EXCIPIENTS STARCH 1500®
PARTIALLY PREGELATINIZED MAIZE STARCH

Technical Data
Direct Compression
Ranitidine Formulation

Direct Compression Formulation Using Starch 1500® with Ranitidine HCl (150 mg) Tablets, Film Coated with Opadry® II (85F Series)

INTRODUCTION

Ranitidine hydrochloride (HCl) is used to treat ulcers, gastroesophageal reflux disease (GERD) (a condition in which backward flow of stomach acid causes heartburn and injury of the esophagus), and conditions where the stomach produces too much acid, such as Zollinger-Ellison syndrome. Over-the-counter ranitidine is used to prevent and treat symptoms of heartburn associated with acid indigestion and sour stomach. Ranitidine HCl is an H_2 blocker which decreases the amount of acid produced in the stomach.

Ranitidine HCl is a moisture-sensitive drug and can be a challenge to formulators because of its tendency to hydrolyze when exposed to humidity and/or high temperatures. The development of a tablet containing a moisture sensitive drug is subject to those high temperatures and high humidity during the film coating process. Therefore, it is important that the core formulation be composed of excipients that will help prevent the drug from decomposing.

Stability of moisture sensitive drugs can be improved by enlisting different techniques. Since humidity in the air can be absorbed by the product, the manufacturing area can be humidity controlled to keep moisture at a low level. Protective packaging, such as foil-foil blisters can be used to prevent transmission of moisture through the package. These two methods are typically very expensive. The selection of ingredients within the dosage form can be optimized in order to reduce the hygroscopicity and to reduce the activity of the water within the product. Also, a moisture barrier film coating can be applied to the product which will allow it to withstand higher humidity environments.

Starch 1500® is a multi-functional excipient designed specifically for use in the formulation of pharmaceutical oral solid dosage forms. Manufactured exclusively for the global pharmaceutical market, Starch 1500® is a pharmaceutical grade of partially pregelatinized maize starch. Starch 1500® brings benefits to formulations through binding capability, improved disintegrant/dissolution properties, enhanced flow and lubricity, as well as moisture protection.

Opadry® II is a custom formulated, dry blend system for the aqueous film coating of solid dosage formulations. Opadry® II film coatings systems provide the user with short process times and superior film finish. Additionally, custom developed systems offer enhanced protection for moisture sensitive cores.

OBJECTIVE

The objective of this study was to evaluate the physical and chemical stability of a core formulation containing Starch 1500® and film coated with Opadry® II for a ranitidine HCl tablet.

MATERIALS AND METHODS

Table 1 lists the formulation used in this study. All materials, with the exception of magnesium stearate, were blended for 10 minutes in a Turbula® T2A blender. Magnesium stearate was added and blended for an additional 2 minutes. Tablets were compressed on an instrumented (SMI) Piccola

Table 1. Formulation

Ingredients [Manufacturer]	Percent	mg / tablet
Ranitidine HCl USP [Orchev Pharma]	54.00	167.39
Microcrystalline Cellulose NF [Avicel® PH-102, FMC]	25.25	78.28
Pregelatinized Starch NF [Starch 1500®, Colorcon]	20.00	62.00
Fumed silica NF [Aerosil® 200, Degussa AG]	0.50	1.55
Magnesium Stearate NF [Peter Greven]	0.25	0.78
Total	100.00%	310.00

Colorcon

(Riva) 10-station, rotary tablet press using 9 mm standard concave tooling at 30 RPM. Tablet hardness, ejection force, weight, thickness, friability, and disintegration times were measured. Tablets were coated to a 4% weight gain in an O'Hara 15" side-vented coating pan with Opadry® II (85F18378 white, suspension at 20%). Table 2 lists the coating parameters used. Tablet weight, diameter, thickness, hardness, and disintegration times were measured after coating. The film coated tablets were packaged in foil-sealed 150-cc HDPE bottles with a desiccant. Stability testing was conducted at 40°C/ 75% RH for 6 months and at 25°C/60% RH for 12 months.

Table 2. Film Coating Parameters

Inlet Air Temperature	60°C
Exhaust Air Temperature	50°C
Air Flow	245 CMH
Spray Rate	6 g/min
Atomization Air	2.0 bar
Pattern Air	2.0 bar
Pan Speed	20 RPM

RESULTS AND DISCUSSION

Table 3 lists the tablet properties measured prior to film coating. The formulation had good powder flow, which allowed the production of tablets with a very low weight variation of 0.6%. The mechanical strength of the tablets was acceptable, yielding a hardness of 11.5 kp before coating (see Figure 1). Friability of the cores was nearly zero for this formulation. Disintegration time of the core formulation (see Figure 2), was rapid, with a value of less than 10 minutes. Ejection force was within acceptable limits, utilizing only a small quantity of lubricant in the formulation, due to the self-lubricating properties of Starch 1500®.

