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WATER UPTAKE AND DISINTEGRATING FORCE MEASUREMENTS: TOWARDS A GENERAL UNDERSTANDING OF DISINTEGRATION MECHANISMS.

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ABSTRACT

Water penetration and disintegrating force measurements were combined with the aim of assessing the role played by various mechanisms in the disintegration process.

Nine tablet series, made of differing base materials (d-lactose monohydrate, dicalcium phosphate dihydrate and acetylsalicylic acid) such as are likely to elicit differing disintegration mechanisms and containing differing disintegrants in varying percentages were prepared and checked for water penetration, disintegrating force development and disintegration time.

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The results obtained show that, in tablets made of dicalcium phosphate dihydrate or acetylsalicylic acid, a correlation exists between disintegration time and disintegrating force kinetics, which indicates that active mechanisms play the prevailing role in the disintegration process.

On the contrary, the lack of such a correlation in α-lactose monohydrate tablets indicates that passive mechanisms are also involved in the disintegration process and prevail over active mechanisms. In this case, water penetration rate, rather than disintegrating force development rate, seems to be the governing factor in the disintegration process.

INTRODUCTION

Recent papers on tablet disintegration reveal an increasing interest in disintegrating force measurements (1-3).
Disintegrating force measures allowed us to provide experimental evidence of the various mechanisms of disintegrant action (4,5). The results obtained in various laboratories indicate that a correlation exists between disintegrating force development rate and disintegration properties (2-4).

However it must be recognized that in certain formulations, besides active mechanisms (i.e, those capable of developing a disintegrating force), passive mechanisms (that is those capable of weakening interparticle bonds without developing any repulsion between particles) may also play an important role (6,7).

Preliminary studies (8) indicated that, in tablet formulations which were based on very soluble materials such as, for example, glucose, disintegrating force development was hindered.
These studies show that, when passive mechanisms are involved, a poor correlation between disintegrating force parameters and disintegration time is to be expected.
Whatever the mechanisms involved, water penetration is a prerequisite for their activation (6,7,9).

In this present study we intended to combine water penetration and disintegrating force measurements with the aim of assessing the role played by active and passive mechanisms in differing tablet base materials (water-soluble, hydrophilic and hydrophobic), such as are likely to elicit different disintegration mechanisms.
Such a study should also assist tablet formulators in the choice of an individualized disintegrant for every tablet base material.
We chose α-lactose monohydrate as a soluble material, dicalcium phosphate dihydrate as a practically insoluble, hydrophilic material and acetylsalicylic acid (ASA) as a practically insoluble, hydrophobic material. Three disintegrants with differing swelling properties (4) (a sodium starch glycolate (Primojel^{R}) with a high swelling volume, a crospovidone (Polyplasdone^{R} XL) with a high swelling force in spite of a moderate swelling volume and a microcrystalline cellulose (Avicel^{R} PH 101) with limited swelling), were employed in varying percentages, to modify formula hydrophylicity opportunely.

Nine tablet series made of either α-lactose monohydrate or dicalcium phosphate dihydrate or ASA, and containing different percentages (1-5-10-20-40) of each disintegrant, were prepared by direct compression under controlled conditions, and checked for both water penetration and disintegrating force development kinetics.

The correlations between disintegrating force development kinetics, water penetration kinetics and disintegration time were sought within every base material formulation tested.

EXPERIMENTAL

Materials

The base materials used were:

- α-lactose monohydrate 100 mesh (DMV, Veghel; The Netherlands)
- dicalcium phopshate dihydrate NF XVI (granulometric fraction 35-400 mesh)
- acetylsalicylic acid FU grade (granulometric fraction 35-400 mesh)

The disintegrants were:

- Primojel® (sodium starch glycolate, Avebe, Foxhol; The Netherlands)
- Polyplasdone® XL (cross-linked polyvinylpyrrolidone, GAF Co., New York; U.S.A.)
- Avicel® PH 101 (microcrystalline cellulose, Prodotti Gianni, Milano; Italy)

Preparation and checking of tablets.

Varying series of tablets, containing 500 mg of base material, 2% of talc and differing percentages of every disintegrant (ranging from 1 to 40) were prepared by direct compression at 20°C and 50% R.H. (compression force level approximately 25.0±0.5 kN).

Tablets were checked for weight, porosity, crushing strength and disintegration time (Erweka apparatus VZ4).

Disintegrating force measures were performed as previously described (1,2).

Water penetration measures were effected using the apparatus described in (7). The kinetic analysis of water penetration curve was performed as described in (10).

