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Influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets

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Abstract

The influence of the composition and properties of pellets on the properties of the tablets prepared from their mixtures has been evaluated. Three types of pellets were prepared, (a) those containing a model drug readily identifiable by colour, to evaluate tablet consistency; (b) those containing a deformable material, glyceryl monostearate, to provide pressure absorbing and binding properties, and (c) those containing an inorganic disintegrating agent. Tablets from various mixtures of these pellets, in a statistical designed manner, were prepared at a known compression force and their weight uniformity, friability, diametral breaking load and disintegration times were measured. The uniformity of composition of selected tablets was also determined. Analysis of variance established that the disintegrant type, the proportion of drug pellets and the proportion of disintegrant pellets influenced the breaking load and the disintegration time of the tablets. The proportion of drug and disintegrant pellets influenced the tablet friability whereas the type of disintegrant did not. Canonical analysis failed to establish an exact relationship between pellet properties and tablet properties. However some conclusions can be drawn from this analysis. First, an increase in either the amount of drug pellets or disintegrant pellets decreases the tablet breaking load, and the disintegration times are reduced. Secondly, disintegration times are increased with disintegrants of a high density. Thirdly, larger amounts of drug and disintegrant pellets increase the tablet friability. © 1997 Elsevier Science B.V.

Keywords: Compaction; Disintegration; Model drug; Pellets; Statistical analysis; Tablets

1. Introduction

The advantages of using small spherical pellets in controlled release dosage forms are well described. Pellets have the following advantages:

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high drug loading capacity, an ideal shape for coating, good flow, and a high surface area to volume ratio, as compared to a tablet (Schwartz et al., 1994). A capsule dosage form containing spherical pellets is the usual drug delivery system as pellets can readily be filled into the capsule shell. However, the main limitation of a pelletized capsule dosage form is that the highest achievable dose is generally around 250 mg, due to pellet packing characteristics and size constraint dictated by the capsule. Rather than using this approach, pellets could be compacted to form a tablet. Then, higher dose strengths could be administered to patients since large volume tablets generally have greater patient acceptability than capsules (Béchard and Leroux, 1992). The phenomena and mechanisms involved during the compaction of pharmaceutical powders and granules have been the subject of numerous publications during the last four decades. However, there is only a limited number of published reports on the compaction properties of pellets. It has been shown that it is possible to compact pellets (Lopéz-Rodríguez et al., 1993; Maganti and Çelik, 1993; Schwartz et al., 1994; Johansson et al., 1995; Wang et al., 1995). However, these compacts generally show different characteristics when compared to powder compacts. Maganti and Çelik (1993) compared the compaction properties of microcrystalline cellulose powder and pellets. They found that the work involved in the compaction of pellets and the tensile strength of the pellet compacts were lower than those of the powder form. The compression mechanisms were also different for powders and pellets. Similar findings were reported by Wang et al. (1995), when comparing compaction of lactose/microcrystalline cellulose mixtures in powder and pellet form and by Schwartz et al. (1994), who showed that the same material in powder form compacts differently from that in pellet form. Johansson et al. (1995) showed that the dominating mechanism of compression for microcrystalline cellulose pellets was deformation and not fragmentation.

Pellets, which are large and spherical in shape as compared to small, irregular powder particles, have a low surface to volume ratio, and this might result in a decreased area of contact between the particles as they consolidate (Maganti and Çelik, 1993). Spheres will thus show different consolidation and deformation characteristics during compaction. During compact testing they will also display different mechanical properties and fracture mechanisms. Evaluation of the role of these parameters on the properties of a compact is an important criterion for successful tablet formation using pellets as excipient and/or drug carriers (Wang et al., 1995).

The deformation mechanisms involved in the compaction of pellets has implications for the drug release characteristics of coated pellets. Gross deformation of the pellets would cause rupture of the coat, with loss of the control of drug release. The compaction of coated drug pellets together with excipients in powder form is one way to achieve controlled release dosage forms (Sandberg et al., 1988). However, the difference in size distribution between powders and pellets might lead to segregation, resulting in tabletting problems, such as weight variation and poor content uniformity. To avoid these problems placebo pellets, with good compaction and cushioning properties, can be used as diluents if the size of the active pellets is much larger than that of the powder excipients (Çelik, 1994). Such soft pellets could, however, prevent disintegration of the tablet with consequent extension of the drug release. An alternative approach is therefore required if coated pellets are to be tabletted and retain their drug release profile. Such an approach was suggested by Pinto (1994) and involves the incorporation into the formulation of three types of pellets; (a) drug pellets, (b) soft pellets, and (c) disintegrant pellets. This study used a single type of disintegrant. The current study investigates the use of alternative types of disintegrant pellets as an initial model. Uncoated drug pellets are used to investigate the ability to form and disintegrate tablets. The model drug used is riboflavin (vitamin B_2). The colour of these pellets provides an easy method of distinguishing them from the other pellets and to detect the absorbance spectrophotometrically (and to monitor drug release). Disintegrant pellets are added in order to break the tablet up into pellets when swallowed (or when put in water). The soft pellets are added to

Table 1
Composition of pellets

No.	Disintegrant	Proportions			
		Disintegrant	Avicel PH101	Water	
Disintegrant pellets					
I	Barium sulphate	5	5	6	
II	Barium sulphate	8	2	3	
III	Calcium carbonate	5	5	6	
IV	Magnesium oxide	5	5	6	
V	Iron oxide	5	5	6	
Drug and soft pellets	Proportions				
Type	Barium sulphate	Glyceryl monostearate	Riboflavinlactose	Avicel PH101	Water
Soft pellets	5	2	—	3	3
Drug pellets	—	—	5	5	6

restrict the drug pellets from deforming and to hold the tablet together by deformation during the compaction.

