dx.doi.org/10.14227/DT320325P122

Development of a Discriminating Dissolution Method Using Apex Vessels for Enzastaurin Tablets

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ABSTRACT

Introduction: This study aims to develop a discriminating dissolution method for 125-mg enzastaurin tablets using a United States Pharmacopeia (USP) apparatus 2 (paddle) with apex vessels. **Methods:** The release rate of enzastaurin tablets was studied using conventional USP vessels and apex vessels. Various dissolution operational parameters were evaluated including rotation speed, media composition, and medium volume. The dissolution method using apex vessels was developed and its discriminating power was evaluated by making deliberate changes in the drug product formulation and manufacturing process. **Results:** Dissolution of the enzastaurin tablets using USP vessels lacked discrimination power at the standard 75 rpm paddle rotation speed; further studies with different rotation speeds and medium volumes also lacked discrimination power. When the rotation speed was below 75 rpm, the drug release rate was slow and incomplete due to a coning effect. When apex vessels were used, the dissolution method was able to discriminate between formulation and manufacturing process changes. **Conclusion:** A discriminating dissolution method for enzastaurin tablets was developed using USP dissolution apparatus 2 with apex vessels at 35 rpm and 500 mL medium volume. The use of apex vessels reduced the coning effect, and this method was able to detect drug product formulation and process changes, while the method using conventional USP dissolution vessels was found to be non-discriminating.

KEYWORDS: apex vessel, dissolution release rate, discriminating, coning effect, PEAK vessel

INTRODUCTION

Dissolution is a critical quality attribute for product development and batch release that can be used to predict in vivo drug release behavior for certain products as well as for biowaiver applications (*1–8*). Regulatory agencies require pharmaceutical companies to have a discriminating dissolution method to ensure product quality and performance, because a discriminating method can indicate possible changes in the quality of the product before in vivo performance is affected (*6*, *9*, *10*). The two most used dissolution apparatus for oral dosage forms are United States Pharmacopeia (USP) apparatus 1 (basket) and apparatus 2 (paddle). Conventional USP vessels are cylindrical, hemispherical and made of glass or other inert, transparent material (*11*).

The current study aimed to develop a dissolution method with discriminatory power for 125-mg enzastaurin tablets (immediate-release formulation) using the paddle apparatus and 25 mM phosphate buffer (pH 2.0) as the medium. Due to the presence of the coning effect and a lack of discriminating power, the use of apex vessels was compared with conventional USP vessels to develop a discriminating dissolution method for enzastaurin tablets.

METHODS

Materials

Enzastaurin hydrochloride (HCl) drug substance was manufactured by Evonik Corp (USA), enzastaurin tablets were manufactured by Lonza (USA), and enzastaurin tablets for the DoE study were manufactured by Alan Laboratories, Inc. (USA). Potassium phosphate monobasic was purchased from Sigma-Aldrich (USA), phosphoric acid was from Supelco (USA), purified water was produced in-house by a Millipore (USA) water purification system, sodium phosphate monobasic monohydrate was from

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VWR (USA), and methanol (HPLC grade) was purchased from Fisher Scientific (USA).

Solubility Study

The equilibrium solubility for enzastaurin HCl in aqueous media was studied to select the dissolution medium.

Dissolution Methods

The dissolution medium was 25 mM phosphate buffer, pH 2.0. To prepare the dissolution medium, 85 g of potassium phosphate monobasic was dissolved into 25 L of purified water, then 80 mL of phosphoric acid was added and mixed well. The pH was adjusted to 2.0 ± 0.05 (if required) by adding either phosphoric acid or 5 N sodium hydroxide. The dissolution medium was degassed by sonication under vacuum prior to use. For a larger volume of dissolution medium, materials volumes and quantities were scaled up as appropriate.

The initial dissolution method for enzastaurin tablets was developed with a USP paddle apparatus (Distek Dissolution System 2100C, Distek Inc., USA) with a rotation speed of 75 rpm in 1000 mL of the dissolution medium at 37.0 ± 0.5 °C. Various paddle rotation speeds and medium volumes were trialed as part of dissolution method development.

