

## Investigation on bonding and disintegration properties of pharmaceutical materials

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### Abstract

The disintegration properties of differing pharmaceutical materials having well-known bonding mechanisms were investigated in various media. The materials were sodium chloride, lactose monohydrate and microcrystalline cellulose. They bind mainly with intermolecular bonds and are therefore supposed to loose bonding strength in media with a suitable dielectric constant. The media used were water, methanol and isopropanol. The tablets were prepared under controlled conditions and checked for disintegration time, liquid penetration and disintegration force development. Whenever disintegration did not occur, the crushing strength after soaking in the various media was measured. For microcrystalline cellulose, the swelling properties of the powder material were also measured. The results obtained show that the annihilation/weakening of intermolecular bonds, which are due to the environmental changes in dielectric constant, may play a role in the disintegration of tablets. However, it has to be taken in consideration that the medium must be capable of penetrating into the tablet, that the extent of bond weakening depends on the dielectric constant of the media and that the mechanical stress is likely to be decisive in provoking tablet disintegration. The type of disintegration that is caused by the annihilation/weakening of intermolecular bonds is not accompanied by any force development, therefore it may be referred to as a passive mechanism of disintegration. Whenever disintegration is accompanied by force development, this may be referred to as an active mechanism of disintegration. Swelling is always present in this mechanism.

**Keywords:** Disintegration; Bonding mechanism; Medium dielectric constant; Liquid penetration; Force development

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### 1. Introduction

The two primary parameters on which the mechanical strength of tablets depend are the dominating bond mechanism and the surface over

which these bonds are active (Nyström et al., 1993). For pharmaceutical tablets, three types of bonds are normally considered (Führer, 1977): solid bridges, mechanical interlocking and intermolecular forces active over distances. Intermolecular forces are believed to be the dominating bonding mechanism.

A method recently proposed for investigating how much intermolecular forces contribute to the

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overall bonding strength implied to evaluate the change in tablet tensile strength in media of different dielectric constants as a function of the calculated Hamaker constant (Luangtana-Anan and Fell, 1990).

The relative importance of bonding with intermolecular forces can also be evaluated through the comparison between the radial tensile strength of compacts compressed in air (under ambient conditions) and in liquids (with different dielectric constants). It was found that the increase in the dielectric constant of the environmental liquid generally caused a decrease in the radial tensile strength of the resulting compacts (Karehill and Nyström, 1990).

The relationship between bond weakening in liquids and disintegration propensity of compacts has been studied lately by Luangtana-Anan et al., 1992; they found a correlation between the disintegration time of tablets and the intermolecular bonding forces existing in the liquid environment.

The disintegration phenomenon, as itself, has been the object of extensive investigation and, as an outcome of these researches, two principal mechanisms of disintegration have been proposed (Guyot-Hermann, 1992). One mechanism refers to the swelling of disintegrants, which results in the development of a swelling force. The other mechanism refers to the annihilation of intermolecular bonds, which results in the development of a repulsion force.

According to both mechanisms, the development of a disintegration force is needed to produce disintegration. Whereas the swelling mechanism has been extensively investigated and has been proved to be capable of producing a force (Caramella et al., 1984a; Caramella et al., 1984b), so far the repulsion force has not been given experimental evidence.

There are indications in the literature according to which some materials, for example lactose and calcium carbonate, are capable of disintegrating even though they are not swelling materials (Guyot-Hermann and Ringard, 1981; Erdos, 1986; van Kamp et al., 1986). This phenomenon is often referred to as self-disintegration or spontaneous disintegration and a

proposed mechanism is bond annihilation and consequent repulsion between particles. However, no attempts have been made to measure force development in these materials. Furthermore, poor knowledge of the bonding mechanism in a given formulation may prevent from a real understanding of self-disintegration processes.

Another reason that may have impaired an exhaustive comprehension of the disintegration process is that disintegration tests are normally performed in water or in aqueous media and rarely in alcohols or other organic solvents (Erdos, 1986). Organic media, in particular alcohols, are capable of changing the dielectric constant of the environment with respect to air and should therefore elicit mechanisms similar to those elicited by water (Guyot-Hermann and Ringard, 1981; Luangtana-Anan and Fell, 1990). The investigation of the disintegration properties of pharmaceutical materials in various solvents should therefore help to understand the underlying mechanisms.

Given these premises, the aim of the present work was to provide an explanation for those cases, like the case of self-disintegrating materials, in which disintegration occurs even though no definite disintegration mechanism has been demonstrated.