2. Experimental

2.1. Materials

For all pellets, distilled water was used as granulating liquid.

The drug pellets consisted of 2% riboflavin (Sigma), 48% hydrous lactose N.F. (Sheffield Products, Norwich, USA) and 50% microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, USA), respectively, of the dry weight. The amount of water required for the process was 37.5% w/w of the total weight.

The soft pellets had the composition described by Pinto (1994), i.e. they consisted of 50% barium sulphate XR ($BaS0_4$, Sachtleben Chemie, Duisburg-Homberg, Germany), 20% microcrystalline cellulose (Avicel PH101, FMC) and 30% glyceryl monostearate, Tech. (Pfaltz and Bauer, USA) respectively of the dry weight. The water content was 23.1% w/w of the total weight.

Microcrystalline cellulose (Avicel PH101, FMC) was used in all disintegrant pellets. Different pharmaceutical excipients were used as disintegrants; $BaSO_4$ XR (Sachtleben Chemie) at two different levels, precipitated heavy calcium carbonate ($CaCO_3$, Sturge Chemicals, Birmingham, UK), heavy magnesium oxide B.P. (MgO, Macarthys, Romford, UK) and precipitated magnetic iron oxide (Fe_3O_4, BDH Chemicals, Poole, UK).

The proportions of disintegrant, microcrystalline cellulose and water were 5:5:6. For $BaSO_4$ an additional formulation with the proportions 8:2:3 was also used. The composition of the pellet formulations are set out in Table 1.

2.2. Methods

2.2.1. Production of pellets

The powders were blended in a planetary mixer (Kenwood Chef, Woking, UK) for 5 min before adding the water and additionally 10 min with the water. In the case of the drug pellets riboflavin was geometrically diluted with lactose before the addition of microcrystalline cellulose. After mixing the wet mass was immediately extruded by a ram extruder fitted to a mechanical testing instrument (Lloyd, MX50, Southampton, UK) using a single hole die of 1.0 mm diameter and 4.0 mm thickness. The extrusion mass was packed into the barrel (2.54 cm internal diameter and 20.3 cm length) and the piston was inserted to partially consolidate the mass. The crosshead speed was set at 250 mm/min. For each material the extrusion

Table 2
Mixture of pellets for tabletting

Mixture number	Disintegrant pellets (%)	Drug pellets (%)	Soft pellets (%)
1	0	40	60
2	15	40	45
3	30	40	30
4	45	40	15
5	60	40	0
6	30	20	50
7	30	30	40
8	30	50	20
9	30	60	10

force was recorded. Immediately after extrusion 400–500 g of the extrudate was spheronised in a 22.5 cm diameter spheroniser (G.B. Caleva, Dorset, UK) with a radial geometry plate. Spheronising time varied between 5 and 30 min. The speed was set at 1000 revs./min. The pellets were dried in a fluidized bed (P.R.L. Engineering, Wrexham, UK) at 60°C (40°C for pellets containing glyceryl monostearate) and the size fraction 1.00–1.40 mm was separated by 10 min of dry sieving with a set of standard sieves (test sieve shaker, Endecott, London, UK).

2.2.2. Shape analysis

Thirty pellets of each pellet formulation were glued on black slides (except Fe_3O_4, which was glued onto transparent slides which were placed on a white background) and analysed with an image analyser (Solitaire 512, Seescan, Cambridge, UK) connected to a black and white camera (CDD-4 miniature video camera module, Rengo, Toyohashi, Japan) and a zoom lens (18-108/2.5 Olympus, Hamburg, Germany). Top light (Olympus cold light source, Hamburg, Germany) was used to reduce the influence of shadows on the image processing, as this has been described previously (Podczeck and Newton, 1995). The two dimensional shape factor e_R was calculated in accordance with the method described by Podczeck and Newton (1994).

2.2.3. Production of tablets

The pellets were mixed in the proportions set out in Table 2.

For all pellets the size fraction 1.00–1.40 mm was used in the tablets.

The pellets were mixed by hand in plastic bags for a few minutes before being compressed in an instrumented single punch press (type F3, Manesty, Liverpool, UK) equipped with round flat faced punches and die, 10.0 mm in diameter. The upper punch force was kept constant at 2.5 kN. The fill volume was adjusted to obtain the required constant pressure, but gave a different fill weight for the different mixtures. Twenty tablets were made from each mixture and for each tablet the upper punch force was recorded. The tablets were weighed on an analytical balance and tablets from each mixture were used to measure the breaking load, friability, content uniformity and disintegration time, respectively, using five tablets for each test.

Tablets are denoted with the same roman numbers as the disintegrant pellets that are presented in Table 1. The numbers 1–9 denotes the proportions of the different types of pellets set out in Table 2. For example formulation II, 3 denotes the pellet mixture of 30% disintegrant pellets, 40% drug pellets and 30% soft pellets, where the disintegrant pellets consists of 8 parts of $BaSO_4$, 2 parts of Avicel and 3 parts of water.