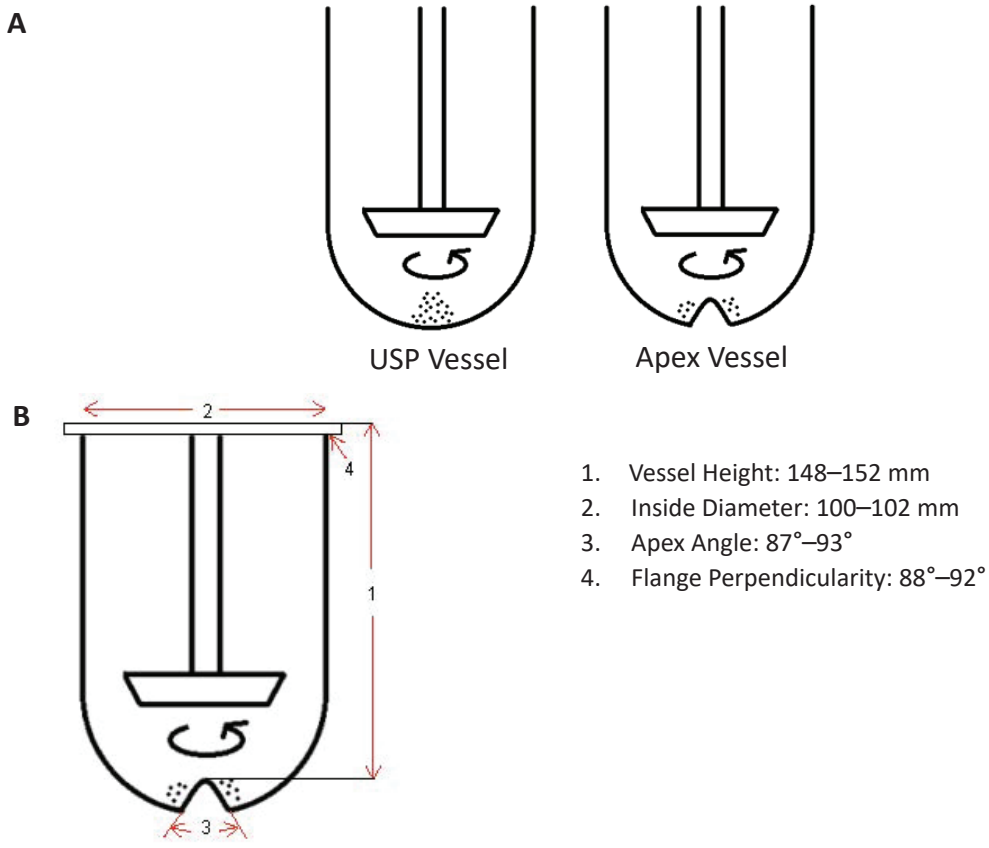
The modified dissolution method was developed using the same USP paddle apparatus, but using apex vessels (Quality Lab Accessories, LLC) instead of conventional USP vessels (round bottom), with a rotation speed of 35 rpm in 500 mL of dissolution medium at 37.0 ± 0.5 °C.

The differences between USP and apex vessels are illustrated in Figure 1.

Dissolution samples of 3.0 ± 0.1 mL (n = 6) were automatically withdrawn via online filters from each vessel at predefined time points of 5, 10, 15, 20, 30, 45, and 60 min. The online filters used for dissolution auto-sampling were 10-µ porous (full flow) filters (Quality Lab Accessories, LLC, PN: FIL010-01, USA). The final paddle speed was increased to 200 or 250 rpm for 15 min immediately after the 45-min sampling timepoint as infinity time, to ensure the full release of enzastaurin tablets.

