

# Pilot and Production Scale Evaluation of an Improved High Productivity Delayed Release Coating for Dietary Supplements

Charles Cunningham, George Reyes and Thomas Farrell

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Nutraferic® II

## Purpose

Nutraferic®, launched in 2003, was a revolutionary alternative to traditional shellac-based systems for enteric coating of dietary supplements. The enhanced aqueous enteric film coating system, Nutraferic® II, has been developed for improved coating productivity. The system is based on Surelease®, aqueous ethylcellulose dispersion, with NS Enteric®, nutritional enteric component as a pH dependent pore-former within the Surelease film. NS Enteric provides resistance to acidic media with disintegration of the film at higher physiological pH.

Using a Design of Experiment (DOE) approach, this study evaluated the optimum ratio of Surelease to NS Enteric to provide protection in simulated gastric fluid (SGF) while allowing acceptable disintegration performance in simulated intestinal fluid (SIF). The effects of coating dispersion solids concentration and coating weight gain were also investigated.

## Methods

The materials used in the study are listed in **Table 1**.

*Table 1.* Substrate and Coating Materials

Materials	Identification	Manufacturer
Fish oil soft gelatin capsules (1000 mg)	#106688	Nutra Manu., Greenville, SC
Surelease, aqueous ethylcellulose dispersion	E-7-19040	Colorcon Inc, West Point, PA
NS Enteric, nutritional enteric component	77U190002	Colorcon Inc, West Point, PA

The DOE consisted of 25 separate coating trials conducted in a 24" fully perforated, side-vented coating pan (Labcoat II, O'Hara Technologies, Richmond Hill, Ontario, CA) equipped with two spray guns (VAU, Spraying Systems Inc. Wheaton, IL, USA). A post DOE production scale confirmatory trial was conducted in a 48" fully perforated, side-vented coating pan (Fastcoat, O'Hara Technologies) equipped with four spray guns (930, Schlick, Düsen-Schlick GmbH, Coburg Germany).

The study variables and process constants are listed in **Table 2**.

*Table 2.* Study Variables and Coating Constants

Experiment Variables			
Variable Name	Units	Range	
		Low	High
Surelease concentration	%	70	85
NS Enteric concentration	%	15	30
Coating dispersion solids concentration	%	10	20
Applied coating weight gain (WG)	%	3	5
Process Constants			
Pan load	kg	12	
Pan speed	rpm	14	
Target product temperature*	°C	32-35	
Spray rate	g/min	70	
Process air flow	cfm / m <sup>3</sup> /hr	275 / 470	
Atomizing air pressure	psi / bar	20 / 1.4	
Pattern air pressure	psi / bar	25 / 1.7	

\* Process inlet temperature was varied as needed to maintain the target product temperature setting for each trial.

## Dispersion Preparation

The Nutratric II coating dispersions were prepared by mixing NS Enteric in deionized water and stirring (low shear) for 30 mins. Surelease was then added to the dispersion, at required level, and mixing continued for an additional 15 mins before coating application.

## Delayed Release Testing

Enteric performance of the coated soft gelatin capsules (softgels), from each trial, was assessed according to USP 32-NF 27, <2040> Disintegration and Dissolution of Dietary Supplements, Delayed Release (Enteric Coated) Tablets.<sup>1</sup>

Testing of the softgels was performed using disintegration Apparatus B, which is required for capsules more than 18 mm long. Delayed release testing consisted of reciprocating the coated softgels (n=6) for 1 hour in simulated gastric fluid (SGF) at  $37 \pm 2^\circ\text{C}$ , followed by reciprocation and rupture in simulated intestinal fluid (SIF) at  $37 \pm 2^\circ\text{C}$ . SGF and SIF were prepared according to the USP.<sup>2</sup>

## Acid Uptake

Acid uptake evaluations provide an indication of the ability of the coating to protect the softgel from the effects of gastric fluid. Coated softgels were individually weighed (n = 6), and fluid uptake measured after exposure to SGF for 60 mins. After removing the samples from SGF and inspecting for any defects (cracking, disintegrating or softening), excess fluid was removed and the samples re-weighed. The amount of SGF taken up by the coated fish oil softgels was determined according to Equation 1.

Equation 1

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

where:

$T_f$  = Final tablet weight (mg)

$T_i$  = Initial tablet weight (mg)

## Disintegration Time

Time of rupture (RT) is the time taken for release of contents into the disintegration vessel. This is determined as the end-point for testing of the coated fish oil softgels.

