PHARMACEUTICAL TECHNOLOGY

Delayed Release Tablet Dissolution Related to Coating Thickness by Terahertz Pulsed Image Mapping

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ABSTRACT: Delayed release dosage forms such as Asacol® employ coatings that are engineered to breakdown and release the drug topically at the nominal pH of the lower intestinal tract. Asacol tablets were found to dissolve in an erratic fashion when they are dissolved in buffers below pH 7 which can occur naturally. In this study Terahertz pulsed imaging (TPI) was used to accurately map the coating thickness of a group of Asacol tablets that were subsequently dissolved using the USP method at pH 6.8. The mean dissolution times were found to correlate with the average coating thickness measured over all surfaces. Thickness values for a single randomly selected face did not correlate well with the dissolution results. The speed and ease of TPI mapping may make it an attractive replacement for wet dissolution testing both in product development and eventually for process analysis. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:1543–1550, 2008

Keywords: Asacol; mesalamine; mesalazine; delayed release; terahertz pulsed imaging; coating mapping; mean dissolution time (MDT); process analytical technology (PAT)

INTRODUCTION

Asacol® is a delayed-release tablet for the treatment of Ulcerative Colitis and Crohn's Disease. To be effective this drug must target the mucosa of the terminal ileum and colon for localized release of the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) or mesalamine. Release of drug in the stomach and upper small intestine is undesirable as this will lead to premature absorption and consequent drug wastage as well as possible systemic side effects. Asacol tablets are coated with an acrylic-based film (Eudragit S®) designed to resist the low pH of the stomach yet release at pH above 7.0. Recent studies showed that treatment with mesalamine had large intra-subject variability which may have been due to differences in physiology (e.g., intestinal transit time, intraluminal pH profiles, fasting state) or disease states.[1–6] Other authors have studied variability in dissolution results by comparing dissolution mechanisms,[7,8] different tablet coating materials,[9,10] and bead formulations.[11]

At pH values above about 7.2 for the final buffer stage (pH 7.2 is stipulated in the USP monograph), Asacol is found to release consistently within the first hour. However, below pH 7.2 the release rate decreases and becomes more

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erratic. Work with ~1 mm pellets coated with Eudragit S®—pH 7 and Eudragit FS 30D®—pH 6 shows similar erratic dissolution behavior in the pH range below the release pH.[12] This study was undertaken to learn whether the erratic dissolution of Asacol at pH values below 7 (pH 6.8 here) can be understood in terms of the relative thickness of the individual tablet coating.

Both near infrared (NIR) and Raman spectroscopy have been applied to the study of tablet coatings,[13–15] tablet dissolution[16] and batch uniformity.[17] These studies were limited to measurement of overall batch properties of dosage forms with coatings much thinner than Asacol.

We employ a new tool, terahertz pulsed imaging (TPI), which can accurately measure and map in 3-D the variations in individual tablet coating thickness.[18,19] In this technique a coherent pulse of terahertz radiation is reflected by the various internal layers of a tablet. The time-delays of the reflected pulses depend on the depth of the features and are used to create a map of the internal structure. Terahertz radiation falls between the infrared and microwave regions of the spectrum. The TPI technique generates very low average powers and therefore does not induce any thermal stress on samples. TPI is also nondestructive so the same tablets can be used in dissolution testing. The method has been applied to enteric, sugar coated, and gelcap dosage forms. It is suited to those forms using single or complex multilayer coatings whose thickness exceeds about 40 μm. Furthermore due to the considerable penetrating power of terahertz radiation, TPI can produce images of the interior structure of complex dosage structures.[20] The purpose of this study is to determine whether mapping the coatings of delayed release tablets such as Asacol can account for their dissolution behavior. TPI provides similar information to NIR and Raman but is distinguished from these methods by the ability to map the detailed thickness over the entire tablet surface. Correlation of tablet coating thickness as measured by TPI with dissolution behavior has not previously been reported.