RESULTS AND DISCUSSION

Porosity and crushing strength values of all the tablets prepared are given in Table I. For glucose tablets see reference (8).

As far as the relationships between disintegration time, disintegrating force development rate and water penetration rate are concerned, the previously obtained (8) and present results have been grouped as follows:

a) Glucose (very soluble material)(8).

Glucose tablets prepared without any disintegrant tend to dissolve in water instead of disintegrating. In the formulations containing a disintegrant, no correlation was found between disintegration time and disintegrating force development rate, even when a disintegrant capable of a rapid

Table I - Porosity and crushing strength values of the tablets

			POROSITY (%)	CRUSHING STRENGTH (N)
ANHYDROUS GLUCOSE	Primojel®	1%	10.0	24
		5%	9.2	46
		10%	7.2	47
		20%	9.0	62
	Polyplasdone® XL	5%	8.7	63
		10%	8.2	94
		20%	9.3	119
		40%	8.1	236
α-LACTOSE MONOHYDRATE	Primojel®	1%	13.7	82
		5%	14.1	85
		10%	13.0	69
		20%	14.3	72
		40%	13.8	74
	Polyplasdone® XL	1%	15.1	64
		5%	15.1	94
		10%	14.3	113
		20%	13.8	196
		40%	12.1	255
	Avicel® PH101	1%	14.2	84
		5%	14.4	108
		10%	14.4	147
		20%	14.9	147
		40%	12.6	260
DICALCIUM PHOSPHATE DIHYDRATE	Primojel®	1%	19.9	51
		5%	18.7	84
		10%	19.8	73
		20%	17.7	101
		40%	14.9	162
	Polyplasdone® XL	1%	21.3	57
		5%	21.3	71
		10%	23.4	85
		20%	21.9	162
		40%	19.6	245
	Avicel® PH101	1%	20.3	76
		5%	20.0	70
		10%	19.9	109
		20%	17.6	148
		40%	14.8	238
ACETYLSALICYLIC ACID	Primojel®	1%	6.3	54
		5%	7.5	48
		10%	7.9	48
		20%	9.8	46
		40%	11.9	36
	Polyplasdone® XL	1%	8.3	48
		5%	8.5	67
		10%	8.8	115
		20%	9.0	95
		40%	9.8	106
	Avicel® PH101	1%	7.0	85
		5%	6.4	103
		10%	7.2	104
		20%	7.2	125
		40%	8.6	125

swelling force development, like Polyplasdone® XL, was present.

b) α-lactose monohydrate (soluble material)

α-lactose monohydrate tablets prepared without any disintegrant are self-disintegrating (7). Water penetration and disintegrating force measures performed on this base material tablet revealed that water penetrates at about 10 mg/sec, whereas no disintegrating force is detectable.

For the tablet series which contains differing % of the various disintegrants no correlation exists between disintegration time and disintegrating force rate (Fig. 1). On the other hand, poor correlation ($r = 0.47$, significant at 0.10 p level) was found, on log-log scale, between disintegration time and water penetration rate (Fig. 2). In this case, water penetration rather than force development kinetics seems to be the governing factor in the disintegration process.

When the three α-lactose monohydrate formulations are considered together, an overall linear correlation (on normal scale) is found between disintegrating force development and water penetration rate ($r=0.72$, significant at $p=0.01$ level). However, within each disintegrant series, a significant correlation (at 0.05 p level) exists only for the formulation which contains a disintegrant with a high swelling force, such as Polyplasdone® XL ($r=0.88$). This indicates that in α-lactose monohydrate formulations, water penetration does not always elicit a proportional force development (and provides