Differing pharmaceutical materials (sodium chloride, lactose monohydrate and microcrystalline cellulose) having well-known bonding mechanisms were checked for their disintegration properties in various media by means of different investigational techniques (disintegration time, liquid uptake and disintegration force development). The materials chosen bind mainly with intermolecular bonds; only in the case of crystalline sodium chloride, the presence of a certain proportion of solid bridges has also been suggested (Karehill and Nyström, 1990), which however provides a small contribution to the total strength of tablets.

Due to their main bonding mechanism, all the three materials examined are supposed to loose bonding strength in media endowed with a suitable dielectric constant. Furthermore, the three

Table 1  
Physical properties of the solvents employed<sup>a</sup>

Solvent	Dielectric constant (25°C)	Density (4°C) (g/cm <sup>3</sup> )	Viscosity (cp)
Water	78.54	1.000	1.14 (15°C) 0.80 (30°C)
Methanol	32.63	0.792	0.63 (15°C) 0.51 (30°C)
Isopropanol	18.30	0.786	2.86 (15°C) 1.77 (30°C)

<sup>a</sup>from Handbook of Chemistry and Physics, 66th edition 1985–1986, Robert C. West Ed., The Chemical Rubber Co. Press Inc., Boca Raton, Florida, USA.

materials are characterised by differing compaction mechanisms and by differing disintegration properties in water. Sodium chloride mainly presents plastic deformation (Rees and Rue, 1978) and is water soluble. Lactose monohydrate is a fragmenting material that disintegrates spontaneously in water (Erdos, 1986; van Kamp et al., 1986), and whose disintegration properties have been attributed to the annihilation of hydrogen bonds. Microcrystalline cellulose is a plastically deforming material whose disintegrating properties in water have been attributed either to capillary action (Lerk et al., 1979) or swelling (Caramella et al., 1984a; Caramella et al., 1984b; Ek et al., 1995).

Tablets were prepared under controlled conditions and checked for weight, dimensions, porosity and crushing strength. Tablet disintegration was investigated both in water and in alcohols. Whenever disintegration did not occur, the crushing strength after soaking in the various media was measured. Measurements of liquid penetration into the tablets were carried out with a modified Enslin apparatus (Ferrari et al., 1988). Measurements of force development in tablets were effected by means of an apparatus previously described (Colombo et al., 1980).

In the case of microcrystalline cellulose, the swelling properties of the powder material were also measured: in particular, swelling in bulk by means of hydration-solvation-capacity (Kornblum and Stoopak, 1973) and intrinsic (particle) swelling (Caramella et al., 1990) were evaluated.

## 2. Materials and methods

### 2.1. Materials

The materials used were:

- (1) — Sodium chloride (cubic crystalline puriss., Kebo, Sweden; granulometric fraction 250–355  $\mu\text{m}$ ).
- (2) — Lactose monohydrate NF XVIII (granulometric fraction 53–125  $\mu\text{m}$ ).
- (3) — Microcrystalline cellulose (Avicel<sup>®</sup> PH 101, Prodotti Gianni, Milan, Italy).

True density was determined by means of a Helium pycnometer mod. 130-20000-01 (Micromeritics, Norcross, Georgia, USA): the values were 2.16 g/cm<sup>3</sup> for sodium chloride, 1.54 g/cm<sup>3</sup> for lactose monohydrate and 1.54 g/cm<sup>3</sup> for microcrystalline cellulose.

The media used were distilled water, methanol and isopropanol (analytical grades). They were previously saturated with each and every material to avoid tablet dissolution, given the fact that dissolution phenomenon is known to interfere with disintegration and force development in tablets (Caramella et al., 1986). The physical properties of the media are presented in Table 1.

### 2.2. Methods

#### 2.2.1. Preparation and checking of tablets

300 ( $\pm 5$ ) mg tablets were obtained by means of an hydraulic press (mod. 15.010, Perkin Elmer, Monza, Italy), equipped with a manometer. A flat punch of 10 mm diameter was used. Sodium chloride tablets were prepared at a compression

Table 2

Physical properties of tablets (mean values  $\pm$  s.e.,  $n = 3$ )

	Porosity (%)	Void volume (mm <sup>3</sup> )	Crushing strength (N)
Sodium chloride	11.1 ( $\pm 1.04$ )	16.6 ( $\pm 3.48$ )	44.1 ( $\pm 3.92$ )
Lactose monohydrate	14.4 ( $\pm 0.91$ )	34.0 ( $\pm 2.55$ )	36.3 ( $\pm 1.96$ )
Microcrystalline cellulose	13.5 ( $\pm 0.95$ )	25.9 ( $\pm 1.45$ )	>200

force of 5 kN, while lactose monohydrate and microcrystalline cellulose tablets were prepared at a compression force of 10 kN.

