Enhancing the Stability of a Famotidine Tablet Formulation through the Use of Starch 1500®
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**Purpose**
To evaluate the influence of Starch 1500 on physical and chemical stability of a formulation containing a moisture sensitive active with a well characterized degradation pathway due to hydrolysis.

**Methods**
To fully assess Starch 1500 in a formulation versus a lactose based formulation currently on the market, three individual studies were conducted: 1. evaluating basic API-excipient compatibility, 2. an open dish stability of four different core formulations and 3. a blister packaging stability study comparing two formulations.

For the API compatibility study, binary blends of famotidine with lactose monohydrate, microcrystalline cellulose or Starch 1500 were prepared and then 10% moisture was introduced into the samples before being sealed in bottles and stored at 50°C for four weeks. All samples were analyzed using HPLC to determine the level of degradants at weekly intervals.

For the open dish study, a formulation containing Starch 1500 and microcrystalline cellulose was compared directly to a marketed formulation containing lactose monohydrate and microcrystalline cellulose. In addition, the Starch 1500 in the formulation was removed and replaced with other ratios of MCC and lactose.

For the blister study, the marketed formulation (containing lactose/ MCC) and the test formulation containing Starch 1500/ MCC, uncoated or coated with a 3% weight gain of Opadry® II (PVA based) were packed in Aclar 2000 blisters and placed on stability at various stability conditions. Samples were analyzed for tablet properties, impurity levels, assay, and dissolution profiles.

**Results**
Degradation of famotidine has been documented in the literature. Four degradants have been reported, where degradant A is due to oxidation while impurities B, C and D are a result of acid catalyzed hydrolysis. Impurity D was most abundant in this work. In the API-excipient compatibility study, all mixtures showed some level of degradation. Lactose produced the highest level of degradation with 2.99% of total impurities while Starch 1500 produced 1.89%.

In the open dish study, the limit of 0.5% for impurity D was exceeded at the following points for the four formulations: Lactose:MCC (1:1 ratio) = 2 weeks, Lactose:MCC (2:1 ratio) = 3 weeks, MCC alone = 5 weeks, Starch 1500:MCC (1:1 ratio) = 9 weeks.

In the blister study, impurity D was the largest single impurity for both formulations. Impurities A, B, and C remained less than 0.50% throughout the six months study. Total impurities represented the sum of the known impurities and did not include unknown compounds. Assay and dissolution passed at the six month time point for both formulations.

For the uncoated tablets, impurity D increased as time progressed. At the 3 month time point the Starch 1500 formulation showed a passing level of 0.49% while the lactose batch failed at 0.65%. At six months both uncoated tablets showed failing results of 0.55% and 0.96% respectively. Applying a moisture barrier film coating to these products showed an improvement in the stability of the Starch 1500 formulation. At the three month point, the Starch 1500 formulation showed 0.44% impurity D while the lactose formulation showed 0.63%. At six months, they showed 0.38% and 1.05% respectively.

The formulations containing Starch 1500 maintained lower impurity levels, as compared to lactose containing formulation. This may be due to the water activity behavior of Starch 1500, where water is tightly bound to it. Whereas, moisture in the formulations containing lactose is more mobile and more reactive, resulting in higher degradation.

Tablet physicals also changed over time. The hardness of the tablets with lactose initially increased and then showed a large drop (-46%) by the end of the six month study. Starch tablets remained fairly stable in hardness dropping by less than 15%. Both coated and uncoated tablets picked up some moisture over time. The uncoated formulations with Starch 1500 picked up the most moisture but this did not result in the highest degradation levels. The formulations with lactose picked up less moisture and resulted in higher impurity levels.

**Conclusion**
Starch 1500 demonstrated the best compatibility with famotidine. In open dish trials, the presence of Starch 1500 in the formulation produced lower levels of famotidine hydrolysis degradants. This is due to the low water activity of Starch 1500 and its potential to scavenge moisture. In the blister study, the only formulation to pass after six month exposure at 40°C/ 75% RH was the one containing Starch 1500 and MCC, coated with Opadry II and packed in Aclar 2000. The lactose monohydrate containing formulation was much less stable with coated and uncoated formulations failing the impurity contents. Hydrolysis in the lactose formulation also resulted in unidentified degradants.