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RESEARCH ARTICLE

# Evaluation of Disintegration Testing of Different Fast Dissolving Tablets Using the Texture Analyzer

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## ABSTRACT

*The in vitro disintegration behavior of fast dissolving systems manufactured by the main commercialized technologies was studied using the texture analyzer (TA) instrument. Quantitative parameters were employed to characterize the effect of the major test variables on the disintegration profiles. The average disintegration profiles of the products were compared using the test conditions that minimized these effects and at the same time mimicked the in vivo situation in the patient's mouth. The differences in the disintegration mechanisms of the fast dissolving systems were reflected in the shape of their disintegration profiles and in the parameters derived from the profiles. The differences were explained in relation to the technology and/or formulation characteristics involved in the manufacture of each product. The in vitro disintegration times obtained under the simulated in vivo conditions were correlated with the reported in vivo disintegration times.*

***Key Words:*** *Disintegration; Fast-dissolving tablets; Texture analyzer method*

## INTRODUCTION

Fast dissolving dosage forms are drug delivery systems that dissolve or disintegrate in the patient's mouth in less than a minute without the need for water. They are prepared by a variety of commercialized technologies and can exhibit different disintegration behaviors.[1,2] The standard compendial test has been used for testing the disintegration time of these forms, however, it may have limitations in discriminating between the disintegration times of the different fast dissolve formulations with very short disintegration times. Recently Dor and Fix[3] and Abu-Izza et al.[4] reported on a disintegration test using the texture

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analyzer (TA) instrument. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, the instrument is set to maintain a small force for a determined period of time. The plots of the distance traveled by the probe, generated with the instrument's software, provide a disintegration profile of the tablets as a function of time. These plots are used to calculate the start and the end point of tablet disintegration. Dor and Fix[3] were able to monitor the changes in the disintegration time of the fast dissolving tablet due to the formulation parameters. Abu-Izza et al.[4] employed the test to compare different products. Both authors obtained a good correlation with the in vivo data.

The objective of the present study is to examine in more detail the TA test and evaluate the disintegration profiles for quantitative measurements of the disintegration behavior of different fast dissolving drug delivery systems.

## Experimental

### Materials

The products used in the present study represent the main commercialized technologies for the fast dissolving delivery systems and were provided by the suppliers:

- Fuisz Technologies Ltd. (currently owned by Biovail Technologies Ltd., Mississauga, ON, Canada): FlashDose® placebos
- Biovail Technologies Ltd.: Nurofen® Meltlets using FlashDose® Technology
- Cima Labs Inc. (Eden Prarie, MN, USA): OraSolv® placebos, DuraSolv® placebos
- Elan Pharma SA (Mezzovico, Switzerland): Children's multivitamins iron and Ca, Nimesulide 100 mg
- Prographarm Group (now owned by Ethypharm/Saint Cloud, France): FlashTab® placebos
- Wowtab®/Yamanouchi (Palo Alto, CA, USA): Benadryl® allergy/cold Fastmelt®

The products are listed in Table 1 and are letter coded for convenience of reference. The tablet dimensions of each product can also be found in Table 1.

## Methods

### Apparatus

The studies were conducted with the TA instrument, model TA-XT2i and the Texture Expert™ software (Texture Technologies Corp., Scarsdale, NY, USA/-Stable Micro Systems, Surrey, England, UK).[3,4] The instrument was calibrated with a 5 kg load cell and fitted with a stainless steel flat-bottomed cylindrical probe with 1 $cm^2$ surface area (Kobe probe). The methodology consists in attaching the tablet to the flat surface of the probe with a double-sided adhesive tape (double-stick tape, 12 mm, 3 M). The probe moves until a trigger force is detected at which point the TA is set to maintain a predetermined nominal force for a given period of time (60 sec). As the tablet starts disintegrating, the TA measures the penetration distance as the tablet is compressed while submerged in the medium.[5]

### Disintegration Medium

To study the disintegration behavior of the tablets in simulated in vivo conditions, the disintegration medium

***Table 1***

*Product Identification and Dimensions*

| Product (manufacturer) | Code | Tablet Dimensions[a] [diameter × thickness (mm)] |
|---|---|---|
| Nurofen (Biovail) | A | 15.0 × 5.0 |
| FlashDose placebo (Fuisz/now owned by Biovail Corp.) | B | 11.1 × 4.9 |
| DuraSolv placebo (Cima) | C | 9.7 × 4.0 |
| OraSolv placebo (Cima) | D | 12.7 × 4.4 |
| Benadryl (Wowtab/Yamanouchi) | E | 11.4 × 4.9 |
| Nimesulide 100 mg (Elan) | F | 13.0 × 5.2 |
| Children's multivitamins iron and Ca (Elan) | G | 16.0 × 6.1 |
| FlashTab placebo (Prographarm Group/now owned by Ethypharm) | H | 11.2 × 4.0 |