High Performance Liquid Chromatography

The buffer for the mobile phase preparation was 17.5 mM sodium phosphate buffer (pH 2.5). This was prepared by dissolving sodium phosphate monobasic monohydrate in 1 L of water, mixing well, and adjusting pH to 2.5 ± 0.05 with phosphoric acid. The mobile phase for HPLC analysis



1. Vessel Height: 148–152 mm
2. Inside Diameter: 100–102 mm
3. Apex Angle: 87°–93°
4. Flange Perpendicularity: 88°–92°

*Figure 1. (**A**) Comparison of bottom geometry between USP and apex vessels. (**B**) Apex vessel dimensions.*

was prepared by mixing 50:50 (v/v) of methanol and 17.5 mM sodium phosphate buffer (pH 2.5).

The dissolution samples were analyzed by a reversed-phase HPLC method using an Agilent (USA) series 1100 or 1200 automatic system and Zorbax SB-C18 column (4.6 × 75 mm, 3.5 µm) at 35 ± 3 °C, with an ambient sample tray. Enzastaurin was detected by ultraviolet (UV) absorbance detection at a wavelength of 220 nm. The mobile phase flow rate was maintained at 1.5 mL/min. The injection volume was 10 µL.

Enzastaurin Tablet Formulation Variations

To study discrimination power of the initial USP vessel method and the modified apex vessel method, enzastaurin tablets were manufactured with deliberate and meaningful variations to the target formulation. All tablets were manufactured by blending on a VH 2 (2 L) blender (Vevor, USA), weighing individual blends equivalent to one tablet, followed by manual compression on a Manesty Betapress tablet press (Syntegon Technology Services, LLC, USA). The target tablet weight was maintained at 550 mg for all formulation variations.

Design of Experiment (DoE) Study

To further evaluate and confirm the discriminating power of the apex vessel method, an extensive DoE study was performed with 11 different tablet batches. All DoE batches except Batch 1 were compressed at two thicknesses: a target core tablet thickness per Lonza batch USTP-5035, and a minimum thickness tablet, representing higher hardness. Batch 1 was only compressed at one target thickness and no minimum thickness tablets were made.

RESULTS AND DISCUSSION

Solubility

The solubility data (supplemental material) showed that enzastaurin HCl is insoluble in aqueous media in general, and the highest solubility of enzastaurin HCl in aqueous media is in phosphate buffer, pH 2.0. Therefore, this was selected as the dissolution medium for enzastaurin tablets.

Dissolution

Initial USP Vessel Method

The dissolution data for enzastaurin tablets (Lonza, lot 190110.3) using the initial method with conventional USP vessels (75 rpm, 1000 mL of medium) are presented in Figure 2A. The dissolution rates were too fast: 85% at 5 min, 95% at 10 min, 98% at 20 min, 99% at 30 and 45 min. Because the initial dissolution method was not discriminating, the effects of paddle speed and medium volume on dissolution rate were investigated further. The dissolution medium was not varied because pH 2.0 was found to be the optimal aqueous medium for enzastaurin dissolution due to its high solubility.

The paddle speed was reduced from 75 to 65 rpm to evaluate the dissolution rate and discriminating power while keeping the other operational parameters unchanged. In separate trials, the volume was reduced from 1000 mL to 900 mL and 500 mL, at 65 rpm.

When the paddle speed was 65 rpm with 1000 mL of medium, the drug product appeared to slow down at 5 min; however, release was greater than 90% at 10 min. When the medium volume was reduced to 900 mL at 65 rpm, the dissolution rate slowed down a little (86% at 10 min); however, the drug release was incomplete (93% at 45 min), which indicated a coning effect. Coning was also observed at 60 rpm with 1000 mL of medium, and the maximum release was 85% at 45 min. Reduction of the medium volume to 500 mL also resulted in incomplete release. Therefore, none of these modifications to the initial dissolution method yielded a desired outcome.

