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Research paper

Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press

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Abstract

Enteric coated bisacodyl pellets were compressed into divisible disintegrating tablets on a high speed rotary tablet press and investigated for pellet damages. The degree of pellet damages was examined via the bisacodyl dissolution during the acid treatment of' the drug release test for enteric coated articles according to USP 23. The damages depended on the type of filler-binder used and settings of the tablet press. Avicel PH 101 proved to be the most suitable filler-binder, effecting homogeneous distribution of the pellets within the tablets, as could be shown by image analysis of coloured pellets. The speed of the tablet press had noo influence on the pellet damages using Avicel PH 101 as a filler-binder, however, tablets containing 70% (w/w) of coated pellets did not fulfil the requirements of USP 23, despite optimum elasticity and coating thickness of a new Eudragit FS 30 D coating. Reducing the proportion of pellets to 60% per tablet, less than 10% of bisacodyl were released within 2 h during acid treatment thus fulfilling the requirements of the USP 23.

Keywords: Pellets; Tableting; Eudragit; Enteric coating; Vicel PH 101;

1. Introduction

Compression of coated particles like pellets to disintegrating tablets combines the advantages of oral, multiple-unit dosage forms [1–5] with those of tablets, i.e. cost effectiveness and divisibility. However, during the compression process, the coated pellets may be damaged either by interactions between feeder, punches and die or between components of the mixture. Therefore the choice of coating polymers [6–8], the pellet size [9,10] and pellet properties [8,11–15], the proportion of pellets in the mixture [8,16,17] and the type of filler-binders [8,9,16,18,19] are as important as the machine parameters, such as production rate and type of feeder [20].

To avoid segregation within the mixture, some authors prefer filler-binders that are almost equal in size to the pellets [13–15,17,21], while others report of reduced segregation tendency especially when using a small-size microcrystalline cellulose (Avicel PH 101) [20,22]. But segregation also depends on the proportion of pellets in the mixture. At 70% (w/w) of pellets, tablets can be obtained that comply with the requirements for mass and content uniformity of Pharm. Eur. This can be explained by percolation theory [16]. However, it is important that the pellets are homogeneously distributed within the tablet, so as to guarantee divisibility and to prevent localized pellet lattices exceeding 71% (v/v). If there is any further reduction of volume once the pellet lattice has reached 71% (v/v), the closest lattice of regular spheres is exceeded and pellet deformation bound to occur. During tableting by means of a single-punch tablet press, no segregation within the die was detected as long as powders of large particle size were used as filler-binders [17]. In a high-speed rotary tablet press, segregation increases with increasing machine speed and/or particle size of the filler-binder. Only Avicel PH 101 as a filler-binder effects homogeneous pellet distribution within the tablet, almost independently of machine speed, as can be shown by image analysis [20]. Reasons are the particle shape, the larger surface area and the fibrous surface texture of the small-size Avicel PH 101 ($x_{50} = 50$ μm). As a result, its infinite cluster in the percolating mixture is particularly compact and stabilizes the mixture against segregation tendencies during tableting [20]. The aim of this study is to correlate the data obtained by image analysis [20] with

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damage to enteric coatings occurring under industrial-scale conditions dependent on:

- pellet distribution within the tablet/segregation tendency;
- type of filler-binder;
- speed of rotary tablet press;
- coating elasticity;
- proportion of pellets.

