ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 369–379

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Compaction of, and drug release from, coated drug pellets mixed with other pellets

Åsa E.K. Lundqvist[1], Fridrun Podczeck, J. Michael Newton*

The School of Pharmacy, University of London, London, UK

Received 13 February 1998; accepted 5 May 1998

Abstract

Tablets have been prepared at known compaction force from three types of pellets in different proportions: (1) pellets containing 80% theophylline as a model drug coated with different thicknesses of a polymer film coat, (2) pellets containing glyceryl monostearate as a deformable material, and (3) pellets containing a disintegrant. The breaking load, friability, disintegration and drug release properties were evaluated, the latter as a mean dissolution time (MDT) and its variance (VDT). The mechanism of dissolution was assessed from the value of the relative dispersion (RD) of the mean dissolution time. The possible relationship between the properties of the pellets and those of the tablets was evaluated by canonical analysis followed by multiple regression analysis. It was found that only about 51% of the tablet properties could be predicted from the properties of the pellets. The quantitative relationship between pellet properties and tablet properties was found to vary in type and level of quality. Reduction of breaking load, friability and disintegration was less predictable than that of dissolution represented as the MDT. The values of RD for the different preparations clearly identified those preparations where the film coat still retained control of the dissolution process. Such formulations contained at least 40% of soft pellets and coated pellets with at least a weight gain of 8%.

Keywords: Drug dissolution; Drug release mechanism; Film Coating; Pellets; Tabletting

1. Introduction

Oral modified release multiple particular dosage forms have gained increasing popularity in recent years. One way to achieve such modified release systems is to coat spherical pellets, which provide the ideal shape for coating. The addition of a coating material can, however, alter the deformation characteristics of uncoated pellets [1].

Although a good deal of work has been done on the compaction characteristics of pharmaceutical powders, much less has been reported on the effects produced on the compaction behaviour of coated pellets. Compression of coated pellets to form tablets can lead to damage to the film coat with a subsequent increase in the dissolution rates from such tablets [2–5].

In a previous study [6] uncoated pellets were used as a model to investigate the ability to form, and disintegrate tablets, from pellets. The current study investigates the effect of compaction of similar multi-component pellet systems in which the drug pellets are coated. The aim of this study was to identify some of the factors which influence the production of modified release multiple-particulate tablets which, on tablet disintegration, release the drug pellets and retain a similar dissolution mechanism. To achieve this, three types of pellets were incorporated in the tablets: (a) coated drug pellets, (b) soft pellets, and (c) disintegrant pellets as described by Pinto [7]. The soft pellets were added to restrict the drug pellets from deforming and to

* Corresponding author. Department of Pharmaceutics, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK. Tel.: +44 171 7535869; fax +44 171 7535942; e-mail: newton@cua.ulsop.ac.uk

[1] Present address: Department of Pharmaceutics, Uppsala University, Box 580, S-751 23, Uppsala, Sweden.

0939-6411/98/$19.00
PII S0939-6411(98)00039-3

hold the tablet together by deformation during the compaction. Disintegrant pellets were added in order to break the tablet up into pellets when swallowed (or when put in water). A statistical design will be employed to consider the effect of type of disintegrant, the relative amount of drug and disintegrant pellets, the variation in compaction pressure and the thickness of the polymer coat applied to the pellets. Identification of the dissolution mechanism will be based on statistical moment analysis as suggested by Voegele et al. [8] and used for pellet formulations by Pinto et al. [9].

2. Materials and methods

2.1. Materials

The granulating liquid used for all the pellets was distilled water. The drug pellets were of the formulation described by Yuen et al. [10], i.e. consisting of 80% theophylline hydrous E.P. (Knoll AG, Ludwigshafen, Germany), 15% microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, USA) and 5% lactose E.P. (Borculo Whey Products, Saltney, UK), respectively, of the dry weight. The amount of water required for the process was 25.4% w/w of the total weight.

The soft pellets had the composition described by Pinto [7], i.e. consisting of 50% barium sulphate (XR, Sachtleben Chemie GmbH, Duisburg–Homberg, Germany), 20% microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, PA) and 30% glyceryl monostearate (Hüls, Witten, Germany), respectively, of the dry weight. The water content was 21.2% w/w of the total weight.

Disintegrant pellets were produced using three different disintegrants. The compositions were as follows. (1) Barium sulphate (Sachtleben Chemie GmbH, Duisburg-Homberg, Germany) 80% and microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, PA) 20%, respectively, of the dry weight with a water content of 23.1% w/w of the total weight. (2) Magnetic precipitated iron oxide, 50%, (Fisons Scientific Equipment, Loughborough, UK) and 50% microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, PA), respectively, of the dry weight with a water content of 37.5% w/w of the total weight. (3) Precipitated calcium carbonate, 50%, (Sturge Chemicals, Birmingham, UK) and 50% microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, USA), water content 36.8% w/w of the total weight.

The coating solution consisted of ethylcellulose (Surelease E-7-7050, Colorcon, Dartford, Kent, UK) and methylcellulose of viscosity grade 400 (Methocel A4C premium, Colorcon, Dartford, Kent, UK). The ratio of methylcellulose to ethylcellulose was 0.16. This ratio was found to be ideal by Yuen et al. [10]. Methylcellulose was dissolved in distilled water prior to mixing with Surelease, resulting in a 1:2 dilution of Surelease before use. This composition has been shown to give controlled release when applied in certain coating thickness to pellets [10].

2.2. Methods

2.2.1. Production of pellets

The powders were blended in a planetary mixer (Model AE200, Hobart, London, UK) for 5 min before the addition of the water and additionally 10 min with the water. The mass was then immediately extruded in a rotary gear extruder (G.B. Caleva, Dorset, UK) through holes of 1 mm diameter and 4 mm length. Immediately after extrusion the extrudate was spheronised in a 22.5 cm diameter spheroniser (G.B. Caleva, Dorset, UK) with a radial geometry plate. The extrudate was spheronised in batches of 400 g at a time with the speed set at 1000 rev./min. The pellets were dried in a conventional hot-air oven at 40°C for 12 h 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, Endecotts, London, UK).

2.2.2. Shape analysis

At least 40 pellets of each formulation were analyzed with an image analyzer (Solitaire 512, Seescan, Cambridge, UK) connected to a black and white camera (CDD-4 miniature video camera module, Rengo Co. Ltd., 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 [11]. The magnification was set so that each pellet outline covered about 12 000 pixels. The two dimensional shape factor e_R was calculated in accordance with the method described by Podczeck and Newton [12].

