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Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration

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Abstract

The assessment of the in vitro disintegration profile of rapidly disintegrating tablets (RDT) is very important in the evaluation and the development of new formulations of this type. So far neither the US Pharmacopoeia nor the European Pharmacopoeia has defined a specific disintegration test for RDT; currently, it is only possible to refer to the tests on dispersible or effervescent tablets for the evaluation of RDT's disintegration capacity. In the present study, we have evaluated the disintegration profile of RDT manufactured by main commercialised technologies, using the texture analyser (TA). In order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. The obtained time–distance profiles or disintegration profiles enabled the calculation of certain quantitative values as the disintegration onset (t_1) and the total disintegration time (t_2). These values were used in the characterisation of the effect of test variables as the disintegration medium and temperature on the disintegration time of RDT. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Results obtained when artificial saliva at 37 °C was employed as disintegration medium were used to correlate the in vitro (t_2) and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouthfeel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile. This method also permitted the discrimination between different RDT, where differences in the disintegration mechanism were reflected on the disintegration profile achieved for each tablet.

Keywords: Rapidly disintegrating tablets; In vitro disintegration profile; Texture analyser; Oral disintegration

1. Introduction

Rapidly disintegrating tablets (RDT) are solid single-unit dosage forms that are placed in the mouth, allowed to disperse/dissolve in the saliva and then

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swallowed without the need for water (European Pharmacopoeia 4.1, 2002). RDT are appreciated by a significant segment of the population, particularly children and elderly who have difficulty swallowing conventional tablets or capsules. Consequently, the development of RDT has recently interested not only the pharmaceutical industry but also academia (Mallet, 1996; Dobetti, 2001).

Commercially available RDT are prepared by various techniques, mainly lyophilisation, moulding and direct compression; thus, they exhibit different disintegration behaviours (Seager, 1998; Sastry et al., 2000; Cremer, 2001). Therefore, the determination of RDT disintegration time and behaviour is very essential in the evaluation and the development of this new dosage form. But so far neither the US Pharmacopoeia nor the European Pharmacopoeia has defined a specific disintegration test for RDT; currently, it is only possible to refer to the tests on dispersible or effervescent tablets for the evaluation of RDT's disintegration capacity. However, this standard compendial test faces many limitations in the discrimination between different RDT as their disintegration time is very short and also because of the strong agitation and large volume of water used during this test (Bi and Hisakadzu, 1996; Hisakadzu and Bi, 2002).

Therefore, it is indispensable to elaborate a new method, not only to determine the disintegration time of RDT but also their behaviour during disintegration, which varies according to the formulation technique employed.

Recently, certain authors (Dor et al., 1999, 2000; Dor and Fix, 2000; Abu-Izza et al., 2000; Mesdjian et al., 2001) have reported on a disintegration test for RDT using the texture analyser (TA) instrument. According to the authors, in this test, the tablet is attached by means of an adhesive tape to a flat-ended cylindrical probe. The tablet under a constant force was emerged in a defined volume of distilled water and the time to disintegrate the tablet versus the distance travelled by the probe into the tablet was monitored. Typical time–distance profiles generated by the texture analyser software enabled the calculation of the beginning and the end point of the disintegration time. The results obtained by the authors were good.

Nevertheless, we find that the operating structure reported by the authors in this method may not cohere with what actually happens in the patient's mouth upon administration of a RDT as when the tablet is placed in the mouth, it is immediately wetted from both sides by the tongue and also slightly by the upper palate of the mouth, which is not the case in the test described by the authors, as the upper surface of the tablet is attached by the tape and hence, it is not wetted. Furthermore, in this test, the tablet is blocked between the probe and the base of the disintegrating recipient; hence, the particles detached during the disintegration process are not progressively eliminated whilst in the mouth, these particles are either diffused or swallowed with the saliva. We also find that the use of an adhesive tape may cause several errors in the results, as its thickness may affect the distance travelled by the probe, in addition the upper surface of the tablet rest attached to the adhesive tape.

In order to better simulate the oral disintegration of RDT, we have completely changed the operating structure of the test where we provided a means for the tablet to be placed on a movable platform without attaching it with an adhesive tape. In addition, our new operating structure mimics the situation in the patient's mouth, where detached particles are gradually eliminated.

The objective of this work is to examine this method with the new operating structure using the texture analyser and to evaluate the disintegration behaviour of different RDT manufactured by different technologies.

In order to accomplish this study, certain commercialised RDT representing the main technologies employed in the fabrication of these dosage forms were selected and in addition, two other RDT were prepared using two different techniques.

Thus, the first part of the study consisted of the preparation of RDT, firstly by a classical wet granulation method and secondly by a granulation using an emulsion as wetting liquid or emulsion granulation (Farah et al., 2001). The preparation of the emulsion used in the granulation, as well the granulation process, was realised according to the method reported by Abdelbary et al. (2004).

The second part of the study encompassed the evaluation of the disintegration behaviour of both prepared and commercialised tablets using texture analyser. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Finally, a correlation between the oral disintegration time and the in vitro disintegration time was achieved.

2. Materials and methods

2.1. Materials

The RDT used in the present study represent the main commercialised technologies for this delivery system. Three different commercially available RDT were selected and are listed hereunder with their suppliers; they are letter coded for convenience of reference.