The coning effect has been reported to affect the dissolution rate (*12–14*). Coning occurs when undissolved material forms a mound in the stagnant zone directly below the paddle, where there is less hydrodynamic flow present, thereby inhibiting drug release (*15*). This phenomenon can be overcome by either changing the stirring speed or using apex vessels, although research has shown that a minimum rotation speed is necessary to prevent coning phenomena in a compendium paddle dissolution apparatus (*16*). Because lowering the stirring speed in our case resulted in an incomplete drug release, and increasing stirring speed would have further reduced the discrimination power of the method, it was determined that the use of conventional hemispherical USP vessels could not address the coning issue in our case. For this reason, an alternative method using apex vessels was developed and studied.

Modified Apex Vessel Method

To address the issue of the coning observed at 60 rpm with USP vessels, the use of apex vessels was investigated, along with paddle speed and medium volume changes, to determine the effect on dissolution rate.

The generic apex vessel has the same design and shape as the patented PEAK vessel (Agilent). Research shows that apex vessels can address the impact of the coning effect on the dissolution rate, and it has been utilized in the dissolution method for some marketed

pharmaceutical products (*12*, *17–22*). However, users need to pay attention to the quality and dimensions of the apex vessels to ensure their performance consistency, as variations in dissolution results due to different apex heights have been observed (*23*).

As shown in Figure 2B, the dissolution profile for enzastaurin tablets using apex vessels with 500 mL and 1000 mL of medium at 35 rpm showed a substantially slower release of drug at all timepoints compared with the initial USP vessel method. Complete dissolution was achieved at 45 minutes for the 35 rpm and 500 mL operating condition.

The observed dissolution profiles are summarized below:

- Too fast: USP vessel, 65 rpm/1000 mL
- Too fast: Apex vessel, 50 rpm/1000 mL
- Optimum: Apex vessel, 35 rpm/500 mL
- Incomplete: Apex vessel, 35 rpm/1000 mL, 25 rpm/500 mL
- Incomplete: USP vessel, 65 rpm/500 mL, 60 rpm/1000 mL

