J Therm Anal Calorim (2012) 108:1287–1292
DOI 10.1007/s10973-011-1477-x

Evaluating drug delivery of solid dose tablets by isothermal mechanical analysis

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Received: 29 November 2010 / Accepted: 9 March 2011 / Published online: 11 April 2011

Abstract The current United States Pharmacopeia (USP) test for the disintegration of drug tablets does not measure initial disintegration times and does not adequately describe tablet disintegration mechanisms. An Isothermal Mechanical Analysis (IsoTMA) method meeting USP specifications has been developed to measure the initial time and rate of drug disintegration. TMA monitors the physical dimension of the formulated drug tablet as a function of time, temperature, applied stress, and pH. TMA can be used to measure the swelling, shrinkage, or disintegration of a formulated tablet in a specified fluid. The focus of this study is to validate an efficient and precise IsoTMA method to measure dimensional stability of solid dose tablets. The precision of the method along with the effect of pH (1–10) and temperature (25–37 °C) on the rate of delivery was determined for nine drugs. Graphical representations of dimensional changes over time were created and compared. Drug delivery in a specific liquid medium was measured by UV analysis for the active pharmaceutical ingredient. An increase in temperature decreased the disintegration time and increased the disintegration rate (mm/min). For the drugs that are studied in this article, pH did not have an appreciable effect on the rate of disintegration.

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Keywords Isothermal mechanical analysis · Drug disintegration · Drug dissolution · Tablet disintegration

Introduction and background

A recent article by Qureshi [1] goes directly to the problem in the development and validation of drug dissolution (disintegration of oral solid dose tablets and capsules): dissolution tests used in quality control testing (QC) can discover variations in product formulations which are not related directly to drug release in humans, also known as the state of bioavailability. Furthermore, observed deviations from expected drug delivery properties do not indicate below average drug release in humans. QC tests may also result in false negatives. What is needed is a test based on bio-relevancy. Qureshi recommends a USP Paddle Apparatus [2] to simulate physical activity of gastrointestinal tract physiology. An in vitro method must be product independent. His crescent-shaped paddle test achieved the objective of product independence while simplifying method development and testing [3].

Additional efforts are underway to investigate disintegration and dissolution of solid dose tablets, many using thermoanalytical techniques [4, 5]. Drebushchak et al. [6] and Bannach et al. [7] used thermoanalytical methods, including TG and DSC, along with X-ray diffraction analysis to evaluate the dehydration and decomposition of various drugs and excipients. It was observed that the crystal structure of cellulose after heating did not change while chitosan contracted, changing its disintegration properties. Solid dose technology was reviewed by Wesolowski [8] based on DSC and TG characterization showing variations in bioavailability with grinding of tablets.

Visible cracks and other alterations in the tablets' appearances also caused variations in disintegration properties. Mechanical preparations of drugs were used to vary their dispersion properties with polyvinylpyrrolidone and polyethylene glycol as excipients. Higher apparent solubility and dissolution rates were measured by this innovative mechanical technique, i.e., applied stress caused the observed changes [9]. Gomes et al. [10] studied the thermal and dissolution kinetics of Ampicillin drugs. The dissolution profiles were obtained using USP 23 method. The results of the study showed a good correlation between the Kitazawa rate constant and the thermal decomposition reaction rate constants. This correlation can be used to confirm pharmaceutical equivalence between reference and test products.

There is an ongoing need to develop a better understanding of how solid dose tablets initially disintegrate and proceed to the final state of disintegration in an aqueous medium of known pH. The proposed new innovative Isothermal Thermal Mechanical Analysis (IsoTMA) method established the relevancy and range of drug dissolution by in vitro examination of the dimensional stability of tablets for a range of drugs. Riga and Alexander [11] introduced this IsoTMA method internationally at the International Congress on Thermal Analysis and Calorimetry (ICTAC) Conference in Denmark. They reported a real world disintegration evaluation that correlated well ($R^2 = 0.92$) with the IsoTMA method (Fig. 1). For example, Olanzapine, an "orally disintegrating drug," disintegrates in 18 s at a dimensional rate change of approximately 6 mm/min. Conversely, Abilify has an IsoTMA disintegration time of 60–70 min and a much slower rate measured in units of microns/min.