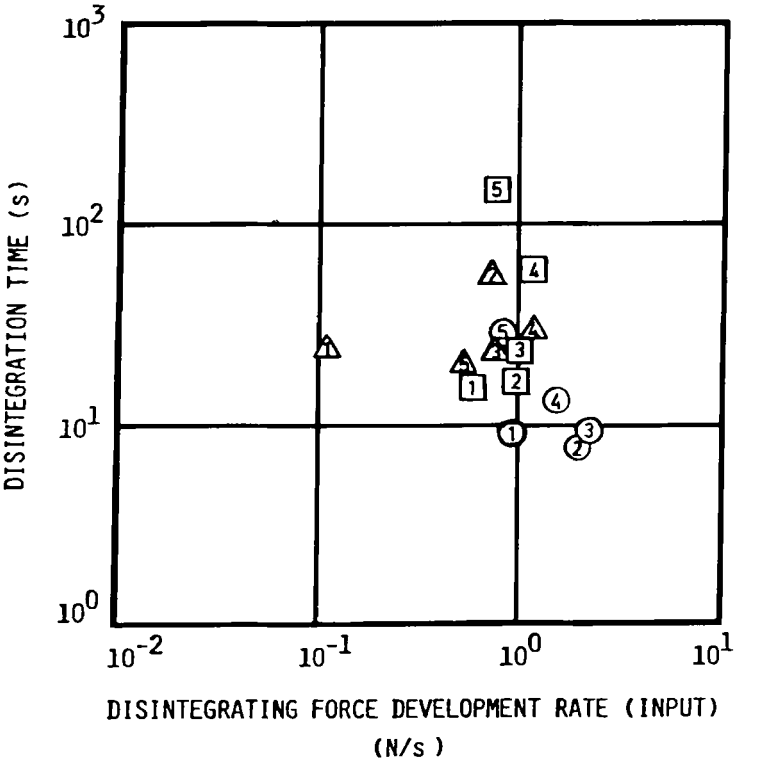

Fig. 1 - Log-log plot of disintegration time versus disintegrating force development rate (input) for Lactose tablets containing differing percentages (□) Primojel®, (◯). Polyplasdone® XL or (△) Avicel® PH 101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part). (r-0.18, not significant).

evidence of the existence of other disintegration mechanisms besides those capable of developing force).

c) Dicalcium phosphate dihydrate (practically insoluble, hydrophilic material)

Plain dicalcium phosphate dihydrate tablets prepared without any disintegrant do not disintegrate (7). Water penetration

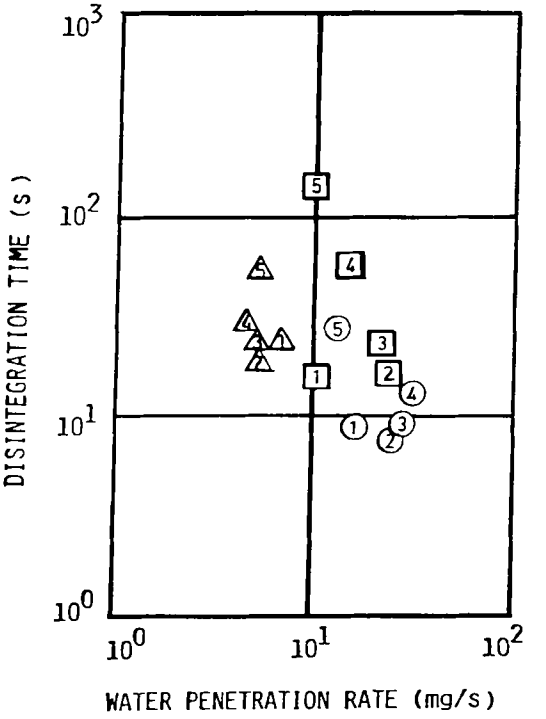

Fig. 2 - Log-log plot of disintegration time versus water penetration rate for Lactose tablets containing differing percentages of (□) Primojel^R, (◯) Polyplasdone^R XL or (△) Avicel^R PH 101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part). (r=0.47, significant at 0.1 p level).

and disintegrating force measures revealed that although water penetration is fairly rapid ($\simeq$5 mg/sec), no disintegrating force is developed.

For the tablet series which contains differing % of the various disintegrants a log-log correlation exists between disintegration time and both disintegrating force development

rate (Fig. 3) and water penetration rate (Fig. 4). This indicates that both water penetration and force development rates may be regarded as the governing factors in the disintegration process.

An overall linear correlation (on normal scale) (r=0.73, significant at 0.01 p level) between water penetration rate and disintegrating force development rate is found. A significant correlation is also found within each disintegrant series. This means that water penetration is accompanied by a proportional force development, indicating the relevance of disintegration mechanisms which are capable of force development.

d) Acetylsalicylic acid (practically insoluble, hydrophobic material)

Plain acetylsalicylic acid tablets prepared without any disintegrant do not disintegrate nor show water penetration nor develop any disintegrating force.

For the tablet series which contains different % of the various disintegrants a log-log correlation is found between disintegration time and both disintegrating force rate (Fig. 5) and water penetration rate (Fig.6). This indicates that both water penetration and force development rates determine the disintegration process.

A linear correlation (on normal scale) exists (r=0.96, significant at 0.01 p level) between disintegrating force rate and water penetration rate, which again indicates that water penetration elicits a proportional disintegrating force development.

