, have improved crack resistance at low humidity, and are rapidly dissolving. Several studies have demonstrated that capsule composition can affect the bioavailability of drugs due to either disintegration rate or interactions between the drug and the capsule materials. One type of interaction is inhibition or delay of precipitation for supersaturating formulations in the presence of certain polymers, such as HPMC. Weakly basic drugs can have much higher solubility in low pH gastric fluid than in intestinal fluids and therefore lead to precipitation upon transfer from gastric to intestinal fluid. The precipitation rate of these drugs in intestinal fluids can impact bioavailability and therefore the impact of capsule material must be understood during development.

**METHODS**
Four model weak bases (erlotinib, gefitinib, ketoconazole, and dipyridamole) were tested as received. Gastric transfer tests were performed by adding fasted state simulated gastric fluid (FaSSGF, pH 2) to the model drug and then transferring to fasted state simulated intestinal fluid (FaSSIF, pH 6.5) with 0.2% SIF (powder) by addition of a concentrated FaSSIF solution. Drug in capsules were tested at 50, 100, to 1000, in a 100 mL USP 2 apparatus. Precipitation inhibition as a function of concentration and HPMC concentration was carried out using the PhenOss Profiler™. Drug and polymer were mixed in pH 2 FaSSGF until fully dissolved and then a concentrated FaSSIF was added to reach a final pH 6.5 and 0.2% SIF. HPMC. All dissolution data was acquired using UV fiber optic probes.

**RESULTS**
Erlotinib, gefitinib, ketoconazole, and dipyridamole all readily dissolve in gastric fluid (FaSSGF) and precipitate on transfer to intestinal fluid (FaSSIF). In this work, we characterize the precipitation of these model compounds as a function of dose and concentration of HPMC. The presence of HPMC, precipitation can be delayed minutes up to greater than two hours depending on the drug and dose. At a concentration between the amorphous solubility half and the amorphous solubility, the in vitro area under the curve (AUC) for 90 minutes in FaSSIF is about two times higher in the presence of 0.2 mg/mL HPMC for all four compounds. Only a minor delay in precipitation occurs in the presence of gelatin. Increasing the concentration of HPMC above 0.1 mg/mL has only a minor effect on precipitation while increasing the concentration significantly increases the precipitation rate in the presence of absence of HPMC.

**CONCLUSIONS**
HPMC-based capsules such as Vcaps® Plus can be used to inhibit precipitation of weak base actives on transfer from gastric to intestinal buffer. The observed enhancement can be understood primarily from the dose and amorphous solubility of the drug and secondarily by the interaction between the drug and HPMC.

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**REFERENCES**
1. D. Cade, "Inhibitors Plus Capsules + Hydrophilic Polymers for Pharmaceutical Products." [capsugel.com](http://capsugel.com)
2. C. et al., "Inhibitors Plus Capsules + Hydrophilic Polymers for Pharmaceutical Products." [capsugel.com](http://capsugel.com)

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**Dissolution of model compounds in FaSSGF followed by transfer to FaSSIF dosed as powder in capsule (PIC) in either gelatin or Vcaps® Plus.**

**Effect of HPMC concentration on the precipitation of erlotinib.**

**Dependence of Supersaturation Parameter 4 on Dose**