

The Influence of Plasticizers and a Stabilizer on Aqueous Delayed Release (DR) Coating Systems on Soft Gelatin Capsules

INTRODUCTION

Polymers commonly used for enteric coating of drug products, such as phthalates and acrylates are not approved for applications in food or nutritional supplements¹. Nutrateric[®], nutritional enteric coating system, is an aqueous DR coating system designed specifically for nutritional supplements. It is comprised of an aqueous ethylcellulose dispersion (Surelease[®]) and NS Enteric[®] (nutritional enteric component).

Nutrateric has been applied in nutritional applications with reliable and reproducible (DR) performance as well as good stability².

The Surelease family of products offers several systems which differ in plasticizer type. The objective of this study was to investigate the influence of different plasticizers and a secondary stabilizer (hypromellose, HPMC) in Nutrateric on the DR performance of coated fish oil soft gelatin capsules (SGC).

METHODOLOGY

The Nutrateric system used in this study consisted of 85% Surelease and 15% NS Enteric. Surelease products containing dibutyl sebacate (DBS), fractionated coconut oil (FCO) or oleic acid (OA) as plasticizers were evaluated in this study. All coating trials were performed at a 10% w/w dispersion solids level and samples were withdrawn at 2.0%-6.0% w/w theoretical weight gain (WG). The impact of a secondary stabilizer (HPMC) in Surelease E-7-19050 was investigated by adding the same level of HPMC to the other Surelease grades for comparison.

MATERIALS

Fish Oil Concentrate 1000 mg SGCs were obtained from LH Valencia. All other materials were provided by Colorcon: Surelease (E-7-19020, E-7-19040 and E-7-19050), NS Enteric and HPMC 6 cPs.

Nutrateric Dispersion Preparation

The enteric coating system was prepared by mixing the NS Enteric powder (15% w/w) in water for 60 to 90 minutes. Surelease (85% w/w) was then added to the dispersion slowly and mixed for an additional 30 minutes before application. When HPMC was added for evaluation, HPMC was mixed with the NS Enteric powder in water. In all cases, the final dispersion solids content was 10% by weight. The dispersion was slowly stirred during spraying.

Coating Conditions

Fish oil SGCs were coated in an O'Hara Labcoat II 15" side-vented coating pan fitted with Spraying Systems 1/8" VAU nozzle. The gun-to-bed distance was 4 inches. Coating parameters are listed in Table 1.

Table 1. Coating Parameters

Coating Parameters	O'Hara Labcoat II
Capsule charge (kg)	2.5
Inlet temperature (°C)	54-56
Exhaust temperature (°C)	39-41
Product temperature (°C)	35-38
Air flow (cfm)	175-180
Atomization air pressure (psi)	25-30
Pattern air pressure (psi)	25-30
Spray rate (g/min)	18-20
Pan speed (rpm)	19

Coating Level

The theoretical weight gain was adjusted based on the different grades of Surelease or the addition of HPMC so that the theoretical coating level of ethylcellulose was equivalent in each case, as detailed in Table 2.

Table 2. Equivalent Coating Weight Gain

Equivalent Coating Levels (%WG) with Respect to Ethylcellulose		
E-7-19020/19040 (DBS/FCO)	E-7-19020/19040 (with 2% HPMC)	E-7-19050 (OA) (with 2% HPMC)
2.00	2.14	2.09
2.50	2.67	2.61
3.00	3.20	3.13
3.50	3.74	3.66
4.00	4.27	4.18
6.00	6.41	6.27

Acid Resistance and Disintegration Testing

The DR coated SGC were reciprocated in a USP-compliant disintegration apparatus for one hour in 0.1N HCl followed by disintegration testing in pH 6.8 phosphate buffer solution. For "acid uptake" determination, the soft gels were removed after one hour testing in the acid media and blotted dry to remove excess liquid on the soft gel surface. The SGCs weight differences before and after the test relative to the initial SGCs weight were recorded as acid uptake.

Penetration Force (PF)

The penetration force was measured using TA.XT Plus Texture Analyser with two different probes (different in size, shape and material). The SGCs were placed in a fixed location centrally under the probe with the capsule seal 90° away from the probe. Testing parameters were setup to measure the penetration force, but not the capsule burst point. Analyzer settings are detailed in Table 3.