[a] Measured with a micrometer.

used was artificial saliva (pH 6) and consisted of: KCl (1.20 g/L); $MgCl_2 \cdot 6H_2O$ (0.05 g/L); $CaCl_2 \cdot 6H_2O$ (0.15 g/L); KSCN (0.10 g/L).[6] A constant temperature of the medium of 33 ± 1°C was maintained during the tests by means of a thermostated double wall cell and a heating bath/circulator (Haake, Karlsruhe, Germany); the set up is shown in Fig. 1. The tests were conducted with a fixed volume of 2 mL. This implies that the volume will be insufficient in some cases for complete submersion of the tablet, due to the different tablet dimensions of the products (Table 1). However, it was necessary to select this parameter as close as possible to the in vivo conditions. The effect of volume (1–6 mL), disintegration medium (water or simulated saliva), and temperature (room temperature and 37 ± 2°C) on the disintegration times was evaluated.

### Nominal Compression Force/Time

The compression force and the time of holding the force were 50*g* and 60 sec, respectively. The effect of larger compression force (250*g*) was evaluated. Four tablets were used for each test measurement.

## RESULTS AND DISCUSSION

### Method of Analysis

The distance–time profile generated by the TA software was used to characterize the behavior of the tablet during the disintegration process. Moreover, an average profile was obtained from the individual distance–time curves of at least four tablets. Thus, the average distance–time profile represents the mean value for each test condition and comprises the tablet to tablet variation. The distance–time profiles are referred to as disintegration profiles. The individual profiles of four FlashDose tablets and the average profile determined from them are shown in Fig. 2a. The obtained profiles are similar in shape to the typical force–displacement curve suggested by Dor et al.[7] They exhibit three characteristic regions: an IR or initial region, where the tablet resists the force applied by the probe before the disintegration starts; an AR or ascending region, where the tablet disintegrates as the probe distance increases sharply in search of the target force; and a PR or plateau region, indicating that the disintegration is complete.[3,7] The following parameters were calculated as illustrated in Fig. 2b:

- disintegration onset ($t_1$)—onset of disintegration, that is the projection on the time axis of the intercept of the slope of the IR with the slope of the AR of the disintegration profile.
- disintegration rate (dr)—the slope of the AR of the disintegration profile.
- extrapolated disintegration time ($t_2$)—duration of disintegration, extrapolated according to Dor et al.[7] from the two intercepts of the slopes of the three main regions of the disintegration plot, IR, AR, and PR (see Fig. 2a).
- penetration distance ($d$)—the maximum distance traveled by the probe into the tablet at the end of the test.

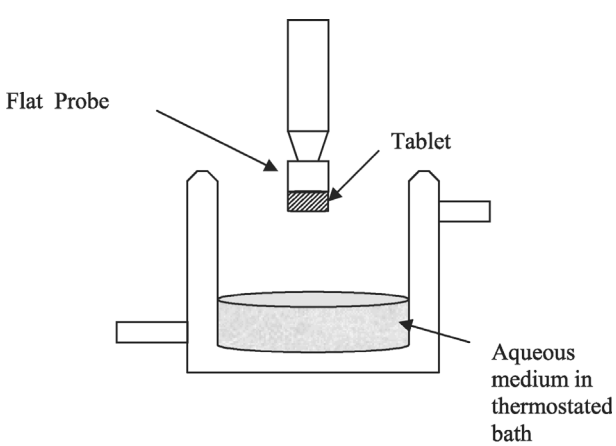


**Figure 1.** Texture analyzer set up for disintegration testing.

### Reproducibility of the Measurements

To estimate the type of variability inherent in the TA-measurements, the extrapolated disintegration times ($t_2$) were calculated from the individual distance–time curves of six FlashDose tablets tested in 3 mL of the disintegration medium (water) at room temperature using a compression force of 50 *g*. The mean and the standard deviation obtained were: $t_{2\,(n=6)} = 9.3 \pm 0.8$ sec (%C.V. = 8.7). Furthermore, the $t_2$-value calculated from the average disintegration profile (the average profile was calculated from the six individual curves with the TA-software) was $t_{2\,(\text{average})} = 10.5$ sec, which is very close to the mean value of 9.3. A similar error was obtained when four tablets were tested instead of six, i.e., $t_{2\,(n=4)} = 9.4 \pm 0.7$ (%C.V. = 7.7) and $t_{2\,(\text{average})} = 11.6$ sec. Generally, the error associated with the other products tested was %C.V. ~ 10. The disintegration