A: Spasfon®, Laboratoire L. Lafon, Maisons-Alfort, France;
B: FlashTab®, Prographarm group (currently owned by Ethypharm), Saint Cloud, France;
C: Wowtab®, Yamanouchi, Tokyo, Japan.

In addition, the following materials were used in the preparation of two other different RDT: crystallised Paracetamol was used as a model drug (acetaminophen, Coopération pharmaceutique Française, France); D-mannitol powder 60 (Roquette, France); sodium carboxymethyl cellulose (AC.DI.SOL.®, Seppic, France); croscarmellose sodium (Vivasol®, JRS, France); PEG-6-stearate (Superpolystate®, Gattefossé, France); aspartame (Quarrechin, France) and magnesium stearate (SPCI, France).

2.2. Methods

2.2.1. Preparation of wet granulation and emulsion granulation tablets

Formulations employed in the fabrication of both RDT are listed in Table 1, and were letter coded D and E for wet granulation and emulsion granulation tablets, respectively.

For wet granulation tablets D, distilled water was used to form granules of the internal phase composed of crystallised Paracetamol and D-mannitol. As for emulsion granulation tablets E, a 12% emulsion of Superpolystate® was used as wetting liquid, where it was added to the internal phase composed of crystallised Paracetamol, D-mannitol and AC.DI.SOL.®, in a way that the obtained granules contained 2.5% Superpolystate®, as reported by the authors (Abdelbary et al., 2004).

Table 1
Percent composition of tablets D and E

Components	D	E
Internal phase		
Crystallised Paracetamol	37.4	37.4
D-Mannitol	50.6	48.6
AC.DI.SOL.®	–	2
Superpolystate®	–	2.5
External phase		
Vivasol®	8.6	8.6
Aspartame	2.9	2.9
Magnesium stearate	0.5	0.5

Both granulations took place in a planetary mixer (Kenwood, UK). The granulation process was standardised on basis of preliminary trials. Paracetamol, D-mannitol and/or croscarmellose sodium were firstly dry blended for 2 min at 60 rpm, and then the granulating liquid (distilled water or emulsion) was added in small quantities under stirring. The formed wet mass was then blended for 5 min at 90 rpm, and dried at 30 °C in a tray oven (Halvatia, France) for 90 min. Finally, granules were sieved through 1 mm mesh in an oscillating calibrator (Erweka-Type FGS).

Prior to compression, both granules were dry blended with the external phase (Table 1), using a flexible mixer (Turbula T2C, Switzerland) for 10 min at 40 rpm. A single punch machine (Korsch KO, France), equipped with flat faced punches with a die diameter of 12 mm, was employed to prepare tablets with an average weight of 600 mg and at a rate of 54 tablets per min.

2.2.2. Tablet properties

The following tests were applied to select commercial RDT (A–C) as well as to prepare tablets (D, E): mean weight and friability of 20 tablets of each were determined using an electronic balance (Mark, Italy) and a friabilator (Erweka TAR, France) at 25 rpm for 4 min, respectively. The hardness, of 10 tablets of each, was measured using a hardness tester (Vanderkamp, Germany). In addition, the thickness and the diameter of each were assessed using a micrometer (Mitotoyo, Japan), as the geometry of tablets may affect their disintegration time.

Finally, the disintegration time was determined using the compendial disintegration test apparatus (Sotax, DT3, France). Distilled water kept at 37 °C was used as a medium and the basket was raised and lowered at a constant frequency of 30 cycles/min. Six tablets were evaluated from each lot (European Pharmacopoeia, 2001).

All measurements were realised in triplicates and the standard deviation was calculated.

2.2.3. Oral disintegration time

Disintegration test in the oral cavity is briefly described in the literature (Watanabe et al., 1995; Dor et al., 2000; Morita et al., 2002). In the present study, oral disintegration time was assessed by 14 healthy volunteers (9 male and 5 female) for a series of different test tablets, following randomised administration.

Prior to the test, all volunteers were asked to rinse their mouth with distilled water. Tablets were placed on the tongue and immediately a chronometer was started. They were allowed to move the tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable granule had disintegrated, the chronometer was stopped and the time recorded. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement. The average of triplicate measurements represented an individual oral disintegration time. For each RDT examined, the mean oral disintegration time was calculated as well as the standard deviation (S.D., $n = 14$) and the variation coefficient (%C.V.).

2.2.4. Determination of in vitro disintegrating time using texture analyser: operating structure

The operating structure used in the in vitro disintegrating test is composed of the apparatus of the texture analyser (TAXT2i, RHEO, France) shown in Fig. 1a. The apparatus was calibrated with a 5 kg load-cell and fitted with a flat-bottomed cylindrical stainless steel probe (P/25, 12 mm in diameter and 25 mm in height).

Fig. 1b and c shows a schematic representation of the detailed and assembled operating structure, respectively, which is used in the disintegration process. It is composed of an elastic spring that maintains the suspension of the cylindrical platform at a distance of 1–5 mm (adjustable by the aid of a screw) from the base of the recipient. This cylindrical platform is movable by the contraction and the expansion of the elastic spring. A perforated grid (30 mm in diameter, 10 mm in height, with several separated upper holes, each 1.5 mm in diameter and four side gaps to enable pressure equilibrium) is placed on the movable platform. The recipient is filled with a predetermined volume of disintegration medium till the upper borders of the grid, in a way that the surface of the grid is not wetted and is absolutely dry.