Tablets were checked for weight and dimensions (with a micrometric device). Percent porosity was calculated according to the following formula:

$$\% \text{ porosity} = (V_b - V_t)/V_b \times 100$$

where:  $V_b$  is the apparent tablet volume, calculated from tablet dimensions, and  $V_t$  is the true tablet volume calculated from the true density of the material.

The difference  $V_b - V_t$  represents the void volume.

Crushing strength was measured immediately after compression using a motorised instrument (Schleuniger apparatus, mod. 2E, Tecno Galenica, Milan, Italy). The physical properties of all tablets are reported in Table 2.

Disintegration time was measured using the USP XXIII apparatus with discs ( $T = 37^\circ\text{C}$ ).

**2.2.1.1. Liquid uptake measurements.** Liquid uptake measurements were effected with a modified Enslin apparatus (Ferrari et al., 1988). To account for weight loss due to evaporation, before each determination a blank measurement was carried out under the same experimental conditions as those used for the tablets (Ferrari et al., 1994). The weight loss was linear with time and was then subtracted from the experimental data.

Liquid uptake versus time profiles were fitted according to the Weibull model as previously described (Ferrari et al., 1988). The following parameters were considered: the maximum amount of liquid taken up at the end of the

experiment and the instantaneous rate of liquid penetration, calculated as the first derivative of the curve at  $t_{63.2}$  (the time needed to take up 63.2% of the maximum amount of liquid).

**2.2.1.2. Force measurements.** Force measurements were effected with a previously described apparatus (Colombo et al., 1980). Similarly to liquid uptake measurements, force versus time profiles were fitted according to the Weibull model (Caramella et al., 1984b). The following parameters were considered: the maximum amount of force developed and the instantaneous rate of force development, calculated as the first derivative of the fitted curve at  $t_{63.2}$  (the time needed to develop 63.2% of the maximum force).

## 2.2.2. Swelling properties of microcrystalline cellulose powder

**2.2.2.1. Swelling in bulk.** Hydration-solvation-capacity measurements were carried out in the various media as described by Kornblum (Kornblum and Stoopak, 1973). The hydration-solvation-capacity was expressed as the volume of solvent taken up per gram of dry material.

**2.2.2.2. Intrinsic (particle) swelling.** A Coulter Counter Multisizer (Coulter Electr. LTD., GB-Luton) was used. The electrolytes employed were: isotonic saline, 5% w/v LiCl in methanol and 5% w/v  $\text{NH}_4\text{SCN}$  in isopropanol. 140, 200 and 280  $\mu\text{m}$  orifice tubes were used after calibration with standard latex suspensions. The particle size distribution of a diluted dispersion of microcrystalline cellulose (containing an accurately weighed amount of material in an accurately measured

Table 3

Disintegration and mechanical properties of sodium chloride tablets and behaviour after liquid penetration test (mean values  $\pm$  s.e.,  $n = 3$ )

Solvent	Disintegration time (s)	Crushing strength <sup>a</sup> (N)	Appearance after liquid penetration
Methanol	> 900	38.2 ( $\pm 0.98$ )	Wet surface and dry inside
Isopropanol	> 900	41.2 ( $\pm 2.45$ )	Wet surface and dry inside

<sup>a</sup>after disintegration test.

electrolyte volume) was determined in each medium with a 128-channel resolution. The total volume of the material was obtained from the particle size distribution and the percentage volume increase in each medium was then calculated as the ratio between the volume measured with the Coulter Counter and the true volume (Caramella et al., 1990).

### 3. Results and discussion

#### 3.1. Sodium chloride

Due to the high water solubility of sodium chloride, disintegration and liquid penetration experiments could be performed only in methanol and isopropanol. Since tablets did not disintegrate in either liquid, crushing strength after disintegration test in each medium was also measured. The disintegration and mechanical properties of sodium chloride tablets and the behaviour after liquid penetration tests are reported in Table 3.