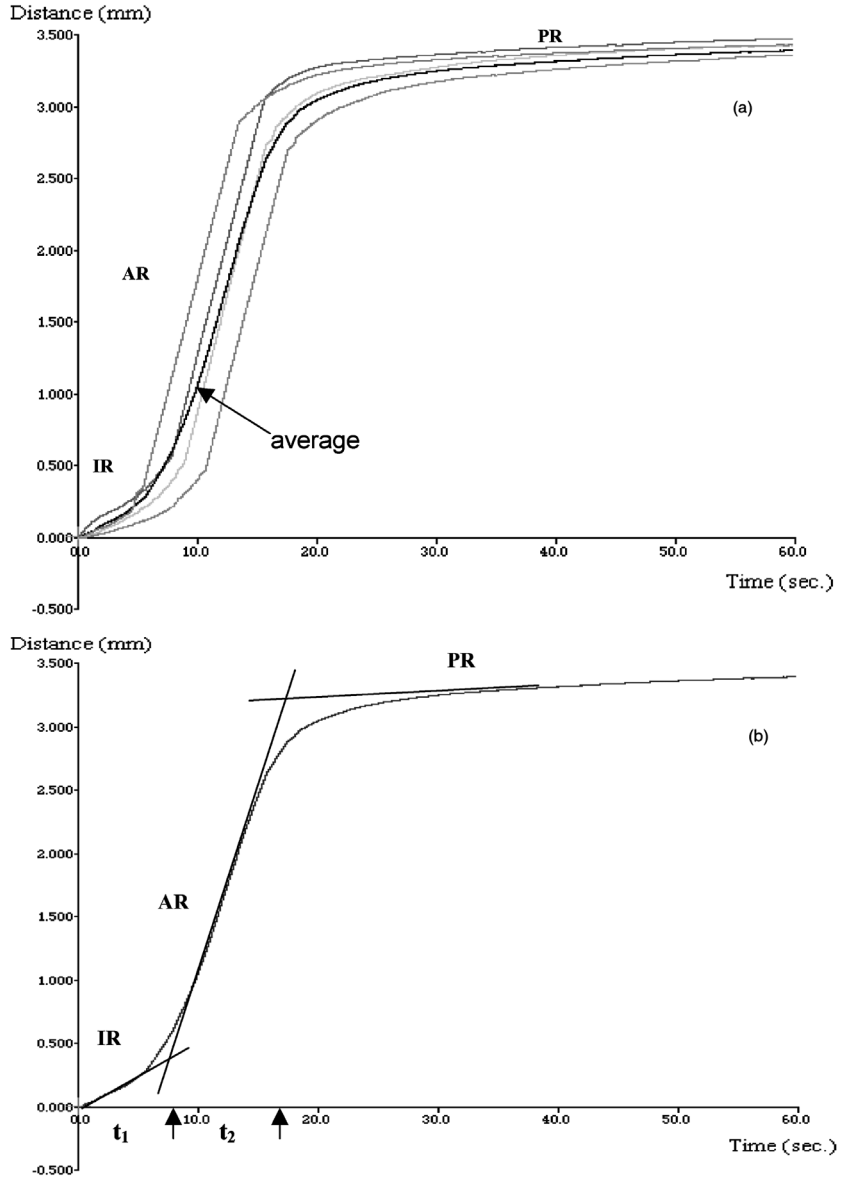


**Figure 2.** (a) Disintegration profiles of FlashDose placebos (B) in 3 mL water. Shown are the individual profiles of the four tablets tested and the average profile (arrow) calculated with the TA-software. The profiles exhibited three regions, i.e., IR = initial region, AR = ascending region, and PR = plateau region. (b) The average profile of FlashDose placebos (B) in 3 mL water from (a) is shown alone, in order to illustrate the intercepts (arrows) used for the extrapolation of the disintegration time according to Dor et al.[7]

times discussed further in the text are obtained from the average profiles. The advantage of using the average disintegration profile for the calculation of the disintegration time is that, while the profile includes the variability inherent in the experimental measurement, it minimizes the error involved in the calculation of the $t_2$ value.