Williams, Alexander, and Riga examined a wide variety of rapidly disintegrating tablets by IsoTMA [12, 13]. They observed a good correlation between the United States Pharmacopeia (USP) dissolution method [14] and the IsoTMA technique with consistent results for enteric coated tablets. However, the USP method [15] only deals with the final disintegration of the tablet while this IsoTMA method reveals the initial time and rate of disintegration. One assumes the dimensional stability, as monitored by IsoTMA, can be correlated to solid dose tablet disintegration in the throat, stomach, or intestines. To-date, we are confident that there is a good relationship with this new analytical tool and drug delivery since, in a number of cases, the drug uptake at pH = 1 was correlated with IsoTMA and ultraviolet spectroscopy.

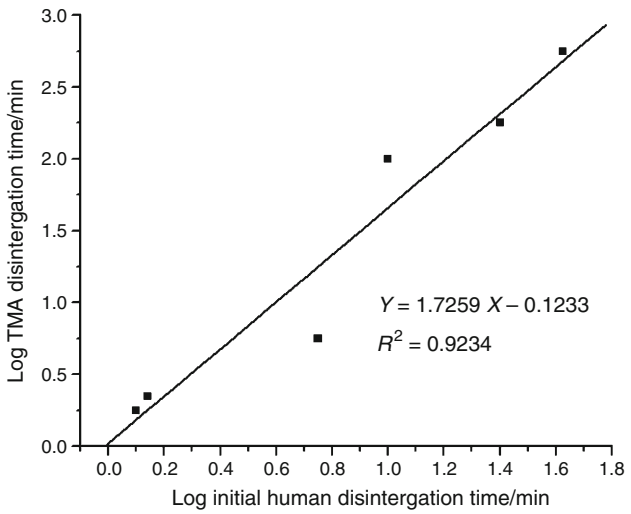

Fig. 1 Log initial TMA disintegration rate vs. Log visual disintegration rate (as judged by a researcher)

The objectives of this study are to evaluate formulated tablet drugs by their disintegration times (min) and dimensional stability rates (millimeters/min = mm/min or microns/min = μm/min). These dimensional stability rates are considered to represent the disintegration rates of the formulated tablets. In addition, we hypothesized disintegration mechanisms might involve swelling in an aqueous fluid followed by disintegration in one or more steps. Independent variables in this study were drug/excipient combinations, pH, and temperature.

Tablets disintegrate and release their active drug while structurally changing. Some tablets expand and thereby allow the active ingredient to be released. Other tablets swell and then disintegrate either rapidly or over a period of time. Measured disintegration times can statistically distinguish between tablets disintegrating in less than 1 min; in between 5 and 10 min; and in more than 10 min. The IsoTMA method can identify the drug delivery target based on disintegration times: oral disintegration occurs between 15 and 30 s; gastric disintegration over 5–10 min; and intestinal disintegration over 10 min. The percent relative error for IsoTMA measured disintegration times was approximately 10–20% and is probably due primarily to non-uniformity of the tablet surface with its curvature and raised letters. The % relative error of the disintegration rate (mm/min) varied more widely than the disintegration time, with a value of 20–30%. Factors to improve the precision and accuracy (relative to the standard USP method) will be discussed.

Experimental procedure

Methods

The Isothermal TMA procedure uses a TA Instruments 943 Thermal Mechanical Analyzer (New Castle, DE, USA). Figure 2 shows the TMA apparatus and a view of the quartz stage before and after a Femhrt tablet has disintegrated.

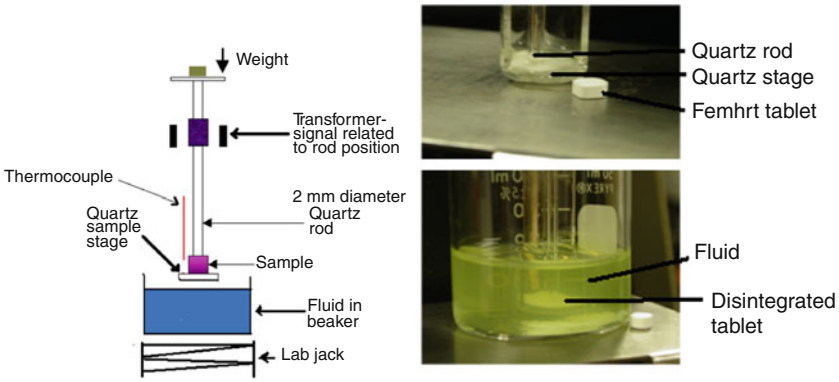

Fig. 2 TMA apparatus (*left*) and disintegration of Femhrt tablet (*right*)