2. Materials and methods

2.1. Materials

Eudragit FS 30 D, a new aqueous 30% dispersion based on polymethacrylates, Eudragit L 30 D-55, Polysorbate 80 and triethyl citrate were supplied by Röhm GmbH (Darmstadt, Germany), Cutina GMS (glyceryl monostearate) by Henkel KGaA (Düsseldorf, Germany), bisacodyl by Ratiopharm GmbH & Co. (Ulm/D., Germany), Aerosil 200 by Degussa AG (Frankfurt/M., Germany), Bayferrox 130, a red iron oxide pigment by Bayer AG (Leverkusen, Germany), Silicone antifoam emulsion SE 2 by Wacker-Chemie GmbH (München, Germany), Kollidon CL (crosspovidone) by BASF AG (Ludwigshafen, Germany), Avicel PH 101 by FMC Corp./Lehmann & Voss & Co. (Hamburg, Germany), magnesium stearate by Bärlocher GmbH (München, Germany), and talc by Talco Val Chisone (Pinerolo, Italy). Avicel granules ($x_{50} = 194$ μm), an excipient for direct compression, were prepared at the Department of Pharmaceutical Technology at the University of Tübingen, Germany [20]. Placebo pellets type 08430 (particle size 90% within 850–1000 μm) were purchased from Hanns G. Werner GmbH (Tornesch, Germany).

2.2. Preparation of colored pellets

Preparation has been described elsewhere [20].

2.3. Preparation of bisacodyl pellets

The bisacodyl pellets were prepared in a fluidized bed coater (WSG 5, Glatt GmbH, Binzen, Germany) by top spraying. Batches of 4500 g of placebo pellets were coated with bisacodyl suspension using Eudragit L 30 D 55 as a binder, talc as a glidant and triethyl citrate as a plasticizer (Tables 1 and 2). The spraying conditions were: 40°C inlet air temperature, 32–34°C outlet air temperature, 2.5 bar atomizing air pressure, 1.8 mm nozzle aperture (Schlick, Coburg, Germany), 60 min coating time, 5 min preheating. After applying bisacodyl, the pellets were dried for 10 min, and the new delayed-release polymer Eudragit FS 30 D was sprayed onto the pellets in amounts of 12.5% (w/w) and 25% (w/w), respectively, based on the ratio of bisacodyl core to dry polymer substance (Tables 1 and 2). The spraying conditions were the same as before, and the coating time was 90–170 min after a preheating period of 15 min. In this way, pellets with a bisacodyl content of 4.4% and 3.9% (w/w) were obtained. To avoid sticking, the pellets were mixed with 0.5% Aerosil 200 for 20 s immediately after coating using the fluidized bed of the coater.

Table 1
Composition of coated pellets

Pellets	A	B	C	D
Bisacodyl pellets				
Placebo pellets (g)		4500.0		
Eudragit®L 30 D-55 (g)		270.9		
Talc (g)		40.5		
Silicone antifoam emulsion SE 2 (g)		q.s.		
Triethyl citrate (g)		8.1		
Water (g)		1305.5		
Bisacodyl (g)		244.0		
Enteric coating				
Bisacodyl pellets (g)	4873.5	4873.5	4873.5	4873.5
4110 D (30% dispersion) (g)	2030.6	4061.2	2030.6	4061.2
Triethyl citrate (g)	30.5	61.0	61.0	122.0
Glycerol monostearate (g)	48.7	97.4	48.7	97.4
Polysorbate 80 (33.3% w/w) (g)	77.0	154.0	77.0	154.0
Water (g)	1383.7	2767.4	1505.7	3011.4
Dry coating substance (% w/w)	12.5	25.0	12.5	25.0
Plasticizer (% w/w based on dry coating substance)	5	5	10	10

2.4. Preparation of coating dispersions

Water, 8% glycerol monostearate, 5 and 10% triethyl citrate, respectively, as well as 4.2% Polysorbate 80 were dispersed and heated up to 65°C until all glycerol monostearate had melted [8]. After cooling down to 30°C, the emulsion was poured into the stirred polymer dispersion. While melting and mixing the emulsion with the coating polymer, stirring was performed with a magnetic stirrer (IKA, Staufen, Germany). All quantities are based on the weight of pure polymer.

2.5. Preparation of filler granules

The preparation of Avicel filler granules has been described elsewhere [20].

2.6. Characterization of components

True density was determined using a Beckman air comparison pycnometer (Model 930, Beckman Instruments, Inc., Fullerton, USA).

Granule size distribution was determined by means of a sieve tower (F. Kurt Retsch GmbH & Co. KG, Haan, Germany).