## Effect of Test Variables

Dor and Fix[3] and Dor et al.[7] used distilled water as the disintegration medium and reported on the effect of the volume and the temperature of the medium as well as on the nominal compression force applied to the TA probe. For a defined tablet geometry, the disintegration time was

independent of the volume, above 0.2 mL, for an applied force greater than 200 *g*. The disintegration time decreased from 23 sec at 5°C to 5 sec at 70°C. These authors employed one particular type of fast dissolving form throughout the study. Abu-Izza et al.,[4] on the other hand, studied different formulations under fixed conditions: 5 mL of water at 37°C and an applied force of 20*g*. Based on our preliminary tests, further consideration must be given to the effect of the various test parameters as the conditions under which the tests are conducted may influence the final result. To compare the performances of the different fast dissolving forms, not only must all the tests be conducted under identical test conditions, they should also mimic the in vivo conditions.

## Effect of the Volume, Temperature, and Compression Force

The effect of the volume, temperature, and compression force was studied using water as the disintegration medium (Figs. 3–5). It can be seen from Fig. 3 that an increase in volume from 1 to 2 mL resulted in a shorter IR of the profiles (i.e., decreased the onset time, $t_1$) and a steeper ascending region of the profile (i.e., increased the rate of penetration, dr). The effect of further increase in the volume (i.e., volume $> 2$ mL) appeared to be less significant. The parameters calculated from the disintegration profiles of the different fast dissolve tablet formulations are shown in Table 2. The disintegration onset ($t_1$) and the disintegration time ($t_2$) decreased whereas the disintegration rate (dr) increased when the volume increased from 1 to 2 mL after which no significant changes could be observed for both the products. Increasing the temperature from room temperature to 37°C decreased the onset time ($t_1$) of both the FlashDose placebos (B) and the Children's multivitamins iron and Ca (G) but did not affect considerably the $t_2$-values or the dr-values (Table 2). The increase in the applied compression force from 50 to 250*g* did not affect the parameters as seen in Table 2, however, increasing the compression force did result in minimizing the dimensional change occurring as a result of effervescence or swelling. For that reason, 50*g* was selected as the preferred compression force. It can be concluded from these findings that a volume larger than 1 mL is necessary to minimize the effect of the volume, and that the effect of the temperature must be taken into account when correlating the results with in vivo data.

