Enhancing the Stability of a Famotidine Tablet Formulation through Use of Starch 1500®

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Purpose

To evaluate the influence of Starch 1500® partially pregelatinized maize starch on the physical and chemical stability of formulations containing the moisture sensitive active, famotidine which has a well characterized degradation pathway due to hydrolysis.

Methods

To fully assess the role of Starch 1500 in place of lactose in a famotidine formulation currently on the market, three individual studies were conducted: 1) Drug/excipient compatibility, 2) an open dish study of four different core formulations and 3) a blister packaging study comparing two formulations.

For the drug/excipient compatibility study, binary blends of famotidine with lactose monohydrate, microcrystalline cellulose (MCC) or Starch 1500 were prepared, then 10% moisture was introduced to the samples prior to sealing in bottles then stored at 50ºC 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 MCC was directly compared to a marketed formulation containing lactose monohydrate and MCC. In addition, the Starch 1500 in the formulation was replaced with further ratios of MCC and lactose (Tables 1 & 2). Tablets of all four formulations were compressed and placed in open containers at 40º/ 75% RH for 16 weeks.

For the blister packaging study, the marketed (containing lactose/ MCC) and test formulations (containing Starch 1500/ MCC), uncoated or coated with a 3% weight gain of a PVA based Opadry® II high performance film coating system were packed in Aclar 2000 blisters and placed on stability at 40ºC/ 75% RH, for six months. Samples were analyzed for tablet properties, impurity levels, assay, and dissolution profiles.

Table 1: Open Dish and Blister Study Formulations

Ingredient	Starch 1500 and MCC Formula		Lactose and MCC Formula (Marketed)	
Famotidine	20.0 mg	6.7%	20.0 mg	6.7%
Microcrystalline Cellulose	135.0 mg	45.0%	78.5 mg	26.2%
Pregelatinized Starch (Starch 1500)	134.5 mg	44.8%	--	--
Lactose Monohydrate	--	--	183.0 mg	61.0%
Sodium Starch Glycolate	--	--	11.0 mg	3.7%
Colloidal Silicon Dioxide	3.0 mg	1.0%	--	--
Talc	6.0 mg	2.0%	6.0 mg	2.0%
Magnesium Stearate	1.5 mg	0.5%	1.5 mg	0.5%
TOTAL	300.0 mg	100.0%	300.0 mg	100.0%

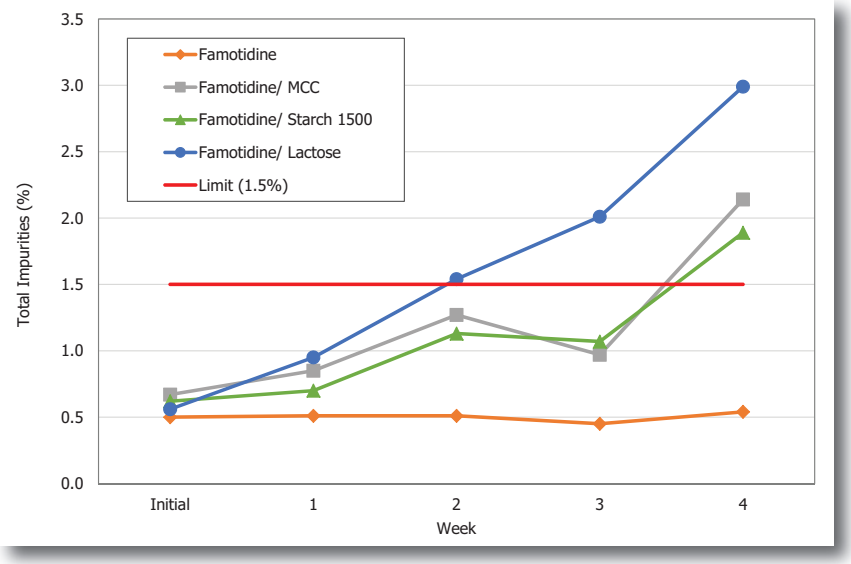
Table 2: Open Dish Study Formulations

Ingredient	MCC Formula		Lactose and MCC Formula	
Famotidine	20.0 mg	6.4%	20.0 mg	6.4%
Microcrystalline Cellulose	269.5 mg	86.7%	135.0 mg	43.4%
Lactose Monohydrate	--	--	134.5 mg	43.2%
Sodium Starch Glycolate	11.0 mg	3.5%	11.0 mg	3.5%
Talc	6.0 mg	1.9%	6.0 mg	1.9%
Colloidal Silicon Dioxide	3.0 mg	1.0%	3.0 mg	1.0%
Magnesium Stearate	1.5 mg	0.5%	1.5 mg	0.5%
TOTAL	311.0 mg	100.0%	311.0 mg	100.0%

Results

Degradation of famotidine has been documented in literature.[1] Four degradants have been reported. 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. Figure 1 shows the drug/excipient compatibility results, where 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%.

