ICH Stability of Dietary Supplements Coated with an Aqueous Ethylcellulose Based Delayed Release Coating for Nutraceutical Applications

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Purpose

Coating solid dosage forms with pH sensitive polymers to deliver drugs to specific sites of the gastrointestinal (GI) tract is a common practice of the pharmaceutical industry.[1] The release of drug is tailored by applying a polymeric coating that is soluble as a function of environmental pH value. Most frequently employed are cellulosic or acrylic-based polymers.[2] Delayed release systems have several applications in pharmacy, both for specific drugs and/or disease states. Among these are; protection of the active substance from degradation by gastric fluids (enzymes or highly acidic gastric fluids), prevention or reduction of nausea and vomiting associated with a drug's irritation, and delivery of the drug to its absorption site in the intestine.[3] Delayed release coatings are also a convenient and effective way to improve consumer appeal of dietary supplement products by reducing unpleasant flavors and odors, enhancing the stability of natural ingredients and by improving overall product performance.

Nutrateric®, nutritional enteric coating system, is an aqueous enteric coating system that meets dietary supplement regulations and enteric disintegration requirements. Garlic tablets and fish oil soft gelatin capsules (softgels) are two common dietary supplements with unpleasant tastes and odors. The purpose of this study was to evaluate the effects of long-term storage on delayed release (DR) performance of garlic tablets and fish oil softgels coated with Nutrateric.

Methods

Materials

Garlic tablets and fish oil softgels were selected as model dietary supplement substrates due to their unpleasant odor and taste. Nutrateric is an aqueous enteric coating system comprised of Surelease®, aqueous ethylcellulose dispersion, and NS Enteric®, nutritional enteric component. Surelease contains water-insoluble ethylcellulose that acts as a barrier while NS Enteric contains a pH dependent pore former, allowing release at the higher pH of the small intestine. Opadry® NS, complete film coating system for nutritional supplements, was also used as a seal-coat.

Materials used in the preparation of the stability samples are listed in **Table 1**.

Methods (cont'd)

Table 1. Materials Used

Product	Supplier	Location
Substrate		
Garlic 250 mg Tablets	Vitaminerals, Inc.	Glendale, CA
Fish Oil 1000 mg Softgels	Nutra Manufacturing, Inc	Greeneville, SC
Coating Formulations		
Surelease	Colorcon, Inc.	Indianapolis, IN
NS Enteric	Colorcon, Inc.	West Point, PA
Opadry NS	Colorcon, Inc.	West Point, PA
Packaging Supplies		
100 cc HDPE Bottles	ALPHA Packaging	St. Louis, MO
Ribbed caps with foam liner	Mold Rite Plastics	Plattsburgh, NY

Preparation of Samples

A seal-coat of Opadry® NS was applied to 3% theoretical weight gain (WG) at 7.5% solids to the garlic tablets in order to provide additional mechanical strength to the core. Nutrateric, prepared using 85% Surelease and 15% NS Enteric, was applied to 4% WG at 10% solids to the seal-coated garlic tablets and fish oil softgels. All coatings were performed in an O'Hara Labcoat II 24-inch, fully-perforated pan. The Nutrateric coating process parameters are listed in **Table 2**.

Table 2. Coating Process Parameters

Process Parameter	250 mg Garlic Tablets	1000 mg Fish Oil Softgels
Equipment	O'Hara Labcoat II, 24"	O'Hara Labcoat II, 24"
Inlet Air Temperature (°C)	65-67	50-52
Outlet Air Temperature (°C)	41-43	31-33
Product Temperature (°C)	38-41	31-33
Spray Rate (g/min)	55-60	49-50
Pan Speed (rpm)	12	12
Atomizing Air Pressure (psi, bar)	25, 1.7	30, 2.0
Pattern Air Pressure (psi, bar)	30, 2.0	35, 2.4
Inlet Air Volume (cfm, m^3/hr)	250, 425	270, 459
Charge (kg)	15	12

Coated and uncoated tablets and softgels were then packaged in 100 cc high-density polyethylene (HDPE) bottles, induction-sealed, and stored at intermediate (30°C/65%RH) for 12 months, and at accelerated conditions (40°C/75%RH) for 6 months, according to ICH guidelines. Samples were pulled at predetermined intervals and subjected to delayed release testing.

Delayed Release Performance Testing

DR performance of coated garlic tablets and fish oil softgels was assessed according to USP 32-NF 27, <2040> Disintegration and Dissolution of Dietary Supplements, Delayed Release (Enteric-Coated) Tablets.[4] Delayed release testing consisted of reciprocation of the coated dosage form (n=6) for 1 hour in simulated gastric fluid (SGF) at 37 ± 2°C. This was followed by reciprocation and complete disintegration or rupture in simulated intestinal fluid (SIF) at 37 ± 2°C. Testing of coated garlic tablets was performed using Apparatus A, which is required for tablets or capsules less than 18 mm long. Testing of coated fish oil softgels was performed using Apparatus B, which is required for tablets or capsules more than 18 mm long.