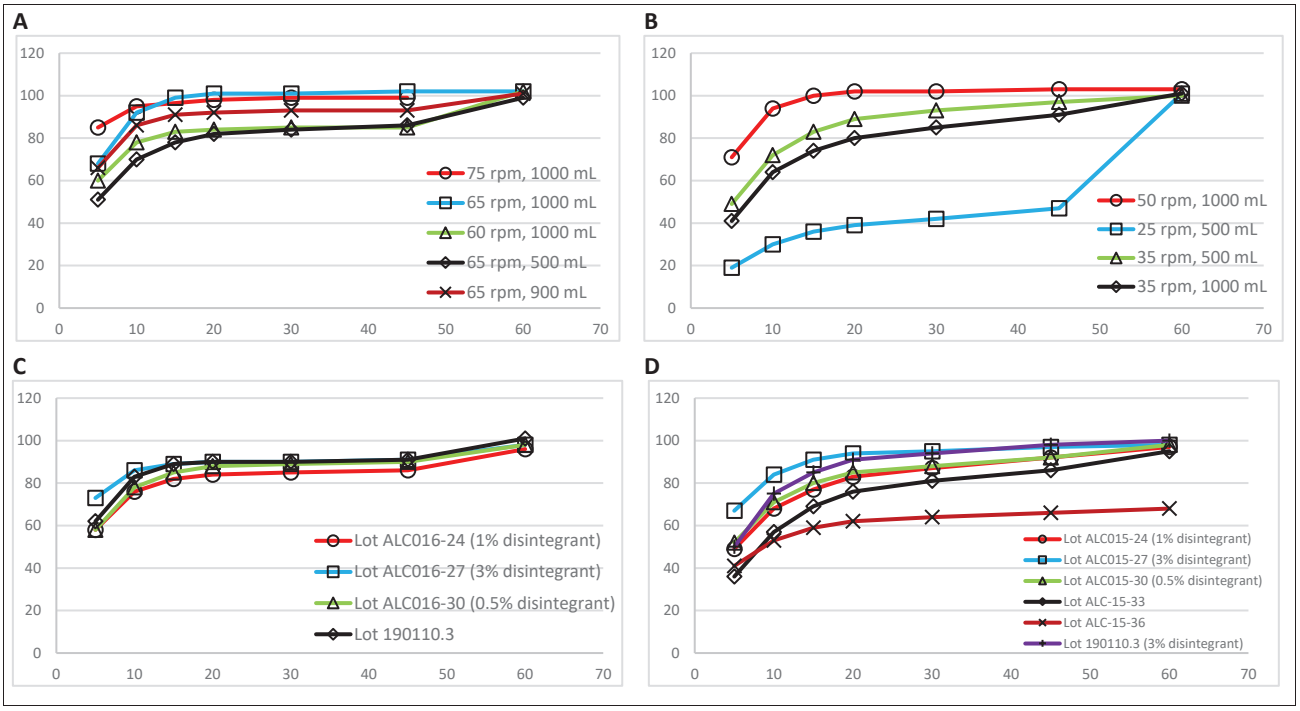


*Figure 2. Cumulative drug release (%) over time (min). Dissolution profiles for Lonza lot 190110.3 in USP Vessel (**A**) and apex vessel (**B**) with various paddle speeds and medium volumes. Dissolution profiles for variant tablets and Lonza lot 190110.3 in USP Vessel (900 mL media, 65 rpm) (**C**) and apex vessel (500 mL, 35 rpm) (**D**) (n = 12).*

Table 1. Composition of Drug Product (Enzastaurin Tablets 125 mg), Core Tablet, and Variant Enzastaurin Tablets Used for Testing Modified Dissolution Method

Lot	Enzastaurin HCl	Filler A	Filler B	Disintegrant	Surfactant	Glidant	Lubricant
Drug Product Current Formula (550 mg)	24.34 (133.85 mg)[a]	37.66 (207.14 mg)	32.00 (176.00 mg)	3.00 (16.50 mg)	1.00 (5.50 mg)	0.25 (1.38 mg)	1.75 (9.63 mg)
ALC-015-27	24.34	37.66	32.00	3.00	1.00	0.25	1.75
ALC-015-24	24.34	37.66	34.00	1.00	1.00	0.25	1.75
ALC-015-30	24.34	37.66	34.50	0.50	1.00	0.25	1.75
ALC-015-33	24.34	41.66	32.00	0.00	0.00	0.25	1.75
ALC-015-36	17.04 (HCl) + 6.82 (free base)	38.14	32.00	3.00	1.00	0.25	1.75

All values are percentages unless otherwise noted.
[a]Equivalent to 125 mg of enzastaurin
ALC-015-27: target formulation, 3% disintegrant, target hardness; ALC-015-24: 1% disintegrant, high hardness; ALC-015-30: 0.5% disintegrant, high hardness; ALC-015-33: 0% disintegrant, 0% surfactant, high hardness; ALC-015-36: target formulation except enzastaurin content was modified to contain 30% free base, high hardness.
HCl: hydrochloric acid