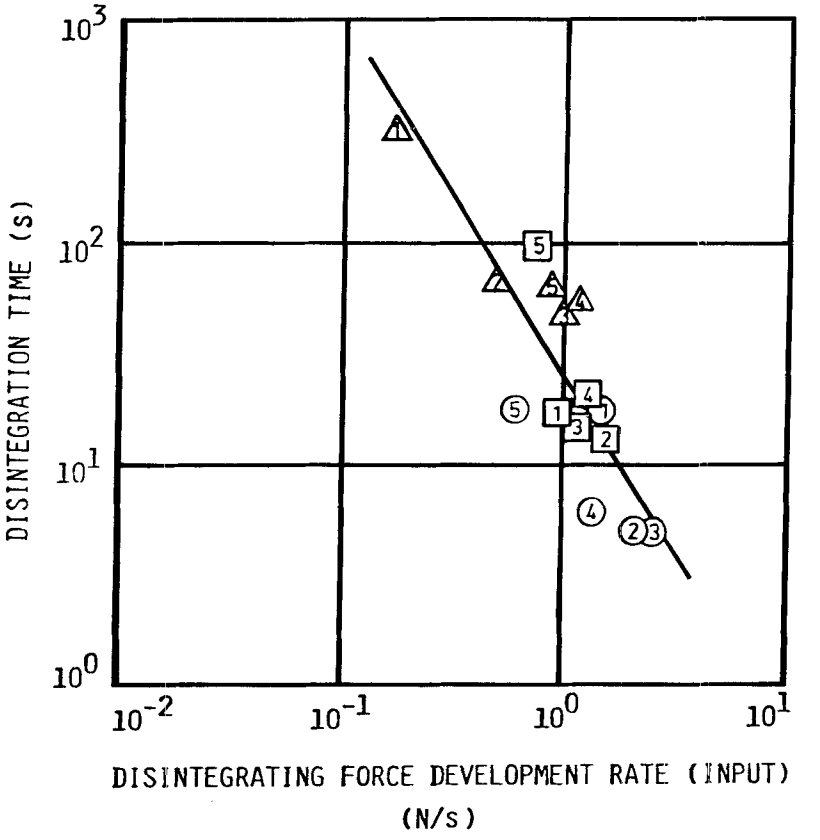

Fig. 3 - Log-log plot of disintegration time versus disintegrating force development rate (input) values for Dicalcium phosphate dihydrate tablets containing differing pecentages of (□) Primojel^R, (◯) Polyplasdone^R XL or (△) Avicel^R PH101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part).
Linear regression equation is: log y = -1.54 log x + 14 (r=0.88)