2.7. Blending and tableting

Coated pellets, Kollidon CL and filler-binder were blended within 10 min using a gyro-wheel mixer. Finally,

Table 2
Composition of tablets

Tablet batch	1	2	3	4	5	6
Pellets (%) (g)	A 1000.0	B 1000.0	C 1000.0	D 1000.0	B 1000.0	D 840.0
Avicel PH 101 (g)	336.0	336.0	336.0	336.0	–	429.8
Avicel granules (g)	–	–	–	–	336.0	–
Kollidon CL (g)	86.0	86.0	86.0	86.0	86.0	84.0
Talc (g)	–	–	–	–	–	35
Aerosil 200 (g)	–	–	–	–	–	4.2
Magnesium stearate (g)	7.0	7.0	7.0	7.0	7.0	7.0
Pellet content (% w/w)	70	70	70	70	70	60

magnesium stearate was passed through a 315-μm sieve onto the mixture and mixing continued for another 5 min (Tables 1 and 2; batches 1–5). Where talc was included in the composition, it was blended with the pellets within 10 min before adding Kollidon CL, filler-binder and magnesium stearate (Tables 1 and 2, batch 6).

Tablets of 400 ± 30 mg were compressed on a Korsch PH230/17 instrumented rotary tablet press (Korsch Pressen GmbH, Berlin, Germany). The die table diameter was 195 mm; eight of the 17 punch stations were equipped with 10-mm flat-face bevelled-edge B-tooling (batches 1–5) or 10-mm concave B-tooling (Batch 6). For filling, a gravity feeder (Art. No. 8590052, Korsch Pressen GmbH, Berlin, Germany) was used. Machine speed levels were set to 26, 50, 75 and 100 rev./min while compressing at 10, 15 and 20 kN. Data acquisition and processing were performed by Compression Research System (Korsch Pressen GmbH, Berlin, Germany).

2.8. Tablet parameters

Mass (AE 200 balance, Mettler-Toledo GmbH, Giessen, Germany), bisacodyl content (UV spectrometer at a wavelength of 264 nm; 550 S, Perkin–Elmer, Stuttgart, Germany) and crushing strength (Model 6D, Dr Schleuninger Pharmatron AG, Solothurn, Switzerland) of 10 tablets and friability (Pharma Test, Hainburg, Germany) of 20 tablets were measured. The disintegration time of six tablets was determined according to Ph. Eur., using a Pharma Test apparatus (Pharma Test). Dissolution assays were performed with three samples on a Sotax AT7 dissolution tester (Sotax AG, Basel, Switzerland). The test medium during the first 2 h was 750 ml of simulated gastric fluid, then 250 ml of 0.2 M trisodium phosphate were added and a pH of 7.2 adjusted using 2 M sodium hydroxide solution. The bisacodyl content of the solutions was measured as mentioned above. Each individual batch of coated bisacodyl pellets was subjected to the complete test. If they released virtually no drug at all in simulated gastric fluid and at least 80% within 45 min at pH 7.2, the pellet tablets were tested for only 2 h in simulated gastric fluid.

2.9. Evaluation of pellet distribution

Colored pellets were blended and tableted as described for bisacodyl pellets. The pellet distribution on the upper and lower tablet surface was ascertained via image analysis as described further above [20].

3. Results and discussion

3.1. Pellet distribution

The pellet distribution in the tablet depended on the machine speed and the size and shape of the filler-binder (Fig. 1). The most homogeneous distribution of pellets, particularly at medium and high machine speed, was achieved using Avicel PH 101. This showed in an almost equal and homogeneously distributed grey scale intensity on the upper and lower surface of the tablets (Fig. 1). Avicel granules gave a homogeneous pellet distribution only at low (26 rev./min) and medium machine speed (50 rev./min). Increasing machine speed (75 rev./min) caused vertical segregation of the pellets to the upper right-hand side, which became worse with increasing machine speed up to 100 rev./min [20].