EXPERIMENTAL

Tablet Dissolution

The current USP dissolution method for mesalamine delayed-release tablets uses a two-stage procedure.[1] These conditions attempt to simulate the physiological conditions that a typical tablet might encounter in the normal gastrointestinal tract. In the Acid Stage (Stage 1) the tablets are placed in 500 mL of liquid at pH 1.2 for 2 h stirring at 50 rpm using USP Apparatus 2 (paddle method). The Buffer Stage (Stage 2) consists of two parts. Initially, stir for 1 h at 100 rpm in 900 mL of 0.16 M phosphate at pH 6.0 and then finally 900 mL of pH 7.2 0.16 M phosphate buffer for 1.5 h at 50 rpm. All solutions were degassed by a standard procedure.[21] Asacol tablets are expected to remain intact at all pHs below 6 and dissolve quickly at pH above 7, as is seen when following the USP procedure. However, gastrointestinal pH in the terminal ileum and colon can drop below 7 in response to dietary variation and/or health conditions.[2,6] For this reason, measurements were also made using a final Buffer Stage at pH values below 7.

As a preliminary to studying the relationship between dissolution and coating thickness, the variability in dissolution behavior as a function of gastric pH was surveyed. Sets of six 400 mg Asacol tablets representing three different manufacturer's lots were dissolved according to the USP method. Three different final dissolution Buffer Stages of pH 6.5, 6.8, and 7.2 were used. Figure 1 demonstrates the pH dependent variability in the mean percentage dissolved versus time. Both the lot-to-lot variation and the large standard deviation within each lot are apparent at the two lower pH values. Complete dissolution at the lower two pH values required considerably more time than the 1.5 h of the USP method. Dissolution at pH 6.8 was selected as the best condition to study whether individual tablet variations in the delayed release coating thickness are responsible for the variability in the dissolution behavior. Only the effect of lower pH in the final dissolution stage is examined in this report.

Terahertz Pulsed Imaging

TPI was performed on the tablets before dissolution using a TeraView TPI imaga 2000 system (TeraView, Cambridge, UK) featuring a programmable 6-axis robotic arm that precisely positioned each tablet in front of a terahertz emitter/receiver. The system has been described in detail by Zeitler et al.[20] The precision and reproducibility have been studied in detail.[22–24] The reflected time-of-flight radiation is analyzed in the time domain to measure the thickness of the tablet coating at

[1] *USP29–NF24*, Page 1355.

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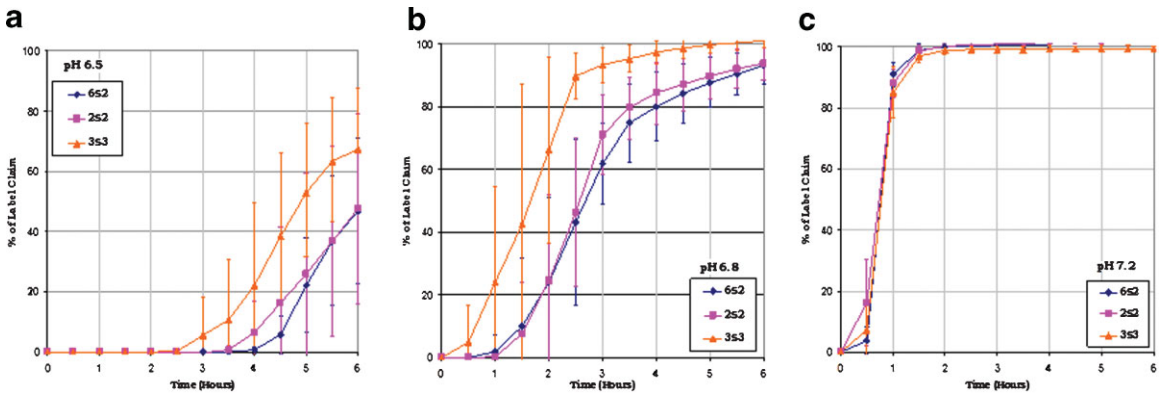

Figure 1. Asacol—Average dissolution curves for three different lots measured at (a) pH 6.5, (b) pH 6.8 and (c) pH 7.2.

points nominally 250 μm apart over the surface. Reflections occurs whenever there is a change in refractive index. The spot size at each location is approximately 100 μm square with a depth resolution of ±2 μm for layers over ~40 μm thick. These individual point measurements are then assembled into a coating thickness map. The two convex faces and the cylindrical centerband of Asacol are separately mapped to simplify the visual depictions as shown in Figure 2. Figure 2 uses a false-color scale for mapping the surface pixels with colors encompassing a range from 30 to 130 μm. The coating thickness for this tablet can be seen to vary from a low of ~60 μm up to ~110 μm. This range agrees with measurements by light microscopy of a sectioned tablet. Figure 3 shows the centerband thickness map unfolded. The coating thickness maps are summarized as histograms of pixel count versus pixel thickness in Figure 4. The mean thickness values used for correlation with the dissolution behavior are calculated from all the pixel thickness values in the image. On the fully scanned tablets the overall mean thickness is the arithmetic average from the three mean thicknesses for the two faces and centerband.