Table 3. Tablet Properties

Weight	310 mg
Weight Variation (RSD)	0.60%
Hardness	11.5 kp
Friability	0.06%
Thickness	3.59 mm
Ejection Force	212 N
Disintegration Time	9.7 min
Dissolution, $T_{80\%}$ in water	13 min
Tooling: Round 9 mm standard concave **Compression Force:** 15 kN	

As expected, application of film coating resulted in a slight increase in tablet hardness (see Figure 1). Tablet disintegration time was not significantly affected by the film coating application, as can be seen in Figure 2. Figure 3 shows the dissolution profiles for the uncoated and coated tablets. The use of Starch 1500® in this formulation resulted in 100% of the drug being released within 25 minutes compared to the USP limit of not less than 80% (Q) in 45 minutes.

Figure 1. Tablet Hardness

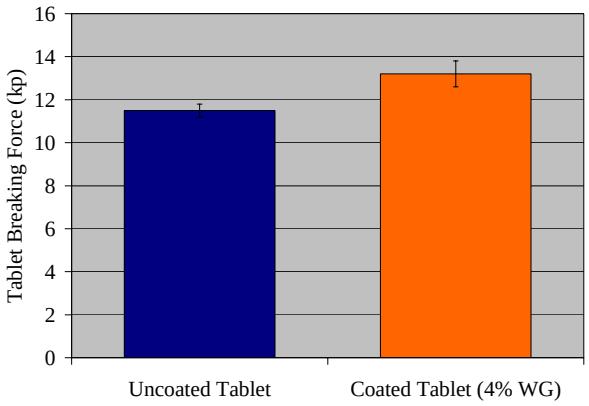


Figure 2. Tablet Disintegration Time

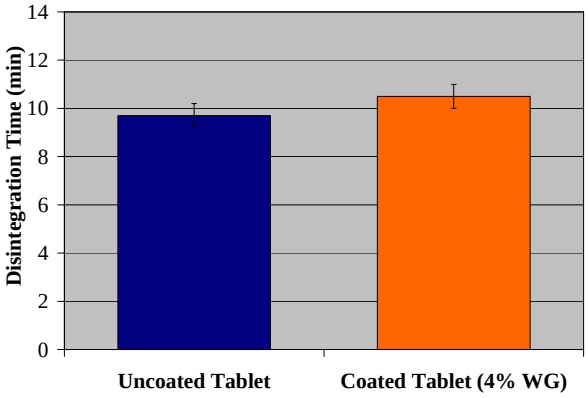
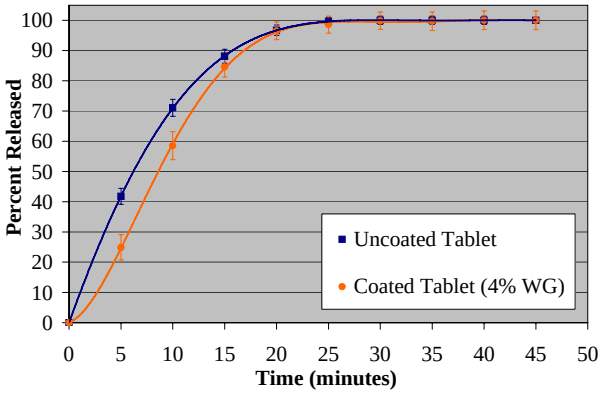


Figure 3. Dissolution: Media DI Water



Tables 4 and 5 show the data generated on storage of the film coated product. No significant changes were recorded for coated tablets after 6 and 12 months of storage for any property measured. Stability of this formulation is in part due to the inclusion of Starch 1500® in the formulation. Starch 1500® acts as a moisture scavenger and retains moisture in its complex structure of glucose polymer chains. These polymers offer many sites for hydrogen bonding of water thereby reducing the water activity of the product. Figure 4 shows the water activity of various excipients in comparison to their moisture content. Even though Starch 1500® has a high moisture content, compared to other excipients, it provides good stability to moisture sensitive drugs due to its low water activity. A slight increase in tablet hardness was seen after storage (see Figure 5). Figure 6 (next page) shows the disintegration time after storage; again, no significant changes were seen.

