Aqueous Enteric Coating Application on Non-Banded Hard Gelatin Capsules

OBJECTIVE

To evaluate the application and performance of an aqueous enteric coating system on non-banded hard gelatin capsules.

METHODOLOGY

Hard gelatin capsules have been produced since the 1840s and are commonly used in Phase I and IIa clinical trials and finished products.[1]

Modifying drug release from capsule dosage forms is commonly achieved through coating pellets which are filled into the hard gelatin capsules. However, this may not be possible if additional equipment for producing and coating pellets is required.

Coating hard gelatin capsules containing active powder is usually considered as a challenging process and use of organic solvent is usually recommended due to moisture sensitivity of gelatin shells.

Banding of the hard gelatin capsules has been recommended to help the uniformity of the film coat covering the seam area. However, additional equipment may be necessary.

In this study non-banded hard gelatin capsules containing 17.5 mg Omeprazole (OMZ) powder were enteric coated with Acryl-EZE®, aqueous acrylic enteric system, 93F19255 in a lab-scale perforated coating pan. Omeprazole was selected to represent a moisture-sensitive, acid-labile active that requires enteric coating.

Capsule Formulations

OMZ capsule formulation is given in Table 1.

Table 1. Omeprazole Capsule Formulation

Material	Supplier	% w/w	mg/capsule
Omeprazole	Medelom	5.53	17.50
Disodium hydrogen phosphate	J.T. Baker	2.50	7.91
Maltose	SPI Pharma	70.97	224.59
StarCap® 1500	Colorcon	20.00	63.29
Cab-O-Sil	Cabot	0.50	1.58
Magnesium stearate	Mallinckrodt	0.50	1.58

Target capsule fill weight: 316.5 mg

Placebo capsules were filled with 100% StarCap 1500®, co-processed starch excipient.

Blending and Encapsulation

Colloidal silicon dioxide was hand sieved through a 30 mesh screen prior to weighing. An 8qt V-shaped blender was charged with the following materials in this order: ~50% part of the maltose, OMZ, Na2HPO4, StarCap 1500, Cab-O-Sil, followed lastly by the remainder of the maltose. The formulation was blended for 15 minutes. Finally, the magnesium stearate was added, and blended for an additional 3 minutes.

Both OMZ powder formulation and placebo were filled into hard gelatin capsules size no.1 using an IN/CAP automatic capsule filling machine (Dott Bonapace, Italy). Placebo capsules were utilized to increase the charge of substrate in the coating pan.

Coating

A mixed batch of OMZ and placebo non-banded capsules (0.44 kg) were coated in a 10" O'Hara Labcoat I side-vented coating pan using one Schlick spray gun model 970/7-1 S75. The capsules were seal-coated with Opadry®, complete film coating system, 03K19229 to a 10% theoretical coating weight gain. A 20% w/w water dispersion of Acryl-EZE 93F19255 was applied onto the seal coated capsules to various theoretical coating weight gains. Seal-coating conditions were 39-41°C capsule bed temperature, 25 psi atomizing air pressure, 25 psi pattern air pressure, 6.5 grams/minute spray rate, and 25 RPM pan speed. Delayed-release coating conditions were 29.5-30.5°C capsule bed temperature, 10 psi atomizing air pressure, 25 psi pattern air pressure, 9 grams/minute spray rate, and 25 RPM pan speed.

Gastro-Resistance Testing

The delayed-release coated OMZ capsules were reciprocated in a USP-compliant disintegration apparatus for 1 or 2 hours in acid media (0.1N HCl or acetate buffer pH 4.5) with discs to keep the capsules immersed in the media; then continued with disintegration testing in pH 6.8 phosphate buffer solution.

After one or two hours testing in the acid media, the capsules were removed and blotted dry to remove excess liquid on the capsule surface. The capsule weight differences before and after the test relative to the initial capsule weight were recorded as liquid (acid)-uptake.

Acid resistance testing was conducted in a USP dissolution (apparatus 1) at 100 rpm for 2 hours in USP pH 4.5 acetate buffer solution. Assay for the remaining drug was conducted according to the USP. "Stressed enteric testing" was performed on 30 enteric coated capsules which were stored for 6 months at 30°C/65%RH conditions. The capsules were subjected to 100 revolutions in a friabilator (25 rpm) followed by disintegration testing in a large basket assembly in pH 4.5 acetate buffer solution for 1 hour. The capsules that were perfectly intact after the acid exposure, were counted and reported as percentage of the number capsules tested.

