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Effect of disintegrant type upon the relationship between compressional pressure and dissolution efficiency

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Four tablet disintegrants: a relatively insoluble sodium carboxymethyl cellulose, casein formaldehyde, calcium carboxymethyl cellulose and a cross-linked polyvinylpyrrolidone have been evaluated. Three widely used disintegrants, sodium carboxymethyl cellulose, sodium starch glycolate and a cation exchange resin were included for comparison. The effect of compressional pressure on the disintegration and dissolution behaviours of a soluble and an insoluble system containing different disintegrants was examined. The results show that disintegrant type can have a pronounced effect upon the relationship between compressional pressure and dissolution efficiency. The significance of this relationship is discussed in terms of the properties of disintegrants and the differing mechanisms by which they act.

The dissolution of a compressed tablet depends to a great extent upon its mode of disintegration. The properties of excipients present, particularly disintegrant, can thus significantly affect the relationship between compressional pressure and dissolution efficiency. Previously, it has been shown by Levy, Antkowiak & others (1963) that when tablets are prepared containing starch an increase in compressional pressure caused an increase in dissolution rate. It was suggested that fragmentation at high pressure was the reason. Ganderton, Hadgraft & others (1967) have recorded a difference between the behaviour of tablets with and without starch. Khan & Rhodes (1972; 1974), using a cation-exchange resin in a dicalcium phosphate dihydrate system, proposed that for tablets made at low pressure, an insoluble, swelling type disintegrant cannot fully exert its disruptive capacity. The same workers (1975) have also reported that disintegrant type can affect the relationship between disintegration time and compressional pressure.

In the current study we have used four tablet disintegrants whose comparative properties have not previously been evaluated. The disintegrants were incorporated into both soluble and insoluble systems.

MATERIALS AND METHODS

Materials

Cross-linked polyvinylpyrrolidone (Polyclar AT: Chemical Division, G.A.F. Limited, Manchester); a relatively insoluble sodium carboxymethyl cellulose, the solubility of which is modified by varying both the degree of substitution of the sodium carboxymethyl groups and the degree of polymerization of the cellulose chain (Nymcel Z.S.D.16: Nyma N.V. Waalbandijk, Nimegen, Holland); calcium carboxymethyl cellulose E.C.G. 505: (Manley Pure Food Ltd, Oxford) and casein formaldehyde (Mann Chemie, Berlin, West Germany). The following disintegrants were included for comparative purposes; sodium starch glycolate (Primojel: Kingsley and Keith Ltd, London); sodium carboxymethyl cellulose (Courlose P20: British Celanese Ltd, Coventry) and cation exchange resin (Amberlite IRP 88: Lennig Chemical Ltd, London). Dicalcium phosphate dihydrate unmilled (Albright and Wilson, Oldbury, Division, Worcestershire). Lactose B.P.; Amaranth B.P.C.; Magnesium Stearate B.P.C.; (Albright and Wilson). Polyvinylpyrrolidone (Kollidon 25: Victor Blagden and Company, London).

Methods

Two types of base formulation were used; lactose was employed in wet granulation and graded, unmilled dicalcium phosphate dihydrate as a diluent in direct compression (particle size distribution is shown in Table 1). The methods of granulation and incorporation of Amaranth as a dye tracer into both systems are described elsewhere (Khan & Rhodes, 1973), the only difference is that the wet mass was dried in a fluidized bed drier (Aeromatic type 515 EX) at 60° for 2 h. The lactose granules

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Table 1. *Particle size distribution of graded dicalcium phosphate dihydrate.*

Size (μm)	222	173	143	119	104	87	64	52	<52
% oversize Cumulative	1·0	4·5	20·0	58·5	69·5	80·0	85·0	95·0	100

were screened using a No. 16 mesh sieve. The materials were blended with lubricant (1% w/w magnesium stearate) and 5% w/w disintegrant in a Turbula mixer. The tablets were compressed on a single punch machine using ½ in flat punches (Manesty type F3: Manesty Limited, Speke, Liverpool, U.K.). The machine was instrumented with strain gauges using a four semi-conductor strain gauge bridge (Kulite D-ACP-120-090: Kulite Semiconductor Ltd., Basingstoke, U.K.) bonded onto the eccentric level. A bridge supply and balance unit (Fylde F.E. 492 B.B.S.) were employed and the signal was fed into an oscilloscope (Tektronix 5103N).