Figure 1: Binary Compatibility Study Results



Each formulation for the blister study ran well on the tablet press. A summary of the average tablet properties from the compression run are shown in Table 3. Tablets showed good hardness and no friability regardless of the formulation. Disintegration times for both formulations were also excellent. One difference noted between the formulations was the higher ejection force seen with the lactose formulation. At the same lubricant level, the Starch 1500 formulation showed considerably lower ejection force due to the self-lubricating properties of the starch.

Table 3: Initial Tablet Properties

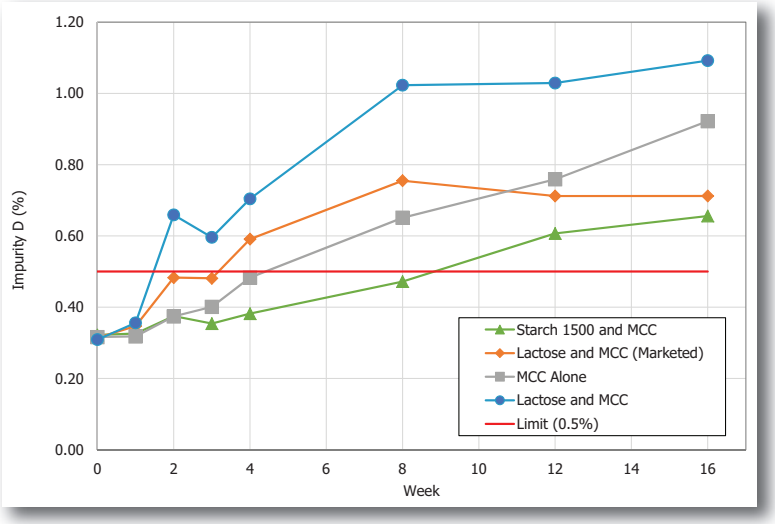
Property	Starch 1500 Formulation	Lactose Formulation
Tablet Breaking Force (kp)	13.3	12.6
Weight (mg)	295.3	298.4
Weight Variation (% RSD)	1.64	1.28
Friability (% loss)	0.00	0.00
Disintegration Time (min)	2.2	2.3
Ejection Force (N)	55	294

In the open dish study, the limit of 0.5% for impurity D was exceeded at the noted time points for all four formulations (Table 4). Figure 2 shows the change in concentration of impurity D in all formulations against the open dish storage time.

Table 4: Open Dish Study Results

Failure Point	Formulation	Reason for Failure	Total Impurities @ 16 weeks USP Limit 1.5%
2 Weeks	Lactose and MCC	Impurity D limit exceeded	1.885
3 Weeks	Lactose and MCC (Marketed)	Impurity D limit exceeded	1.093
5 Weeks	MCC Alone	Impurity D limit exceeded	2.252
9 Weeks	Starch 1500 and MCC	Impurity D limit exceeded	1.598

Figure 2: Open Dish Impurity D Results



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, (Figure 3), impurity D increased as time progressed. At the 3 month time point, the Starch 1500 formulation showed a pass level of 0.49% while the lactose batch failed at 0.65%. At six months, both uncoated tablets showed fail results of 0.55% and 0.96% respectively. Applying a film coating with moisture barrier properties to these products showed an improvement in the stability of the Starch 1500 formulation (Figure 4). 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.

Figure 3: Aclar Blister Stability of Uncoated Tablets

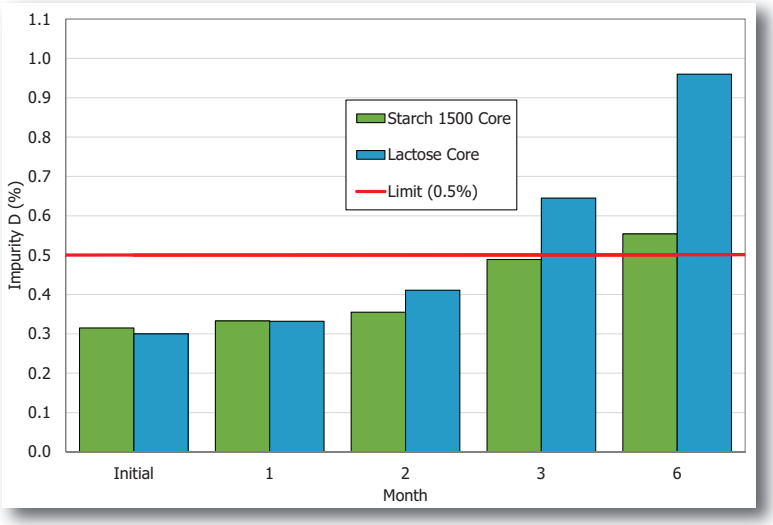
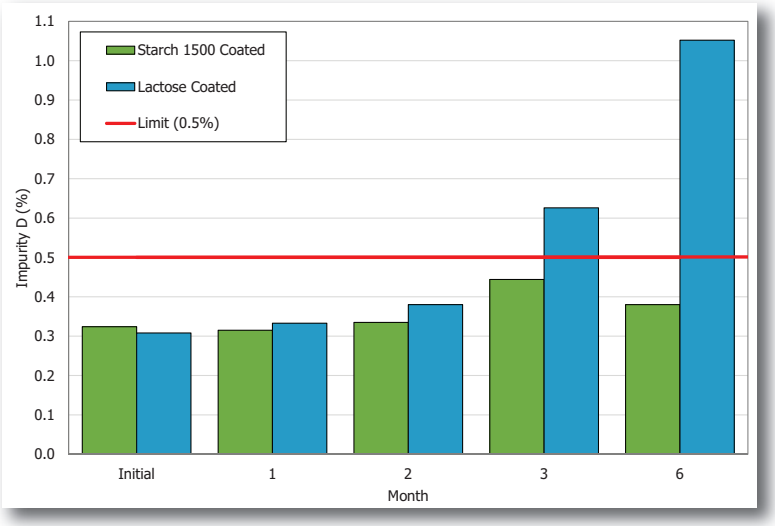