2.2.3. Coating of drug pellets

The drug pellets were film coated in a fluidized bed coating apparatus (Aeromatic AG, Muttenz, Switzerland) with the bottom spray technique [10]. The drying temperature was set at 60°C and the capacity of the fan at 18 units. The atomizing pressure was 0.4 bar and the spray rate was about 2 g/min. In each batch 50 or 100 g of pellets were coated. The coating solution was stirred with a magnetic stirrer for 5 min before the coating was started and continuously during coating. The different coat thicknesses were 1.17% total weight gain (twg), 4.38% twg and 8.27% twg, respectively. After coating, the pellets were dried and cured in a conventional hot-air oven at 60°C for 24 h [10].

2.2.4. Production of tablets

The pellets were mixed in different proportions, as set out in Table 1. The statistical design used is a fractionated composite design, which included the content of drug pellets (five levels), disintegrant pellets (three levels), the table-

tting pressure (three levels), the coat thickness, expressed as percentage weight gain (three levels) and the type of disintegrants (three levels) as main factors, and the interaction between type of disintegrant and tabletting pressure. Such fractionations are useful and estimate similar relationships as that of a full composite design as long as restrictions with respect to further possible interactions are considered [13]. To adjust the ratio of number of experiments to number of levels, no interaction term was calculated in the regression analyses. The mixture with 30% disintegrant pellets, 40% drug pellets and 30% soft pellets was the centre point mixture, which was used for most of the tablets.

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

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 normal concave faced punches and die, 12.5 mm in diameter. Due to differences in the excipient composition each variety of pellets showed distinctive differences in colour and grey shade, which allowed the detection and prevention of mixing inhomogeneities. The content uniformity of the mixtures was also confirmed during the dissolution studies (see Section 2.2.8.). For each tablet 1000 mg (±5 mg) of pellets was weighed and manually filled in the die. The weight was kept constant in order to obtain constant pressure. Three different compaction pressures were used for each of the disintegrants. Twenty tablets were made for each tablet mixture and for each tablet the upper punch force was recorded.

Tablets from each tablet formulation were used to measure the breaking load, friability, disintegration time and dissolution rate, respectively, using five tablets for each test.

2.2.5. Pellet and tablet strength

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

2.2.6. Tablet friability

Five tablets were run in a Roche friabilator for 5 min and the proportion that did not pass the 1.40 mm sieve was weighed on an analytical balance. The friability was subsequently calculated as percentage of weight lost.

2.2.7. 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.

2.2.8. Pellet and tablet dissolution rate

Drug release was studied in an automated paddle dissolution apparatus (type PTWS, PharmaTest Apparatebau, Hamburg, Germany) set at 37°C and 100 rev./min for 12 h. One tablet, or 400 mg of drug pellets, was placed in 1.00 l of distilled water. The absorbance was measured spectrophotmetrically (PU8620 UV/VIS/NIR Spectrophotometer, Philips, Cambridge, UK) at 274 nm wavelength at certain predetermined times. Each test was run in sets of five, and the percentage of theophylline released over time was calculated. From the release curves the mean dissolution time, MDT, its variance, VDT, and the relative dispersion RD were calculated as previously described [8,9].

Table 1

Experimental design. The type of disintegrant pellets, coat thickness, formation pressure and the proportion of disintegrant, drug and soft pellets evaluated

Exp. no.	Disintegrant in pellets	Coat thickness (%)	Upper punch force (kN)	Proportions (disintegrant/drug/soft pellet)
1	$CaCO_3$	4.38	23.48	30:20:50
2	$CaCO_3$	4.38	22.94	30:30:40
3	$CaCO_3$	4.38	21.84	15:40:45
4	$CaCO_3$	1.17	21.90	30:40:30
5	$CaCO_3$	4.38	6.80	30:40:30
6	$CaCO_3$	4.38	23.51	30:40:30
7	$CaCO_3$	4.38	38.62	30:40:30
8	$CaCO_3$	8.27	21.38	30:40:30
9	$CaCO_3$	4.38	23.44	45:40:15
10	$CaCO_3$	4.38	22.26	30:50:20
11	$CaCO_3$	4.38	23.38	30:60:10
12	Fe_3O_4	4.38	6.58	30:40:30
13	Fe_3O_4	4.38	23.66	30:40:30
14	Fe_3O_4	4.38	39.40	30:40:30
15	$BaSO_4$	4.38	6.86	30:40:30
16	$BaSO_4$	4.38	22.82	30:40:30
17	$BaSO_4$	4.38	38.90	30:40:30

For pellet formulations see text.

3. Results and discussion

3.1. Analysis of the size distribution of the pellets

For all pellet formulations most of the pellets were in the sieve fraction 1.00–1.40 mm (Table 2). This was what was expected since the diameter of the extrusion die holes was 1 mm. This size fraction was therefore chosen for the tabletting. The disintegrant pellets with calcium carbonate gave the most uniform size distribution, with 96.1% of the pellets in the 1.00–1.40 mm, size fraction.

3.2. Shape of the pellets

The two dimensional shape factor of the pellets was between 0.36 and 0.60, as seen in Table 2. The iron oxide pellets were clearly not spherical. All other pellet formulations had a shape factor above 0.5, which, although not perfectly spherical, were of acceptable quality.

3.3. Breaking load

As expected, the soft pellets had the lowest strength (Table 2) and they were extensively deformed during the diametral compression test. None of the other pellet formulations showed any deformation during testing. The barium sulphate pellets had a much lower strength than the other disintegrants. This can be attributed to the lower proportion of microcrystalline cellulose, which contributes significantly to the mechanical strength [4,14] and therefore gives hard pellets [5]. The iron oxide pellets had the highest breaking load, probably because they were the least spherical.

The coating did not change the strength of the drug pellets, regardless of the thickness of the coat. This indicates that the core of the pellets fractures before the coat breaks, which is a typical occurrence for pharmaceutical pellets and film coats [15]. Rupture of the film is thus a result of the excessive deformation process of the pellet core under load, which leads to defects due to adhesion between contacting pellets and overstretching of the film. Therefore, two possibilities can be considered to prevent film damage: first, an increased rupture strength of the film, usually achieved by an increase in film thickness, and secondly the prevention of pellet deformation using cushioning i.e. an increased number of soft pellets. Both constellations are incorporated as independent variables into the statistical design (see Table 1).