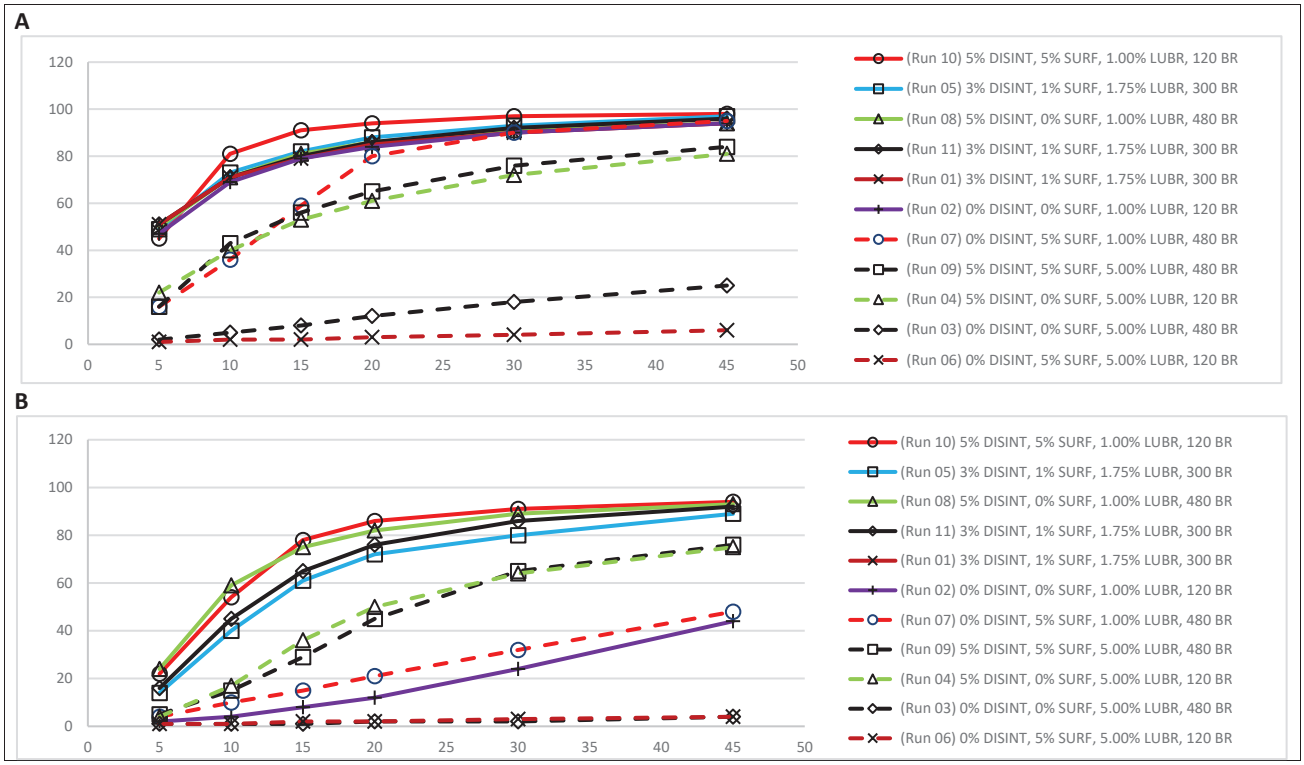


*Figure 3. Cumulative drug release (%) over time (min). Dissolution profiles for Design of Experiment batches 1–11: target thickness (**A**) and minimum thickness (**B**) (n = 3). DISINT: disintegrant; SURF: surfactant; LUBR: lubricant. BR: blender revolutions.*

Discrimination Power

To demonstrate the discrimination potential of the modified method using apex vessels, enzastaurin tablets were manufactured with deliberate variations to the current formulation and manufacturing process (Table 1).

To compare the dissolution profiles obtained with the USP vessel versus the apex vessel, 65 rpm and 900 mL of medium was used instead of the initial method (75 rpm and 1000 mL in the USP vessel). This is because the dissolution profile obtained by using 65 rpm and 900 mL with the USP vessel was found to be more discriminatory than the initial method; however, the 65 rpm/900 mL method was found to be an unsatisfactory method due to incomplete release.

The dissolution data for the USP vessel and apex vessel are presented in Figures 2C and 2D, respectively. The dissolution data further confirmed that the modified apex vessel method was more discriminating than the initial USP vessel method.

DoE Study and Additional Experiments

The composition and properties of the 11 DoE batches are shown in Table 2. The dissolution data for the DoE batches according to tablet thickness are presented in Figure 3.

Several additional formulation variation experiments were carried out (i.e., changes in lubricant, hardness, coating, free base, and disintegrant), which further demonstrated the discriminating power of the modified dissolution method (Fig. 4).