Analytical protocol

The 2-mm diameter TMA quartz rod was first zeroed on the quartz sample stage. After calibrating the TMA with an aluminum height standard, the zeroed probe was placed on top of the test tablet in order to measure its thickness in mm. A load was applied to the probe by placing a weight on the top tray. This load varied from 2 to 100 g, with 20 g being typical. A scan of tablet dimension versus time was then begun. The tablet was immersed in a beaker of de-ionized water after a 2 min interval at ambient conditions. The pH of the water used had been adjusted to 1, 4, 7, and 10, with pH = 7 being typical. The temperature of the water was set at 24 or 37 °C with a hot plate to investigate the effect of temperature. 37 °C was chosen as the biologically relevant temperature of the human body; 24 °C (ambient temperature) was chosen as a control for comparison to the 37 °C results. The formulated drugs evaluated by this in vitro method are summarized in Table 1.

Three apparent drug disintegration mechanisms measured by IsoTMA are as follows:

- Tablet releases the drug while structurally disintegrating.
- Tablet swells, subsequently allowing the active ingredient to be released.
- Tablet swells and then disintegrates either rapidly or over a period of time.

Table 1 Solid dose tablets studied

Trade name	Generic name
Abilify	Aripiprazole
Aspirin	Acetylsalicylic acid
Cardura	Doxazosin mesylate
Femhrt	Ethinyl estradiol + norethindrone acetate
Hytrin	Terazosin
Norvasc	Amlodipine besylate
Proscar	Finasteride
Ritalin	Methylphenidate HCl
Zyprexa	Olanzapine

Results and discussion

The IsoTMA curves for Femhrt at pH 5.5 and 7.0 (24 °C) are seen in Fig. 3. A slight swelling occurs before disintegration after about 1 min immersion. Disintegration is faster at the lower pH. The time to complete disintegration decreased with increasing temperature.

Abilify, at pH 7 and 24 °C, swelled and then disintegrated over a period of 68–90 min (Fig. 4).

Ritalin, at pH 7 and 24 °C, disintegrated in multiple stages over a period of time ranging from 31 to 100 min (Fig. 5). The derivative of the dimensional change shows eight peaks (microns/min) representing different stages of disintegration. The three major disintegration rate peaks are at 35, 56, and 85 min with a standard deviation of ±5.5%. The dimensional rate change (derivative) values corresponding to three peaks are 620, 605, and 200 microns/min with a standard deviation of ±20%.

Other formulated tablets had disintegration times of 1 to 4 min with accompanying maximum rates of 1.2 to 3.2 mm/min, significantly higher than either Ritalin or Abilify.

Doxazosin at pH 4.0 and 24 °C was a 3.0 min disintegration time tablet with three different peak rate values: 1.0, 2.1, and 3.2 mm/min.

Proscar at pH 4.0 and 24 °C was a 4.0 min disintegration time tablet with three different peak rate values: 1.2, 2.5, and 3.0 mm/min.

Norvasc was evaluated at pH = 1, 4, 7, and 10 at 24 °C. Mechanistically, it swelled and then disintegrated. The swelling rate at all pH values was 1.4 mm/min and the disintegration rate was 2.0 mm/min. It was observed that the disintegration rate at pH 4, 7, and 10 was 7.7 mm/min while at pH 1 it was 5.4 mm/min. This variation in IsoTMA behavior at pH 1 can be attributed to the salt-like structure of Norvasc.