3.4. Mean dissolution time and variance in dissolution time of the pellets

The properties of the pellets prepared from the different formulations are set out in Table 3. The uncoated pellets showed a fast dissolution rate, and released 75% of the theophylline within 1 h, as seen in Fig. 1. The mean dissolution time (MDT) for these pellets was 0.69 h and the variance in dissolution time (VDT) was 1.66 h^2. The MDT is a measure of the rate of the dissolution process; the higher the MDT, the slower the release rate. The 1.17% thickness was not enough to give controlled release. Almost all the theophylline was released within 5 h the value of the MDT was 1.60 h and that of the VDT was 1.19 h^2. As the thickness of the coating increased, the linearity of the release curves also increased and the 4.38% twg gave nearly linear dissolution curves. The values of the MDT were 5.55 h and 6.07 h, respectively, for the 4.38% and 8.27% coatings. The difference in dissolution rate between these two coatings was small, with the thicker coat giving a slightly more linear release profile. The variances in dissolution times were 10.31 h^2 and 10.47 h^2, respectively, for the 4.38% and 8.27% coatings. Neither of these pellet types, however, reached 100% release within the 12 h recorded.

Table 3 also lists the release mechanisms derived from the cumulative dissolution profile of multiparticulate pellet dispersions (zero-order release). It is known from basic mathematics that averaging of a set of individual time-dependent probability distributions leads to a population time law which does not necessarily represent the underlying time function of each individual distribution [16]. For some distribution functions this has been shown experimentally, comparing individual release profiles of microspheres with those obtained from the population means [17]. Two reasons, however, justify the use of dissolution studies on multiparticulate pellet dispersions in this study: first, the pellets will be compacted into tablets, which have to disin-

Table 2

Pellet properties. Median and inter quartile range (IQR) derived from cumulative percentage of pellets vs. size graphs. Shape factor and breaking load of the sieve fraction 1.00–1.40 mm

Pellet type	Pellet size distribution				Shape factor e_R		Breaking load	
	Median diameter (mm)	Modal diameter (mm)	Modal fraction (%)	IQR (mm)	Mean (n = 40)	Variation coefficient (%)	Mean (n = 5) (kg)	Variation coefficient (%)
$BaSO_4$	1.20	1.00–1.40	94.3	0.24	0.506	31.7	0.88	9.9
$CaCO_3$	1.20	1.00–1.40	96.1	0.22	0.578	22.1	1.81	3.9
Fe_3O_4	1.23	1.00–1.40	75.1	0.26	0.358	29.3	2.26	17.9
Soft	1.26	1.00–1.40	68.7	0.30	0.595	27.0	0.16	21.1
Drug (uncoated)	1.27	1.00–1.40	76.9	0.27	0.562	22.7	1.78	15.2

For pellet formulations see text.

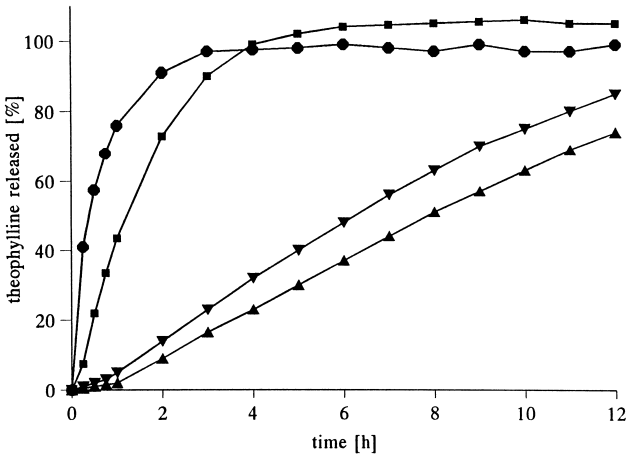

Fig. 1. Drug pellet dissolution profiles. Release of theophylline vs. time: ●, uncoated pellets; ■, 1.17% total weight gain (twg); ▼, 4.38% twg; ▲, 8.27% twg.

tegrate before a truly individual pellet drug release can begin. The measurement of individual pellet release profiles is hence impossible, plus there will always be an initial phase of drug release controlled by the tablet rather than by individual pellets. Secondly, in vitro drug release aims to assess the pharmaceutical bioavailability of the dosage form, which is here a tablet, not a single pellet. In vivo, the drug that can be absorbed will be a function of the multiparticulate pellet release, i.e. it is the average dissolution process that needs to be evaluated and described, even if the release mechanism derived is not necessarily reflecting a single pellet release mechanism.

3.5. Properties of tablets

The properties of the tablets prepared from the different formulations are set out in Table 4. This represents the total set of values for the tablet properties. It is useful, however, to consider the influence of the properties in association with a given combination of input variables. In this respect it has to be remembered that the experiments are outlined using a type of composite design. As long as only one influence factor is studied at the time, which appears useful to derive basic, preliminary conclusions, one has to extract those experiments from the design for which all other influence factors were kept constant [13]. For example, if the influence of the film thickness alone on the MDT is to be investigated, only the results of experiments 4, 6 and 8 can be compared to fulfil this requirement. However, the statistical design gives the essential foundation for the use of multivariate statistical methods such as the canonical analysis, which will be employed here. Multivariate statistical methods allow the identification of interactions and combined effects of all influence factors which are studied at the same time. Hence, modelling of the relationships between influence factors and properties of the dosage form becomes possible.

3.6. Breaking load

The tablet strength, as indicated by the load necessary to cause failure in diametral compression, decreased when the proportion of drug pellets was increased and the proportion of soft pellets was decreased (Fig. 2a). The breaking load was not influenced by changing the proportion of disintegrant pellets (Fig. 2b) or by different coat thicknesses (Fig. 2c). As expected, increasing the upper punch force gave an increased strength (Fig. 2d).

3.7. Friability

As expected, the friability decreased with increasing upper punch force (Table 4). A thicker coat also reduced the friability. There was no clear trend in friability when the proportions of drug or disintegrant pellets were changed. A limiting value of 1% for friability tests of tablets has been suggested by the European Pharmacopoeia [18]. In experiments 1, 7, 14, 16 and 17, tablets provided a friability of ≤0.5%, thus satisfying expectations of a good tablet formulation, while in other experiments medium or large friability values were found. The aim of a sophisticated statistical design is to cover the full range of possible values for a variable with its experiments to allow the use of the results in a predictive manner (Table 5) without extrapolations outside the variable space. With about one-third of all formulations providing an acceptable friability value, the design reported in this study satisfies this statistical requirement.

Table 3
Pellet dissolution characteristics and dissolution mechanisms for uncoated and coated drug pellets

Pellet coat thickness (weight gain)	MDT (h)		VDT (h^2)		RD	Mechanism of drug release
	Mean (n = 5)	Variation coefficient (%)	Mean (n = 5)	Variation coefficient (%)		
Uncoated	0.69	5.83	1.66	41.90	3.487	–
1.17%	1.60	2.56	1.19	11.10	0.465	Non-fickian
4.38%	5.55	0.68	10.31	0.54	0.335	Zero order
8.27%	6.07	0.35	10.47	0.49	0.284	Zero order

MDT, mean dissolution times; VDT, variance in dissolution time; RD, relative dispersion of the MDT.