CONCLUSION

The DoE study and additional formulation variation experiments demonstrated the discriminating power of the modified dissolution method with apex vessels for enzastaurin tablets. The dissolution method with apex vessels was sensitive to changes in the formulation and manufacturing process and provided consistent results. Therefore, the apex vessel method is suitable as a quality control tool for enzastaurin tablets. Additionally, this data support the use of apex vessels as an effective alternative method to provide discriminating power when there is a prominent coning effect in the dissolution test. The 35 rpm/500 mL dissolution method using apex vessels was accepted by the FDA and is the current dissolution method for enzastaurin tablets.

SUPPLEMENTAL MATERIAL

Supplemental material is available from the corresponding author upon request.

Table 2. Composition and Properties of Tablet Batches 1–11 (Design of Experiment)

Batch	Enzastaurin HCl		Filler A		Filler B		Disintegrant		Surfactant		Glidant		Lubricant		BR[a]	Thickness[a] (mm)		Weight Range[a] (mg)	Disintegration Time Range (minute:second)
	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%					
1	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.85–5.86	549–553	2:38–2:53
2	133.85	24.34	233.27	42.41	176.00	32.00	0.00	0.00	0.00	0.00	1.38	0.25	5.50	1.00	120	Target	5.87–5.88	550–551	1:34–1:34
																Min	5.44–5.45	550–551	N/A
3	133.85	24.34	211.27	38.41	176.00	32.00	0.00	0.00	0.00	0.00	1.38	0.25	27.50	5.00	480	Target	5.89–5.90	549–551	23:02–54:50
																Min	5.43–5.45	549–551	> 270:00 (30% remaining)
4	133.85	24.34	183.77	33.41	176.00	32.00	27.50	5.00	0.00	0.00	1.38	0.25	27.50	5.00	120	Target	5.88–5.88	551–551	3:25–3:25
																Min	5.49–5.50	549–552	13:10–13:50
5	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.86–5.87	550–550	2:15–2:30
																Min	5.48–5.49	550–551	10:15–10:20
6	133.85	24.34	183.77	33.41	176.00	32.00	0.00	0.00	27.50	5.00	1.38	0.25	27.50	5.00	120	Target	5.85–5.87	550–551	> 180:00 (60% remaining)
																Min	5.50–5.50	550–551	> 180:00 (90% remaining)
7	133.85	24.34	205.77	37.41	176.00	32.00	0.00	0.00	27.50	5.00	1.38	0.25	5.50	1.00	480	Target	5.86–5.87	550–551	8:25–8:40
																Min	5.43–5.45	550–551	52:10–52:30
8	133.85	24.34	205.77	37.41	176.00	32.00	27.50	5.00	0.00	0.00	1.38	0.25	5.50	1.00	480	Target	5.86–5.88	550–550	1:20–1:20
																Min	5.48–5.49	549–550	7:10–7:15
9	133.85	24.34	156.27	28.41	176.00	32.00	27.50	5.00	27.50	5.00	1.38	0.25	27.50	5.00	480	Target	5.87–5.88	549–551	6:45–7:20
																Min	5.56–5.58	550–551	16:40–17:10
10	133.85	24.34	178.27	32.41	176.00	32.00	27.50	5.00	27.50	5.00	1.38	0.25	5.50	1.00	120	Target	5.86–5.88	551–551	3:20–3:30
																Min	5.51–5.53	550–551	8:40–8:50
11	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.87–5.88	550–551	2:35–2:40
																Min	5.47–5.50	549–552	10:30–10:45

[a]*Thickness and weight range data were as recorded at the time of manufacture.*
HCl: hydrochloric acid; BR: blender revolutions; Min: minimum