Table 4. Stability Data Summary – Test Results for 40°C/ 75% RH Storage Conditions

Test	USP limits	Initial	1 month	3 months	6 months
Breaking force (kp)		13.2	14.9	14.9	14.9
Friability (%)	NMT 1.00%	0.00	0.00	0.00	0.00
Disintegration (min)		11	12	12	12
Dissolution, $T_{85\%}$ (min)	NLT 85% in 45 min	15	15	15	15
Assay (%)	90 - 110	105	100	98	98
Impurities (%)	NMT 2%	0.5	0.8	0.8	1.3

Table 5. Stability Data Summary – Test Results for 25°C/ 60% RH Storage Conditions

Test	USP limits	Initial	1 month	3 months	6 months	12 months
Breaking force (kp)		13.2	14.0	14.0	14.6	14.5
Friability (%)	NMT 1.00%	0.00	0.00	0.00	0.00	0.00
Disintegration (min)		11	11	12	12	12
Dissolution, $T_{85\%}$ (min)	NLT 85% in 45 min	15	15	15	15	15
Assay (%)	90 - 110	105	104	100	100	100
Impurities (%)	NMT 2%	0.5	0.8	0.8	0.8	0.8

Figure 4. Water Activity vs. LOD

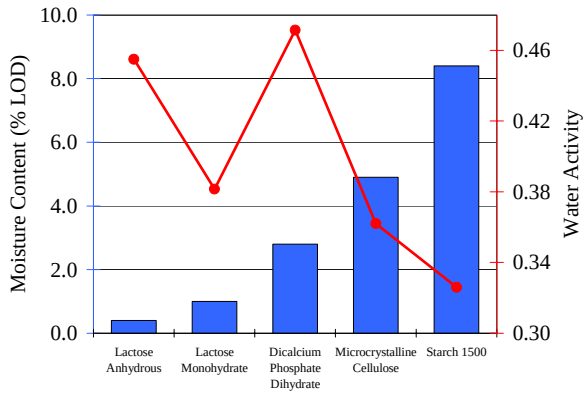


Figure 5. Tablet Hardness on Storage

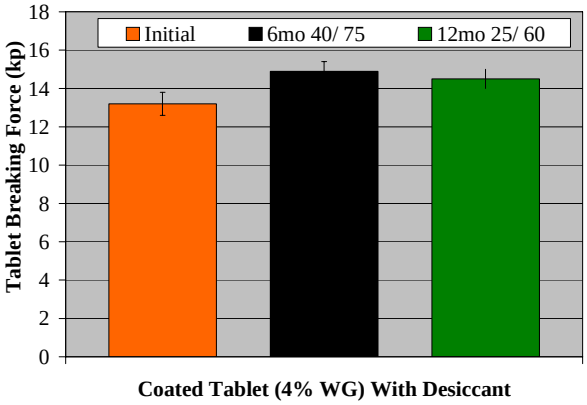
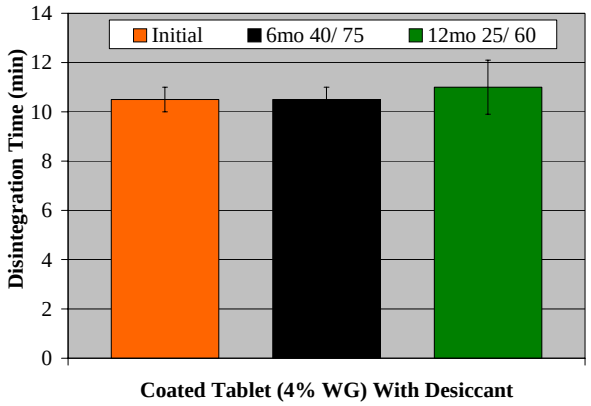


Figure 6. Tablet Disintegration Time on Storage



CONCLUSIONS

A relatively simple formulation of microcrystalline cellulose and Starch 1500® was found to produce robust tablets with high mechanical strength and low friability. The use of Starch 1500® as a filler-disintegrant in the ranitidine formulation was responsible for rapid tablet disintegration and drug dissolution. Starch 1500® also provided good stability results in this formulation due to its ability to reduce the water activity of the formula. Application of Opadry® II (85 series) film coating provided an elegant finish to the product. The film coating showed little effect of the disintegraton and dissolution of the cores. The stability data presented, shows that the combination of core formulation, processing conditions, and film coat produced a stable product maintaining values within USP limits for accelerated and room temperature conditions. Further evaluation of film coating level and type of Starch 1500® used in the core can be found in the Colorcon AAPS 2004 poster reprint “The Influence of Core Formulation, Film Coating Level and Storage Conditions on Stability of Ranitidine Tablets”.

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