3.8. Disintegration time

The European Pharmacopoeia [18] requires tablets to disintegrate in not more than 15 min (i.e. 900 s), if they are to be used as rapid-release dosage forms. While it is questionable whether one can apply this rule as it stands to tablets consisting of pellets for multiple-dose prolonged-release formulations, disintegration time measurements, as such, are indicative of whether, and when, the tablet formulations start to act as true multiple-dose preparations. Seven of the 17 formulations tested provided tablets which disintegrated in less than 900 s, thus conforming to the requirements of the European Pharmacopoeia mentioned above. The longest disintegration time of 37 min was found for formulation 1. However, here as well as in all other experiments, the disintegration time was much smaller than the mean dissolution time, indicating that the release was governed by single pellets over the majority of the time.

The disintegration time decreased when the proportion of drug pellets was increased and the proportion of soft pellets was decreased (Fig. 2a). Thus, the soft pellets hold the tablet together. As expected, the disintegration time decreased when the proportion of disintegrant pellets increased and the proportion of soft pellets decreased (Fig. 2b). The disintegration time was not influenced by coat thickness (Fig. 2c) but it increased with increasing upper punch force, as expected (Fig. 2d).

3.9. Mean dissolution time and variance in dissolution time

The mean dissolution time (MDT) decreased as the proportion of drug pellets was increased and the proportion of soft pellets was decreased (Fig. 3a). When the proportion of disintegrant pellets increased and the proportion of soft pellets decreased, the MDT decreased (Fig. 3b). This indicates that the dissolution rate is linked to the disintegration time. As expected, the dissolution rate decreased with increasing coat thickness (Fig. 3c), and, when the tabletting pressure increased, the value of the MDT increased very slightly (Fig. 3d). This indicates that there is some coat rupture even at the lowest upper punch force used. The slight

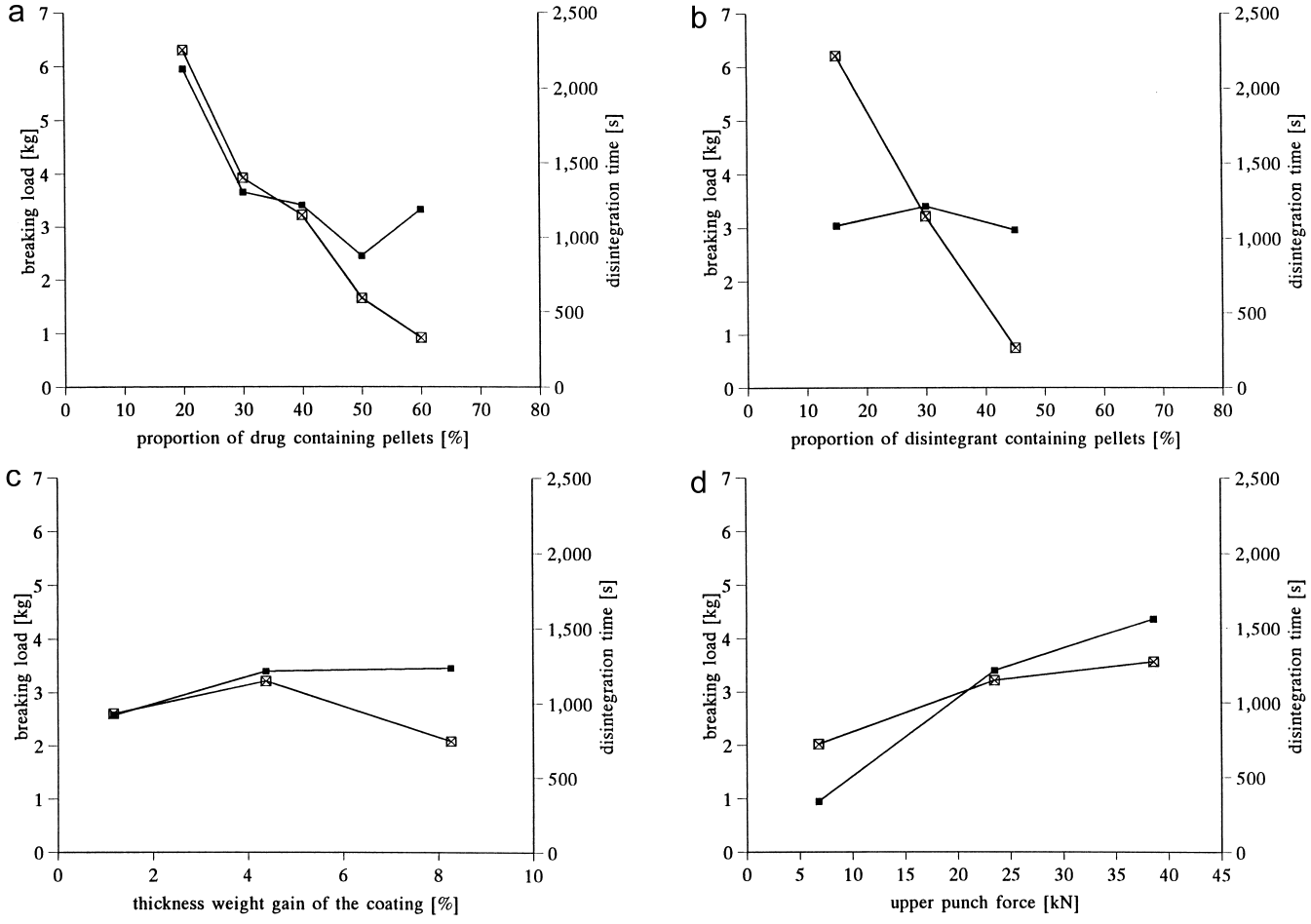

Fig. 2. Variation in tablet properties as a function of: (a) the proportion of drug pellets in the tablets (exp. no. 1, 2, 6, 10, 11), (b) the proportion of disintegrant pellets in the tablets (exp. no. 3, 6, 9), (c) the total weight gain of the coated drug pellets in the tablets (exp. no. 4. 6. 8), and (d) the upper punch tabletting force (exp. no. 5, 6, 7): ■, breaking load; ☒, disintegration time.

