Drug Development and Industrial Pharmacy, 32:287–296, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500518781

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Important Parameters for the Manufacture of Slow-Release Matrix Pellets With an Aqueous Dispersion of Quaternary Poly(meth)acrylates in the Rotary Fluidized Bed

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ABSTRACT The manufacture of slow-release matrix pellets with an aqueous dispersion of quaternary poly(meth)acrylates was investigated in the rotary fluidized bed. By considering the moisture content of the fluidized bed to be the key process parameter, it was measured on-line throughout the whole manufacturing process. A specially designed sampling device opened new ways to apply NIR spectrometry in laboratory scale processes. It was shown that reproducibly improved pellet properties can be achieved by reproducing the moisture content of the (rotary) fluidized bed. Moisture plateaus proved to be a suitable way to optimize the sphericity of the pellets. Premoisturizing was found to be a very effective tool to achieve slow-release dissolution of the model drug theophylline.

KEYWORDS Aqueous polymer dispersion, Curing, Direct pelletization, Matrix pellets, Plasticizer, Rotary fluidized bed, Slow release

INTRODUCTION

In previous studies we had investigated the suitability of conventional fluidized bed granulation for the manufacture of slow-release matrix granules with aqueous polymer dispersions (Radtke et al., 2002). As a major outcome of our studies, a high terminal moisture content (TMC) of the fluidized bed (e.g., 20 %) proved to be the most important factor for the achievement of slow-release dissolution of the model drug theophylline out of granules. Other findings were high amounts of polymer (e.g., 40%) in the granules, and subsequent curing of the granules at temperatures of, for example, 70°C are essential factors for a pronounced retardation of drug release. Despite very encouraging first results, repeatability tests showed that conventional fluidized bed granulation does not meet the needs for reproducibility of the drug release rate and sphericity of the granules.

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In this study, improvement of the sphericity of the granules, reproducibility of the drug release rate, and retardation efficiency (reduction of polymer needed for sufficient slow release) were investigated in detail. The release rate, expressed as MDT80–mean dissolution time for 80% of the drug–is regarded to be the most important pellet property. Looking for the optimal process technology, *rotary* fluidized bed granulation seemed to have the highest potential for achieving sphericity and reproducibility (Bauer, 1979; Hinderer, 1987). Considering the moisture content of the fluidized bed as the most important factor throughout the pelletization process, we developed a powerful on-line in-process control method based on NIR spectrometry. A specially designed sampling device enabled measurements at short intervals without having to interrupt the fluidization and suffer considerable losses of fluidized material (Radtke et al., 1999; Radtke, 1998).

OBJECTIVES

The aim of this study was the optimization of the manufacture of slow-release matrix pellets by wet granulation with an aqueous dispersion of quaternary poly(meth)acrylates in the rotary fluidized bed. The impact of quantity of plasticizer, moisture content of the fluidized bed, and curing conditions on the pellet properties were investigated, evaluated, and discussed.

EXPERIMENTAL PROCEDURE

Materials

Starting Materials

Theophylline, anhydrous (Knoll, Ludwigshafen, Germany) mean particle size $d_{1,3} = 30$ µm, microcrystalline cellulose (Avicel PH 101, Lehmann & Voss, Hamburg, Germany) mean particle size $d_{1,3} = 80$ µm.

Polymer Dispersion

Aqueous dispersion of quaternary poly(meth)acrylates (Eudragit RS 30 D, Röhm GmbH & Co. KG, Darmstadt, Germany).

Plasticizer

Triacetin (Riedel-de Haän, Seelze, Germany).

METHODS

Direct Pelletization

Equipment

Rotary fluidized bed granulator (GPCG1, Glatt, Binzen, Germany, fed with air of standardized humidity of 40 ± 5% RH at 21 ± 1°C).