2.2.4. Pellet and tablet strength

The breaking load for the pellets and the tablets was measured by diametral crushing test (CT40 Engineering systems, Nottingham, UK) at a compression rate of 1 mm/min.

2.2.5. Tablet weight uniformity

Twenty tablets from each tablet formulation were weighed on an analytical balance, to the nearest milligram, and the mean and coefficient of variation was calculated.

2.2.6. Tablet content uniformity

The tablets were placed separately in 1.00 l of distilled water and left in a paddle dissolution bath (type PTWS, PharmaTest, Apparatebau, Germany) for 16 h at 37.5°C and 100 revs./min. The solutions were then placed in an ultrasonic bath for 2 min before the absorbance was measured spectrophotometrically (Perkin–Elmer 554 UV/vis. Spectrophotometer, UK) at 266 nm wavelength. A calibration curve of absorbance vs. concentration riboflavin was made and used to determine the concentration of riboflavin for each tablet.

2.2.7. Tablet friability

Five tablets were tumbled in a Roche friabilator for 2 min and the proportion that did not pass the 1.40-mm sieve was weighed on an analytical balance. The friability was thereafter calculated as the percentage of weight lost.

2.2.8. Tablet disintegration time

The disintegration time was tested according to the British Pharmacopoeia (BP 1993) disintegration test for tablets, in a disintegration apparatus (Copley, Nottingham, UK) with discs. Water was used as disintegration medium and the temperature was set at 37°C. The time taken until no material from any of the tablets was left on the mesh was recorded.

3. Results and discussion

3.1. Pellets

3.1.1. Extrusion properties

The MgO mixture was difficult to extrude. Air bubbles occurred in the mixture, leading to 'explosions' during the extrusion that caused the crosshead to stop. It was, however, still possible to produce a sufficient amount of extrudate. The high level of $BaSO_4$ and the $CaCO_3$ showed both steady state and forced flow during extrusion. All other formulations showed only steady state extrusion.

It was found that when the extrusion force exceeded about 10 kN the extrudate was too hard to round into spheres and the pellets obtained were oblong or dumbbell shaped. The properties of the pellets are recorded in Table 3.

3.1.2. Analysis of size distribution

For most of the formulations most of the pellets were in the sieve fraction 1.00–1.40 mm (Table 3). This was to be expected since the diameter of the extrusion die was 1.0 mm. This size fraction was therefore chosen for the tabletting. Since the first batch of drug pellets was insufficient, a second and a third batch were produced. These gave different size distributions compared to the first batch with higher proportions of large pellets. The reason for this difference in size distribution is so far not known. Sufficient drug pellets in the range 1.00–1.40 mm were however obtained in the three batches produced.

The disintegrant pellets with the high proportion of $BaSO_4$ (formulation II) gave the most uniform size distribution and these were also the most spherical pellets.

3.1.3. Shape

The shape factor of the pellets used for tabletting was between 0.46 and 0.60, as seen in Table 3. The disintegrant pellets with the high proportion of $BaSO_4$ had the highest value of e_R, i.e. were the most spherical, and the disintegrant pellets with MgO had the lowest value of e_R.

3.1.4. Breaking load

As expected the soft pellets had the lowest strength (breaking load 0.16–0.19 kg, Table 3) and they were extensively deformed during the diametral compression test. None of the other pellet formulations showed any deformation during testing. There was little difference in breaking load between the different disintegrants. The disintegrant pellets with the high proportion of $BaSO_4$ had a lower strength than the other disin-

Table 3
Pellet properties

Pellet size distribution					Shape factor		Breaking load	
Pellet formulation	Diameter median (mm)	Diameter mode (mm)	% in mode	I.Q.R. (mm)	Mean ($n = 30$)	Variation coefficient (%)	Mean (kg, $n = 5$)	Variation coefficient (%)
I	1.10	1.00–1.40	65.2	0.35	0.484	30.2	1.37	7.6
II	1.20	1.00–1.40	99.8	0.20	0.600	12.0	0.89	20.0
III	1.20	1.00–1.40	95.8	0.20	0.587	12.9	1.43	4.5
IV	1.20	1.00–1.40	96.6	0.20	0.464	29.2	1.63	13.1
V	1.3	1.00–1.40	53.6	0.36	0.500	32.6	1.55	5.1
Soft a	1.19	1.00–1.40	90.3	0.21	0.596	8.82	0.16	23.4
Soft b	1.19	1.00–1.40	91.5	0.21	0.591	15.4	0.19	21.6
Drug a	1.22	1.00–1.40	89.2	0.23	0.544	20.4	1.62	6.2
Drug b	1.47	1.40–1.70	53.6	0.34	0.573	17.8	1.42	4.7
Drug c	1.48	1.40–1.70	54.6	0.33	0.566	18.5	1.39	6.7

I.Q.R., inter quartile range.
Median and I.Q.R. derived from cumulative percentage of pellets versus size graphs.
Shape factor and breaking load from sieve fraction 1.00–1.40 mm.
Pellet formulations as in Table 1.

tegrant pellets (breaking load 0.89 kg compared to 1.37–1.63 kg). This is explained by the lower proportion of microcrystalline cellulose in these pellets. Microcrystalline cellulose has been found to be a very effective binder and contributes significantly to the mechanical strength (Aulton et al., 1994; Wang et al., 1995), and water granulated microcrystalline pellets are very hard (Schwartz et al., 1994).