Data Collection and Processing

Four different lots of 400 mg Asacol tablets were obtained from commercial sources for use in this study. A total of 54 tablets were selected for the terahertz coating thickness measurements. Tablets were randomly selected from the four lots and individually identified by placing them in

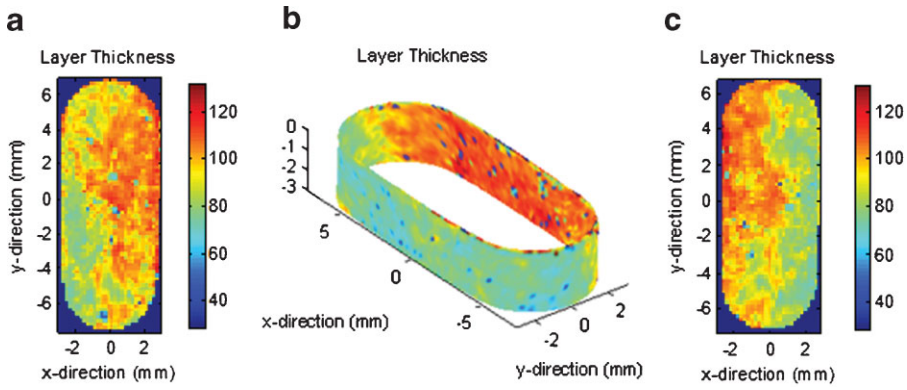

Figure 2. TPI coating maps of a 400 mg Asacol tablet, Sample 2S2_5/Run G2 Sample 3: (a) convex top, (b) centerband and (c) bottom surfaces. The false colors in the thickness maps range from 30 (blue) to 130 (red) μm. The darkest blue represents the edge of the tablet.

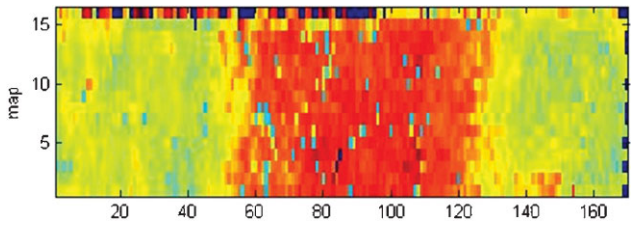

Figure 3. Centerband map from Figure 2b unwrapped The x, y units are relative. The same false color mapping is used as in Figure 2.

labeled plastic zip-lock bags. Eighteen tablets randomly selected from all four lots were mapped by TPI on a single convex face to survey the lot-to-lot variance in the coating thickness (sets D1–D3, see Tab. 1). The overall variance in each lot was similar, and therefore two lots were selected for full surface mapping to better characterize the tablet-to-tablet variation in coating thickness. Eighteen tablets were fully mapped by TPI on all surfaces (sets G1–G3, see Tab. 2).

Eighteen tablets that were measured by TPI on one face and eighteen additional tablets that were measured by TPI on all surfaces were randomly selected for dissolution. All the dissolution studies were performed with a second stage 2 buffer of pH 6.8. Dissolution analytical data were taken every 15 min over 10 h for the samples in Table 1 (D1–D3) and at half-hour intervals over 6 h for the samples in Table 2 (G1–G3). Typical sets of dissolution curves are shown in Figure 5. A suitable method to measure a consistent 'dissolution time' is the Mean Dissolution Time (MDT).[25,26] This was calculated for each run using the ratio of the area beneath the curve (ABC) calculated by trapezoidal approximation to the maximum percent released (W_{lim}) where $\text{MDT} = \text{ABC}/W_{\text{lim}}$. In addition, the fully-mapped tablets (Runs G1–G3) were visually observed to determine the time interval to the point when a breach in the coating was directly observable. This was termed the 'onset' time of dissolution and has also been recorded in Table 2. The onset times were found to be indicative but too imprecise to use to characterize the dissolution process. However direct observation was useful in spotting outlier tablets that split prematurely like 2S2_4n in run G3, tablet 4.