The methodology of the test consists of placing the tablet on the perforated grid. The tablet is completely dry and is not in contact with the disintegration medium. The probe descends until a trigger force is detected where it gets in contact with the tablet placed on the grid and pushes the whole system downwards, where the elastic spring contracts. Hence, the tablet touches the medium and starts disintegrating. At this point, the TA apparatus is set to maintain a predetermined nominal force (50 g) for a given period of time (60 s). As the tablet disintegrates, the particles detached during the process pass through the holes of the grid, hence simulating oral disintegration where these particles are progressively swallowed or diffused in the mouth.

The TA measures the penetration distance as the tablet is compressed whilst submerged in the medium. Typical time–distance profiles generated by the texture analysis software are obtained, thus enabling the calculation of the starting and ending disintegration times.

2.2.5. Disintegration medium and temperature

During the study of the disintegration behaviour of different RDT, distilled water was firstly used as disintegration medium. But in order to simulate the oral disintegration as much as possible, artificial saliva (pH 5.8) was then used. It was composed of NaCl (0.4 g/L); KCl (0.4 g/L); $CaCL_2{\cdot}2H_2O$ (0.8 g/L); $NaH_2PO_4{\cdot}2H_2O$ (0.78 g/L); $NaS{\cdot}9H_2O$ (0.005 g/L); urea (1 g/L) (Gal et al., 2001).

For both mediums (artificial saliva and distilled water), the test was carried out at room temperature (RT) and then at $37 \pm 2\,^{\circ}C$. This temperature was maintained during the test by means of a thermostated double wall cell and a heating bath circulator (Haake, D-8, Germany) (cf. Fig. 1b and c). All tests were conducted with a fixed volume of 18 mL. This volume was predetermined on basis of preliminary studies and assures the submersion of the tablet in the medium.

The effect of disintegration medium and temperature on the disintegration time was evaluated. For each test tablet, at least three measurements were effectuated (at the same conditions) and average time–distance curves were obtained from individual profiles.

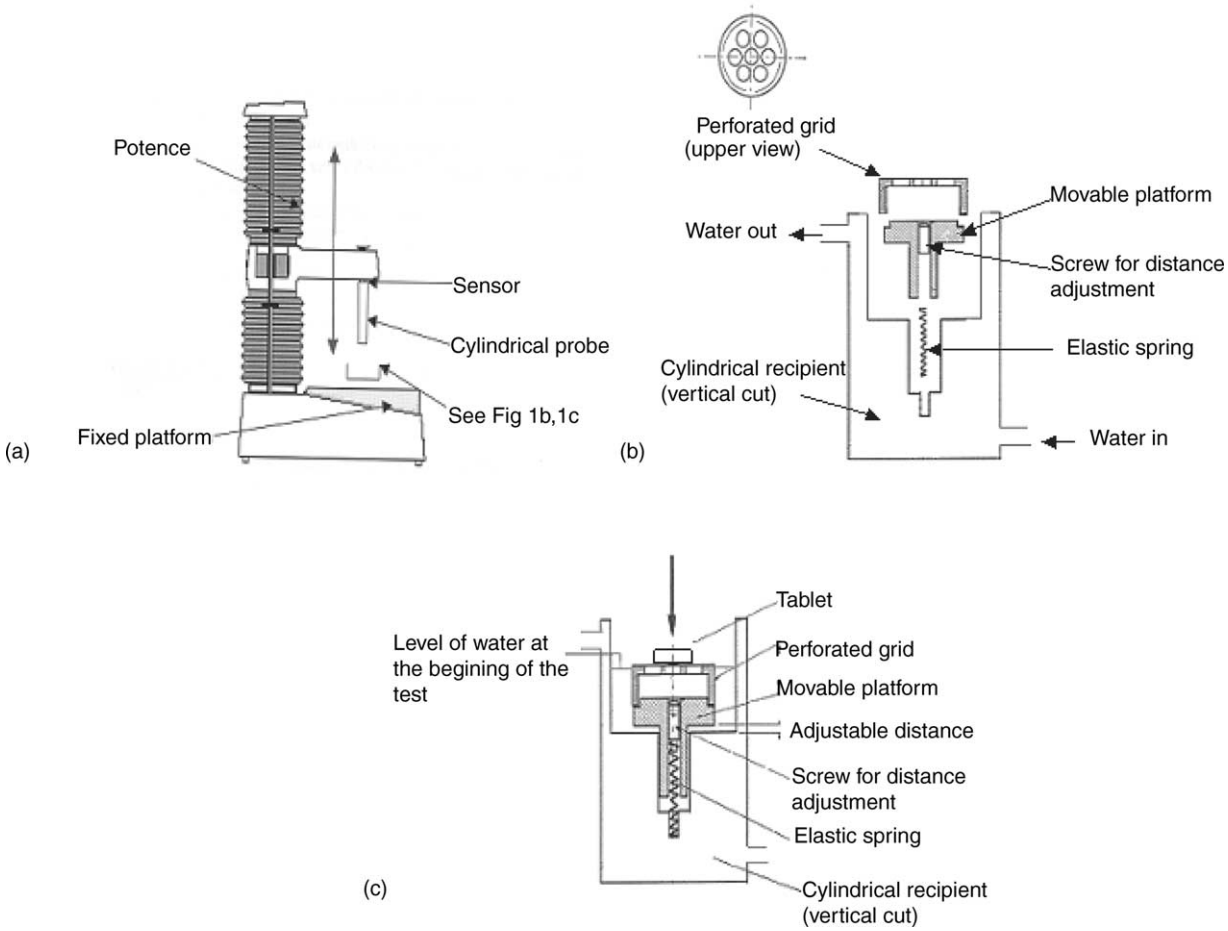

Fig. 1. (a) Schematic representation of texture analyser used in the in vitro disintegration test; (b) schematic representation of the detailed operating structure of the disintegration recipient; (c) schematic representation of the assembled operating structure of the disintegration recipient.