3.2. Tablets

3.2.1. Weight and weight variability

There was little difference in tablet weight when the proportion of drug pellets was varied (Figs. 1 and 2). The proportion of disintegrant pellets did however influence the tablet weight as Fig. 1 shows. When the proportion of disintegrant pellets was increased, the weight increased accordingly. The tablet weight varied for the different disintegrant pellets due to the differing densities of the disintegrants as seen in Fig. 2. The tablets with $BaSO_4$ as disintegrant had the highest weights, and the ones with Fe_3O_4 or MgO had the lowest. The tablets showed good uniformity of weight, with a coefficient of variance of between 0.9 and 4.2% (Table 4). In some cases, especially with the tablets containing $BaSO_4$ pellets of the low disintegrant proportion, the tablets started falling apart before they were being weighed, and

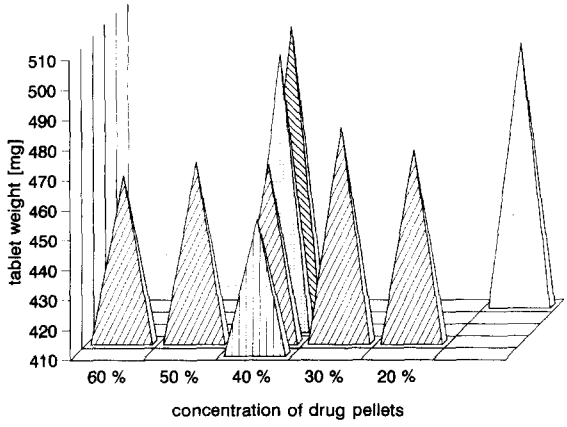

Fig. 1. Influence of concentration of drug and disintegrant pellets on the weight of tablets with magnesium oxide; □ no disintegrant, ▨ 15%, ▨ 0%, ■ 45%, and ▧ 60% disintegrant.

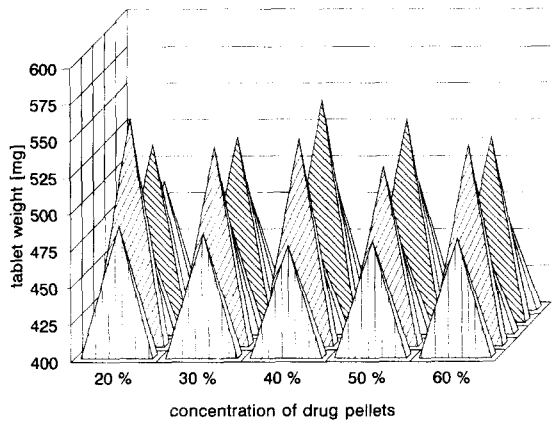

Fig. 2. Influence of concentration of drug and type of disintegrant in pellets on the weight of tablets (30% disintegrant pellets); ▨ $CaCO_3$, ▧ $BaSO_4$ (1:1), ■ MgO, ▨ $BaSO_4$ (8:2), and ▨ Fe_3O_4 as disintegrant.

this can have influenced the variation coefficient for the weight.

3.2.2. Content uniformity

The content uniformity for a selection of the tablet formulations are set out in Table 5. The variation coefficient for the amount of riboflavin in the tablets was below 10% in most cases. The theoretical amount riboflavin was only reached in one case, for formulation I, 6, which is also the formulation with the highest coefficient of variation.

3.2.3. Friability

Some of the tablets were nearly intact after the 2 min but some tablets fell apart almost totally into pellets. This was related to the proportion of soft pellets, the lower this proportion, the higher the friability. The following tablet formulations gave an acceptable friability (less than 10% for all five tablets) nos: 1; II, 2; II, 6; II, 7; III, 2; III, 6; III, 7; IV, 2; IV, 3; IV, 6; IV, 7; V, 2; V, 3; V, 6 and V, 7 (Table 4). Only formulation number 1 (without any disintegrant pellets) had a friability of less than 0.4% for all five tablets, although some formulations (II, 2; II, 6; IV, 2 and V, 2) had a mean friability of less than 1% (Table 4).

When the proportion of disintegrant pellets was increased the friability increased as seen in Fig. 3.

Table 4
Tablet characeristics: weight and weight variability, friability, tablet strength as breaking load and disintegration time. For tablet formulations see text.