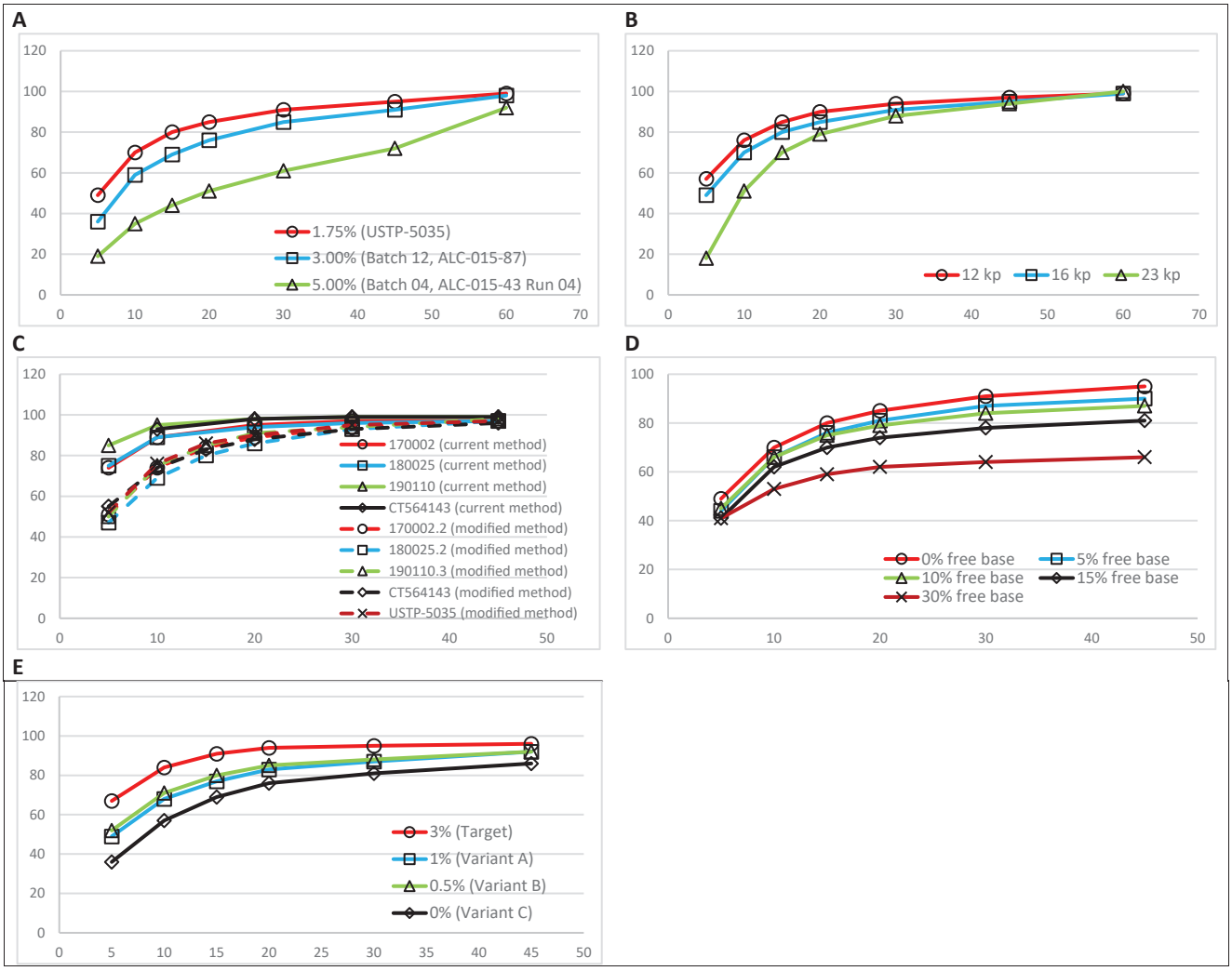


*Figure 4. Cumulative drug release (%) over time (min). Dissolution profiles for lubricant variation tablets (**A**), tablets with varying hardness, Lonza lot USTP-5035 (**B**), historical coated tablets (**C**), % free base variation tablets (**D**), and disintegrant variation tablets (**E**) (n = 12).*

DISCLOSURES

The study was conducted at Alan Laboratories, Inc. and was funded by Denovo Biopharma LLC. The authors have no conflicting interests.

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