Figure 4: Aclar Blister Stability of Film Coated Tablets



The formulations containing Starch 1500 maintained lower impurity levels, as compared to lactose containing formulations. This may be due to the water activity behavior of Starch 1500, where water is tightly bound.[2] Whereas, moisture in the formulations containing lactose is more mobile and reactive, resulting in higher degradation.

Figures 5 & 6 show that tablet physical properties also changed over time. The hardness of the tablets with lactose initially increased, then showed a large drop (minus 46%) by the end of the six month study. Starch 1500 containing tablets remained fairly stable in hardness dropping by less than 15%. Over time, both coated and uncoated tablets picked up some moisture. 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.

Figure 5: Change in Tablet Hardness

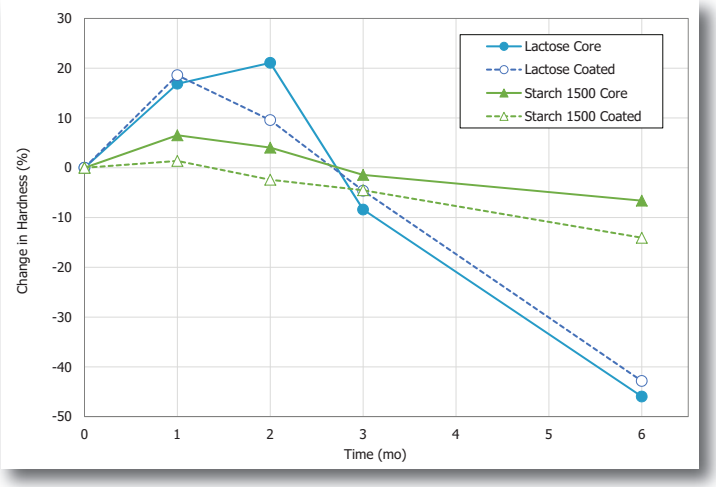
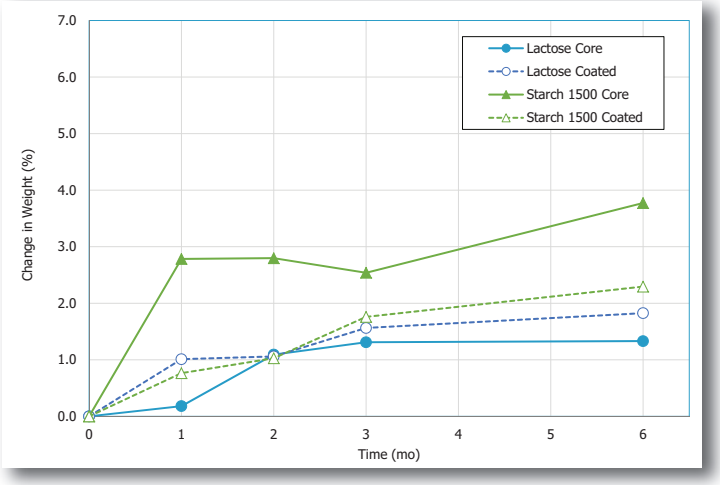


Figure 6: Change in Tablet Weight



Conclusions

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 tablets, coated with PVA based Opadry II and packed in Aclar 2000. The formulation containing lactose monohydrate was less stable with both coated and uncoated formulations failing for impurity content. Hydrolysis in the lactose formulation also resulted in unidentified degradants.

References

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2. Ali R. Rajabi-Siahboomi, Marina Levina, Sampada B. Upadhye and Jason Teckoe, 'Excipient Selection in Oral Solid Dosage Formulations Containing Moisture Sensitive Drugs in; Excipient Applications; editors: Narang AS and Boddu SHS, Formulation Design and Drug Delivery, ISBN: 978-3-319-20205-1.