Zyprexa was listed as an "orally disintegrating tablet." IsoTMA measured its disintegration time as 18 s for a whole tablet with a rate of 1.5 mm/min. A half tablet, with a noted degree of surface roughness, had the same 18 s

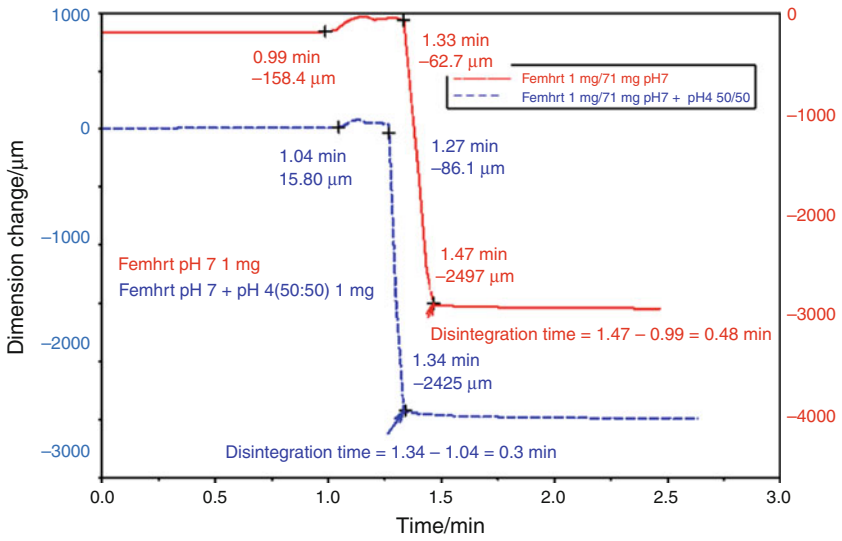

Fig. 3 Femhert IsoTMA profile at pH 5.5 and 7.0 (24 °C)

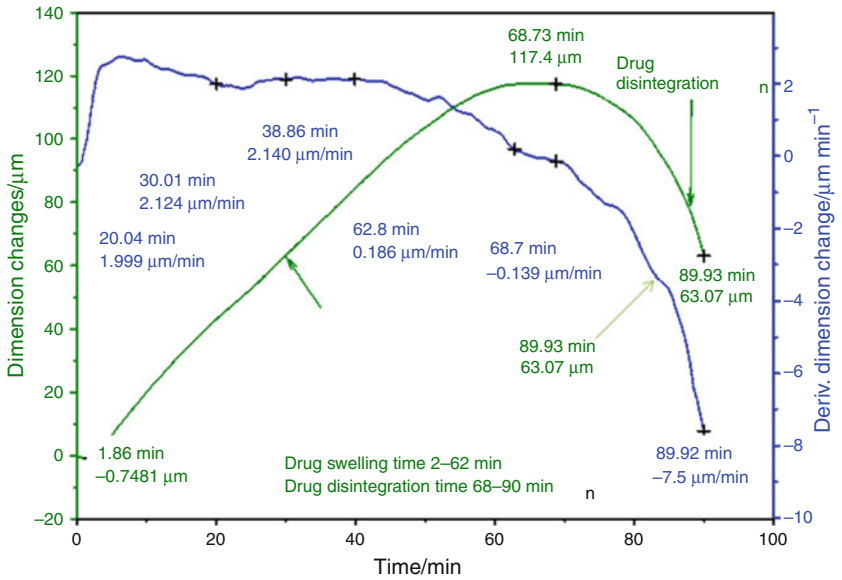

Fig. 4 IsoTMA profile at pH 7.0 (24 °C)

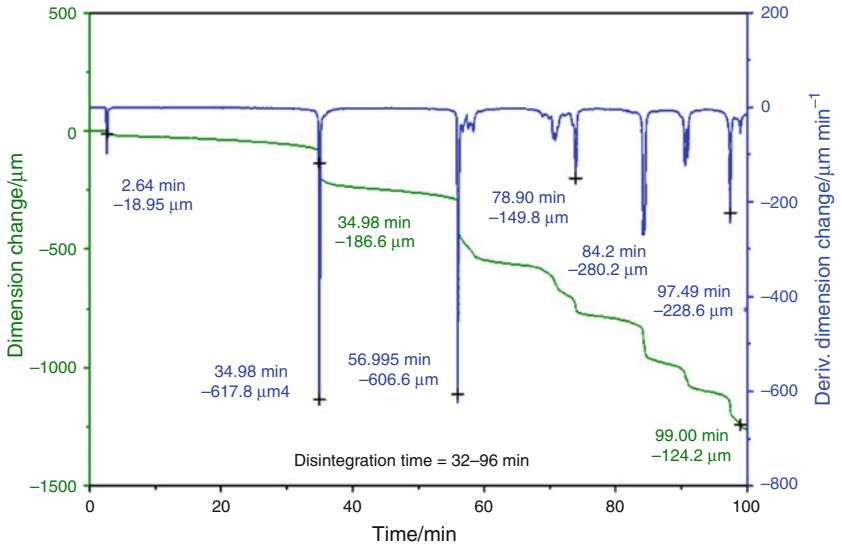

Fig. 5 Ritalin IsoTMA profile at pH 7.0 (24 °C)