3.2. Dissolution

Before testing the pellet-loaded tablets, all pellet batches (A, B, C and D) were examined following the specifications of USP 23 that enteric coated cores liberate no more than 10% of drug within 2 h in simulated gastric fluid and at least 80% within 45 min in buffer at pH 7.2 (USP 23: pH 6.8). The new polymer dissolves completely above pH 7.0. Therefore, the pH of intestinal fluid was set at 7.2 instead of 6.8. All pellets released less than 1.5% of drug within 2 h in simulated gastric fluid and over 95% after 45 min at pH 7.2. Thus, liberation of bisacodyl from compressed pellets after 2 h in simulated gastric fluid indicates the extent of coating damage done during filling of the die cavity and compression of the tablets.

Liberation of bisacodyl from tablets (batch 2) containing 70% (w/w) of pellets depended on the pellet distribution within the tablets (Fig. 2). Tablets made with Avicel PH 101 as a filler-binder released bisacodyl independently of machine speed between 26 and 75 rev./min, while tablets prepared with Avicel granules showed increasing bisacodyl liberation at higher machine speeds. This correlated well

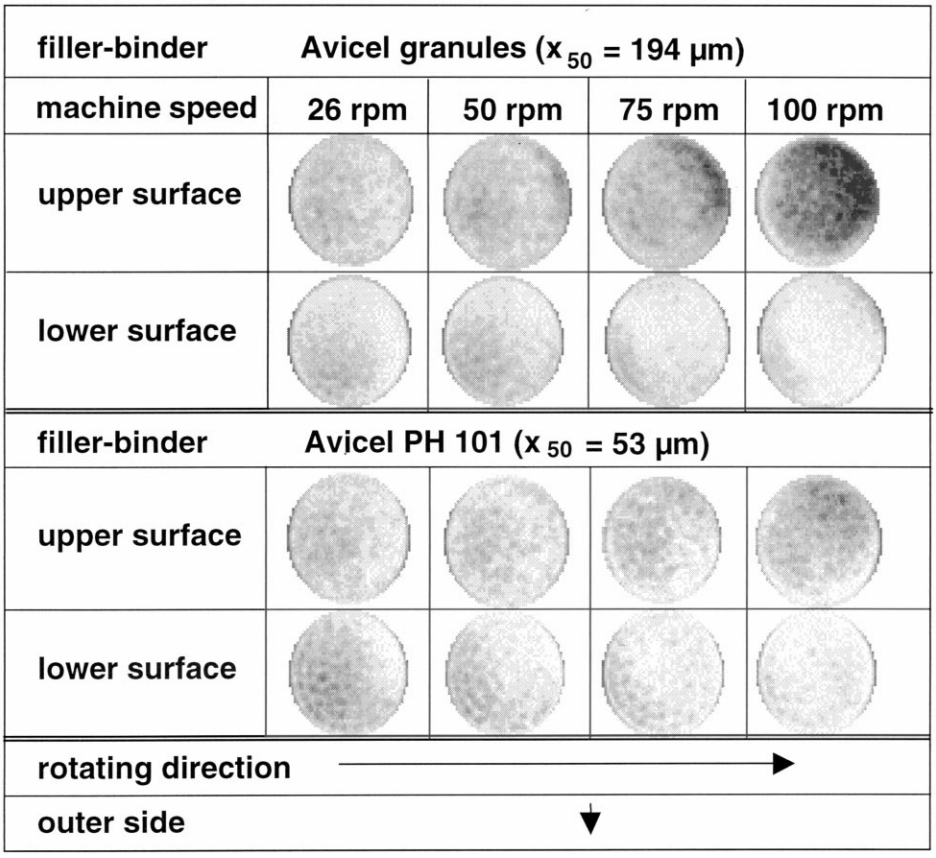

Fig. 1. Normalised pellet densities of upper and lower tablet surfaces using Avicel-granules and Avicel PH 101 as filler binder.

with the pellet distribution data (Fig. 1). With regard to scale-up problems and high production rates, we chose Avicel PH 101 as the most suitable filler-binder for further investigations.