3. Results and discussion

3.1. Evaluation of tablet properties and oral disintegration

Table 2 shows the technological characteristics of all tested tablets. All tablets were acceptable in terms of uniformity of mass (European Pharmacopoeia, 2001). For prepared tablets (D, E), we notice that the incorporation of Superpolystate® has improved tablet's physical resistance, where the hardness has increased from 33.4 N to 47.9 N and their friability decreased from 1.43% to 0.56% (Abdelbary et al., 2004).

Although the compendial test was used in the evaluation of the in vitro disintegration time of RDT, we find that this method is neither convenient nor sufficiently precise. It only permits an approximate evaluation of the actual disintegration time. In addition, the disintegration time is assessed by visual observation over a series of six tablets, which is not very precise as the disintegration time is very short. Moreover, the large volume of water and the strong agitation applied by the apparatus over the tablets are not coherent with the situation in the patient's mouth.

Oral disintegration results are shown in Table 3. We note that, effectively, the disintegration time obtained by the compendial test is only approximate and in some cases, much higher or lower times than oral disintegration were obtained.

Table 2
Technological characterisation of tablets ($n = 3$)

	A	B	C	D	E
Diameter (mm)	15.7	14.4	7.5	12	12.1
Thickness (mm)	6.1	5.2	3.1	4.9	3.9
Mean weight (mg) ± S.D.	700 ± 16.3	801 ± 23.5	120 ± 3.1	624 ± 4.9	598 ± 7.6
Friability (%) ± S.D.	12.65 ± 0.6	6.55 ± 0.21	0.68 ± 0.03	1.43 ± 0.04	0.56 ± 0.02
Hardness (N) ± S.D.	32.4 ± 1.6	25.7 ± 1.3	32.7 ± 2	33.4 ± 1.7	47.9 ± 2.6
Disintegration time (s) ± S.D.	10 ± 0.4	11 ± 0.7	28 ± 1.8	27 ± 2	42 ± 1

Oral disintegration of RDT reveals unsatisfactory reproducibility (%C.V. ∼ 25), which may be caused by the variation that exists between individuals. Hence, the utilisation of this method alone in the evaluation and development of RDT may not be sufficient. Moreover, the in vivo test is characterised by intrinsic limitations from the perspective of ethics and the safety of volunteers.

3.2. Disintegration testing using texture analyser

3.2.1. Method of analysis

The time–distance profiles or disintegration profiles obtained by the TA software enabled the characterisation of the tablets' disintegration behaviour. For each test tablet, at least three measurements were effectuated and the average time–distance curve was obtained (Fig. 2a). The average disintegration profile was used to calculate by extrapolation the start or onset of disintegration (t_1) and the end point of disintegration (t_2), as shown in Fig. 2b.

Table 3
Oral disintegration of tablets by 14 volunteers ($n = 14$)

Volunteers	A	B	C	D	E
1	8	14	12	27	38
2	9	14	15	24	36
3	9	13	16	28	27
4	14	18	14	27	48
5	12	10	9	26	32
6	8	15	12	20	48
7	10	13	17	25	35
8	11	13	14	24	32
9	8	25	9	21	42
10	14	16	11	26	37
11	15	20	12	23	55
12	10	14	9	21	53
13	9	13	11	19	47
14	8	13	10	20	49
Mean	10.36	15.07	12.21	23.64	41.36
S.D	2.47	3.75	2.64	3.00	8.69
%C.V.	23.83	24.89	21.58	12.70	21.01

We can notice that the curve (Fig. 2b) is characterised by three distinct regions, which are: firstly an initial region (IR) where the tablet resists the force applied by the probe and its disintegration has not yet started. Secondly, an ascending region (AR) where the tablet starts to disintegrate gradually and the probe travels a certain distance, to maintain the constant force. At the end, a plateau is reached, which is the final region (FR) where the tablet is disintegrated and no further descent of the probe is possible (Dor et al., 2000; El-Arini and Clas, 2002).

For each tested tablet, average disintegration profile of at least three measurements was obtained. This average profile represents the mean value for each test condition and includes tablet-to-tablet variations; hence, it was used to calculate the following values by means of the TA software (Fig. 2b):

- disintegration onset (t_1), which is calculated by the extrapolation on the time axis of the intercepts of IR and AR slopes;
- end point disintegration time (t_2), which is calculated using the interception of the slopes of AR and FR;
- time (t) the tablet takes to disintegrate from the onset to the end point, which is equal to ($t_2 - t_1$);
- disintegration rate (dr), which is the slope of the AR;
- maximum penetrated distance (d), which is the distance travelled by the probe during the disintegration process.

In addition, the residue (r) that remains at the end was assessed by subtracting the value of the distance (d) from the initial thickness of the tablet (h).