Even though bond weakening was expected to occur in alcoholic media (due to the increase in the dielectric constant with respect to air), no decrease in tablet crushing strength could be observed after soaking in the above mentioned liquids. This behaviour was explained by liquid penetration measurements. A typical liquid penetration curve in isopropanol is given in Fig. 1; after an initial rapid liquid uptake, which may be attributed to a surface tension phenomenon, the tablets do not absorb liquid any more; in fact the curve of the tablet runs parallel to the curve of the blank. This may be attributed to the fact that the solvent does not penetrate into the tablet pores,

possibly due to the unfavourable wettability of the material, which seems to have a 'skin' hindering liquid penetration.

The dry state of the tablets at the end of the experiments (Table 3) also confirmed the conclusion that the solvents did not penetrate into the tablets.

#### 3.2. Lactose monohydrate

The disintegration properties of lactose monohydrate tablets and the results of liquid penetration tests are given in Table 4. The experiments were performed in saturated water, methanol and isopropanol.

Disintegration occurred both in water and in methanol, whereas in isopropanol the tablets did not disintegrate but appeared to be totally wet and soft. This means that the liquids employed are capable of weakening intermolecular bonds to some extent, but not necessarily of producing tablet disintegration.

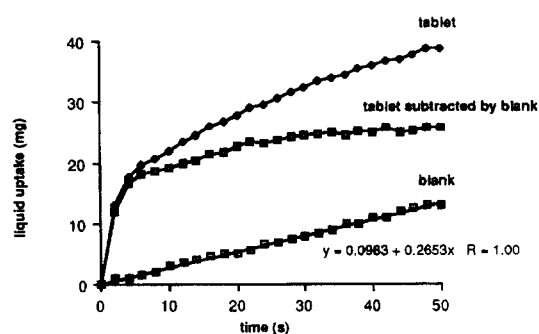


Fig. 1. Mean liquid (isopropanol) penetration curves of sodium chloride tablets (C.V. < 5%,  $n = 3$ ).

Table 4

Disintegration properties and liquid penetration parameters of lactose monohydrate tablets (mean values  $\pm$  s.e.,  $n = 3$ )

Solvent	Disintegration time (s)	Maximum amount of liquid taken up (mm <sup>3</sup> )	Liquid pen. rate (mg/s)	Appearance after liquid penetration
Water	63.9 ( $\pm 1.96$ )	134.0 ( $\pm 8.13$ )	1.36 ( $\pm 0.074$ )	No swelling, totally wet, collapse upon touching
Methanol	82.7 ( $\pm 6.15$ )	60.5 ( $\pm 3.24$ )	0.65 ( $\pm 0.003$ )	No swelling, totally wet
Isopropanol	> 900 <sup>a</sup>	57.7 ( $\pm 2.58$ )	0.35 ( $\pm 0.005$ )	No swelling, totally wet

<sup>a</sup>crushing strength after disintegration test not detectable ( $\sim 0$  N): tablets totally wet and soft.

Liquid penetration and force development tests were instrumental in understanding more about the mechanism involved in such a behaviour.

The liquid penetration profiles obtained in the various media are shown in Fig. 2. The results obtained in water confirm the data already given in the literature (van Kamp et al., 1986), according to which water penetration into lactose monohydrate tablets occurs in two steps. In the first step water penetrates into the tablet due to capillarity; then, the breaking of intermolecular bonds causes the widening of the pores, which allows further uptake of water. This explanation is in line with the bimodal pattern of the curve (Fig. 2). No swelling of the tablets was observed during water penetration. At the end of the experiment, the tablets appeared to be totally wet and disintegrated by simple touching. The maximum amount of water taken up was about fourfold the initial void volume of the tablets (Table 2). The liquid penetration curves obtained in methanol and iso-

propanol are very similar to each other, and the total volume of liquid taken up is in the same order of magnitude as the initial void volume of the tablets. The excess of liquid with respect to the void volume is in the same order as that observed with sodium chloride and is possibly due to surface wetting. It can be concluded that these liquids penetrate mainly by capillarity. The weakening of tablet structure, evidenced by the fact that tablets were totally wet and soft at the end of the liquid penetration test, confirms that liquid penetration is capable of producing, to some extent, the weakening of intermolecular bonds. The differences between water and alcohols are rather quantitative than qualitative and may be attributed to the differences in dielectric constant. Water promotes a more rapid loosening of the structure and a certain degree of pore enlargement, which is not the case with methanol and isopropanol.

When force measurements were performed, no measurable force could be detected either in water or in alcoholic media, even though the experiments were carried out for a long time (5 h). The absence of force indicates that the breaking of intermolecular bonds, which is due to environmental changes, is not capable of producing any repulsive force between particles. Therefore, when disintegration occurs with this material, it must be due to a passive phenomenon, namely a collapse of the structure. Disintegration takes place more or less rapidly depending on the extent of bond annihilation provoked by the medium and on the mechanical stresses applied.