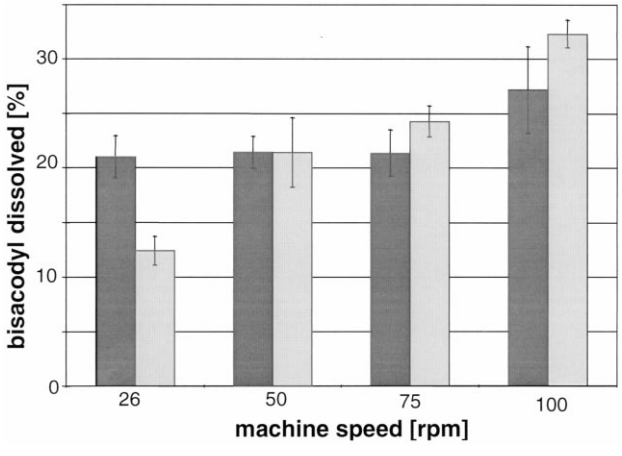

Fig. 2. Release of bisacodyl from pellet-loaded tablets after 2 h in simulated gastric fluid as a function of machine speed. □ = tablets compressed with Avicel PH 101 (x_{50} = 50µm (Batch 2), ■ = tablets compressed with Avicel granules (x_{50} = 194µm (Batch 5) as a filler-binder. The bisacodyl pellets were coated with 25% (w/w) Eudragit® FS 30 D at a plasticizer level of 5% TEC. Compressional force applied: 20 kN. Error bars represent 95% confidence interval.

The dissolution data (Fig. 3) showed a low bisacodyl release rate within the first 15 min and an almost linear increase, indicating formation of small cracks in the coating. Pronounced damage caused by mechanical treatment during filling of the die resulted in a high initial bisacodyl liberation rate. However, in our case, initial release was less than 10%. Thus, it can be assumed that the pellet coating had cracked, causing drug release controlled by diffusion.

This damage did not depend on the compressional force

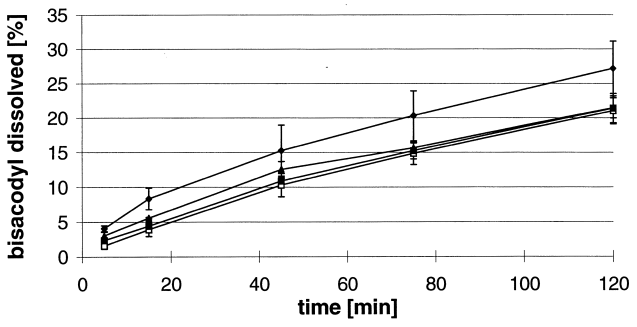

Fig. 3. Release of bisacodyl from tablets compressed with Avicel PH 101 and pellets coated with 25% (w/w) Eudragit® FS 30 D at a plasticizer level of 5% TEC (Batch 2) after 2 h in simulated gastric fluid as a function of machine speed: □ 26 rpm, ▲ 50 rev./min, ■ 75 rev./min, ◆ 100 rev./min. Compressional force applied: 20 kN. Error bars represent 95% confidence interval.

applied between 10 and 20 kN. A tendency to lower release rates at higher compressional forces would not be confirmed statistically.