RESULTS

Asacol tablets in all six sets show considerable tablet-to-tablet variance in the dissolution profiles at pH 6.8. USP Stage 1 pH 1.2 acid solution conditions and pH 6.0 initial buffer were used in all cases. Various tablet coating measurements and corresponding dissolution times measured by the Mean Dissolution Time are collected in Tables 1 and 2. Plots of MDT versus coating thickness are shown in Figure 6 for the tablets mapped on a single face. Similar plots for fully mapped tablets are shown in Figure 7. Correlation coefficients for the two sets of three dissolution runs are collected in Table 3. Clearly, the correlation of dissolution time with the coating thickness of a randomly selected single face is considerably inferior to that based on the mean thickness averaged over all surfaces.

The general conclusion is that tablets with the thinner coatings ($\sim$<80 μ) usually released earlier than those with thicker coatings (>80 μ), where 80 μ represents the median coating thickness in this group of samples. Visual inspection of the various details of individual tablet maps did not reveal any subtleties that could be used to predict the fate of any single tablet. Since the nominal

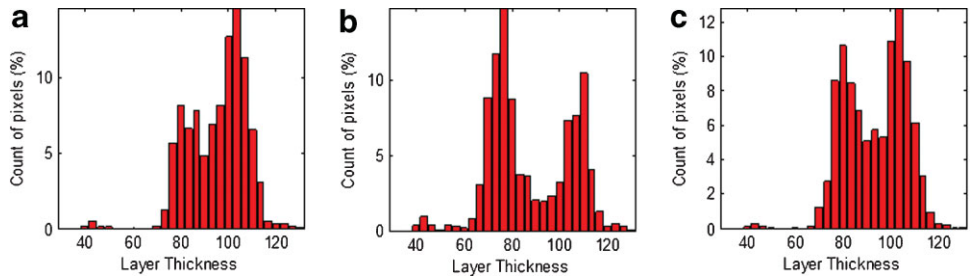

Figure 4. Histograms of coating thickness for the tablet in Run G2 Sample 3 surfaces, (a) top, (b) centerband, and (c) bottom. Mean thicknesses are in Table 2.

Table 1. Summary of Three Dissolution Runs Where One Tablet Face was Mapped With TPI

		Thickness (Microns)		
Run	Sample	Face	±Std. Dev.	MDT (Hours)
D1				
1	6S2_2	66	14	4.0
2	6S2_5	77	9	3.7
3	6S2_6	100	11	4.9
4	3S3_5	80	10	3.2
5	3S2_4	66	12	2.9
6	2S2_11	80	9	3.8
D2				
1	6S2_8	90	14	5.0
2	4S4_3	74	8	2.1
3	3S3_12	81	8	3.7
4	2S2_7	92	12	3.7
5	3S3_8	109	9	4.8
6	4S4_11	83	14	3.5
D3				
1	4S4_15	82	8	5.1
2	6S2_15	74	12	3.8
3	3S3_10	68	14	1.9
4	6S2_12	81	13	3.3
5	3S3_3	92	11	4.2
6	2S2_14	78	10	1.0

Samples were randomly selected from four different lots.

surface resolution of the TPI mapping is on the order of 250 μ, the coating imperfections that sponsor the permeation and rupture of the coating are assumed to be smaller than this dimension.

DISCUSSION

For an enteric coated tablet like Asacol, the coating is designed to produce specific dissolution behavior. The mesalamine tablet core dissolves readily once exposed. The coating thickness, composition and particularly the polymer cross-linking, affect the final product dissolution. Here we have assumed all tablets in a lot are coated with the same homogeneous Eudragit polymer. The thickness of the polymer layer as measured by TPI was found to vary considerably both over an individual tablet surface as well as from tablet-to-tablet. Hence it was reasonable to ask whether this coating variation was the root-cause of the observed differences in dissolution at pHs below 7. This work indicates that coating thickness is indeed a factor in the dissolution variance but clearly not the sole factor.

There is a modest correlation between the overall mean tablet coating thickness as measured by the TPI mapping and the dissolution rate derived from the Mean Dissolution Time. Monitoring the coating thickness of a single face of tablets such as these is insufficient to predict the dissolution behavior. Based on our visual observations of the onset of dissolution, this variability seems to be influenced by the details of the permeation, swelling and subsequent rupture of the Eudragit S coating. In spite of our ability to accurately measure and map coating thickness using TPI, uniform thinning of the coating by erosion/dissolution of the Asacol tablet coating is not wholly responsible for the dissolution behavior.