Tablet hardnesses were determined using an Erweka motorized hardness tester and disintegration times measured by the B.P. method. The dissolution rate determinations were carried out using a stirred flask method. Single tablets were dropped into the dissolution medium (distilled water) which was stirred by a centrally held paddle revolving at a speed of 30 rev min^{-1}. All dissolution studies were carried out at 37° ± 0·5° and in quadruple. Monitoring of the dissolution was conducted by continuous flow analysis through a spectrophotometer set at 520 nm and recorded on a chart recorder (Vitatron, Fison Limited, U.K.). The dissolution results are expressed as dissolution efficiencies as described previously (Khan & Rhodes, 1972), taken after 30 min. The results of the effect of pressure on the disintegration and dissolution properties of the two systems are presented in Table 2. The relation between dissolution efficiency and hardness of both systems is shown in Figs 1 and 2.

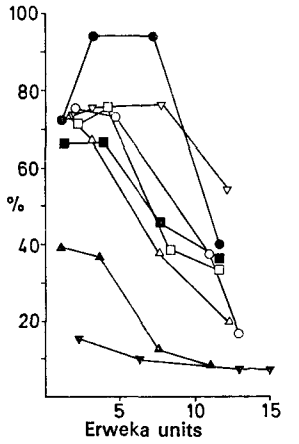

FIG. 1. The effect of hardness (Erweka) on the dissolution efficiencies (%) of tablets prepared from lactose system (1% w/w amaranth and 2% w/w polyvinylpyrrolidone) containing several disintegrants (5% w/w). ● Cross-linked polyvinylpyrrolidone. ▽ Cation exchange resin. ○ Casein formaldehyde. ■ Relatively insoluble sodium carboxymethyl cellulose. □ Sodium starch glycolate. △ Calcium carboxymethyl cellulose. ▲ Sodium carboxymethyl cellulose. ▼ Without disintegrant.

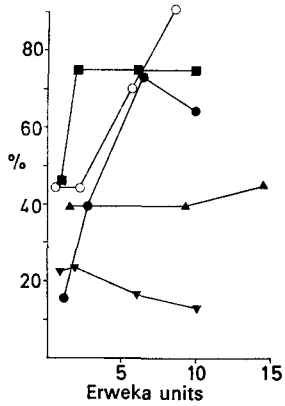

FIG. 2. The effect of hardness (Erweka) on the dissolution efficiencies (%) of tablets prepared from unmilled dicalcium phosphate dihydrate (1% w/w Amaranth) containing several disintegrants (5% w/w). ○ Cross-linked polyvinylpyrrolidone. ■ Relatively insoluble sodium carboxymethyl cellulose. ● Calcium carboxymethyl cellulose. ▲ Casein formaldehyde. ▼ Sodium carboxymethyl cellulose.

RESULTS AND DISCUSSION

The effect of pressure upon the disintegration times of tablets is shown in Table 2. In the dicalcium phosphate dihyrate system we examined, an increase in pressure reduces the disintegration time of tablets containing cross-linked polyvinylpyrrolidone and calcium carboxymethyl cellulose. Tablets containing casein formaldehyde show minima at compression pressures of 1000–2000 kg cm^{-2} after which disintegration time increases. It is interesting to see that the well known supposition, 'harder tablets take longer to disintegrate', is not applicable to the dicalcium phosphate dihydrate system. In fact, Table 2 shows that the converse may be true. In the lactose system studied the disintegration time generally increases with pressure except for tablets containing cross-linked polyvinylpyrrolidone and

Table 2. *The effect of applied pressure on the disintegration times (D.T.) (min) and dissolution efficiencies (D.E.) (% at t 30) of tablets prepared from A lactose (1% w/w amaranth and 2% w/w polyvinylpyrrolidone) and B tablets prepared from dicalcium phosphate dihydrate.*