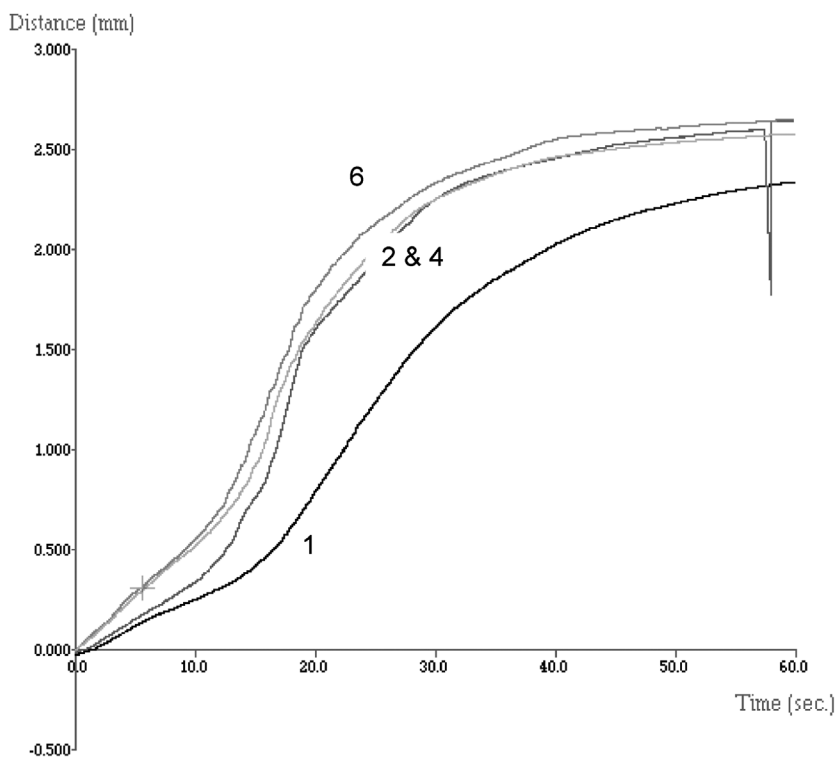


**Figure 3.** Average disintegration profiles of Children's multivitamins iron and Ca (G) in 1, 2, 4, and 6 mL of water.

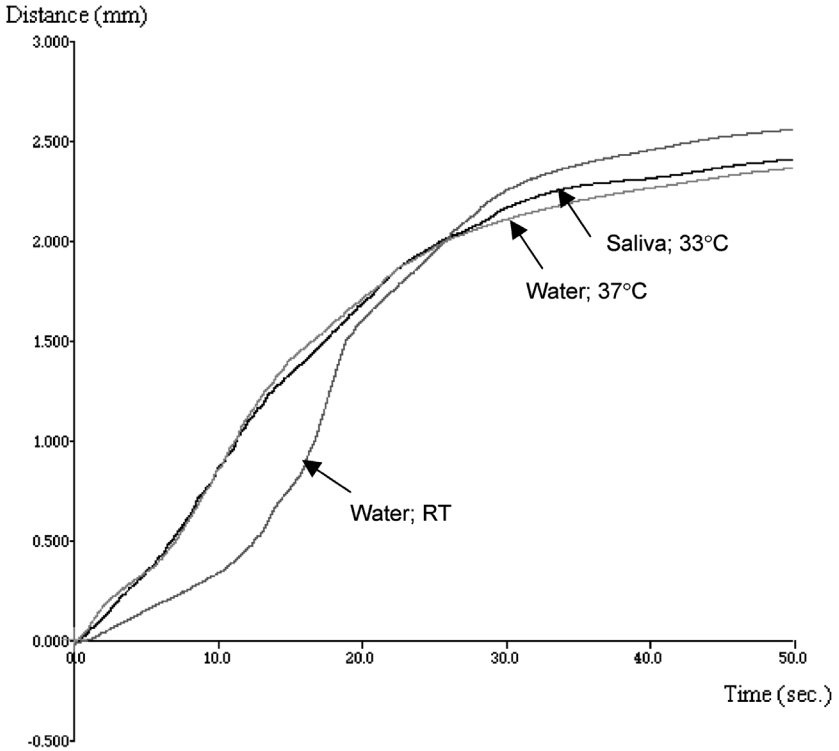


**Figure 4.** Average disintegration profiles of children's multivitamins iron and Ca (G) in 2 mL of: water at room temperature; water at 37°C; and artificial saliva at 33°C.

***Table 2***

*Effect of Test Variables on the Disintegration Characteristics of Fast Dissolving Tablets*

| Product Code | Test Variable | Disintegration Onset, $t_1$ (sec) | Disintegration Rate, dr (mm/sec) | Extrapolated Disintegration Time, $t_2$ (sec) |
|---|---|---|---|---|
| Volume of water (mL) | | | | |
| B | 1 | 16 | 0.06 | 21 |
| | 2 | 6 | 0.18 | 14 |
| | 3 | 7 | 0.21 | 12 |
| | 4 | 5 | 0.13 | 16 |
| | 5 | 8 | 0.18 | 15 |
| G | 1 | 16 | 0.07 | 19 |
| | 2 | 13 | 0.10 | 13 |
| | 4 | 13 | 0.09 | 13 |
| | 6 | 11 | 0.08 | 13 |
| Temperature of water (°C) | | | | |
| B | Room temperature | 8 | 0.18 | 15 |
| | 37 | 5 | 0.18 | 15 |
| G | Room temperature | 13 | 0.10 | 15 |
| | 37 | 4 | 0.09 | 18 |
| Compression force (*g*) | | | | |
| D | 50 | 23 | 0.11 | 18 |
| | 250 | 24 | 0.11 | 17 |