Weight			Friability(%) ($n = 5$)	Breaking load		Disintegration time	
Formulation	Mean weight (mg, $n = 20$)	Variation coefficient (%)		Mean load (kg, $n = 5$)	Variation coefficient (%)	Mean time (s) ($n = 5$)	Variation coefficient (%)
1	493	1.8	0.3	4.55	10.2	1765	35.9
I, 2	527	4.1	24.8	2.38	22.8	886	11.7
I, 3	548	2.8	45.3	1.68	30.9	707	27.9
I, 4	565	3.5	64.2	0.59	53.9	306	23.6
I, 5	596	2.8	85.3	0.50	36.2	6	42.2
I, 6	515	4.2	10.8	3.42	29.9	1455	12.2
I, 7	524	2.3	13.3	2.86	31.6	1350	16.4
I, 8	538	1.2	41.5	2.17	24.8	572	17.4
I, 9	525	1.3	58.6	2.10	54.7	339	38.4
II, 2	507	2.1	0.4	3.89	18.7	1531	24.9
II, 3	541	2.8	10.1	3.42	28.2	1166	24.1
II, 4	556	2.4	53.7	2.17	12.2	301	11.8
II, 5	604	2.6	77.1	1.08	40.7	5	11.9
I, 6	555	1.4	0.7	4.31	15.8	879	7.2
I, 7	531	2.1	6.2	3.81	16.3	811	32.2
II, 8	518	1.9	33.7	2.49	15.6	393	32.0
II, 9	539	2.0	63.4	1.76	23.2	340	48.8
III, 2	477	1.2	1.7	4.50	10.2	1694	17.1
III, 3	490	1.1	22.3	2.77	23.8	585	32.6
III, 4	502	1.2	49.9	1.61	28.6	259	16.3
III, 5	506	1.8	82.7	0.50	22.9	4	34.5
III, 6	486	1.4	1.4	3.63	21.7	1167	32.0
III, 7	482	1.6	1.3	3.73	14.8	1108	10.9
III, 8	485	1.2	33.2	2.82	24.7	420	3.6
III, 9	472	0.9	46.3	2.75	30.2	297	20.8
IV, 2	454	1.2	0.7	4.71	9.0	1069	19.7
IV, 3	467	1.0	7.8	3.67	21.1	807	4.7
IV, 4	506	1.3	50.7	1.75	39.6	223	24.8
IV, 5	509	1.9	76.6	0.90	55.0	6	29.5
IV, 6	474	3.9	1.7	3.29	25.9	1267	24.7
IV, 7	481	0.9	2.8	3.29	10.6	593	33.5
IV, 8	470	1.6	15.3	3.41	19.9	423	13.1
IV, 9	466	1.2	28.3	2.44	22.5	261	31.8
V, 2	463	1.3	0.4	4.22	9.0	1198	10.7
V, 3	475	1.6	9.6	3.50	19.8	826	22.0
V, 4	495	1.2	46.8	2.11	31.9	409	23.8
V, 5	523	1.6	61.6	0.54	35.0	4	31.7
V, 6	488	1.1	1.5	3.25	12.3	860	22.8
V, 7	479	1.4	3.3	3.09	25.3	925	24.7
V, 8	475	1.3	25.2	2.97	9.9	606	19.7
V, 9	476	1.3	47.1	1.77	38.3	208	20.3

Table 5
Content uniformity.

Formulation	Mean amount released ($n = 5$)	Variation coefficient (%)	Mean theoretical amount (mg, $n = 5$)
I	3.35	9.2	3.91
V, 2	2.79	8.8	3.64
V, 3	2.72	6.6	3.80
V, 4	3.30	6.5	3.99
V, 5	3.06	6.8	4.20
I, 6	2.02	17.1	2.02
II, 6	1.72	10.4	2.22
III, 6	1.58	5.2	1.95
IV, 6	1.20	13.0	1.85
V, 6	1.63	7.3	1.96
V, 7	2.04	10.1	2.88
V, 8	3.84	3.0	4.74
I, 9	5.13	3.3	6.17
II, 9	5.46	6.4	6.26
III, 9	5.15	4.4	5.65
IV, 9	4.67	4.3	5.56
V, 9	4.48	4.4	5.69

Amount of riboflavin released from different tablet formulations with coefficient of variation, and calculated amount riboflavin for the tablets on a selection of tablet formulations.

This graph also shows that an increased amount of drug pellets leads to an increased friability. Fig. 4 shows that the lower the proportion of drug pellets, the lower the friability. The tablets containing $BaSO_4$ (5:5:6) pellets as disintegrant had the highest friability and the tablets with MgO disintegrant pellets had the lowest friability.

3.2.4. Breaking load

The tablet strength as indicated by the load necessary to cause failure in diametral compression was highly dependent on the proportion of the different pellet types. Fig. 5 shows that the breaking load decreased as the proportion of disintegrant pellets was increased. When the proportion of drug pellets was increased the breaking

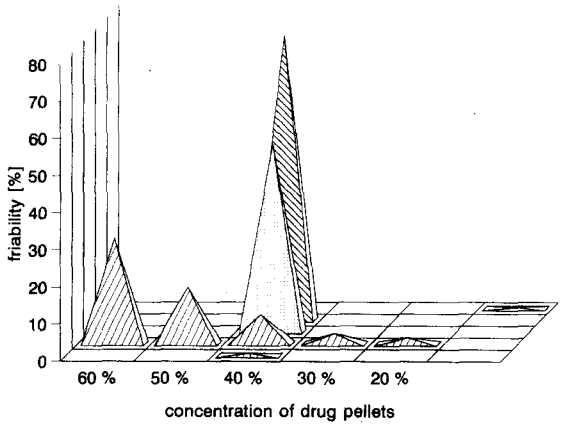

Fig. 3. Influence of concentration of drug and disintegrant pellets on the friability of tablets with magnesium oxide; □ no disintegrant, ▥ 15%, ▨ 30%, ■ 45%, and ▧ 60% disintegrant.