	A Applied pressure kg cm^{-2}								B Applied pressure kg cm^{-2}							
Disintegrant 5% w/w	500		1000		2000		3000		500		1000		2000		3000	
	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.	D.T.	D.E.
Without disintegrant	10·50	15·00	20·00	9·60	31·00	7·06	31·50	7·06								
Sodium carboxymethyl cellulose (Nymcel ZSD 16)	1·40	66·26	3·25	66·26	3·25	45·30	5·50	36·54	3·50	46·03	1·00	74·90	0·85	74·90	1·25	74·90
Calcium carboxymethyl cellulose	1·25	73·53	1·33	67·50	4·50	38·14	7·25	20·20	20·00*	16·14	2·50	39·82	1·10	73·61	1·25	64·80
Cross-linked polyvinyl-pyrrolidone	0·80	72·45	0·67	94·33	0·70	94·33	2·00	40·36	3·75	44·53	7·00	44·53	1·00	70·00	0·87	91·07
Casein formaldehyde	0·80	75·18	0·80	73·17	4·00	37·50	9·50	16·73	2·40	39·37	1·60	39·37	1·60	39·37	2·75	44·77
Sodium carboxymethyl cellulose (Courlose P20)	2·00	39·40	3·50	36·90	14·50	12·50	21·00	8·30	30·00*	22·54	30·00*	23·45	30·00*	16·43	30·00*	13·12
Sodium starch glycolate	0·87	71·96	0·92	75·63	2·30	38·71	5·50	33·53					1·40	64·06		
Cation-exchange resin	1·20	73·31	1·10	75·40	1·00	76·44	2·00	54·25								

* Particles remaining.

cation exchange resin for which there is an initial decrease.

The dissolution results given in Table 2 follow the disintegration results pattern. In the dicalcium phosphate dihydrate system, tablets containing disintegrants for which swelling is perhaps the most dominant mechanism, i.e. calcium carboxymethyl cellulose, relatively insoluble sodium carboxymethyl cellulose and cross-linked polyvinylpyrrolidone, an increase in pressure causes an increase in dissolution efficiency. This increase is more pronounced for the tablets containing cross-linked polyvinylpyrrolidone: here dissolution efficiency increases progressively with increasing pressure.

The dissolution behaviour of tablets containing the three forms of carboxymethyl cellulose elucidates the differences between their disintegrant action (Table 2). It is obvious that as the solubility improves (sodium carboxymethyl cellulose > relatively insoluble sodium carboxymethyl cellulose > calcium carboxymethyl cellulose), the swelling effect decreases. The dissolution efficiency of dicalcium phosphate dihydrate tablets containing calcium carboxymethyl cellulose increases from 16·14%, for tablets compacted at 500 kg cm^{-2} to 73·6%, for those compacted at 2000 kg cm^{-2}, i.e. an increase of 57·4%. For tablets containing relatively insoluble sodium carboxymethyl cellulose, there is initially a rapid increase in dissolution efficiency to a maximum value at 1000 kg cm^{-2} pressure, above which there is no change. The tablets containing sodium carboxymethyl cellulose show a slight initial increase followed by a progressive decrease in dissolution efficiency with increasing pressure. These results confirm previous findings of Khan & Rhodes (1972; 1974). They have shown that the efficiency of a swelling type disintegrant was impaired in insoluble tablet systems compacted at low pressure due to their higher porosity. The dissolution efficiency of tablets containing casein formaldehyde remains largely unchanged over the pressure range studies in this investigation.

Since the dissolution of a soluble system takes place by erosion at the outer surfaces, swelling of disintegrant particles is not expected to play a major role. Therefore the tablets prepared from lactose would be expected to show a different behaviour from that shown by dicalcium phosphate dihydrate. For lactose systems the dissolution properties appear to fall into two groups. Group one contains cation exchange resin and cross-linked polyvinylpyrrolidone which are basically swelling type disintegrants and relatively nonadhesive in the hydrated state. The maximum in dissolution effici-

ency of tablets containing these materials is probably caused by the effect of swelling as described previously. The second group includes tablets containing sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium starch glycolate and casein formaldehyde. Initially there appears to be no appreciable difference between the dissolution efficiencies of tablets compacted at 500 and 1000 kg cm^{-2}, however at higher pressure a reduction in pore size, porosity and penetration rate decreases the dissolution efficiencies. The dissolution efficiency of lactose tablets without a disintegrant show a progressive decrease with increasing pressure.

An examination of both dissolution efficiency versus compressional pressure (see Table 2) and dissolution efficiency *vs* tablet hardness (Figs 1 and 2) reveals that although significant differences in relative efficiencies of disintegrants exist at certain pressures, at others the gap is narrow. This emphasizes, therefore, the necessity of full compressional studies for disintegrant evaluation.

This report hypothesizes that the effect of pressure combined with the inherent properties of a disintegrant in a tablet formulation can exert a very significant effect upon the dissolution and compressional pressure relationship. Therefore, an understanding of the disintegrant mechanism and the factors controlling its action in a disintegrating tablet system would be useful.

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