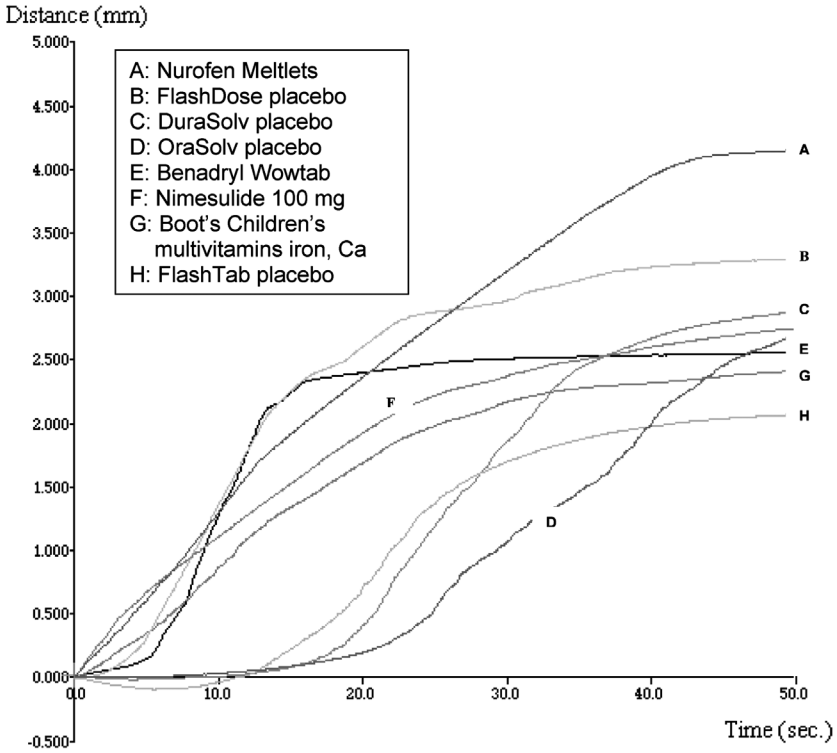


**Figure 5.** Average disintegration profiles of the fast dissolving tablets (each of at least 4 tablets) manufactured by different technologies in 2 mL simulated saliva pH 6.0 at 33°C with 50*g* probe force and 60 sec hold. Key: A—Nurofen (Biovail); B—FlashDose placebo (Fuisz); C—DuraSolv placebo (Cima); D—OraSolv placebo (Cima); E—Benadryl (Wowtab); F—Nimesulide 100 mg (Elan); G—Children's multivitamins iron and Ca (Elan); H—FlashTab placebo (Prographarm/Ethypharm).

## Effect of Disintegration Medium

The effect of the medium was studied in 2 mL of either water or artificial saliva. The average profiles for the product G are shown in Fig. 4. It can be seen that the profiles of the artificial saliva and water at 37°C were very similar, however, if water was used at room temperature a different result was obtained (i.e., a longer onset time). Thus, the temperature of the medium has a predominant effect over the type of the medium.

In view of the findings discussed above, it was necessary to keep the test conditions constant and as close as possible to the in vivo conditions in the patient's mouth.

## Disintegration Tests in Simulated In Vivo Conditions

In order to select the volume parameter as close as possible to the in vivo conditions, the studies were conducted in 2 mL of artificial saliva. While, the commercial products come in different sizes and dimensions, resulting in different degrees of submersion of the tablet in the medium, the 2 mL volume was found to be sufficient to observe the following trends (Fig. 5):

(a) Wowtab Benadryl tablets (E) and FlashDose placebos (B) exhibited a typical disintegration profile[3,7] with: a short IR, where the tablet resists the force before disintegrating (parameter: onset, $t_1$); a fast AR, where the tablet disintegrates (parameters: disintegration rate, dr and extrapolated disintegration time, $t_2$); a PR, where the disintegration is complete.
(b) Nurofen Meltlets (A) and the two Elan's products (F, G) had disintegration profiles without the initial onset region.
(c) DuraSolv (C), OraSolv (D), and FlashTab (H) had disintegration profiles with comparatively longer onset regions which exhibited negative distance values.

The quantitative parameters calculated from each average curve, $t_1$, dr, and $t_2$ are shown in Table 3. In addition, the total disintegration time, $T = t_1 + t_2$ was

***Table 3***

*Disintegration Parameters of Fast Dissolving Tablets*

| Product (Manufacturer); [Thickness $h$ (mm)] | Code | Onset $t_1$ (sec) | Rate dr (mm/sec) | EDT[a] $t_2$ (sec) | Total Disintegration Time $T$ (sec) | Penetration Distance $d$ (mm) (std. dev.) | $\Delta$[b] (mm) | In Vivo Disintegration Time (sec) [Ref] |
|---|---|---|---|---|---|---|---|---|
| Nurofen Meltlet (Biovail); (5.0) | A | ~0 | 0.10 | 31 | 31 | 4.2 (2.0) | 0.8 | |
| FlashDose placebo (Biovail); (4.9) | B | 4 | 0.15 | 14 | 18 | 3.3 (0.1) | 1.6 | |
| DuraSolv placebo (Cima); (4.0) | C | 17 | 0.13 | 18 | 36 | 3.0 (0.1) | 1.0 | 5–30,[1] 52[c] |
| OraSolv placebo (Cima); (4.4) | D | 22 | 0.09 | 30 | 52 | 3.0 (0.1) | 1.4 | |
| Benadryl allergy/cold fastmelt (Wowtab/Yamanouchi); (4.9) | E | 6 | 0.19 | 8 | 14 | 2.6 (0.2) | 2.3 | |
| Nimesulide 100 mg (Elan); (5.2) | F | ~ 0 | 0.09 | 25 | 25 | 2.8 (0.9) | 2.4 | |
| Children's multivitamins iron and Ca (Elan); (6.1) | G | 0.2 | 0.08 | 27 | 27 | 2.5 (0.2) | 3.6 | |
| FlashTab placebo (Prographarm); (4.0) | H | 12 | 0.09 | 15 | 27 | 2.1 (0.1) | 1.9 | <60,[1] 41[c] |