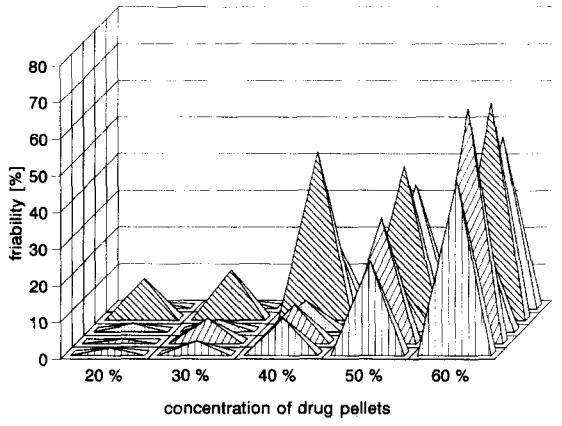

Fig. 4. Influence of concentration of drug and type of disintegrant in pellets on the friability of tablets (30% disintegrant pellets); □ $CaCO_3$, ▧ $BaSO_4$ (1:1), ■ MgO, ▨ $BaSO_4$ (8:2), and ▥ Fe_3O_4 as disintegrant.

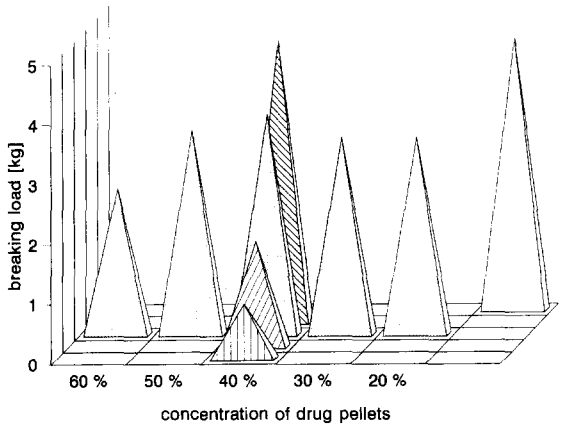

Fig. 5. Influence of concentration of drug and disintegrant pellets on the breaking load of tablets with magnesium oxide; □ no disintegrant, ▨ 15%, ■ 30%, ▨ 45%, and ▯ 60% disintegrant.

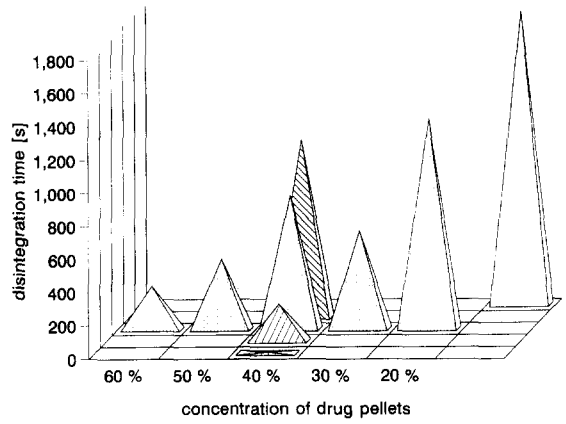

Fig. 7. Influence of concentration of drug and disintegrant pellets on the disintegration time of tablets with magnesium oxide; □ no disintegrant, ▨ 15%, ■ 30%, ▨ 45%, and ▯ 60% disintegrant.

load decreased as seen in Fig. 6. The difference between different types of disintegrant was slight, and varied with the proportion of drug pellets (Fig. 6). The formulations with a low proportion of soft pellets had low strengths, as expected.

3.2.5. Disintegration time

When the proportion of disintegrant pellets was increased the disintegration time decreased as expected (Fig. 7). This graph also shows that when the percentage of drug pellets was increased, while the proportion of disintegrant pellets was held constant, the disintegration time decreased. When the proportion of soft pellets was low the disintegration time was short. This indicates that the soft pellets hold the tablets together, as expected. Fig. 8 shows that the lower the proportion of drug pellets, the longer the disintegration time and it can also be seen that the influence of disintegrant type varied with the proportion of drug pellets.

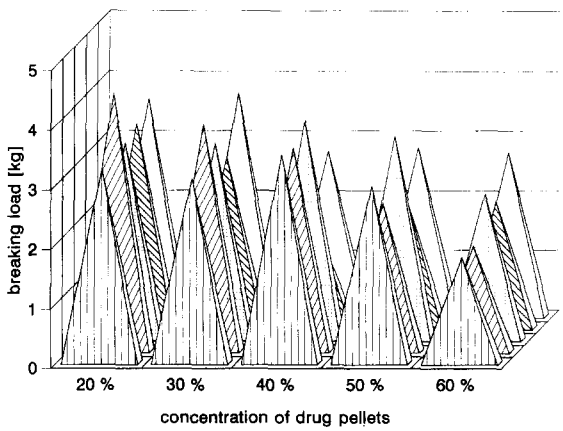

Fig. 6. Influence of concentration of drug and type of disintegrant in pellets on the breaking load of tablets (30% disintegrant pellets); □ $CaCO_3$, ▨ $BaSO_4$ (1:1), ■ MgO, ▨ $BaSO_4$ (8:2), and ▯ Fe_3O_4 as disintegrant.

