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Partially Pregelatinized Maize Starch

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Stability Improvement of a Moisture-Sensitive Drug, Ranitidine HCl, with the Inclusion of a Partially Pregelatinized Starch

Authors: Raxit Y. Mehta, James Henry, Manish Ghimire, Maureen Vander Fliet and Ali R. Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA | AAPS Poster Reprint 2020

Introduction

Ranitidine HCl has been widely used as a prescription and over the counter medicine for the treatment of stomach and intestinal ulcer, gastroesophageal reflux disease (GERD) and erosive esophagitis. It has been reported that the stability of ranitidine HCl is significantly affected by elevated humidity and temperature. Recently, the FDA advised pharmaceutical companies to recall ranitidine HCl formulations from the market over concern of the presence of N-nitrosodimethylamine (NDMA) impurity. This recall presents an opportunity for pharmaceutical companies to reformulate ranitidine HCl core using excipients to help improve the stability of the drug. It has been shown that Starch 1500®, partially pregelatinized maize starch has moisture scavenging properties and its inclusion within the formulation may enhance drug stability[1].

Hence, the purpose of this study was to investigate the influence of Starch 1500 on the stability of ranitidine HCl, a moisture sensitive drug. The stability of coated ranitidine HCl tablets, containing Starch 1500 was evaluated in comparison to a marketed product. Ranitidine HCl tablet samples were dispensed into a pill organizer (also known as multidose compliance aid) and exposed to 40°C/75% RH storage conditions for 14 days. Tablets were tested for drug assay and impurities each day for one week and then at 14 days.

Methods

Ranitidine HCl Tablet Formulation

A marketed ranitidine HCl (150 mg) tablets consisting of drug and MCC, as per the drug label information, was purchased from a pharmacy store and use in this study. Also, two alternative formulations were developed using ranitidine HCl and microcrystalline cellulose (MCC), with and without Starch 1500 together with colloidal silicon dioxide and magnesium stearate (Table 1). Powders were blended in a twin shell blender for 10 mins, followed by lubrication with magnesium stearate for 3 mins. The blends were compressed to a target tablet weight of 311 mg with a drug dose of 150 mg ranitidine HCl, then they were film coated.

Table 1: Formulation of Ranitidine HCl 150 mg Tablets

Ingredients	Formulation 1: Starch 1500: MCC, 1:2 ratio, %	Formulation 2: MCC, %
Ranitidine HCl	54.00	54.00
Partially Pregelatinized Maize Starch (Starch1500, Colorcon, USA)	15.08	—
Microcrystalline Cellulose (Avicel PH-102, Dupont Nutrition & Bioscience, USA)	30.17	45.25
Colloidal silicon dioxide (CAB-O-SILM5P, Cabot Corporation, USA)	0.50	0.50
Magnesium Stearate (Peter Greven GmbH, DE)	0.25	0.25
Total	100.00	100.00

Open Dish Stability Study Design

The two ranitidine HCl tablet test formulations and the marketed product were stored in a pill organizer at 40oC/75% RH conditions as shown in Figure 1. Samples were pulled every day, for the first 7 days, then following 14 days of storage. The samples were analyzed for ranitidine assay as well as impurities, using high performance liquid chromatography (HPLC).

Figure 1: Pill Organizer for Open Dish Stability Evaluation

Drug Assay and Impurity Evaluation

Stability of the 3 formulations in the pill organizers were evaluated through assay of ranitidine and degradant using the HPLC gradient method. Sample solution was prepared by dissolving 10 tablets in 98:2, pH 7.1 phosphate buffer: acetonitrile solvent system. The sample and standard solution were analyzed by C18 column using gradient of mobile phase A of 98:2 pH 7.1 phosphate buffer: acetonitrile and mobile phase B containing 78:22 pH 7.1 phosphate buffer: acetonitrile injected at the flow rate of 1.5 mL/min. Ranitidine peak was detected using the LC UV detector at 230 nm.

Results

Tablet Property and Disintegration Time

- Application of 12KN or higher compression force resulted in the tablet hardness>10KP (>2MPa) for both formulations (with and without Starch 1500 inclusion).
- Tablet formulations, with and without Starch 1500, produced low friability tablets (<0.15% w/w).
- Inclusion of Starch 1500 to MCC resulted in lower ejection force of the tablets indicating the lubricity of Starch 1500 (189N with Starch 1500 vs 288N without Starch 1500 inclusion).
- The disintegration time for the Starch 1500 formulation was low, demonstrating the additional benefit of Starch 1500 inclusion on the disintegrant property for the ranitidine HCl tablets.

Drug Assay and Impurity Analysis

- Figures 3 and 4 display the reduction of drug content and the growth of total impurities of the samples, respectively.
- The loss of drug was less for the formulation containing Starch 1500 with 85% w/w of drug remaining after 14 days of storage, while the formulation without Starch 1500 contained 60% w/w of the drug and the marketed product contained 59% w/w of the drug.
- The rate of degradation followed the sigmoidal shape; hence, the drug assay remained constant for the first 4 days. After the initial appearance of impurities, the degradation rate appeared to increase. The level of impurities in the Starch 1500 containing formulation was significantly lower (12% w/w).

Visual Observation of the Tablet Formulations during Stability Testing

- Coated tablets in the pill organizer, exposed to the open dish 40°C/75% RH conditions, led to coating rupture within 4-6 h for the marketed product and within 24h for the two developmental formulations.
- The color of the core composition changed from pale white to brown after 4 days and progressively worsened during the remainder of the study.