Table 4

The properties of the tablets (mean values of five replicates) prepared according to the experimental design in Table 1

Exp.	BL (kg)	VC (%)	F (%)	DT (s)	VC (%)	MDT (h)	VC (%)	VDT (h^2)	VC (%)	RD	Mechanism of drug release
1	5.95	14.6	0.2	2250	23.5	2.68	10.4	3.77	28.6	0.525	Non-fickian
2	3.65	27.0	16.9	1399	25.7	2.22	12.2	4.76	18.4	0.966	First order
3	3.04	9.1	18.6	2217	25.6	2.87	4.0	6.37	4.1	0.773	Non-fickian
4	2.58	20.0	39.3	932	16.8	1.09	2.5	0.49	2.2	0.412	Non-fickian
5	0.95	30.9	52.4	722	35.4	1.79	8.8	2.04	40.0	0.637	Cube-root
6	3.40	16.1	15.7	1148	19.1	1.91	3.1	3.13	8.6	0.858	Square-root
7	4.37	21.1	0.3	1274	20.4	2.13	7.9	2.57	13.1	0.566	Cube-root
8	3.46	9.2	7.3	746	29.4	2.46	3.4	6.41	4.2	1.059	First-order
9	2.96	13.9	16.5	268	19.5	1.40	6.1	2.07	32.4	1.056	First-order
10	2.45	15.4	22.4	591	18.6	1.55	3.0	3.39	42.5	1.411	Destroyed
11	3.32	6.3	7.0	327	15.7	1.30	3.8	5.11	4.7	3.024	Destroyed
12	0.84	35.7	60.9	723	21.5	1.88	5.1	5.00	26.8	1.415	Destroyed
13	3.16	12.7	22.3	1403	17.0	2.18	9.4	4.92	10.3	1.035	First-order
14	4.35	21.1	0.1	1616	34.4	2.46	6.4	3.75	10.5	0.620	Cube-root
15	1.51	15.4	51.2	887	26.4	2.31	1.8	4.63	18.6	0.868	Square-root
16	4.42	9.9	0.5	1192	16.3	2.54	13.2	5.19	25.0	0.804	Square-root
17	4.18	16.8	0.0	1425	32.5	2.69	9.6	5.85	23.2	0.808	Square-root

VC, variation coefficient; BL, breaking load; F, friability; DT, disintegration time; MDT, mean dissolution time; VDT, variance of dissolution time; RD, relative dispersion of the mean dissolution time; 'destroyed', film destroyed.

increase in MDT could be linked to the slower disintegration at higher tabletting pressure. Decreased dissolution rates have been reported when pellets have been compressed without any excipient to ensure the disintegration of the tablets [19–22].

There was no trend in the variance in dissolution time (VDT) when the proportion of drug pellets was increased and the proportion of soft pellets was decreased (Fig. 3a), or when the upper punch force was changed (Fig. 3d). When the proportion of disintegrant pellets increased and the proportion of soft pellets decreased, the value of the VDT decreased (Fig. 3b). This could again be attributed to the faster disintegration of the tablets. The VDT increased with increasing coat thickness (Fig. 3c).

3.10. Different disintegrants

There was almost no difference between calcium carbonate and iron oxide. Except for the highest pressure, tablets containing barium sulphate as disintegrant gave higher breaking loads (Fig. 4a). This could be attributed to the lower amount of microcrystalline cellulose in these pellets, which gives weaker pellets which are more extensively deformed and therefore give stronger tablets. For the middle pressure, barium sulphate- containing pellets gave tablets with much lower friability than those containing calcium carbonate and iron oxide (Table 4). At the highest tabletting pressure, all three disintegrants provided non-friable tablets ($<0.5\%$), while, at the lowest tabletting pressure, all three disintegrants gave tablets with a friability greater than 50%. There were only small differences in disintegration time between the types of disintegrant pellets (Fig. 4b). The value of the MDT was slightly higher for barium sulphate than for the other disintegrants (Fig. 4c). The value of VDT was lowest for calcium carbonate and highest for barium sulphate.

Table 5

Regression models.

Parameter	Equation	R^2	F	P	RMS (%)
MDT, pellets	$-6.162(1/t) + 6.878$	0.999	11363.55	<0.001	1.6
VDT, pellets	$-13.302(1/t) + 12.662$	0.992	851.47	<0.001	7.5
Breaking load, tablets	$0.100u - 0.064y + 3.469$	0.787	66.75	<0.001	26.5
Disintegration time	$21.267u - 46.365y - 66.088x + 4476.721$	0.854	72.64	<0.001	28.9
Friability	$42.601(1/t) + 417.260(1/u) - 15.914$	0.884	145.96	<0.001	35.6
MDT, tablets	$0.014u + 0.002z - 0.034y + 0.188t - 0.050x + 3.594$	0.926	95.00	<0.001	9.7
VDT, tablets	$0.818t - 0.143x + 0.006z + 4.227$	0.769	39.14	<0.001	27.8

MDT, mean dissolution time; VDT, variance in dissolution time; t, thickness (%); u, upper punch force (kN); x, disintegrant (%); y, drug pellets (%); z, disintegrant type; R^2, linear determinant; F, variance ratio; P, probability level; RMS, root mean square deviation (residual analysis).

3.11. Statistical analysis

Statistical analysis of the data was undertaken using the 'Statistical Package for Social Sciences' (SPSS 4.0.1., SPSS Inc. Ltd., Chicago, IL).

Canonical analysis can be used to identify possible relationships between factors and the properties of the tablets [23]. 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 barium sulphate, twice the molar mass was entered, since the proportion of barium sulphate was higher than that of the other two disintegrants. This gives an order of disintegrants as follows: calcium carbonate (M = 40), iron oxide (M = 56) and barium sulphate (M = 274). Canonical analysis was performed thus with X = (% drug pellets, % disintegrant pellets, molar mass, coat thickness, upper punch force) and Y = (breaking load, disintegration time, friability, mean dissolution time, variance in dissolution time). The relationship between X and Y as defined above was found to be highly significant (Wilks's multivariate test criterion $\Lambda = 0.0069$, approximation onto F-distribution: $F = 31.60$, $P < 0.001$). However, the measure of redundance ($g^2_{YIU} = 0.512$) implies that one can predict the tablet properties only to about 51%. For breaking load, the concentration of drug pellets and upper punch force were identified as highly significant influence factors ($P < 0.001$), but the type of disintegrant, proportion of disintegrant pellets and coat thickness appeared to have no effect on this property. For disintegration time, the proportions of drug and disintegrant pellets and the upper punch force were identified as highly significant influence factors, but disintegrant type and coat thickness appeared not to influence the disintegration time. The disintegrant type and the upper punch force were highly significant influence factors on friability, whereas the proportions of drug and disintegrant pellets and the coat thickness were not. For mean dissolution time all five influence factors were highly significant. The disintegrant type, proportion of drug pellets and coat thickness were identified as