The coated softgels were examined for rupture (n=6) and % acid uptake after 60 min in simulated gastric fluid (SGF). Disintegration time (DT) in simulated intestinal fluid (SIF) was also tested (n=6).

## Results

The DOE coating trials resulted in coated softgel acid uptake values from 3.49% with no signs of rupture, up to 10.0% when some softgels exhibited slight leakage of fish oil. The rupture time of the coated softgels in SIF ranged from 18 to 58 mins. Analysis of % acid uptake and disintegration time in SIF, indicated the effects of Surelease:NS Enteric ratios and applied weight gain were interdependent. Higher concentrations of Surelease in the coating improved gastric resistance, but lengthened disintegration time in SIF. Increasing coating weight gain resulted in lower acid uptake with prolonged disintegration time of the softgels in SIF.

Response surface graphs (**Figures 1-6**) were developed to illustrate these interactive effects and aid in determining the optimum Surelease:NS enteric ratios, and weight gain, that would provide robust protection in SGF while still resulting in acceptable disintegration times in SIF.

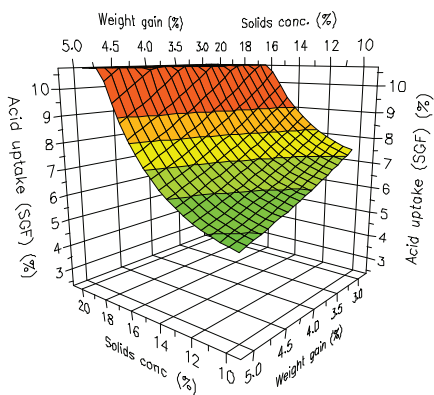
The criteria for determining the optimum Surelease:NS Enteric ratio was to obtain > 60 mins of protection from rupture in SGF, with disintegration times (DT) of < 30 mins in SIF.

As shown in **Figures 2 and 4**, a ratio of 75:25 Surelease:NS Enteric was found to provide the optimum balance between low % acid uptake in SGF and acceptable (<60 min.) DT in SIF. At up to 15% solids concentration, this ratio resulted in <5% acid uptake with no ruptures after 60 min in SGF and < 25 min DT in SIF.

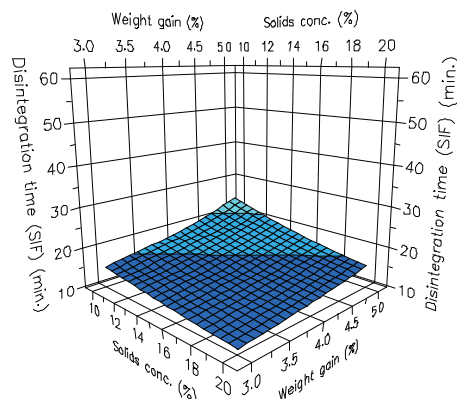
Increasing acid uptake values, as solids concentrations exceed 15%, is attributed to reductions in coating time, resulting in reduced coating uniformity at low weight gains.

At ratio of 75:25 and 15% solids concentration, the Nutrateric II coating dispersion viscosity was 204 cP. This is a substantial reduction in viscosity vs the original Nutrateric system which was limited to 10% solids application level due to its higher viscosity. This lower dispersion viscosity alone reduces application time by 33% for Nutrateric II.

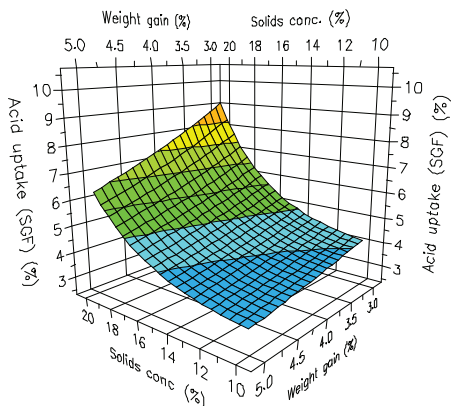
**Figure 1. Acid Uptake (SGF)**  
Surelease:NS Enteric 70:30 ratio



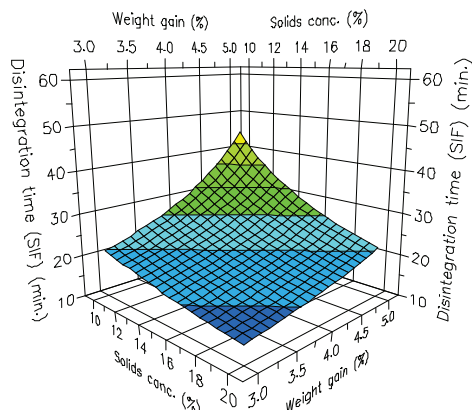
**Figure 4. Disintegration time (SIF)**  
Surelease:NS Enteric 70:30 ratio