Table 3. Texture Analyzer Settings

TA Settings	Probe TA-8A (2 mm, round, s. steel)	Probe TA-10 (10 mm, flat, plastic)
Mode	Compression	Compression
Pre-test speed:	1.00 mm/sec	1.00 mm/sec
Test speed:	2.00 mm/sec	2.00 mm/sec
Post-test speed:	10.00 mm/sec	10.00 mm/sec
Distance:	8.00 mm	5.00 mm
Trigger type:	Auto/Force 5 g	Auto/Force 5 g

RESULTS AND DISCUSSIONS

Acid Resistance vs. Plasticizer and Stabilizer

Leakage of drug and "acid uptake" greater than 10% are considered failures in acid resistance tests. The results detailed in Table 4 indicated that:

- DBS or FCO provided similar and good acid protection even at relatively low coating levels.
- HPMC significantly influenced the acid resistance and showed different degrees of impact with different plasticizers (DBS>OA>FCO).

Table 4. Acid Uptake Results

Coating Level* (%)	Average Acid Uptake% in 0.1N HCl for 1 Hour**				
	DBS	DBS+ HPMC	FCO	FCO+ HPMC	OA & HPMC
2.0	6.8	Leak	7.2	16.9	Leak
2.5	6.4	Leak	5.7	10.7	Leak
3.0	4.6	29.4	5.2	9.6	Leak
3.5	4.1	25.7	4.5	8.0	14.0
4.0	4.2	19.7	4.1	7.6	Leak
6.0	3.3	13.5	3.4	5.5	6.8

* With respect to E-7-19020 and E-7-19040. ** n= 3 to 11

Disintegration Test (DT) Results

DT results demonstrated that the coated films from different plasticizer systems all disintegrated in a reasonable time frame after the acid phase with up to 6% w/w coating weight gain as detailed in Tables 5 and 6, respectively.

Tables 5. Uncoated SGC Disintegration Time (minutes)

Media	Lot A	Lot B
In 0.1 N HCl Buffer	8.38 ± 2.12	9.00 ± 1.50
In pH 6.8 Buffer	9.59 ± 3.41	10.68 ± 3.50

Table 6. Coated SGC Disintegration Time (minutes)

System	DT (minutes) in Buffer, pH 6.8 after exposure to 0.1N HCl (1 Hr)		
	3% WG	4% WG	6% WG
DBS	17	20	29
FCO	13	14	33
FCO+HPMC	-	-	17
OA+HPMC	-	-	15

Penetration Force and Film Properties

The PF on the coated capsules by TA can be affected by both film strength and flexibility. PF data showed similar trends using either TA-8A or TA-10 probes. Both plasticizer and HPMC affected the coated film flexibility based on the film cracking observation.

Results from Table 7 indicate that inclusion of HPMC with FCO had a significant influence on the film property compared to DBS. It also resulted in more brittle and weaker films. The PF trend seemed to agree with the findings from the cast film physical properties (see Figure 2) with film strength in rank order of FCO>OA>DBS and film flexibility in a rank order of DBS>OA≈ FCO.

Table 7. Penetration Force and Film Cracking Observation

System (at 6% WG)	PF (Newton)		Film Cracking ^a
	TA-8A (n=10)	TA-10 (n=5)	# of Failures (n=5)
Uncoated	39.1 ± 0.9	117.4 ± 2.7	0/5
FCO+HPMC	46.6 ± 1.6	129.9 ± 5.1	5/5 ^b
DBS	52.5 ± 1.1	144.6 ± 9.7	0/5
DBS+HPMC	74.6 ± 1.4	168.3 ± 4.0	5/5 ^b
OA+HPMC	67.5 ± 1.8	176.0 ± 5.2	4/5 ^c
FCO	73.5 ± 3.5	183.2 ± 2.6	0/5

^a Pressed by fingers and rotated for 30 seconds. ^b Film cracking was obvious.

^c Film cracking was minor.

CONCLUSIONS

Different plasticizers used in Surelease products had substantial influence on the film properties and DR performance of Nutratric systems. Surelease 19040 (commonly recommended for use in Nutratric) with FCO as a plasticizer provided excellent acid protection on the soft gelatin capsules. The inclusion of 2% HPMC to the system showed a large impact on the coated film acid resistance, which also varied with the type of plasticizer.

REFERENCES

- 1 Porter, S.C. "Coating of Pharmaceutical dosage Forms", Remington: The Science and Practice of Pharmacy, 20th ed., Lippincott Williams & Wilkins, 897-898 (2000).
- 2 Lawrence Martin, Budi Simon and Thomas Farrell. "New Enteric coating System (Nutra[®]treric) for Nutritional Supplements", Controlled Release Society Annual Meeting, June, 2005.

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