3.2.2. Reproducibility of the method

In order to estimate the variations and the error that may be caused by the TA measurements using

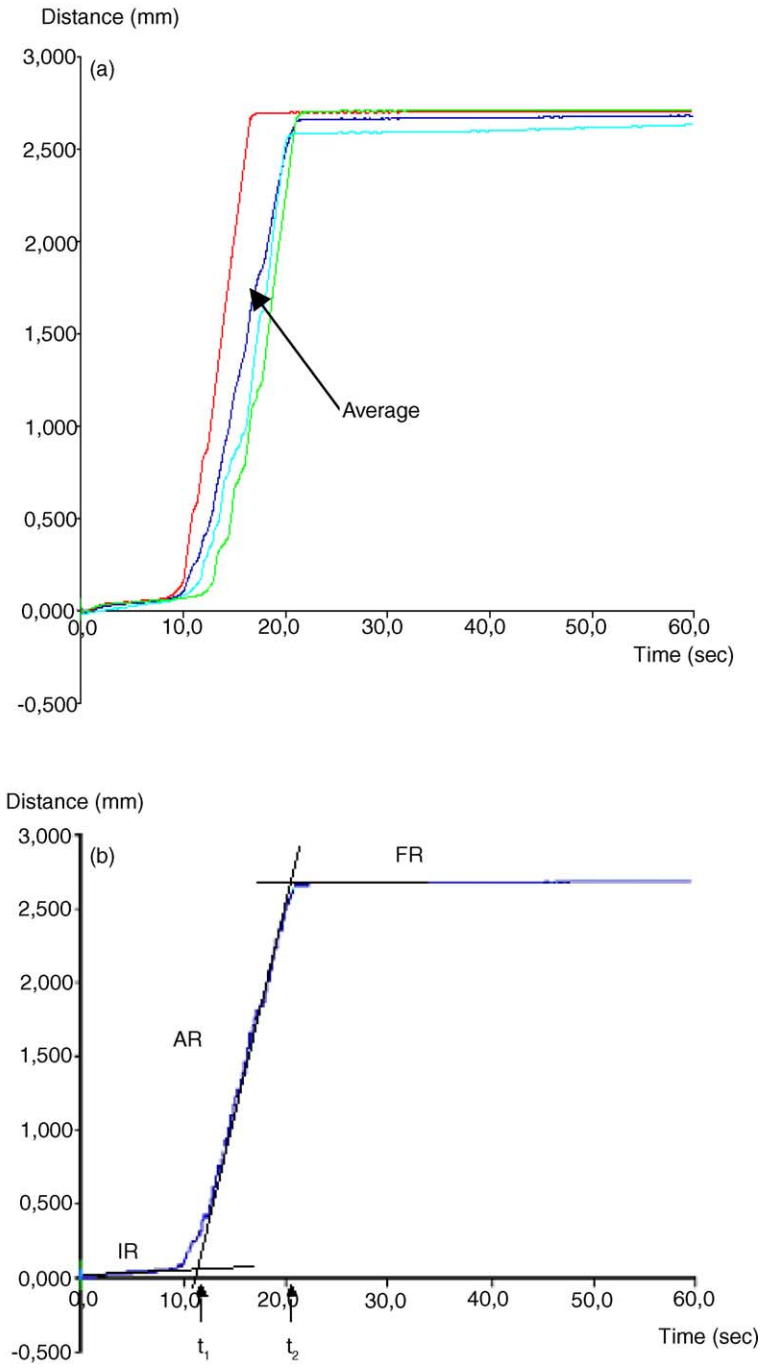

Fig. 2. (a) Disintegration profile of Wowtab® (C) in distilled water at room temperature; shown are the individual profiles of three tested tablets and the average (arrow) profile calculated by the TA software. (b) Average disintegration profile of Wowtab® (C) in distilled water at room temperature is shown alone in order to illustrate the intercepts used for the extrapolation of the disintegration time.

the new operating structure, the end point disintegration time t_2 was determined for tablets B and D, tested in distilled water at room temperature. The mean and standard deviation of each was calculated using the individual profiles of six consecutive measurements. Disintegration times obtained for tablets B and D were $t_{2(n=6)} = 22.4 \pm 0.9$ s (%C.V. = 4.01) and $t_{2(n=6)} = 45.4 \pm 3.5$ s (%C.V. = 7.7), respectively. Furthermore, the disintegration end point t_2 was also calculated from the average disintegration profiles of tablets B and D where $t_{2(\text{average})} = 22.3$ s and 46.3 s, respectively. Hence, we notice that $t_{2(\text{average})}$ is very similar to the mean disintegration time and that the reproducibility obtained is satisfactory.

The same test was repeated with both tablets (B, D) at different conditions, in order to be sure that the test conditions will not affect the reproducibility of the method. Obtained disintegration times for a series of six tablets of B and D in distilled water at $37 \pm 2\,^{\circ}$C were $t_{2(n=6)} = 20.8 \pm 1.4$ s (%C.V. = 6.7) and $t_{2(n=6)} = 36.7 \pm 0.95$ s (%C.V. = 2.6), respectively. In both test conditions, similar results were obtained with a series of three tablets instead of six. Generally, the errors obtained with other studied products did not in any case exceed %C.V. ~ 10.

Throughout the study, the average disintegration profile (at least three tablets) calculated by the TA software was used to calculate all values. The advantage of using this average profile is that it minimises the error involved in the calculation of the disintegration time and includes variability inherent in the experimental measurement (El-Arini and Clas, 2002).