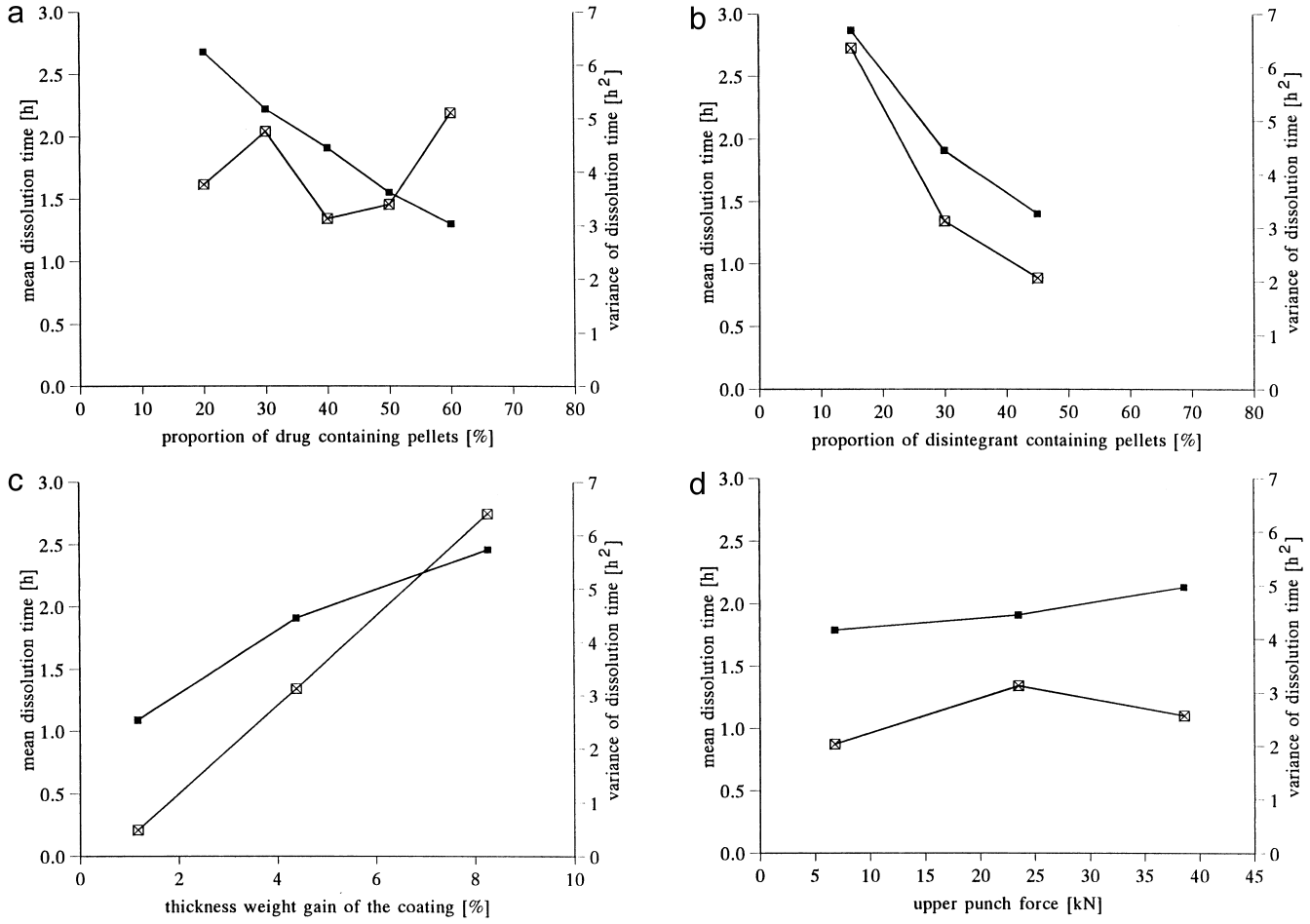

Fig. 3. Mean dissolution time (■) and its variance (☒) as a function of: (a) the proportion of drug pellets in the tablets (exp. no. 1, 2, 6, 10, 11), (b) the proportion of disintegrant pellets in the tablets (exp. no. 3, 6, 9), (c) the total weight gain of the coated drug pellets in the tablets (exp. no. 4, 6, 8) and (d) the upper punch tabletting force (exp. no. 5, 6, 7).

highly significant influence factors on variance in dissolution time, whereas the proportion of disintegrant pellets and upper punch force were not.

From analysis of variance and the canonical analysis, linear regression models were derived to predict the response of a given factor from the input variables of proportion of drug and disintegrant pellets, molar mass, coat thickness and upper punch force. The regression model that gave the best result for the dissolution of the pellets was a reciprocal function (Table 5), i.e. the mean dissolution time and variance in dissolution time are inversely related to the coat thickness of the pellets. Thus, as the coat thickness increases, the dissolution rate decreases.

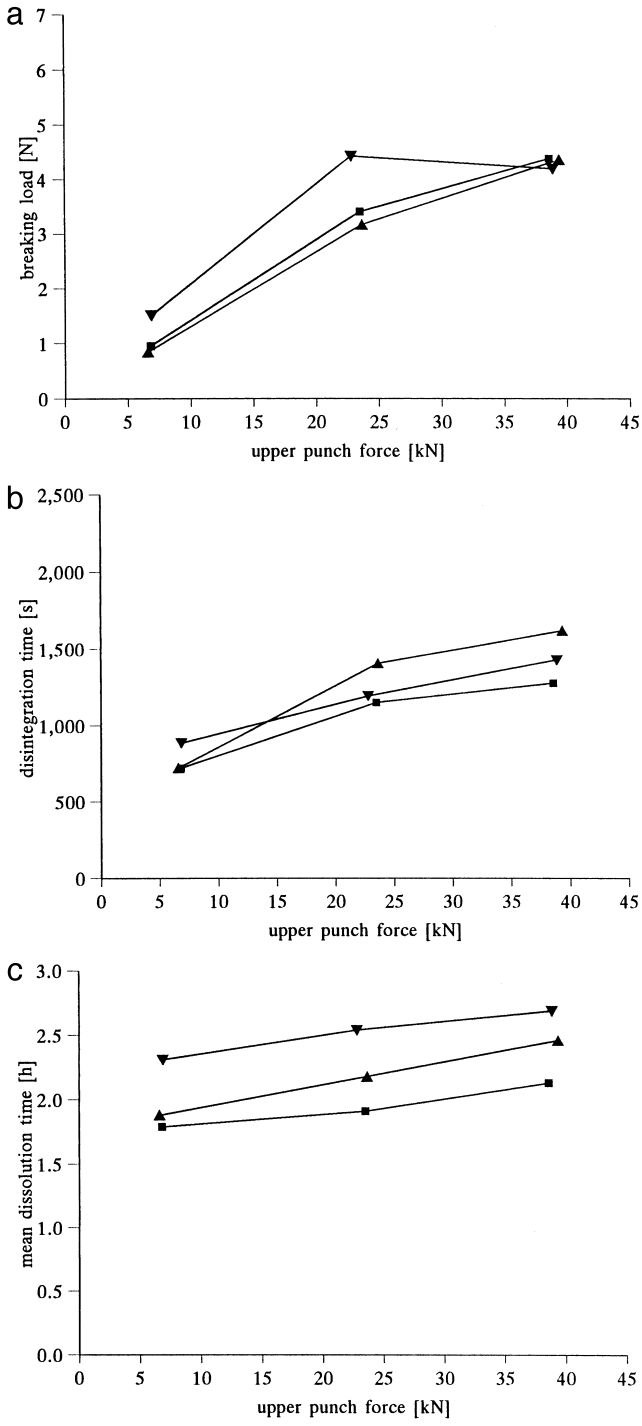

Fig. 4. The combined effect of disintegrant type and upper punch tabletting force on (exp. no. 5, 6, 7, 12–17): (a) the breaking load, (b) the disintegration time, and (c) the mean dissolution time: ■, calcium carbonate; ▲, iron oxide; ▼, barium sulphate.

