Postprandial Enteric Performance of Enteric Coated Omeprazole Multiparticulate Systems

George Reyes[1], Daniel To[1], Vaibhav Ambudkar[2], Shantanu Damle[2], Ali Rajabi-Siahboomi[1]
[1]Colorcon Inc., Harleysville, PA, USA. [2]Colorcon Asia Pvt. Limited, Verna, Goa, India

AAPS
Poster Reprint 2020

Introduction

Acryl-EZE® II, aqueous acrylic enteric system, is an easy to use, fully formulated coating system designed for enhanced enteric protection of proton pump inhibitors (PPIs) in intermediate acidic pH media. In this study, seal-coated omeprazole multiparticulates (MP), were coated with either (i) Acryl-EZE II or (ii) Eudragit L30D-55 and acid resistance was investigated, using both visual examination and analytical determination of drug assay. Preferred coating weight gains were selected for a postprandial in vivo enteric performance in 18 healthy volunteers.

Methods

Formulation

Disodium phosphate as an alkalizer and Opadry® as a binder were dissolved into water followed by the addition of the API, omeprazole. The resulting dispersion was then spray layered onto 18/20# sugar spheres (Suglets®, 850-1000 µm) in a Vector VFCLab3 fluid bed coater, with Wurster insert. The multiparticulates were then seal-coated with a plasticizer free Opadry system followed by enteric coating with either the Acryl-EZE II coating system, or with Eudragit L30D-55 with the addition of talc and triethyl citrate (TEC). The multiparticulates were encapsulated in hard gelatin capsules (20 mg dose) and packaged into 100 mL PET bottles with a 2 g desiccant. The packed capsules were stored for stability study at 30°C/65% RH and 40°C/75% RH for 3 months.

In Vitro Evaluations

The enteric dissolution performance of the capsules in 0.1N HCl acid followed by pH 6.8 phosphate buffer were evaluated by measuring drug assay and total impurities following the USP monograph specifications, at the initial and 3-month storage time points. In separate evaluations, enteric coated beads were exposed to intermediate pH values of 4.9, 5.0 or 5.1 acetate buffer for up to two hours. The samples were visually assessed for color change every 15 minutes, as a simple mean to identify degradation of omeprazole, since degradation of the drug causes a color change from white to purple. Drug assays were performed using HPLC after exposure to different acidic conditions.

In Vivo Evaluations

The in vivo performance of the two enteric coated omeprazole formulations were evaluated in 18 healthy human volunteers. The study protocol was reviewed and approved by an independent Ethics Committee (Aavishkar Ethics Committee). The equivalent of 20 mg of omeprazole capsules was orally ingested by each volunteer, 30 minutes after a standard breakfast.

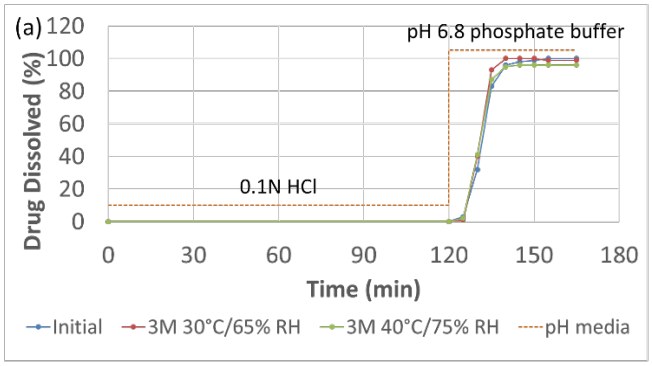
A total of 21 blood samples were taken per subject over a time period of 12.5 hours. The amount of omeprazole present in the blood samples was determined by first centrifuging the samples to separate the plasma. 1 mL of plasma was removed and mixed with 50 µL of 0.4M sodium bicarbonate solution and stored at -70±15°C until analysis. Samples were analyzed by HPLC-MS under sodium vapor lamp light.