3.2.3. Effect of disintegration medium and temperature

The effect of changing the nature and the temperature of the disintegration medium was evaluated for all test tablets. Fig. 3a and b shows the average disintegration profiles of tablets (A–E) in distilled water at room temperature and at $37 \pm 2\,^{\circ}$C, respectively.

We notice that as the temperature increases from room temperature to $37 \pm 2\,^{\circ}$C, the disintegration onset t_1 as well as the end disintegration time t_2 decreased whilst the disintegration rate, dr, slightly increased for all tested tablets (Table 4).

Fig. 4 shows the average disintegration profiles of tablets tested in artificial saliva at room temperature. We can observe the effect of changing the disintegration medium by comparison with Fig. 3a where a similar effect is observed as when the temperature is increased (Table 4).

Table 4
Effect of disintegration medium and temperature on the disintegration of tested RDT

Tablet	Medium	Temperature (°C)	t_1 (s)	t_2 (s)	dr (mm/s)
A	Distilled water	RT	0.14	14.22	0.334
		$37 \pm 2\,^{\circ}$C	0.12	11.86	0.384
	Artificial saliva	RT	0.13	11.06	0.379
B	Distilled water	RT	3.28	22.16	0.211
		$37 \pm 2\,^{\circ}$C	1.84	20.6	0.217
	Artificial saliva	RT	2.54	16.02	0.260
C	Distilled water	RT	10.02	21.70	0.219
		$37 \pm 2\,^{\circ}$C	5.64	16.82	0.228
	Artificial saliva	RT	9.14	18.12	0.281
D	Distilled water	RT	8.80	46.02	0.107
		$37 \pm 2\,^{\circ}$C	7.90	37.08	0.140
	Artificial saliva	RT	5.40	31.00	0.154
E	Distilled water	RT	4.90	59.04	0.068
		$37 \pm 2\,^{\circ}$C	1.54	52.98	0.071
	Artificial saliva	RT	2.50	54.48	0.069

Accordingly, we can conclude that both disintegration medium and temperature have an effect on the disintegration onset, end time and rate obtained by the texture analyser, and that neither of these two variables is predominant over the other, as the effect of each is clearly observed.

3.2.4. Correlation of in vitro results of texture analyser with oral disintegration time

In view of the results discussed above, it is necessary to maintain the test conditions constant and as close as possible to the in vivo conditions in order to be able to correlate the in vitro (t_2) and oral disintegration times. Hence, the in vitro test conducted using artificial saliva at $37 \pm 2\,^{\circ}$C as a disintegration medium was used to correlate with oral disintegration.

Fig. 5 shows the average disintegration profiles obtained with tablets A–E in artificial saliva at $37 \pm 2\,^{\circ}$C. The quantitative parameters obtained with each tablet from their corresponding average disintegration profile

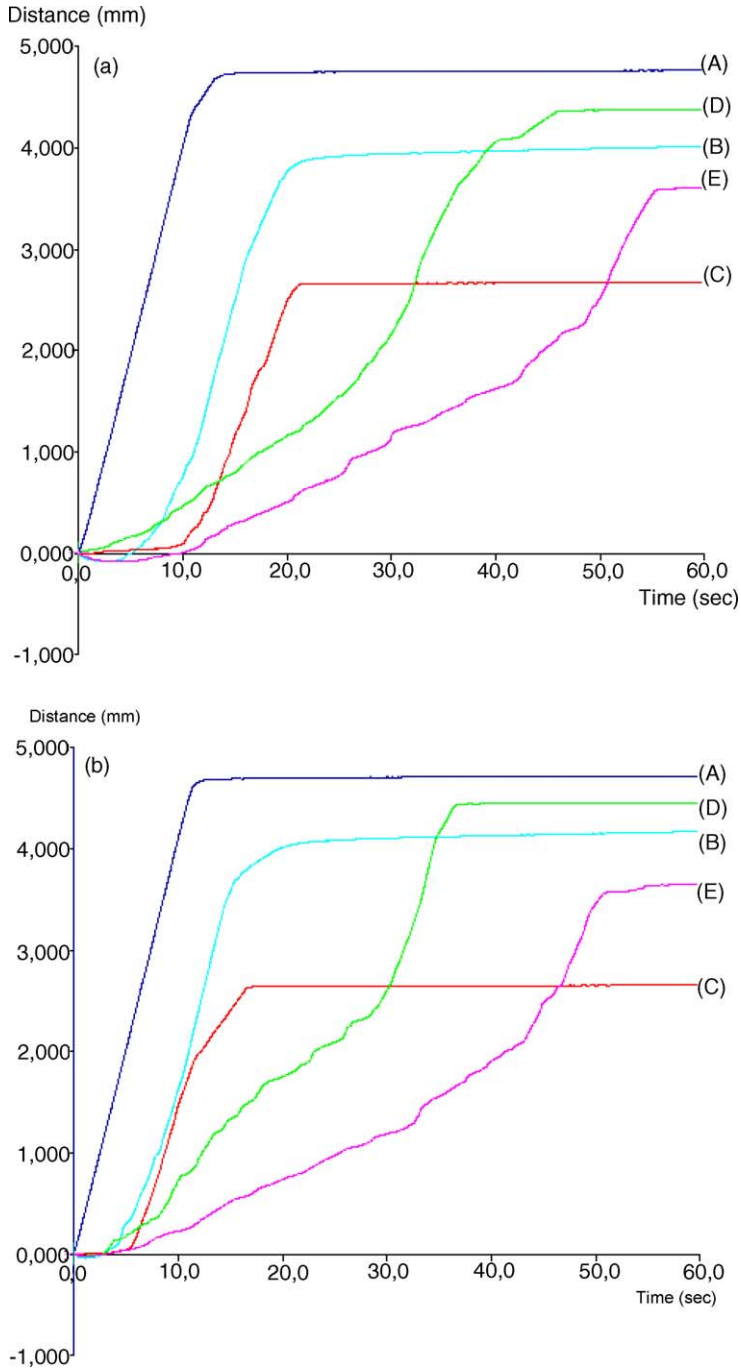

Fig. 3. Average disintegration profiles of all tablets tested in distilled water at (a) room temperature and (b) $37 \pm 2\,^{\circ}C$.