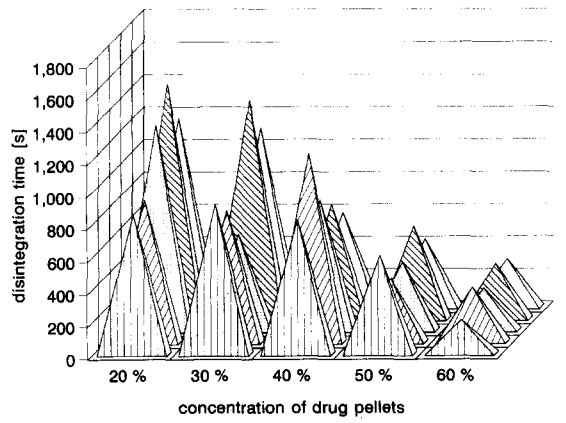

Fig. 8. Influence of concentration of drug and type of disintegrant in pellets on the disintegration time of tablets (30% disintegrant pellets); □ $CaCO_3$, ▨ $BaSO_4$ (1:1), ■ MgO, ▨ $BaSO_4$ (8:2), and ▯ Fe_3O_4 as disintegrant.

Table 6
Analysis of variance

	Parameter	Variance ratio (F)	Probability level (P)
Disintegrant type	Breaking load	5.32	<0.001
	Disintegration time	5.20	<0.001
	Friability	3.11	0.013
	Weight	67.83	<0.001
% Drug pellets	Breaking load	7.50	<0.001
	Disintegration time	13.74	<0.001
	Friability	6.87	<0.001
	Weight	2.51	0.043
% Disintegrant pellets	Breaking load	62.77	<0.001
	Disintegration time	60.37	<0.001
	Friability	40.13	<0.001
	Weight	14.79	<0.001

Probability levels: $P<0.05$, significant; $P<0.001$, highly significant.

3.3. Statistical analysis

3.3.1. Analysis of variance

Statistical analysis of the data was undertaken using the 'Statistical Package for Social Sciences' (SPSS 4.0.1., SPSS, UK). The combination of proportions of different types of pellets was such that analysis of variance (ANOVA) could be undertaken to establish which important factors influenced the properties of the tablets. The influence of disintegrant type, percentage of drug pellets and percentage of disintegrant pellets on the breaking load, disintegration time and friability of tablets was tested.

The ANOVA test, Table 6, shows that all parameters were statistically significant. It also shows that the disintegrant type, the proportion of drug pellets and the proportion of disintegrant pellets all influence the breaking load, the disintegration time and the friability of the tablets act independently from each other, because the first order interaction terms were all found to be not significant ($P \gg 0.05$).

3.3.2. Canonical analysis

Canonical analysis can be used to identify possible relationships between factors and the properties of the tablets (Podczeck et al., 1993). While the concentrations of the drug and disintegrant pellets can be used in the analysis as influence factors as they are, the type of disintegrant is a qualitative factor only. Thus, an appropriate coding had to be found to transform the factor levels into numerical data. In the first place, the molar mass of the positive ion of the disintegrant was used, and for the double concentration of $BaSO_4$, twice the molar mass was entered. This gives an order of disintegrants as follows: no disintegrant (M = 0), MgO (M = 24), $CaCO_3$ (M = 40), Fe_3O_4 (M = 56), $BaSO_4$ (M = 137) and $BaSO_4$/double concentration ('M = 274'). Canonical analysis was performed thus with X = {% drug pellets, % disintegrant pellets, molar mass} and Y = {breaking load, disintegration time, tablet weight}. 'Friability' was here excluded due to about 50% of the experiments leading to 100% friability. The relationship between X and Y as defined above was found to be highly significant (Wilks' $\Lambda \approx 0.069$, $F = 106.41$, $P < 0.001$). However, the measure of redundance ($g^2 = 0.492$) implies, that one can predict the tablet properties only to about 50%. For 'breaking load' and 'disintegration time', the concentrations of drug and disintegrant pellets were identified as highly significant influence factors ($P < 0.001$), but the type of disintegrant appeared to have no effect on the formulations. For a reduced set of data, i.e. exclusion of experiments leading to a friability of 100%, a similar relationship was found for the variable 'friability'. The total exclusion of the disintegrant type appeared

Table 7
Linear regression models

Parameter	Equation	r	B	F	P
Breaking load	$-0.069x-0.023y+6.107$	0.783	0.604	61.14	<0.001
Disintegration time	$-35.714x-17.054y+17.705z+2282.891$	0.820	0.660	52.04	<0.001
Weight	$1.118x+0.269z+443.192$	0.807	0.647	188.24	<0.001
Friability	$1.397x+1.222y-65.989$	0.919	0.841	212.64	<0.001

x, % disintegrant pellets; y, % drug pellets; z, disintegrant type; r, coefficient of multiple correlation; B, adjusted linear determinant; F, variance ratio; P, probability level.
The adjusted linear determinant describes the variability explained by the regression, corrected for the number of variables and measurements included in the model.

at least unacceptable for the disintegration time. Hence, it was assumed that the coding of the disintegrant type by the molar mass of the positive ion is not an appropriate measure. The disintegrants are different in density and thus take up different volume in the tablets. For this reason, a second coding — the quotient of the percentage of disintegrant and the true density of the disintegrant — led to the following order: for no disintegrant (Q = 0), Fe_3O_4 (Q = 9.62), $BaSO_4$ double concentration (Q = 11.44), MgO (Q = 13.70), $BaSO_4$ (Q = 18.31) and $CaCO_3$ (Q = 18.38). Using this coding in the canonical analysis, the type of disintegrant was identified to be a significant influence factor for the disintegration time ($P = 0.039$), but still of no importance for the 'breaking load' and 'friability'.