Compared with the previous findings [6] an increase in the proportion of drug pellets was also found to decrease the breaking load of the tablets. An increase in the proportion of disintegrant pellets was not found to influence tablet breaking load in the current study. In this case only the proportions of one type of disintegrant were varied, whereas, previously, all types had been changed. An increase in forming pressure was found to increase the tablet breaking load. The type of disintegrant was not found to have a significant influence on the disintegration of the tablets, which contrasts with the previous findings [6]. However, the two other factors of the proportions of disintegrant and drug pellets were again found to decrease the disintegration time as their proportions increased. As the compaction pressure increased, there was a significant increase in disintegration time. The friability of the tablets was found to be not significantly affected by the proportion of disintegrant or drug pellets which had been reported in the previous study [6]. In this case, tablets were produced at only one upper punch pressure, whereas in the current experiments the upper punch pressure was varied and shown to make a significant contribution to the tablet friability, as did the coat thickness. These two factors could therefore dominate the property of friability, removing the significance of the other factors. The level of performance of the regression models for breaking load, disintegration time and friability were not good, as indicated by values of the root mean square (RMS) being greater than 25% (Table 5). That the value of RMS for the MDT was better, at 9.7%, gives a clear indication of how the factors can be used to predict the dissolution performance of the formulation.

3.12. Dissolution performance of the tablets

The comparison of the results for the MDT of the tablets and the pellets from which they are made (Fig. 3, Table 3) clearly shows that tabletting resulted in an increase in drug release. Examination of the equation relating tablet formulation and MDT clearly indicated that modification of the input parameters would not result in a value which was exactly equivalent to that for the pellets. Thus it would be necessary to change other parameters to ensure that there is an equivalent performance. The obvious choice is to change the type of coating applied. It would appear that, while the current coating is appropriate to control the release performance of the pellets, it is not totally appropriate to ensure that the coat is free from damage during the compaction process.

From experiments 4, 6 and 8, the effect which an increase in thickness of the coat around the drug particles has on the

release mechanism can be seen in Table 4. The resistance of the film against damage during tabletting although not fully prevented, increases with film thickness, as can be seen from the increase in the value of the MDT. This was expected considering the breaking load of the coated pellets in comparison to uncoated pellets (see Section 3.3). Consequently, tablets with very thin films around the drug pellets (formulation 4) release the drug in a non-fickian manner, which is indicative of extensive damage to the film during tabletting. For an average film thickness, consistent with the centre point of the design (experiment 6), the release mechanism from tablets follows the square root law. According to Higuchi [24] this is typical for a drug dissolution mechanism, where the penetration of the liquid into the pellets is the dissolution limiting step. Often such a mechanism is obtained for insoluble matrix tablets. The disintegration time of tablets of formulation 6 is higher than for the reference formulations with respect to film coat thickness, i.e. formulations 4 and 8. Hence the alteration in dissolution mechanism could simply be an expression of a prolonged disintegration, and is not directly indicative of an improved film stability and therefore of less damage to the film coat during tabletting. In this respect, however, the influence of a reduced tabletting pressure on the release mechanism can be considered. For an identical ratio of the pellets, a decrease in tabletting pressure (experiment 5) does not alter the release mechanism to one that is comparable to that of the untabletted drug pellets. On the contrary, the drug release follows the cube root law. Therefore the pellets must have disintegrated rapidly into their primary powder particles, which can only occur if considerable damage to the film during tabletting has taken place. A further increase in film thickness (experiment 8) alters the release mechanism again. Here, a first-order release was obtained. This shows that the film became more resistant against damage during tabletting. Although some damage has still occurred, most likely to those drug pellets at the interface between pellets and the punch and die, the drug release is still controlled by the film as a first-order process. The loss of zero-order release may also be associated with the more complex tablet system, where both disintegration and dissolution are involved. The other experiments can now be used to identify constellations, which would further improve the ability of the film to control drug release.

An increase in the proportion of drug pellets (experiments 1, 2, 6, 10, 11) necessitates a decrease in the proportion of soft pellets, resulting in a reduction in the cushioning material to prevent damage of the film during tabletting. Interestingly, the protective function of the soft pellets is not a linear one. At the highest amount of soft pellets (formulation 1), the drug release is non-fickian, i.e. the film around the drug particles has been damaged to a large extent. This could be explained by the fact that, during tabletting, the soft pellets deform greatly and the area of contact between these pellets and the drug pellets increases accordingly. At the same time the adhesion between the film around the drug pellets and the surfaces of the soft pellets increases. As a consequence, the generally occurring elastic recovery of the tablet structure, after the tabletting pressure has been removed, can lead to a peeling effect, i.e. parts of the film are pulled off the surfaces of the drug pellets and now adhere to the surfaces of the soft pellets. The control of the drug release by the film is thus impossible. The slightly smaller concentration of the soft pellets (experiment 2) provides an optimal protection of the film. Here the release mechanism is first-order, as obtained for the tablets made from drug pellets with increased coat thickness. Thus, the film is able to control the release of the drug, although slight damage has occurred during tabletting. Very low concentrations of soft pellets lack the protecting function during tabletting. The relative dispersion coefficient exceeds unity, which is characteristic for a total damage to the film coat during tabletting.

An increase in the amount of disintegrant pellets (experiments 3, 6, 9) also alters the dissolution characteristics of the drug from the tablets from non-fickian finally into first-order kinetics. However, this is not a measure of elasticity, but of brittleness. One possible explanation could be that these pellets are fairly elastic and thus can act as a cushion during the tabletting process. Another possible explanation could be that disintegration of the tablets occurs more and more due to rupture of the disintegrant pellets instead of a separation at the interfaces between the pellets. Film defects would become less important, because the interfaces would not separate and the crack would therefore not be freely exposed to the dissolution medium.