[a] EDT = Extrapolated disintegration time.
[b] $\Delta = h - d$.
[c] Internal market research evaluation.

also calculated and is shown in Table 3. It is evident from the analysis of Fig. 5 and the data in Table 3 that the disintegration occurs by different mechanisms. This can be related to the different manufacturing technologies and/or different formulation factors involved, bearing in mind that the test conditions were kept constant and the effect of the test parameters was minimized.

The FlashDose (B) and the Wowtab (E) tablets had short onset times ($t_1 = 4-6$ sec) and fast disintegration. The disintegration times ($t_2$) were 14 and 8 sec and the disintegration rates (dr) were 0.15 and 0.19 mm/sec, respectively, for B and F. The total disintegration time ($T$) was 18 sec for FlashDose and 14 sec for Wowtab. In the Fuisz technology for the FlashDose, a saccharide-based matrix is subjected to a fluid shear force ("flash flow processing") to produce a candy floss matrix ("shearform matrix"). The amorphous floss is molded using low compression force and recrystallized to form a continuous crystalline structure throughout the tablets. This gives rapidly disintegrating tablets, which possess satisfactory mechanical strength. The patent, assigned to the Fuisz Technologies claims that the dissolution in the patient's mouth is 10 sec or less.[8] These characteristics of the FlashDose systems were reflected in the $t_2$ value (fast disintegration) and the $t_1$ value (some mechanical resistance) shown in Table 3. The in vitro parameters of the FlashDose tablet correlated well with the in vivo requirement for this product. The Wowtab tablet is a compression molded multiparticle system made of granules of saccharides of "low" and "high" compressibility. The "low" compressibility component provides the fast dissolution, the "high" compressibility component is of slower dissolution but improves the compressibility. The patent, assigned to the Yamanouchi Pharmaceutical Co., claims that the product dissolves rapidly in the mouth (i.e., within 1–40 sec) and has adequate hardness.[9] The in vitro characteristics of the Wowtab system shown in Table 3 were within the range of the in vivo disintegration time claimed for this product.

Although the Nurofen Meltlets (A) are manufactured using the FlashDose technology, their profile (Fig. 5) differed from the FlashDose placebos (B). The $t_1$ value was $\sim 0$ and the $t_2$ value was 31 sec. The disintegration rate was 0.10 mm/sec. It can be speculated that the drug loading of the system led to lower mechanical strength (decrease in $t_1$) and slower disintegration (increase in $t_2$ and decrease in dr) vis-à-vis that of the placebos. The Elan's products (F and G) exhibited disintegration profiles without onset time, i.e., $t_1 \sim 0$. The disintegration time and rate were similar for both products: $t_2 = 25$ sec and dr $= 0.09$ mm/sec for the product F and $t_2 = 27$ sec and dr $= 0.08$ mm/sec for the product G. The Elan's FastMelt tablets are prepared by fluid-bed granulation of polyalcohols (e.g., sorbitol, xylitol) using a spraying solution of water-soluble/water-dispersible polymers. The granules obtained in the fluid-bed process have a very high porosity, which is maintained even after compression of the tablets. The porous structure (i.e., large surface area) promotes fast disintegration in the mouth without the need of an effervescent agent. The patent claims in vivo disintegration time ranging from 30 sec to 3 min depending upon the formulation, e.g., 30 sec for the Nimesulide 100 mg FastMelt tablets.[10] This is in agreement with the in vitro data obtained in this study. (N.B.: It is worth noting that the Zydis® delivery form—a freeze-dried porous matrix which requires special packaging due to its poor mechanical properties[1]—exhibited a similar type of disintegration profile (not shown) with zero onset time, although the corresponding disintegration time was considerably shorter, i.e., $t_2 = 8$ sec).