Results

In Vitro Evaluations

Both enteric coated formulations met USP specifications1 for dissolution (< 10% release in acid phase, and > 80% release in buffer phase), assay (90-110%) and total impurities (< 2%) at the initial time point and after storage for 3 months at 30°C/65% RH and 40°C/75% RH. Dissolution, assay and total impurity results are shown in Figures 1, 2 and 3, respectively.

Figure 1. Enteric Dissolution Profile of Capsules Containing Omeprazole MP Enteric Coated with (a) Acryl-EZE II or (b) L30D-55



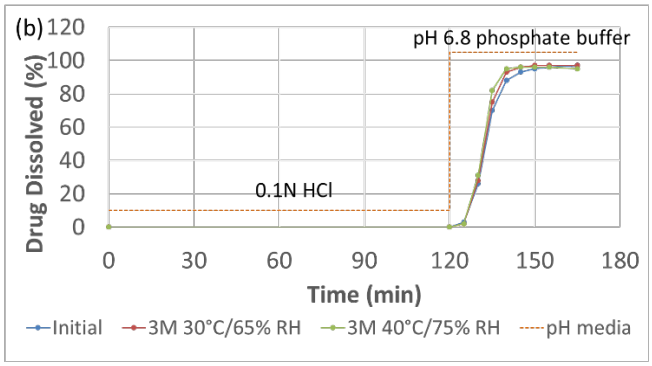


Figure 2. Drug Assay of Omeprazole DR Capsules Before and After Storage at 30°C/65% RH and 40°C/75% RH

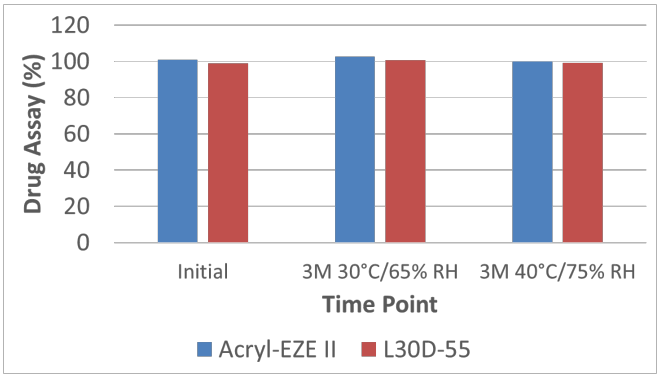
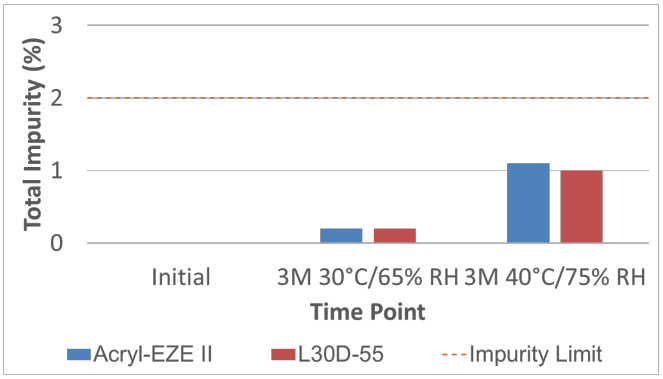


Figure 3. Total Impurities of Omeprazole DR Capsules Before and After Storage at 30°C/65% RH and 40°C/75% RH



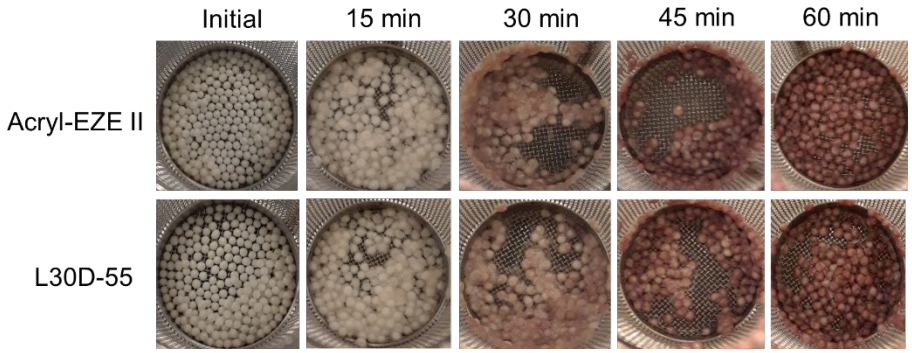
Enteric coated omeprazole multiparticulates were also evaluated by acid resistance testing in intermediate acidic pH media for up to 2 hours. All exposed beads showed a shift in color from white to purple indicating some omeprazole degradation had occurred. Acryl-EZE II and Eudragit L30D-55 coated beads had similar appearances at various time points through 60 minutes as shown by images of multiparticulates exposed to pH 5.1 acetate buffer in Figure 4.