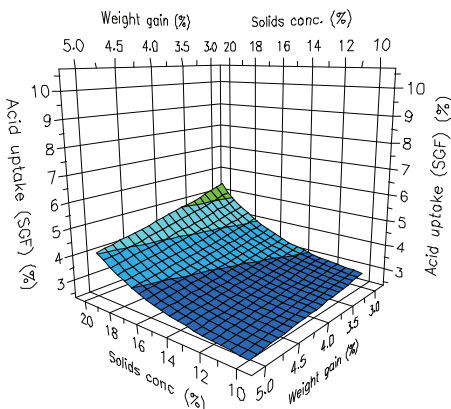
**Figure 2. Acid Uptake (SGF)**  
Surelease:NS Enteric 75:25 ratio



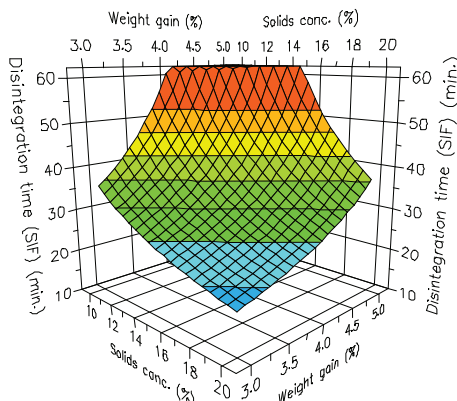
**Figure 5. Disintegration Time (SIF)**  
Surelease:NS Enteric 75:25 ratio



**Figure 3. Acid Uptake (SGF)**  
Surelease:NS Enteric 80:20 ratio



**Figure 6. Disintegration Time (SIF)**  
Surelease:NS Enteric 80:20 ratio



## Production Scale Trial

A 48" scale coating trial was conducted using the optimum Nutrateric II formulation ratio, as identified from the 24" scale DOE. The coating parameters are listed in **Table 3**.

**Table 3. Production Scale Coating Parameters**

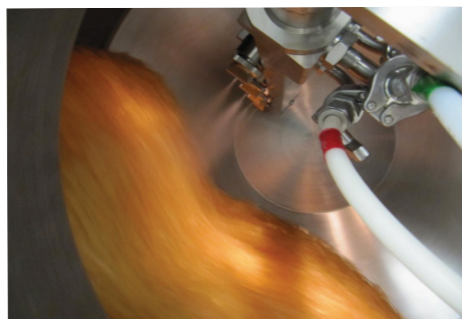
Coating Parameters	Units	Values
Surelease : NS Enteric	ratio	75:25
Coating dispersion solids concentration	%	15
Applied coating weight gain	%	3.5
Pan load	kg	100
Pan speed	rpm	7
Target product temperature*	°C	32-35
Spray rate	g/min	400
Process air flow	cfm /m <sup>3</sup> /hr	1800 /3060
Atomizing air pressure	psi / bar	25 /1.7
Pattern air pressure	psi / bar	30 / 2.1
Total coating time	minutes	58.3

The production scale trial was problem free, with the coating pan remaining clean and no clogging or build-up on the spray guns (**Figure 7**).

The Nutrateric II coated soft gelatin capsules were smooth in appearance, with no visible defects. No evidence of spray drying or non-uniformity of film in the capsule seams was seen, which could be a problem with coating of soft gelatin capsules (**Figure 8**).

The delayed release testing results were consistent with the coating trial run at optimum conditions of 24" scale. At 3.5% WG, acid uptake (SGF) was <5.0% with no ruptures observed, and DT in SIF was 35min.

**Figure 7.** Application of Nutrateric II in Production Scale Pan



**Figure 8.** Nutrateric II Coated Soft Gelatin Capsules (48" scale /100kg charge)



## Conclusions

Optimum formulation parameters were determined for Nutrateric II nutritional enteric coating system. These parameters were successfully transferred to production scale with consistent disintegration results. Application of Nutrateric II at 15% solids concentration with a higher spray rate (400g/min in 48" pan) resulted in a 41% reduction in coating time, compared to the first generation Nutrateric system. These efficiency improvements result in increased coating productivity and could reduce the need or delay expensive capital investments in expanding coating capacity.

## References

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

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For more information, contact your Colorcon representative or call:

North America  
+1-215-699-7733

Europe/Middle East/Africa  
+44-(0)-1322-293000

Asia Pacific  
+65-6438-0318

Latin America  
+54-1-5556-7700

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