Figure 2: Images of Tablets Retained for Stability Study

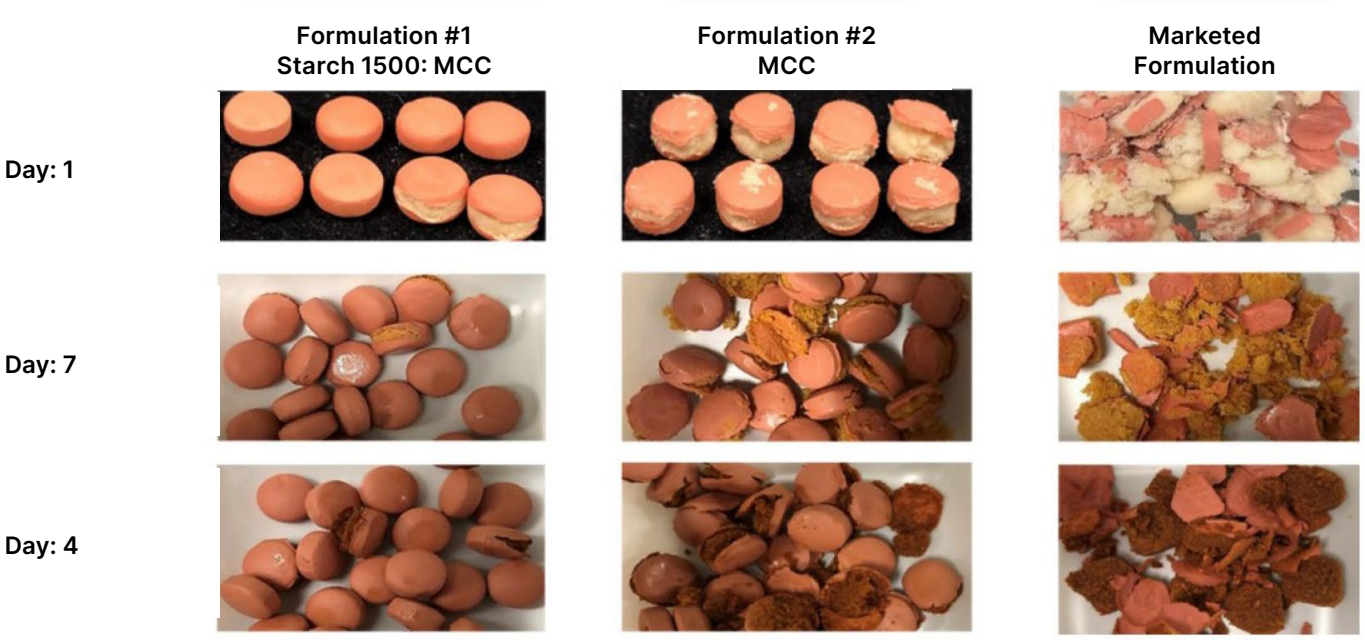


Figure 3: Drug Content of Ranitidine HCl Tablet on Stability

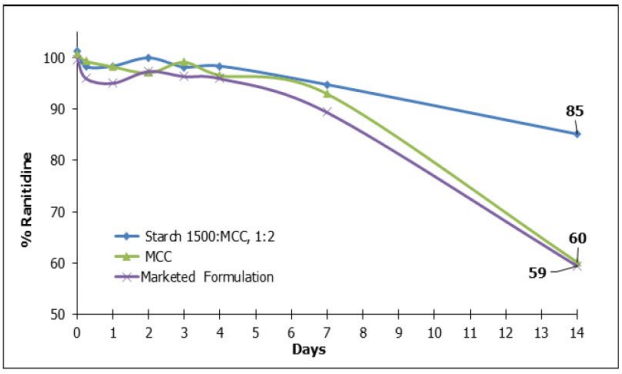
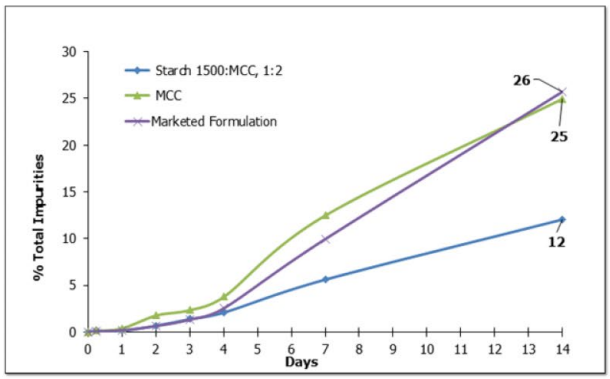


Figure 4: Total Impurity of Ranitidine HCl Tablet on Stability



Conclusions

- Ranitidine HCl tablet formulations using MCC, with and without the inclusion of Starch 1500 as fillers were investigated for drug stability when dispensed in a pill organizer at 40oC /75% RH.
- The inclusion of Starch 1500 within the core formulation reduced the rate of degradation of ranitidine and led to lower levels of total impurities.
- The enhanced stability of ranitidine HCl tablets is attributed to the moisture scavenging property of Starch 1500 to reduce drug hydrolysis and degradation.

References

1. Cunningham CR, Kinsey B, Scattergood LK. Formulation of Acetylsalicylic Acid Tablets for Aqueous Enteric Film Coating. Pharmaceutical Technology, DRUG DELIVERY 2001, pp 38-43.

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North America	Europe/Middle East/Africa	Latin America	India	China
+1-215-699-7733	**+44-(0)-1322-293000**	**+54-1-5556-7700**	**+91-832-6727373**	**86-21-61982300**

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