The mechanical resistance of pellet coatings can be improved in two different ways: by increasing the thickness and/or elasticity of the polymer film [6,7]. The elasticity of Eudragit FS 30 D can be increased by a considerable margin via the plasticizer content. The elongation at break of Eudragit FS 30 D films containing 5% TEC was 50%. Doubling the amount of plasticizer from 5 to 10% TEC, increased the elongation at break 6-fold, from 50 to 300% (Fig. 4). However, it is not sufficient to use a highly elastic polymer in order to protect the coating against damage. Only from a specific thickness of the polymer film onward has elasticity the synergistic effect of reducing coating damage during tableting of coated pellets. Bisacodyl pellets coated with 12.5% Eudragit FS 30 D at a plasticizer content of either 5 or 10% TEC (batches A and C) had a coating thickness of 25–30 μm. Tableting these pellets in a proportion of 70% (w/w) together with Avicel PH 101 at a compressional force of 20 kN led to a similarly high drug release of 35 to 44% after 2 h in simulated gastric fluid (Fig. 5). Increasing the amount of polymer applied from 12.5% to 25.0% (batches B and D) at both plasticizer levels (B and D) resulted in a coating thickness of 50–60 μm. Compared with tablets containing pellets A or C, drug release from tablets containing pellets B after 2 h in simulated gastric fluid was nearly halved (21–27%), and in the case of tablets containing pellets D it reduced to almost a quarter (12–15%) (Fig. 5). When tableting pellets with a thin coating layer (A and B), frictional interactions between turret and pellets, feeder and pellets and/or filler-binder and pellets may be so very pronounced that a higher elasticity of the coating cannot avoid pellet damage. Thicker polymer films should offer better resistance to frictional forces, so that cracks appearing after compression do, in fact, depend on the elasticity of the film.

However, it was not possible to produce tablets containing 70% (w/w) of coated pellets (850–1120 μm) and Avicel

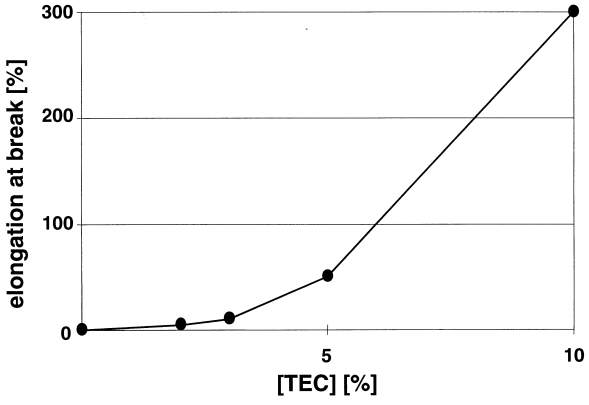

Fig. 4. Elongation at break of 4110 D polymer films (DIN 53455) as a function of plasticizer content (triethlyl citrate), calculated on dry polymer substance.

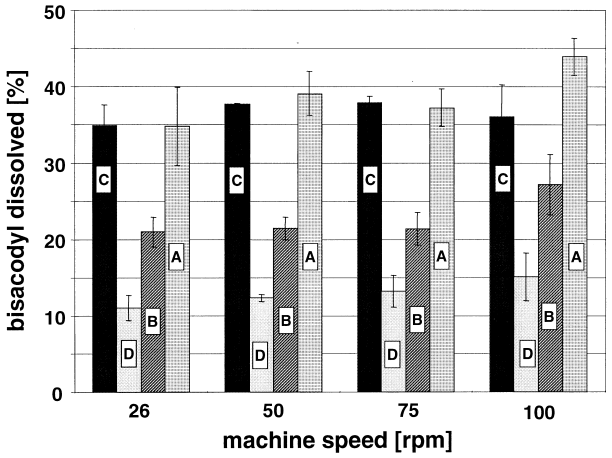

Fig. 5. Release of bisacodyl from tablets (70% (w/w) pellets, Avicel PH 101) after 2 h in simulated gastric fluid as a function of machine speed, coating weight and plasticizer content. A = coating weight 12.5% (w/w) (Batch 1), B = coating weight 25.0% (w/w) Eudragit® FS 30 D (Batch 2), plasticizer content: 5% TEC; C = coating weight 12.5% (w/w) (Batch 3), D = coating weight 25.0% (w/w) Eudragit® FS 30 D (Batch 4), plasticizer content: 10% TEC. Compressional force applied: 20 kN. Error bars represent 95% confidence interval.