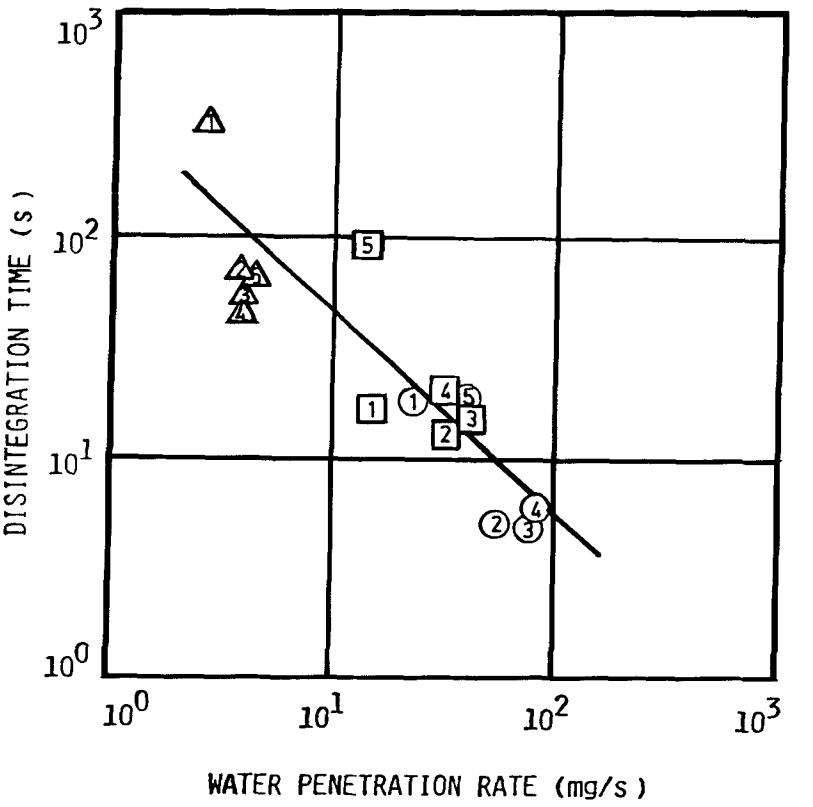

Fig. 4 - Log-log plot of disintegration time versus water penetration rate for Dicalcium phosphate dihydrate tablets containing differing percentages of (□) Primojel^R, (◯) Polyplasdone^R XL or (△) Avicel^R PH 101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part). Linear regression equation is: $\log y = -1.14 \log x + 2.87$ ($r=0.82$)

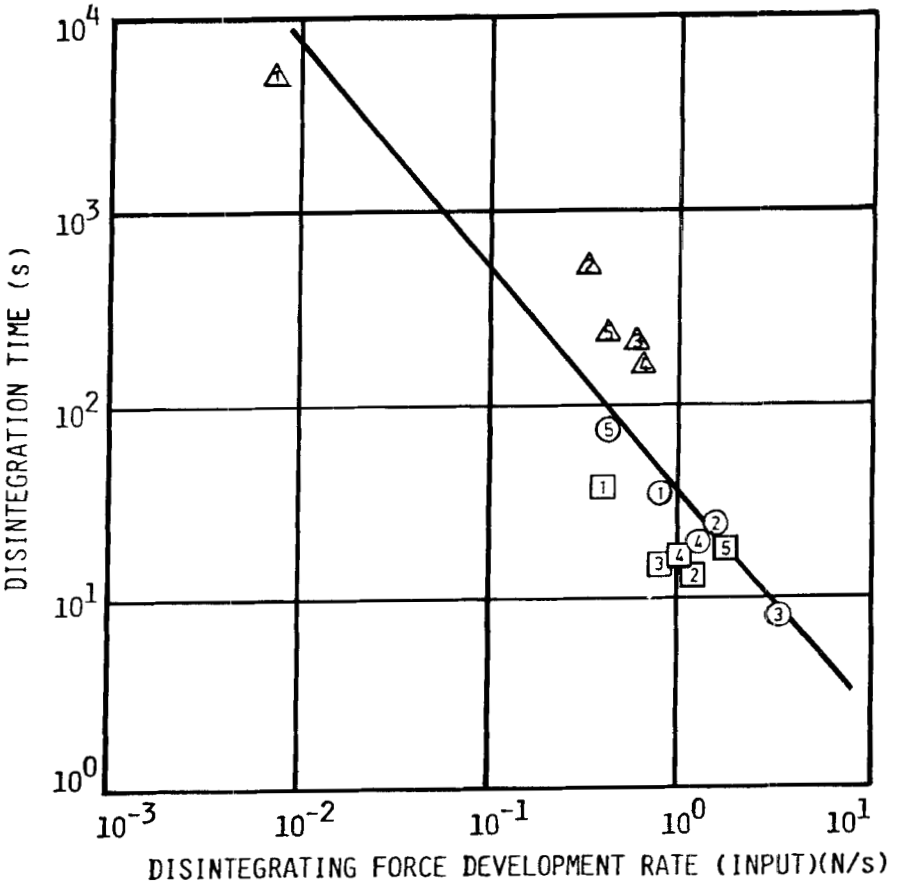

Fig. 5 - Log-log plot of disintegration time versus disintegrating force development rate (input) for ASA tablets containing differing percentages of (□) Primojel^R, (◯) Polyplasdone^R XL or (△) Avicel^R PH 101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part).
Linear regression equation is: $\log y = -1.1 \log x + 1.56$ ($r=0.89$)