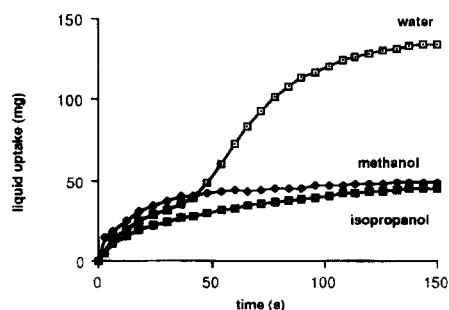


Fig. 2. Mean liquid penetration curves of lactose monohydrate tablets (C.V. < 5%,  $n = 3$ ).

Table 5

Disintegration properties and liquid penetration measurements of microcrystalline cellulose tablets (mean values  $\pm$  s.e.,  $n = 3$ )

Solvent	Disintegration time (s)	Maximum amount of liquid uptaken ( $\text{mm}^3$ )	Liquid pen. rate (mg/s)	Appearance after liquid penetration
Water	298.3 ( $\pm 7.81$ )	548.7 <sup>b</sup> ( $\pm 8.82$ )	5.77 ( $\pm 0.31$ )	Disintegration
Methanol	> 900 (‘capping’)	272.4 <sup>b</sup> ( $\pm 3.24$ )	0.23 ( $\pm 0.03$ )	“capping” then break down to small pieces
Isopropanol	> 900 <sup>a</sup>	51.8 <sup>c</sup> ( $\pm 2.58$ )	0.0028 ( $\pm 0.0008$ )	No disintegration

<sup>a</sup>crushing strength after disintegration test =  $118 \pm 7.5$  N.<sup>b</sup>at saturation.<sup>c</sup>after 1500 s.

### 3.3. Microcrystalline cellulose

In Table 5, the disintegration properties of microcrystalline cellulose tablets are given together with the results of the liquid penetration tests. Tablets disintegrate in water, although very slowly due to their high crushing strength (Table 2). Disintegration did not occur either in methanol or in isopropanol, but tablets showed capping in methanol and a reduction in crushing strength in isopropanol. This indicates that alcoholic solvents are capable of weakening to a certain extent the structure of the tablets.

Liquid penetration curves in the various media are shown in Fig. 3. Measurements in water confirms data already given in the literature (Lerk et al., 1979; van Kamp et al., 1986), according to which microcrystalline cellulose tablets take up an amount of water which is much greater than the

initial void volume of the tablets (Table 2). This rapid water uptake is not due only to capillarity, but can be explained only by the assumption of pore widening and extensive swelling of the powder bed (Caramella et al., 1984a; Ek et al., 1995). Liquid uptake in methanol was less rapid; however the amount of liquid taken up at the end of the experiment was one order of magnitude greater than the initial void volume of the tablets. This accounts for a rather extensive swelling of the tablet in methanol. In isopropanol, a slow liquid uptake was observed; the amount of liquid taken up in about half an hour was the same order of magnitude as the initial void volume of the tablets. However, the liquid uptake process continued to take place during the whole period of observation (4 h) and was linear with time.

The results of force measurements are given in Table 6 and Fig. 4. They show that the penetration of liquid in microcrystalline cellulose tablets is accompanied by force development. The force develops to a higher extent and more rapidly in water than in methanol, as expected on the basis of liquid penetration tests. In isopropanol a very low force develops, which is in line with the slow liquid uptake. It has to be pointed out that a quantitative correlation between liquid penetration and force development is not possible because the two experiments are effected in different experimental conditions. In particular, the differences in the rate of liquid penetration, observed for the different solvents, are much higher than

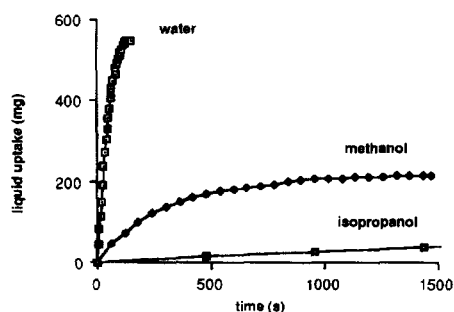


Fig. 3. Mean liquid penetration curves of microcrystalline cellulose tablets (C.V. < 5%,  $n = 3$ ).