PH 101 which satisfied the requirement for release of less than 10% bisacodyl within 2 h, not even when we used pellets coated with 25% Eudragit FS 30 D at a plasticizer content of 10% TEC. If the pellet size is not be changed, the only way to reduce damage is by decreasing the proportion of pellets. Lowering their quantity from 70% (w/w) to 60% (w/w) resulted in a reduction of the tablet content from 66 ± 0.5% to 59 ± 0.7% by volume. Thus, the lattice of spheres was not as close and less damage was to be expected. Tablets made of 60% (w/w) of pellets D and Avicel PH 101 as a filler-binder confirmed this impression, as they released far less than 10% bisacodyl within 2 h in

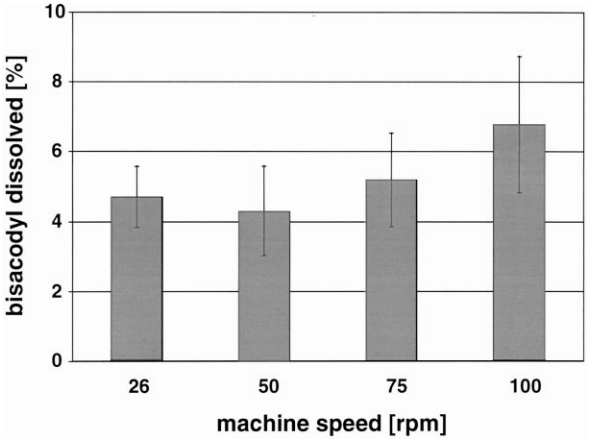

Fig. 6. Release of bisacodyl from tablets containing 60% (w/w) of pellets coated with 25.0% Eudragit® FS 30 D at a plasticizer content of 10% TEC, 30.7% Avicel PH 101, 2.5% talc and 0.3% Aerosil 200 (Batch 6), after 2 h in simulated gastric fluid as a function of machine speed. Compressional force applied: 20 kN. Error bars represent 95% confidence interval (5 replications with 3 samples each).

Table 3
Properties of pellet tablets containing 70% of pellets (Batch No. 2, 4 and 5)

Machine speed	26 rev./min			50 rev./min			75 rev./min			100 rev./min		
Batch	2	4	5	2	4	5	2	4	5	2	4	5
Crushing strength (N)	124	178	70	109	152	53	99	127	44	99	100	38
s	13	19	5	9.5	11	7	5.9	9	4	7	10	5
s_{rel} (%)	10.5	10.4	7.3	8.8	7.1	13.4	6.0	6.7	8.7	6.7	9.6	11.8
Disintegration time (min)[a]	1.0 (0.9–1.3)	>15 (no distint.)	0.4	1.2 (1.0–1.3)	>15 (no disint.)	0.4	1.0 (0.9–1.1)	>15 (no disint.)	0.6 (0.4–1.0)	0.7 (0.5–0.8)	>15 (no disint.)	0.86 (0.5–1.3)
Tablet weight (mg)	414	447	437	415	439	436	411	426	435	412	394	431
s	6	7	4	5	3	3	4	5	3	4	8	3
s_{rel} (%)	1.4	1.6	1.0	1.3	0.8	0.6	1.0	1.2	0.6	1.0	2.1	0.7

[a] Ranges given in parentheses.

simulated gastric fluid at all machine speeds and a compressional force of 20 kN (Fig. 6).

3.3. Disintegration time

According to the specifications of the European Pharmacopoeia for uncoated tablets, all samples must disintegrate within 15 min. For tablets prepared with Avicel PH 101 and Avicel granules, short disintegration times (<1.5 min) were achieved at 70% (w/w) pellets of batch B (5% TEC) (Table 3). At the optimum machine speed identified for homogeneous pellet distribution in the tablets, the tablets disintegrated as quickly as required.