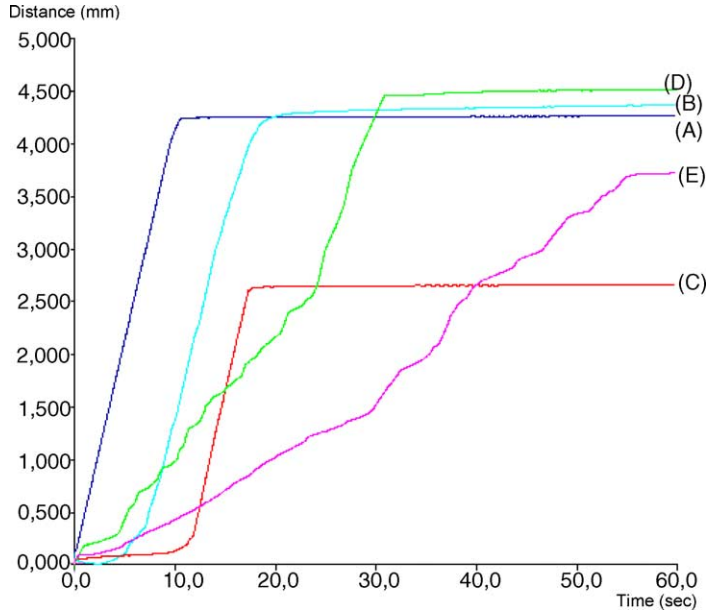

Fig. 4. Average disintegration profiles of all tablets tested in artificial saliva at room temperature.

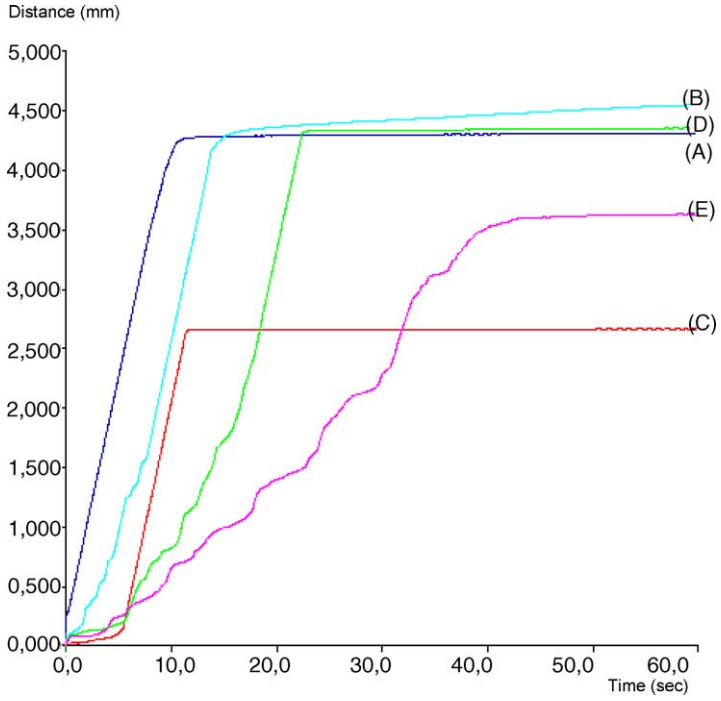

Fig. 5. Average disintegration profiles of all tablets tested in artificial saliva at $37 \pm 2\,^{\circ}C$.

Table 5
Disintegration parameters of all tablets tested in artificial saliva at 37 °C

Tablet	t_1 (s)	t_2 (s)	t ($t_1 - t_2$) (s)	dr (mm/s)	d (mm)	r ($\Delta h - d$)
A	0.12	10.34	10.22	0.394	4.4	1.7
B	0.42	15.06	14.64	0.286	4.6	0.6
C	4.86	11.66	6.80	0.376	2.6	0.5
D	4.02	23.06	19.04	0.219	4.5	0.4
E	0.64	42.50	41.86	0.085	3.7	0.2

are shown in Table 5. We can notice here again the effect of the temperature of the medium (cf. Table 4), where the disintegration times (t_1, t_2) were less than those obtained with artificial saliva at room temperature. It is evident that by the analysis of the data in Fig. 5 and Table 5, we can easily differentiate between the different disintegration behaviours of tablets where the disintegration of each product occurs by a different mechanism according to the manufacturing technology and/or different formulation factors involved.