Table 2 Solid dose drug tablets evaluated by IsoTMA times versus delivery target

Brand name	Generic name	Disintegration time	Delivery target
Abilify	Aripiprazole	60–96 min	Intestines
Asprin	Acetylsalacylic acid	7–10 s	Oral
Femhrt	Ethinyl estradiol + norethindrone acetate	18–29 s	Oral
Cardura	Doxazosin mesylate	3–5 min	Stomach
Hytrin	Terazosin	48–60 s	Oral
Norvasc	Amlodipine besylate	2–3 min	Stomach
Proscar	Finasteride	4–6 min	Stomach
Ritalin	Methylphenidate·HCl	31–100 min	Intestines
Zyprexa	Olanzapine	18–22 s	Oral

Table 3 Statistical analysis of IsoTMA of Femhrt at pH 7 and 37 °C

Test no.	Disintegration rate/μm/min	Disintegration time/s
1	12	10.2
2	16	6.0
3	15	6.0
4	14	9.0
5	14	7.8
6	12	9.6
7	15	5.4
8	12	5.4
9	13	8.4
10	14	7.2
11	15	6.6
Average	14	7.2
STDV	1.2	1.8
% Error	8.9	2.3

disintegration time but the rate increased to 7.2 mm/min. The surface area increase in the half tablet is likely responsible for the increased rate.

Four Aspirin tablets were sampled by IsoTMA. The average disintegration time was 7.0 s at 37 °C and pH = 7. The average rate was 2.6 microns/min with a 7.4% standard deviation.

Hytrin was also sampled for four runs and had an average disintegration time of 48 s for a dry tablet. The average rate was 6.9 μm/min with a standard deviation of 7.2%. An additional two runs of a Hytrin tablet exposed to a moist environment had a 22 s disintegration time and an average rate of 9.0 μm/min (±10% standard deviation). Therefore, the disintegration time and rate of Hytrin were both affected by previous exposure to moisture.

Conclusions

The IsoTMA protocol is fairly simple and yields direct information on formulated drug delivery. Tablets can

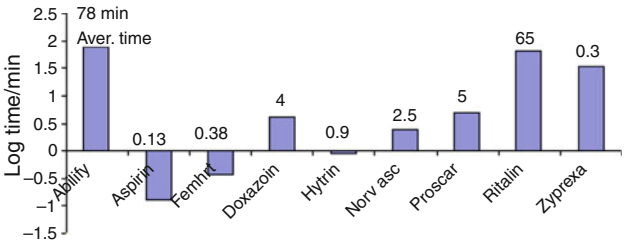

Fig. 6 Average disintegration times of solid tablets

disintegrate rapidly in less than 2 min, corresponding to an oral mechanism, or disintegrate over a longer period of time, 40–90 min, corresponding to an intestinal drug delivery process (see Table 2). The disintegration times as determined by using the IsoTMA method can aid in determining drug delivery target times. The statistical analysis summary indicates that, for Femhrt (Table 3), Hytrin, and Aspirin, the average % standard deviation for the disintegration rate (mm/min) was 11%. For these same drugs, the average % standard deviation for the disintegration time was 20%. This repeatability was poorer than we had anticipated. However, there are some contributing factors that undoubtedly inflated the % standard deviation.

There is a difficulty in obtaining consistent IsoTMA probe placement that may be due to the convex nature of many solid dose tablets. Another problem in using dimensional stability as a measure of drug disintegration and subsequent delivery is the embossed logo on the pill causing variations in IsoTMA probe measurements.

We are currently assessing these problems with a wide variety of tablet drugs. We are evaluating disintegration properties of formulated tablets with longer dissolution times, tablets with minimum curvature and imprinted logos and the effect of applying a higher applied stress to fix the tablet in place while being submersed in a fluid. Another possible improvement in the IsoTMA precision might result from increasing the contact surface area of the quartz probe from 3.1 to 19.6 mm^2.

This data may be visually represented as the log of the average disintegration time for the respective tablets (Fig. 6).

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