Omeprazole Assay and Impurity Testing

Assay and impurities of OMZ were determined according to the USP-29 methods. Content uniformity was determined by assaying each of 20 OMZ uncoated capsules.

Delayed release coated capsules (12%WG Acryl-EZE) were stored for 6 months at 30°C / 65%RH conditions in heat sealed HDPE bottles with desiccant and cotton.

RESULTS

Gastro-Resistance Testing Results

Acryl-EZE 93F19255 coated from 10-18% theoretical coating weight gain onto 10% seal-coated OMZ capsules provided sufficient enteric protection. All coated capsules were intact after 2-hour testing in pH 4.5 USP acetate buffer solution (Table 2).

Table 2. Acid Uptake and Disintegration Time of Coated OMZ Capsules

Enteric Coating Weight Gain	Acid Uptake in pH 4.5 Acetate Buffer Solution		Disintegration Time in pH 6.8 Phosphate Buffer Solution
	1 Hour	2 Hours	
10%	6.5%	9.4%	NMT* 28 minutes
12%	5.9%	8.5%	NMT 29 minutes
14%	7.2%	10.4%	NMT 30 minutes
16%	8.1%	15.0%	NMT 35 minutes
18%	4.0%	7.1%	NMT 34 minutes

Omeprazole Stability

Chemical stability of OMZ powder in a delayed release capsule dosage form is demonstrated by the assay and impurity data obtained at time zero and after a 6-month storage at 30°C/65%RH conditions in heat sealed HDPE bottles with desiccant and cotton (Table 3).

Table 3. Storage of the Enteric Coated OMZ Capsules in 30 °C/65%RH - 6 months

Time (Month)	Assay (%)	Impurities (%)	
		Individual	Total
0	97.8	NMT* 0.1	0.2
6	98.2	NMT* 0.2	0.6

*NMT = not more than

OMZ drug assay after 6-month storage at 30°C/65%RH conditions met the USP 29 specification of 90-110%.

OMZ individual and total impurities also were within specification of individual (0.5%) and total (2.0%) impurity levels.

Relative standard deviation for the content uniformity of the uncoated capsules at initial time was 1.9%.

Gastro-Resistance – Stability

After 6-month storage at 30°C / 65%RH, acid uptake of the OMZ enteric coated capsules in various acid media up to pH 4.5 for either 1 hour or 2 hours testing are less than 10% which historically correlates to acceptable acid protection (Table 4).

Table 4. Acid Uptake of OMZ Enteric Coated Capsules After 6-Month Storage at 30oC/65%RH Conditions

Acid Solution	Acid Uptake	
	1 Hour	2 Hours
0.1 N HCl	2.7%	5.3%
pH 4.5 USP Acetate Buffer	5.0%	8.1%

Visual observation of the coated OMZ capsules after 2-hour exposure in each media yielded no signs of softening, bloating, or disintegration.

Disintegration times of the OMZ enteric coated capsules in pH 6.8 USP phosphate buffer solution after the capsules were subjected to pH 4.5 USP acetate buffer solution for 2 hours were 21-29 minutes.

To simulate the effects of mechanical handling during distribution, the 6 month old enteric coated OMZ capsules were subjected to stressed enteric testing.

The results show that testing in pH 4.5 USP acetate buffer solution, 28 out of 30 capsules (93.6%) were perfectly intact without any signs of softening or bloating.

Acid resistance testing of enteric coated OMZ capsules (at 12% enteric coated w.g.) both at initial time and after the 6-month storage shows that no omeprazole was released after 2-hour dissolution testing in pH 4.5 USP acetate buffer solution.

CONCLUSIONS

Non-banded hard gelatin capsules containing OMZ powder have been successfully enteric coated with aqueous Acryl-EZE 93F19255 in a lab-scale side-vented coating pan. The coating provides sufficient enteric protection in various acid media up to pH 4.5. The enteric protection and subsequent disintegration times were stable after 6-months storage at 30°C/65%RH conditions in heat sealed HDPE bottles with desiccant and cotton.

Future work is intended to look at larger scale coating trials and a comparison between banded and non-banded capsules to further study the feasibility of this technology. Appropriate selection of seal-coat and enteric layer, can lead to successful delayed release of an active powder in hard gelatin capsules via a simple, efficient, and economical unit operation.

Reprint of poster presented at AAPS – Nov 2006. Authors: Kurt A. Fegely, Budhi H. Simon, and Ali R. Rajabi-Siahboomi.

REFERENCES

1. Encyclopedia of Pharmaceutical Technology, 2002, Marcel Dekker.

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