Table 6

Results of force development tests on microcrystalline cellulose tablets (mean values  $\pm$  s.e.,  $n = 3$ )

Solvent	Maximum amount of force developed (N)	Force development rate (N/s)
Water	107.9 ( $\pm 6.88$ )	0.30 ( $\pm 0.025$ )
Methanol	82.5 ( $\pm 4.34$ )	0.25 ( $\pm 0.017$ )
Isopropanol	11.3 ( $\pm 1.05$ )	$1.0 \times 10^{-3}$ ( $\pm 0.005 \times 10^{-3}$ )

the corresponding differences in the rate of force development. This can be explained by the fact that in liquid uptake experiments the tablets are free to expand, whereas in the force experiments they are constricted; consequently, the differences in force development may be reduced.

The development in microcrystalline cellulose

Table 7

Swelling properties of microcrystalline cellulose powder (mean values  $\pm$  s.e.,  $n = 3$ )

Solvent	Hydration (solvation) capacity (ml)	Particle swelling %
Water	2.8 ( $\pm 0.15$ )	39.2 ( $\pm 8.61$ )
Methanol	2.3 ( $\pm 0.20$ )	22.5 ( $\pm 5.27$ )
Isopropanol	2.0 ( $\pm 0.13$ )	5.5 ( $\pm 4.28$ )

tablets of a force is definitely linked to the swelling of the material (Table 7) (Caramella et al., 1984b, Ek et al., 1995). Even though microcrystalline cellulose is commonly believed to be a non swelling material, the results of both hydration (solvation) capacity and particle swelling measurements demonstrate that it swells to a significant extent both in water and in methanol. It has to be stressed that, as already demonstrated for disintegrants (Caramella et al., 1984b), even a small increase in particle volume is capable of developing a high swelling force. This appears to be the case with microcrystalline cellulose, for which a relatively limited particle swelling (about 40% in water) is accompanied by a high swelling force.

The overall results indicate that, although the breaking of intermolecular bonds may also play a role, the disintegration of microcrystalline cellulose tablets is mainly due to material swelling, which provokes force development. Therefore, disintegration or capping are the results of an active mechanism.

#### 4. Conclusions

The annihilation/weakening of intermolecular bonds, that takes place between particles when air is replaced by a liquid with a suitable dielectric constant, plays a role in the disintegration of tablets. However, it has to be taken in consideration that:

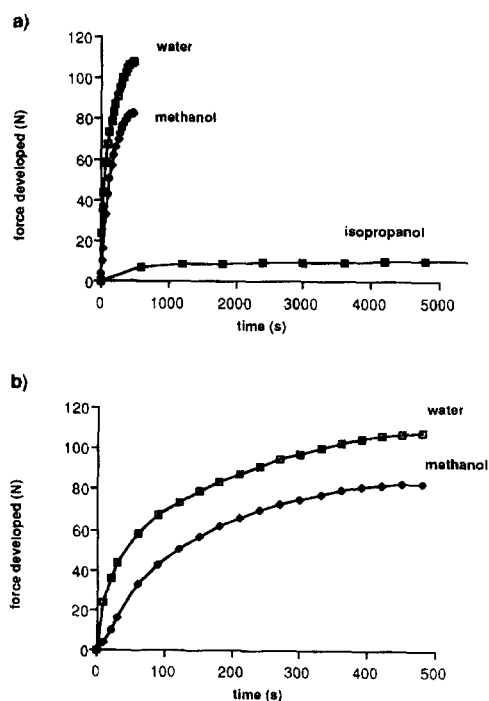


Fig. 4. Mean force development profiles of microcrystalline cellulose tablets (C.V. < 5%,  $n = 3$ ): (a) normal scale; (b) expanded scale.



- (1) — in order to produce bond weakening, the liquid must be capable of penetrating into the tablet. Whenever it penetrates, its ability to disrupt intermolecular bonds also depends on its dielectric constant; the higher the dielectric constant, the greater the capability of bond weakening;
- (2) — the mechanical stress is likely to be decisive in provoking tablet disintegration, especially with liquids like methanol and isopropanol, having a low dielectric constant;
- (3) — the type of disintegration that occurs with this mechanism is not accompanied by force development, meaning that it may be referred to as a passive mechanism of disintegration. This mechanism may not be sufficient to counteract the negative effects that tablet hardness and tablet hydrophobicity may have on the disintegration properties of a given formulation.

Whenever disintegration is accompanied by force development, this may be referred to as an active mechanism of disintegration. Material swelling is responsible for this mechanism. Or, better to say, swelling is the only mechanism that have so far been demonstrated capable of force development.

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