Pelletization Process

Starting materials 400–600 g were premixed (fluidized) and heated in the granulator. The granulation fluid (polymer dispersion: water ratio = 1:1 with different amounts of plasticizer) was sprayed onto the fluidized bed continuously (approximately 22 g/min). The amount of polymer dispersion was adjusted to the amount of starting materials so that the final pellets contain 30, 35, or 40% of polymer by theory. After spraying, the pellets were dried under smooth agitation (for precise parameter settings, see Radtke, 1998).

On-Line NIR Moisture Control

Equipment

- NIR-VIS spectrometer (Bühler AG, Uzwil, Switzerland),
- Fiber-optic probe for touchless measurement (remission); chemometric software: FCAP Ver. 2.00; PCR (Optan AG, Bubikon, Switzerland)
- Sampling device for standardized presentation and reintegration of samples (Radtke et al., 1999; Radtke, 1998).

On-line Measurement

Samples were drawn from the rotary fluidized bed and transferred to the measurement position using the sampling device. Three subsequent measurements were initiated via PC, each calculated as the mean value of three different scans. Standard error of prediction (SEP) of the measurement = 0.5% (Radtke et al., 1999; Radtke, 1998).

Curing

The pellets were all cured on trays in an oven (Hereaus RVT 360, Hanau, Germany).

Pellet Characterization

Sieve Analysis

Representative samples of 150 to 200-g size were sieved for 5 min in accordance with DIN 54377 using a Retsch AS 200 control (Retsch, Haan, Germany). Mean ±s, n = 4; standard error of the method = 0.6%.

Mean Particle Size

The mean particle size was calculated according to Eq. (1):

$$d_{1,3} = \sum_{i=1}^{n} \frac{x_i \cdot m_i}{e} \ (\mu m) \qquad (1)$$

where is number of fractions, x_i is mean particle size of fraction i in μm, m_i is weight of sieve fraction i in g, and e is total sample weight in g.

Poured/Tapped Density

Approximately 70 g of pellets were analyzed in accordance with EP4.0, 2.9.15. Mean ±s, n = 3; standard error of the method = 0.002 g/mL, and sieve fraction is 630–800 μm.

Flowability

Flowability was measured in accordance with EP4.0, 2.9.15. In contrast to the method, flowability is expressed as a velocity [$g \times min^{-1}$]; mean ±s, n = 3; standard error of the method = 0.06 $g \times min^{-1}$; and sieve fraction is 630–800 μm.

Attrition

Ten grams of pellets (sieve fraction: 800–1000 μm) were filled into the attrition tester TAP (Erweka, Heusenstamm, Germany). After addition of three stainless steel balls (∅ = 13 mm, weight = 11.2 g), the test container was rotated for 5 min (125 revolutions). Attrition is defined as the sieve fraction less than 630 μm after 125 revolutions. Mean ±s, n = 3; standard error of the method = 1%.

Resistance to Crushing

Single pellets (sieve fraction: 800–1000 μm) were tested with the hardness tester TB 24 (Erweka, Heusenstamm, Germany). Mean ±s, n = 20; standard error of the method = 0.23 kp.

Drug Dissolution

Dissolution apparatus DT6 (Erweka, Heusenstamm, Germany) conditions: basket, 100 min^{-1}, 0.1 N-HCl, 37 ± 0.5°C, λ = 243 nm.

MDT_{80}

The mean dissolution time to achieve dissolution of 80% (MDT_{80}) (Radtke, 2002) was calculated to describe the release rate of different formulations; n = 3–6.

Characterization of the Release Profile, Exponent n_f

The exponent n_f was calculated according to Eq. 2. (Lindner and Lippold, 1995). This exponent is used to characterize the dissolution kinetics of drug release. Values of 0.5 describe square root of time kinetics, which are typical for matrix controlled release from planar systems. For ideal spherical dosage forms, 0.43 stands for matrix control. Values close to 1.0 describe zero-order kinetics, which are typical for film-coated slow-release formulations.

$$F(t) = \frac{Q}{Q_\infty} = k \cdot t^{n_f} + b \qquad (2)$$

where F(t) is fraction released at time t, Q is quantity released at the time t, Q_∞ is total quantity released, n_f is exponent without dimension and describes release mechanism, k is release constant of the nth order (dimension: t^{-n}), and b is y-axis intercept (burst effect).