For calcium carbonate-containing disintegrant pellets, an increase in tabletting pressure (experiments 5–7) leads initially to an apparent improvement in the release characteristics. However, as discussed above with respect to the film thickness, the film is increasingly damaged if the tabletting pressure is set to higher levels, so that the tabletting pressure should be kept to a minimum to obtain mechanically stable, wear-resistant tablets. Unfortunately, improvement of the release characteristics requires rather higher tabletting pressures (experiment 7). An exchange of the disintegrant (experiments 12–17) does not result in changes in the general situation with respect to film damage. All release mechanisms obtained indicate more or less damage to the film coat during tabletting, although the extent of damage obviously varies with the disintegrant used. Barium sulphate appears to be the most appropriate disintegrant, because a change in the tabletting pressure appears not to alter the release mechanism, which can be interpreted as an indication that the amount of film damage caused did not change. One has, however, to remember that barium sulphate is also the main excipient in the soft pellets. The disintegrant pellets are therefore presumably soft and act as an additional cushion. Iron oxide pellets are the least useful disintegrant pellets. Here the damage of the film during tabletting appears to be extensive.

4. Conclusion

The combination of three types of pellets namely, film-coated drug-containing, soft deformable, and disintegrant pellets, formed tablets whose properties were related to the proportions of the different pellets included, type of disintegrant pellets, the coat thickness of the drug-containing pellets and the force used to form the tablets. In quantitative terms, only about 51% of the tablet properties could be related to the input variables. The factors which influenced the tablet characteristics and the extent of the reliability of the prediction varied with the characteristic being measured. The breaking load and disintegration time of the tablet was reasonable, related to the upper punch force, the proportion of drug pellets and disintegrant pellets. The dissolution of the tablets was related to the upper punch force, the type of disintegrant, the proportion of drug and disintegrant pellets and, in particular, the thickness of the film coating surrounding the pellets.

While the pellets themselves gave a controlled release performance, the tabletting decreased the value for the MDT. From the range of formulations tested, an optimal formulation should contain about 40% of soft pellets, and the drug pellets should be coated with sufficient film material to give a weight gain of at least 8%. Both optimal values are inside the experimental design and can therefore form the basis for further experiments. The damage caused to the film in these cases will be minimal. The protecting mechanism proposed can hence be regarded as a potential method for the tabletting of controlled release pellets.

Acknowledgements

The authors wish to thank FMC for the gift of Avicel PH101, and Colorcon for the gift of Surelease and Methocel.

References

[1] M. Çelik, L. Maganti, Formulation and compaction of microspheres, Drug Dev. Ind. Pharm. 20 (1994) 3151–3173.
[2] S.R. Béchard, J.C. Leroux, Coated pelletized dosage form: effect of compaction on drug release, Drug Dev. Ind. Pharm. 18 (1992) 1927–1944.
[3] F.J. Lopéz–Rodríguez, J.J. Torrado, S. Torrado, C. Escamilla, R. Cadórniga, L.L. Augsburger, Compression behaviour of acetylsalicylic acid pellets, Drug Dev. Ind. Pharm. 19 (1993) 1369–1377.
[4] M.E. Aulton, A.M. Dyer, K.A. Khan, 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.
[5] J.B. Schwartz, N.H. Nguyen, R.L. Schnaare, Compaction studies on beads: compression and consolidation parameters, Drug Dev. Ind. Pharm. 20 (1994) 3105–3129.
[6] Å.E.K. Lundqvist, F. Podczeck, J.M. Newton, The influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets, Int. J. Pharm. 147 (1997) 95–107.
[7] J.F. Pinto, Formulation and tabletting of controlled release pellets produced by extrusion/spheronisation, Ph.D. Thesis, University of London, 1994, pp. 33–34.
[8] D. Voegele, D. Brockmeier, H.M. von Hattingberg, Modelling of the input function to drug absorption by moments, in: Proceedings of the Symposium on Compartmental and Noncompartmental Modelling in Pharmacokinetics, Smolenice, Czechoslovakia, 1988, pp. 1–14.
[9] J.F. Pinto, F. Podczeck, J.M. Newton, The use of statistical moment analysis to elucidate the mechanism of release of a model drug from pellets produced by extrusion and spheronisation, Chem. Pharm. Bull. 45 (1997) 171–180.
[10] K.H. Yuen, A.A. Deshmukh, J.M. Newton, Development and in-vitro evaluation of a multiparticulate sustained release theophylline formulation, Drug Dev. Ind. Pharm. 19 (1993) 855–874.
[11] F. Podczeck, J.M. Newton, 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.
[12] F. Podczeck, J.M. Newton, A shape factor to characterize the quality of spheroids, J. Pharm. Pharmacol. 46 (1993) 82–85.
[13] L. Davies, Efficiency in Research, Development and Production, Royal Society of Chemistry, Cambridge, 1993, pp. 97–100.
[14] C. Wang, G. Zhang, N.H. Shah, M.H. Infield, A.W. Malick, J.W. McGinity, Compaction properties of spheronized binary granular mixtures, Drug Dev. Ind. Pharm. 21 (1995) 753–779.
[15] P. Stanley, R.C. Rowe, J.M. Newton, Theoretical considerations of the influence of polymer film coatings on the mechanical strength of tablets, J. Pharm. Pharmacol. 33 (1981) 557–560.
[16] F. Podczeck, J.M. Newton, Letters to the Editor, J. Controlled Release 41 (1996) 291–293.
[17] A. Hoffman, M. Donbrow, S.T. Gross, S. Benita, R. Bahat, Fundamentals of release mechanism interpretation in multiparticulate systems: determination of substrate release from single microcapsules and relation between individual and ensemble release kinetics, Int. J. Pharm. 29 (1986) 195–211.
[18] European Pharmacopoeia, third ed., Amtliche Deutsche Ausgabe: Deutscher Apotheker Verlag, Stuttgart und Govi-Verlag-Pharmazeutischer Verlag GmbH, Ettlingen, 1997.
[19] I. Jalsenjak, J.R. Nixon, R. Senjkovic, I. Stivic, Sustained-release dosage forms of microencapsulated isoniazid, J. Pharm. Pharmacol. 32 (1980) 678–680.
[20] C. Chemtob, J.C. Charnmeil, M. N'Dongo, Tablets of metronidazole microcapsules; release characteristics, Int. J. Pharm. 29 (1996) 83–92.
[21] J. Akbuga, Some factors affecting properties and dissolution behaviour of tableted furosemide microspheres, Pharmazie 47 (1992) 128–131.
[22] T. Baykara, S. Karatas, Preparation of acetaminophen microcapsules by coacervation-phase separation method, Drug Dev. Ind. Pharm. 19 (1993) 587–601.
[23] F. Podczeck, G. Merkel, P. Révész, 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.
[24] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.