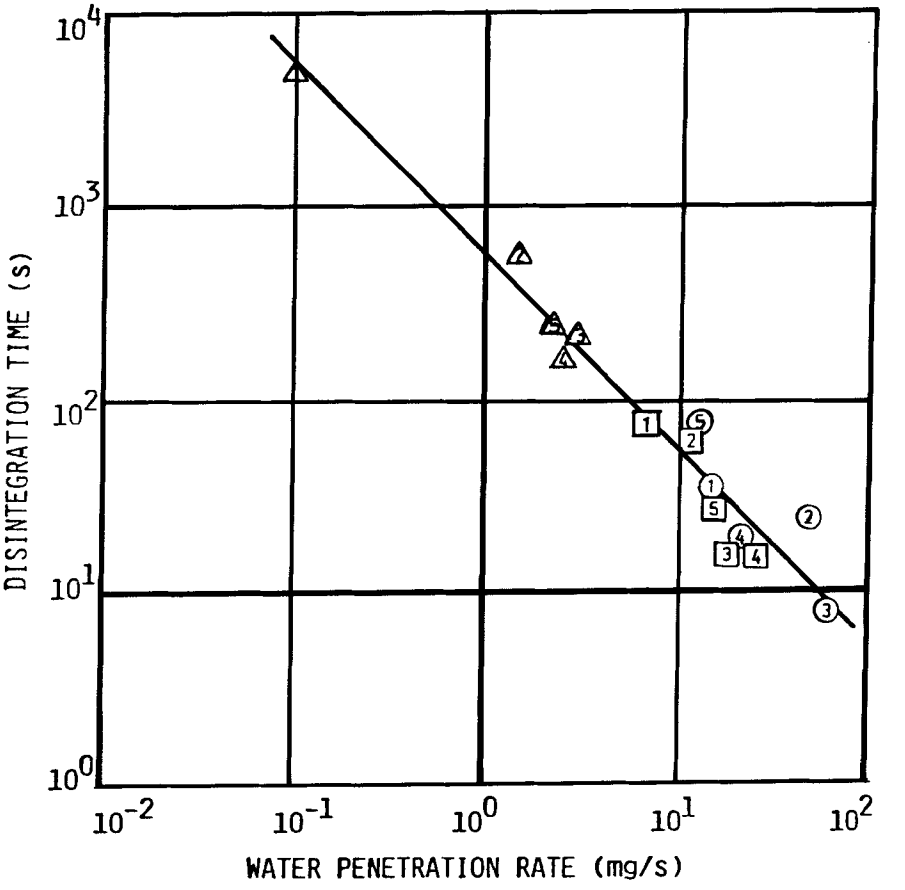

Fig. 6 - Log-log plot of disintegration time versus water penetration rate for ASA tablets containing differing percentages of (□) Primojel^R, (◯) Polyplasdone or (△) Avicel^R PH 101. Figures within the symbols indicate the increasing order of disintegrant concentration (from 1 to 40%, see experimental part).

Linear regression equation is: $\log y = -0.99 \log x + 2.75$ ($r=0.98$)

CONCLUSIONS

The observation that, in tablets made of water insoluble and/or hydrophobic materials (such as dicalcium phosphate dihydrate and acetylsalicylic acid) a correlation exists between disintegration time and disintegrating force development kinetics indicates that the prevailing role in the disintegration process is played by active mechanisms.

On the other hand, the lack of such a correlation in tablets made of hydrophylic, water-soluble materials indicates that passive mechanisms (such as dissolution or hydrogen bond annihilation) are also involved in the disintegration process and may prevail over active mechanisms. In these cases, water penetration measures allow a better understanding of the disintegration properties of a formula. When disintegrants with a high swelling force development rate are present, active mechanisms seem to prevail even in water-soluble formulas.

The linear correlation found between water penetration and force development kinetics, seems to become increasingly significant as the base material passes from lactose to dicalcium phosphate dihydrate to acetylsalicylic acid, i.e. as one increases formula hydrophobicity. This indicates that, in formulas exhibiting optimum hydrophobicity, water is uptaken only by the disintegrant; this, by swelling, completely transforms the water penetrated into a force. From a practical point of view, this implies that, inside a given base formulation, an optimum hydrophylic /hydrophobic balance should be built up by appropriate formula modifications (addition of excipients, granulation...). This may improve the force development caused

by water penetration and consequently, improve disintegration (obviously when disintegration represents a problem).

In hydrophobic and/or water insoluble base formulations, the disintegrant (which is always needed to promote disintegration), is capable of developing its maximum swelling force, besides drawing water inside the compact. Therefore, highly hydrophylic and strongly swelling disintegrants are to be preferred as confirmed by certain examples from the literature (11,12). On the other hand, in hydrophylic and water soluble formulations, the disintegrant, when needed, assists in the drawing of water inside the compact, but is not always able to develop its maximum swelling force. This suggests that limited swelling disintegrants should work as well as, and even better than, strongly swelling materials. This is confirmed by certain examples from the literature (11,12).

Of course, since such conclusions have been drawn from, and on, very simple model formulations, it is conceivable that the addition of an active principle or of such other excipients as are capable of modifying formula hydrophylicity, would change the relationships between water penetration, force development and disintegration time, thus necessitating further considerations.

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