DuraSolv (C), OraSolv (D) of Cima and FlashTab (H) of Prographarm all exhibited relatively slow disintegration onsets, i.e., long IR regions ($t_1 = 17$ sec for C, $t_1 = 22$ sec for D, and $t_1 = 12$ sec for H). The shape of the disintegration profiles indicates a different mechanism of disintegration than that observed previously, whereby, the tablets effervesce or "explode" as they come in contact with water (C and D) or swelled (H) before disintegrating. This is observed as the negative value of the distance on the profile in Fig. 5, which resulted from the counteracting force due to the effervescence/swelling that pushed upward on the probe. Indeed, literature data indicate that the Cima technology uses saliva-activated effervescent agent to promote rapid disintegration in the mouth.[1,2] OraSolv represents a mixture of microparticles and at least one effervescent agent. The patent claims that the effervescent agent is effective in obtaining complete disintegration in the patient's mouth, by providing effervescence in contact with saliva, promoting secretion of saliva, and further disintegration. The disintegration time is claimed to be between 30 sec and 7 min.[11] DuraSolv is the most robust Cima form, which is claimed to achieve the primary benefits of OraSolv, but is capable of being packaged in conventional packaging. The DuraSolv technology uses a matrix composed of nondirect compression sugars (i.e., having particles in the range of 10–80 $\mu$m), an effervescent agent, a wicking agent, and a lubricant. The patent claims a dissolution time in the patient's mouth of 45–90 sec.[12] The in vivo disintegration times for the Cima products were reported

to be between 5 and 30 sec depending on the tablet size.[1] Other sources reported a value of 52 sec for the product C.* The in vitro disintegration times ($t_2$) obtained in this study were 18 and 30 sec for DuraSolv (C) and OraSolv (D), respectively, and the total disintegration times ($T$) were 36 and 52 sec for C and D, respectively. These findings indicate that the in vitro data obtained in the present study lie within the range of the reported in vivo data. The disintegration rate was 0.13 mm/sec for C and 0.09 mm/sec for D (Table 3). The slightly higher rate of the product C could be due to its smaller tablet size (Table 1). The Prographarm technology for the FlashTab incorporates both a disintegrating agent and a swelling agent; the rapid disintegration is due to the simultaneous action of the formulation agents, which also render satisfactory physical characteristics to the tablet. The patent claims that the tablet disintegrates in the mouth in less than 60 sec.[13] Table 3 shows that the FlashTab had a disintegration rate, $\mathrm{dr} = 0.09\ \mathrm{mm/sec}$ close to that of the Cima products. The in vitro disintegration times were: $t_2 = 15$ sec and $T = 27$ sec. The results are within the range of the reported in vivo disintegration time, i.e., $< 1$ min[13] and 41 sec.*

### Penetration Distance ($d$)

In order to further characterize the disintegration behavior, the penetration distance ($d$) was determined from the average disintegration profiles. The penetration distance is the maximum depth traveled by the Kobe probe from the time the tablet hits the medium until the end of the run (i.e., 60 sec). The penetration distance corresponds to the value of the PR of the disintegration profile (see Fig. 2). If one assumes that the tablet dissolved completely within 1 min, theoretically the $d$ value will correspond to the tablet thickness. The actual penetration distances, however, were found to be a certain fraction of the tablet thickness as shown in Table 3. This is because the fast dissolving systems may contain insoluble components, which do not dissolve in the patient's mouth, and the patient swallows the insoluble excipients as a suspension. Thus, the difference ($\Delta$) between the tablet thickness ($h$) and the penetration distance ($d$) can be related to the bulkiness of the remaining suspension—possibly a qualitative measure of the "mouthfeel". Although the tablet dimensions can affect the $\Delta$-values, it can be seen from Table 3 that the $\Delta$-value of the product H is almost twice that of the product C although they have the same thickness. This discrepancy can be related to the different formulation characteristics of the two products.

*Internal market research evaluation.

## CONCLUSIONS

The in vitro disintegration test using TA apparatus can provide useful information about the disintegration behavior of different fast dissolving drug delivery systems. The present study showed that the shape of the distance vs. time profile and the quantitative parameters calculated from the profile depend on the disintegration mechanism involved. By conducting the tests under conditions, which mimic the in vivo situation, it was possible to employ the profiles for comparison of the different products and to correlate the in vitro disintegration times with the reported in vivo data. The method may also find useful application in development studies to identify the changes in the disintegration behavior due to the formulation factors.

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