For tablets A (Spasfon®), the oral disintegration time was 10.36 ± 2.47 s and the end point disintegration time t_2 obtained by the texture analyser was 10.34 s which is almost the same. The obtained disintegration onset is 0.12 s, which is very short, and the disintegration rate is 0.394 mm/s, which is the fastest rate obtained in comparison with other tablets. In fact, Spasfon® are porous solid RDT obtained by lyophilisation of an oil-in-water emulsion placed directly in the blister alveolus due to its poor mechanical properties (Laboratoire and Maisons-Alfort, 1985). This explains its rapid onset of action (~0 s) and rapid disintegration rate, as when the tablet gets in contact with the disintegration medium, it absorbs the medium and instantly starts disintegrating without resistance.

The shape of the average disintegration profile of tablets B (FlashTab®) indicates a different mechanism of disintegration than that observed previously. We notice a negative value on the distance axis (Fig. 3a and b) in the average disintegration profiles obtained with distilled water as a disintegration medium. This could be explained by the fact that the tablet swells when it gets in contact with the medium, and the counteracting force due to this swelling pushes the probe slightly upwards, which is reflected by a negative distance value. This swelling is attributed to the Prographarm technology involved in the fabrication of FlashTab® (Bruna et al., 1995; Demichelis et al., 1997; Barbero et al., 1998), as their formulation incorporates a disintegrating agent and a swelling agent; thus, the simultaneous action of both is responsible for rapid disintegration as well as satisfactory physical characteristics. However, this negative value was not obtained when artificial saliva at 37 °C was used as a disintegration medium but we can still note the swelling of tablets (Fig. 5), where the disintegration time t_2 obtained was 15.06 s, which is again very well correlated with the oral disintegration time (15.07 ± 3.75 s).

Tablet C (Wowtab®) is a compression-moulding tablet, comprising granules made with saccharides having low and high mouldabilities (Mizumoto et al., 1996; Muraoka and Fukui, 1996). According to the patents assigned by Yamanouchi, mouldability is defined as the capacity of the compound to be compressed. Hence, the low mouldability saccharide provides fast disintegration whilst the high mouldability saccharide provides high compressibility. The in vitro results obtained with Wowtab® (Fig. 5) show an IR that is characterised by a plateau, which illustrates the physical resistance of the tablet before the beginning of the disintegration. Thus, the disintegration onset t_1 (Table 5) is relatively slower than A and B tablets. Nevertheless, the disintegration results obtained from the in vitro characteristics (t_2) using texture analyser are largely within the range of oral disintegration results (Table 4) and also of the in vivo disintegration time claimed for this product in the patent assigned by Yamanouchi (Mizumoto et al., 1996).

For prepared tablets D and E, similar disintegration behaviours were obtained, where for both tablets, we notice a negative distance value at the beginning of the average disintegration profile (Fig. 3a and b), which could be attributed to the utilisation of a powerful disintegrating agent (croscarmellose) that absorbs a large quantity of water causing the swelling of the tablet; hence, the counter force pushes the probe upwards. Tablets E had a shorter disintegration onset t_1 than D, but the end point disintegration time was $t_2 = 42.50$ s

and 23.06 s for E and D, respectively. Both results are very well correlated with the oral disintegration results (Table 4). In addition, we can observe the effect of the incorporation of Superpolystate® (tablets E) as the disintegration time did not exceed 45 s and at the same time, the hardness and friability were considerably improved (Table 2) (Abdelbary et al., 2004).

Therefore, we can conclude that for all tablets, an excellent correlation was obtained between the in vitro disintegration results of the texture analyser and the oral disintegration results as well as in vivo disintegration times claimed for products A–C.

3.2.5. Penetration distance

The penetration distance (d) is the maximum depth travelled by the probe from the moment where the tablet gets in contact with the disintegration medium till the end of the rum (i.e. 60 s). This distance has been calculated for all tested tablets from their average disintegration profiles and it corresponds to the value of the FR of the profile (Table 5). The assessment of this distance is very interesting as it enables further evaluation of the disintegration behaviour of different RDT.

Normally, the distance (d) should be equal to the thickness of the tablet (h) in the case where the tablet completely dissolves within 1 min. However, this is not the case, as when we calculate the difference between both values ($\Delta h - d$), we observe that there is always a remaining fraction (Table 5). This is due to the presence of insoluble components in the formulation of RDT that will not dissolve in the patient's mouth and will be swallowed as a suspension. Thus, the ($\Delta h - d$) value may be considered as a qualitative measure of the mouthfeel and certainly of the remaining residue in the mouth.

The tablet dimension may affect this distance as we can observe in Table 5 where tablet D, which is thicker than tablet E, has the double ($\Delta h - d$) value than the later. In addition, it may also be influenced by the formulation technology as observed with the other tablets.

4. Conclusions

The use of the texture analyser in the in vitro determination of the disintegration behaviour of different RDT was shown to be very successful, convenient and precise. In fact, the new operating structure enabled a better simulation of the in vivo conditions, where the use of the perforated grid on which the tablet is placed minimises the operating error that might occur when using an adhesive tape. Moreover, this structure mimics the situation in the patient's mouth.

We have shown in the study that the obtained time–distance profiles or disintegration profiles and the calculated values reflected the mechanism of disintegration of different RDT and gave a qualitative measure of their mouthfeel.

By conducting the test using artificial saliva at $37 \pm 2\,^{\circ}C$ as disintegration medium, excellent correlation was obtained between the oral disintegration results and the in vitro disintegration times calculated by the TA software. Furthermore, this method may also be very useful during the formulation of new RDT in the determination of the effect of various excipients and actives on the disintegration behaviour.

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