3.3.3. Linear regression models

Finally, an attempt was made to model the relationships between X and Y, as identified by the canonical analysis, using linear regression. Table 7 summarizes the results. Residual analysis has shown that these equations represent only an overall trend and cannot be used for predictions, as this was already indicated by the low measure of redundance in the canonical analysis. However, some conclusions can be drawn. First, an increase in either the amount of drug pellets or disintegrant pellets decreases the breaking load of the tablets, thus weakens their structure. Similarly, the disintegration time becomes reduced. However, the disintegration time increases for disintegrants, which have a higher true particle density. Secondly, larger amounts of drug or disintegrant pellets increase the friability of the tablets. Thus the mechanical properties of the tablets are governed mainly by the amount of soft pellets, which were initially included to protect the drug pellets from damage during tabletting. The type of disintegrant is able to affect the disintegration time of the tablets independently from the weakening effect of the amount of drug or disintegrant pellets in the tablets. Disintegrants such as $BaSO_4$ or $CaCO_3$ are more effective than for example MgO or Fe_3O_4. However, the concentration of these disintegrants in the disintegrant pellets should not be too high, because on comparing the two concentrations of $BaSO_4$ used it appears as if higher concentrations have an adverse effect due to the large increase in pellet density.

4. Conclusions

It was possible to obtain tablets made entirely out of mixtures of the different pellets, but in some cases the tablets were too weak to hold together after compression. This was due to a low proportion of soft pellets.

By observing the pellets which disintegrated from the tablets it was possible to see that the drug pellets were deformed when compacted into tablets.

The soft pellets held the tablet together and the lower the proportion of soft pellets, the higher the friability, the lower the breaking load and the shorter the disintegration time.

The disintegrant pellets clearly did break the tablet. The higher the proportion of disintegrant

pellets, the higher the friability, the lower the breaking load and the shorter the disintegration time. This was exactly what was expected.

The disintegrant materials that from the statistical analysis seems to be best suited are $CaCO_3$ and $BaSO_4$, the worst formulations were found to be Fe_3O_4 and $BaSO_4$, the latter in the high proportion.

The optimum level of disintegrant pellets to ensure adequate disintegration was in this study found to be 30%, and the maximum level of drug pellets that gives tablets which are strong enough was found to be 40%.

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References

Aulton, M.E., Dyer, A.M. and Khan, K.A., The strength and compaction of millispheres. The design of a controlled-release drug delivery system for ibuprofen in the form of a tablet comprising compacted polymer-coated millispheres. *Drug Dev. Ind. Pharm.*, 20 (1994) 3069–3104.

Béchard, S.R. and Leroux, J.C., Coated pelletized dosage form: effect of compaction on drug release. *Drug Dev. Ind. Pharm.*, 18 (1992) 1927–1944.

Çelik, M., Compaction of multiparticulate oral dosage forms. In Ghebre-Sellassie, I. (Ed.) *Multiparticulate Oral Drug Delivery*, Marcel Dekker, New York, 1994, p. 211.

Johansson, B., Wikberg, M., Ek, R. and Alderborn, G., Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. *Int. J. Pharm.*, 117 (1995) 57–73.

Lopéz-Rodriguez, F.J., Torrado, J.J., Torrado, S., Escamilla, C., Cadórniga, R. and Augsburger, L.L., Compression behavior of acetylsalicylic acid pellets. *Drug Dev. Ind. Pharm.*, 19 (1993) 1369–1377.

Maganti, L. and Çelik, M., Compaction studies on pellets I. Uncoated pellets. *Int. J. Pharm.*, 95 (1993) 29–42.

Pinto, J.F. de A. Formulation and tabletting of controlled release pellets produced by extrusion/spheronisation. PhD Thesis, 1994, University of London.

Podczeck, F. and Newton, J.M., A shape factor to characterize the quality of spheroids. *J. Pharm. Pharmacol.*, 46 (1994) 82–85.

Podczeck, F. and Newton, J.M., The evaluation of a three-dimensional shape factor for the quantitative assessment of the sphericity and surface roughness of pellets. *Int. J. Pharm.*, 124 (1995) 253–259.

Podczeck, F., Merkel, G. and Révész, P., The application of canonical analysis to the evaluation of the influence of changes in components of standard direct compression tablet formulations. *Int. J. Pharm.*, 97 (1993) 15–28.

Sandberg, A., Ragnarsson, G., Jonsson, U.E. and Sjögren, J., Design of a new multiple-unit controlled-release formulation of metoprolol–metoprolol CR. *Eur. J. Clin. Pharmacol.*, 33 (1988) S3–S7.

Schwartz, J.B., Nguyen, N.H. and Schnaare, R.L., Compaction studies on beads: compression and consolidation parameters. *Drug Dev. Ind. Pharm.*, 20 (1994) 3105–3129.

Wang, C., Zhang, G., Shah, N.H., Infeld, M.H., Malick, A.W. and McGinity, J.W., Compaction properties of spheronized binary granular mixtures. *Drug Dev. Ind. Pharm.*, 21 (1995) 753–779.