The acid resistance of omeprazole multiparticulates coated with either Acryl-EZE II or with Eudragit L30D-55 was evaluated at pH 4.9, 5.0 and 5.1 acetate buffer. Table 1 shows the remaining omeprazole after exposure to acid generally decreased with increasing pH, for both enteric coating formulations.

Table 1. Acid Resistance of Enteric Coated Omeprazole MP in Intermediate pH Media

Sample Name	Omeprazole Remaining After Exposure to Acid for 120 mins(%)		
	pH 4.9 Acetate Buffer	pH 5.0 Acetate Buffer	pH 5.1 Acetate Buffer
Acryl-EZE II	96	81	49
L30D-55	86	72	48

Figure 4. Color Change of Enteric Coated Omeprazole Multiparticulates, Over Time in pH 5.1 Acetate Buffer



In Vivo Evaluations

Figure 5 shows the plasma concentration profiles with an average omeprazole concentration over time for the across all volunteers. The two plasma concentration profiles are considered similar, providing either a low or no release within the first two hours after ingestion, followed by a quick release and absorption. The pharmacokinetic parameters such as C_{max}, T_{max} and AUC are shown in Table 2, indicating similar in- vivo performance for the two delayed release omeprazole capsule formulations.

Figure 5. Average Plasma Concentrations for 12 h after Administration

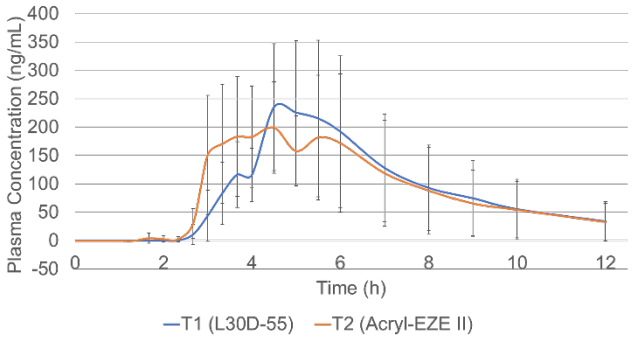


Table 2. Pharmacokinetic Parameters of Omeprazole DR Capsules

PK Parameter	Acryl-EZE II (Mean ± SD)	Eudragit L30D-55 (Mean ± SD)
C_{max} (ng/mL)	362.21 ± 280.36	365.56 ± 300.20
AUC_{0-t} (hr-ng/mL)	1042.43 ± 1146.93	1026.54 ± 1209.11
$AUC_{0-\infty}$ (hr-ng/mL)	1302.42 ± 1625.98	1104.72 ± 1536.28
T_{max} (hr)	4.18 ± 0.97	4.43 ± 0.73

Conclusions

Acryl-EZE II is a formulated enteric coating system that provides delayed release coating suitable for use in the formulation of proton pump inhibitor drug products. The enteric protection of omeprazole coated multiparticulates was observed in vivo, where no or small concentration of drug appeared in the blood plasma samples during the first 2 hours, followed by a fast release and drug absorption in healthy volunteers.

References

1. United States Pharmacopeia and National Formulary (USP 42-NF 37 2S). Rockville, MD: United States Pharmacopeial Convention; 2018. https://online.uspnf.com/uspnf/document/1_GUID-71E87DD7-0164-42C0-8027-A9211B069968_1_en-US. Accessed August 19, 2020.

For more information, contact your Colorcon representative or call:

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**

You can also visit our website at **www.colorcon.com**