The dissolution results demonstrate the delayed-release behavior of Asacol (mesalamine) is affected by the pH of the final dissolution medium. All dissolution profiles were run with the same preprocessing before dissolution at pH 6.8. In the course of the study one tablet (of 36) released the API in the acid phase and three others began to release within 15 min in the pH 6.8 medium. It seems the earlier stages at pH 1.2 and 6.0 can affect some tablets. None of these tablets exhibited anything unusual in their thickness maps. So we make no conclusions about effects from the preliminary phases of the dissolution procedure. Whether final pH is the sole contributing factor to the erratic dissolution times can not be established from this study.

In light of this work and various studies on the variability of pH in the lower gastrointestinal tract,[1–4] it is suggested that dissolution methods for delayed-release dosage forms should specify dissolution profiles of products across the physiologically relevant pH range associated with gastrointestinal processing. Several steps between pH 6.0 and 7.5 should be examined at least in the development of the final marketed product.

Tablets mapped on a single face gave very poor correlation to the dissolution times whereas those fully mapped showed a stronger correlation. The minimum coating thickness of 40 μm limitation in TPI mapping is generally not a problem in delayed release dosage forms since the pH dependent polymer coatings are typically at least this thick. Our spatial step size of 250 μ limits our resolution of finer details that may be able to account for the more nuanced variation in dissolution. Future use of TPI coating mapping in process development or as a PAT tool should make note of the need for full

Table 2. Summary of Three Dissolution Runs Where all Three Tablet Faces Were Mapped With TPI

		Thickness (Microns)						
Run	Sample	Upper Face	Centerband	Lower Face	Mean	±Std. Dev.	MDT (Hours)	Onset Time (Obs., Hours)
G1								
1	3S3_1[a]	95	91	99	95	4	5.3	4.20
2	3S3_2	65	65	57	62	5	1.2	0.07
3	3S3_4	82	68	71	74	7	3.6	2.72
4	3S3_6	81	72	76	76	5	3.4	2.50
5	3S3_7	97	89	96	94	4	4.4	3.00
6	3S3_9	61	60	60	60	1	2.1	1.20
G2								
1	2S2_2	83	72	73	76	6	4.0	3.00
2	2S2_3	70	69	79	73	6	4.0	3.50
3	2S2_5	95	87	93	92	4	4.8	4.00
4	2S2_6	82	77	84	81	4	4.2	4.00
5	2S2_8	80	68	72	73	6	3.5	2.50
6	2S2_9	80	69	70	73	6	3.4	2.75
G3								
1	2S2_1n	73	66	66	68	4	2.9	2.50
2	2S2_2n	96	86	97	93	6	4.1	3.00
3	2S2_3n	75	75	91	80	9	3.6	2.75
4	2S2_4n[b]	82	75	82	80	4	0.5	0.00
5	2S2_5n	94	79	71	81	12	3.6	2.25
6	2S2_6n	81	75	86	81	6	3.5	2.40

Run G3 used a new set of tablets from the same lot as G2.
[a]Sample G1-3S3_1 was not fully dissolved after 6 h.
[b]Sample G3–2S2_4n breached in acid solution and was not included in the correlation analysis.

mapping of coatings with sufficient thickness and spatial resolution.

Correlation of the statistical properties of coating thickness maps with dissolution times, though modest at this early stage in the development of the technology, illustrates the role that TPI can play in product development and in the study of delayed release properties of coated tablets. Refined methods for predicting dissolution times from coating thickness maps would be especially welcome because typical delayed release dissolution protocols call for tedious procedures requiring multiple media stages and 8–10 h of observation.