Inhomogeneous pellet distribution provided small non-disintegrating agglomerates of coated pellets (3–5 pellets), especially if Avicel granules were used at higher machine speed (75 and 100 rev./min). Raising the proportion of plasticizer in the coating polymer increased both elasticity and tack [23]. Thus, tablets containing 70% (w/w) of pellets coated with 25% Eudragit FS 30 D at a plasticizer content of 10% TEC (Batch 4) failed to disintegrate within 15 min. To reduce tack, the pellets were blended with 2.5% talc (batch 6) before adding the remaining excipients. At a reduced pellet proportion of 60% (w/w), tablets (batch 6) were obtained that disintegrated within less than 15 min (Table 4).

3.4. Crushing strength

The crushing strength of pellet tablets did not depend on the pellet distribution, but decreased with increasing machine speed. This might be a result of the shorter residence time at higher production rates. However, the filler-binders showed significant differences in the crushing strength they produced. Using Avicel PH 101 as a filler-binder, tablets with a crushing strength between 90 and 130 N (batch 2) or 100 and 180 N (batch 4) were obtained independent of whether the plasticizer content in the coating was 5% (B) or 10% (D). The increased tackiness of the more flexible film (B) entailed higher values of crushing strength. Tablets with Avicel granules as filler-binder (batch 5) showed lower values of crushing strength of 70–75 N, due to the larger particle size and the associated smaller surface area per mass.

3.5. Mass and content uniformity

All mixtures containing 70% (w/w) of pellets passed the percolation threshold, thus providing good mass uniformity.

Table 4
Properties of tablets containing 60% pellets (Batch 6)

Machine speed	26 rev./min	50 rev./min	75 rev./min	100 rev./min
Crushing strength (N)	132	107	96	110
s	12	13	10	11
s_{rel} (%)	9	12	11	10
Disintegration time (min)	10	9.3	9.26	10.2
Range	5.9–14.8	5.3–11.75	3.3–11.5	8.25–10.5
Tablet weight (mg)	400.2	394.7	388.5	389.7
s	4.1	5.2	6.3	7.6
s_{rel} (%)	1.0	1.3	1.6	1.9
Drug load (mg)[a]	7.9	8.0	7.6	7.1
s	0.3	0.2	0.3	0.4
s_{rel} (%)	4.1	2.1	4.4	6.0
Friability (% w/w)	0.10	0.08	0.09	0.07

[a] Mean of ten tablets, all tablets confirm to content uniformity test of Ph. Eur.

Two infinite and mutually stabilizing clusters were formed [16]. The true volume of 70% (w/w) of pellets in the mixture was 35% (v/v); the corresponding volume of filler-binder, 14% (v/v, calculated as Avicel PH 101). Consequently, the pellets had a great influence on the properties of the mixture, causing good flow. The mixture nevertheless remained stable against segregation while being processed to tablets. Blends containing 60% (w/w) of pellets at a true volume of 29% (v/v) and a proportion of filler-binder of 18% (v/v) showed less favorable flow properties, due to the increased proportion of Avicel PH 101. Thus, 0.3% Aerosil 200 had to be added to achieve adequate flow, resulting in tablets of good mass and content uniformity (Table 4).

4. Conclusions

The correlation between pellet distribution and damage to coated pellets confirms that Avicel PH 101 is the most suitable filler-binder for industrial-scale production of divisible pellet tablets. Homogeneous distribution of the pellets within each tablet and little damage to the pellet coatings, almost independently of machine speed, add up to a calculable system for easy scale-up. For the production of delayed-release pellet tablets, the new coating polymer Eudragit FS 30 D is the only suitable option because of its high elasticity at a plasticizer content of 10% TEC. Pellet coatings with Eudragit FS 30 D withstand the stress of tableting. However, increasing the proportion of plasticizer enhances the tackiness of the coating, and disintegration at a pellet content of 70% (w/w) fails to occur. Overall, it has been shown that using 70% (w/w) of pellets approximately 1.0 mm in size, a critical level is exceeded which results in more pronounced damage to the coating. If the proportion is reduced to 60% (w/w) of pellets, pellet tablets of good mass and content uniformity are obtained, which fulfill the requirements of USP 23 by not liberating more then 10% of drug within 2 h in simulated gastric fluid. However, in this case good flow of the mixture is essential.

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