SGF and SIF were prepared according to the USP.[5]

Fluid Uptake

Fluid uptake evaluations provide an indication of the ability of the coating to protect the active from the effects of gastric fluid. Coated tablets and softgels for evaluation were individually weighed and fluid uptake was measured after exposure to SGF for 60 minutes. After removing the samples from SGF and inspecting for any defects (cracking, disintegrating, or softening) excess fluid was removed and the samples were reweighed. The amount of SGF taken up by the coated garlic tablets and fish oil softgels was determined by calculating the percent difference between weights before and after exposure according to **Equation 1**.

Equation 1.

$$Fluid\ Uptake(\%) = \left[\frac{T_f - T_i}{T_i}\right] \times 100$$

where:

T_f = Final tablet weight (mg)
T_i = Initial tablet weight (mg)

Disintegration

Complete disintegration (DT), the state in which any residue of the unit is a soft mass having no palpably firm core, was determined as the endpoint for testing of the coated garlic tablets. Time of rupture (RT), the time at which the softgel capsule allowed the release of the softgel contents into the disintegration vessel, was determined as the endpoint for testing of the coated fish oil softgels.[4] Time of disintegration or rupture was recorded for garlic tablets and fish oil softgels respectively.

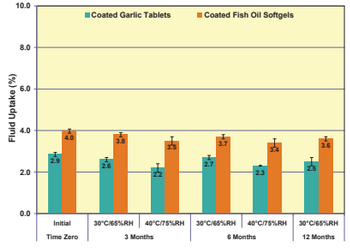
Results

All coated garlic tablets and fish oil softgels were observed to be physically intact, showing no signs of cracking, disintegrating, or softening after fluid uptake testing in SGF. Samples were then transferred to SIF for disintegration and rupture testing during which all samples tested reached their specified end point.

Fluid uptake values for both coated tablets and softgels showed no increase after 6 months of storage at accelerated conditions, and 12 months of storage at intermediate conditions. These stable values for fluid uptake show exceptional enteric protection and robustness provided by the Nutrateric enteric coating. The fluid uptake data is shown in **Figure 1**.

Results (cont'd)

Figure 1. Influence of Storage Time and Condition on Fluid Uptake.



After 1 hour in SGF, the disintegration time for coated tablets or rupture time for coated softgels, was recorded. The DT of coated garlic tablets decreased by 4 minutes after 6 months and increased by 4 minutes after 12 months of storage at 30°C/65%RH, and increased by 40 minutes after 6 months of storage at 40°C/75%RH. Although there is a 40 minute increase in DT of coated garlic tablets observed after 6 months storage at accelerated conditions, no increase is noted in the DT of coated garlic tablets after 12 months storage at intermediate conditions. The rupture time of coated softgels, however, decreased 4 minutes and 13 minutes after 6 and 12 months storage at intermediate conditions, respectively, and increased 2 minutes after 6 months storage at accelerated conditions. The disintegration and rupture times are shown in **Figure 2** and **Figure 3**.

Figure 2. Influence of Storage Time and Condition on Disintegration/Rupture Time on Garlic Tablets

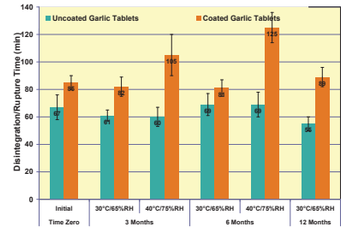
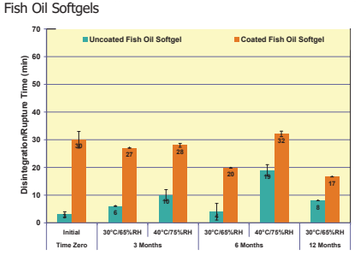


Figure 3. Influence of Storage Time and Condition on Disintegration/Rupture Time on Fish Oil Softgels



Conclusions

This study demonstrated the stability of garlic tablets and fish oil soft gelatin capsules when coated with Nutrateric, nutritional enteric coating system. Nutrateric-coated garlic tablets and fish oil softgels maintained delayed release performance characteristics following storage at intermediate and accelerated ICH conditions. This ensures that consumers will avoid the undesirable taste and odor of these dietary supplements, while still attaining the nutritional benefits.

References

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4. USP 32-NF 27 specifications; <2040> Disintegration and Dissolution of Dietary Supplements: Delayed Release Tablets
5. USP 32-NF 27; Reagents: Test Solutions