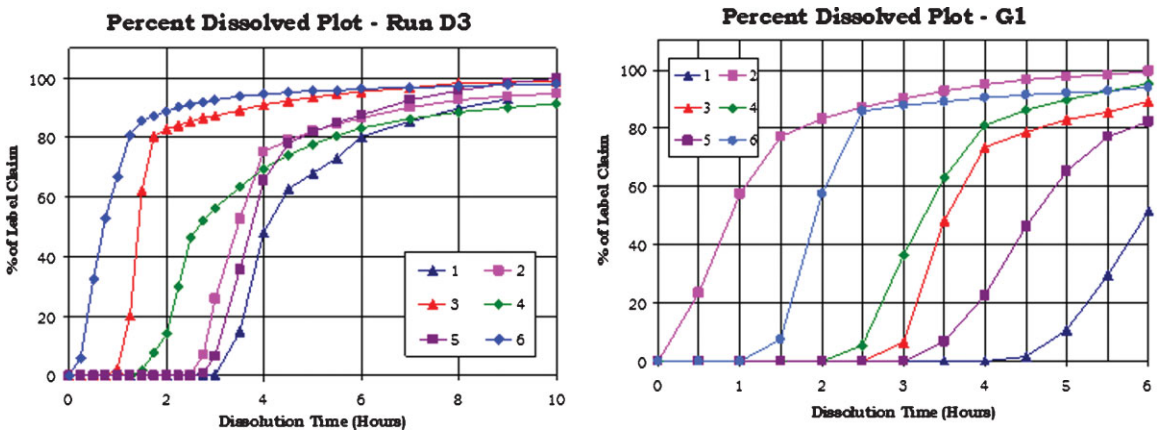

Figure 5. Typical dissolution curves for two of the runs. Run D3 was on tablets scanned on one face for 10 h. Run G1 observed fully scanned tablets for 6 h.

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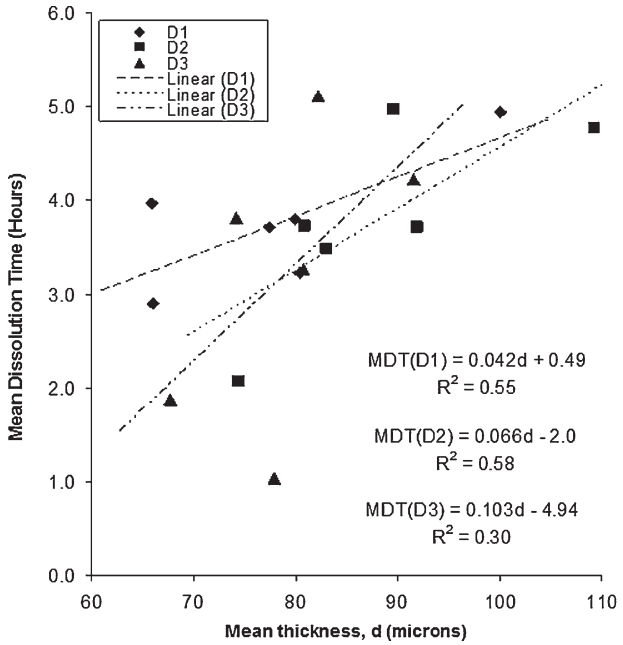

Figure 6. Mean dissolution time as a function of thickness of a single randomly selected tablet face.

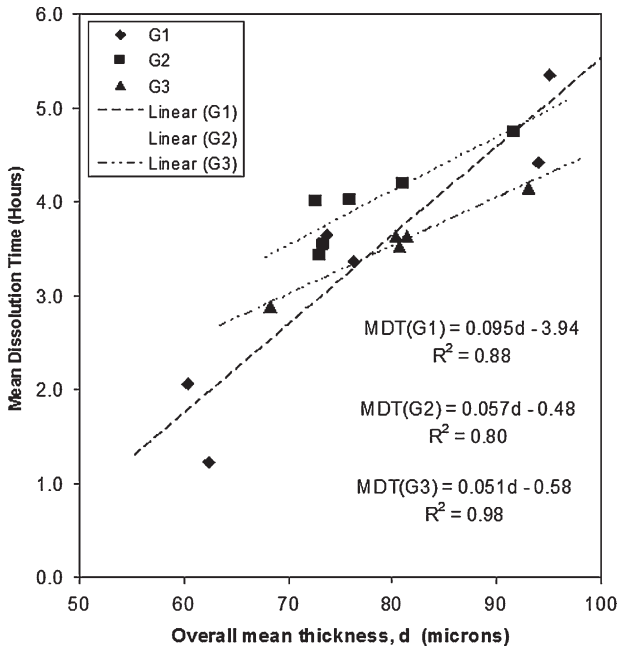

Figure 7. Mean dissolution time as a function of the overall mean tablet coating thickness measured by terahertz pulsed imaging.

Table 3. Summary of Linear Statistical Fit Results for MDT Versus Coating Thickness in Figures 6 (D1-3, Single Facial Map) and 7 (G1-3, Mean of all Three Surface Maps)

Run	# Samples	r^2
D1	6	0.55
D2	6	0.58
D3	6	0.30
G1	6	0.88
G2	6	0.80
G3	5	0.98

Calculated by MS Office Excel 2003.

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