Spericity

Photographs of the pellets (sieve fraction: 800–1000 μm) were inspected visually. Six different levels of sphericity were defined. Level 1 describes spherical pellets with a smooth surface, whereas Level 6 means irregular shaped pellets with a rough surface. Mean ±s, n = 10; standard error of the method = 0.2 levels of sphericity.

Parameters Investigated

A series of experiments focussed on the following parameters:

- Quantity of plasticizer
- Moisture content in the fluidized bed
- Curing conditions
- Reproducibility

Quantity of Plasticizer

The quantity of triacetin in the polymer dispersion was varied to provide different conditions for the formation of the polymer matrix within the pellets. As in film-coating technology, the minimum film-forming temperature (MFT) was used for setting different plasticizer levels (Amighik and Moes 1996). A range of 0–33 g of triacetin, corresponding to MFT values of between 15 and 45°C, was investigated. The process temperature (PT) was kept constant at 21°C in all the trials.

Curing Conditions

The pellets were cured at temperatures of 70–100°C for 2–24 h.

Moisture Content

The moisture content of the fluidized bed was modified in three different ways:

1. In line with previous investigations, the pelletization process was stopped when a target **terminal moisture content (TMC)** (Radtke et al., 2002) had been reached. The TMC was varied between 21 and 31%.
2. At the end of the direct pelletization process, the moisture content of the fluidized bed was kept constant (±1%) for 30 min, before drying of the pellets was initiated. This process step, characterized by almost constant moisture in the fluidized bed, is called "moisture plateau." Different **moisture plateaus** were applied during the pelletization process. The moisture levels 24% and 27% were investigated.
3. At the beginning of the direct pelletization process, the fluidized bed had been **premoisturized** before the polymer dispersion was added. Different amounts and types of spraying solutions were tested. The effect of 5 or 10 min of premoisturization on several pellet properties was investigated.

Reproducibility

Reproducibility was tested for each of the above three parameters by repeating trials (n = 2–4).

RESULTS AND DISCUSSION

Quantity of Plasticizer

MDT_{80}

As shown in Table 1 and Fig. 1, the MDT_{80} and the dissolution profile largely depend on the quantity of plasticizer used. It is surprising that the MDT_{80} increases with decreasing quantities of triacetin, corresponding to an increase of the MFT. The highest MDT_{80} of approximately 90 min (lowest dissolution rate) was observed when the polymer dispersion was free of plasticizer. The process was not feasible with use of high amounts of triacetin: In our study, 33 g of triacetin, corresponding to an MFT of about 6°C lower than the PT, caused pronounced stickiness of the fluidized bed. At this plasticizer level, no controlled pellet growth was possible. Reducing the amount of triacetin, thus increasing the MFT, resulted in reduced stickiness. An MFT equal to the PT seemed to be boarderline. In principle, the process was feasible; particle (respectively pellet) growth occurred, but

TABLE 1 **Influence of the Quantity of Triacetin on the MFT and MDT_{80}**

Batch	Amount of triacetin (g)	Triacetin [in polymer dispersion] (%)	Triacetin [in polymer matrix] (%)	MFT [of polymer dispersion] (°C)	(MFT–PT) (°C)	MDT_{80}** (min)
RW3*	33	2.5	10	15 ± 1	–6	—***
RW2*	26	2.0	8	21 ± 2	0	22 ± 3
RW1*	13	1.0	4	31 ± 2	+10	44 ± 1
RW0**	0	0.0	0	45 ± 1	+24	86 ± 4

Composition of pellets: 42% theophylline, 40% polymer (including triacetin), 18% microcrystalline cellulose.
*Pellets cured for 2 h at 70°C.
**Pellets cured for 2 h at 90°C.
***Not feasible due to sticking and lumping.

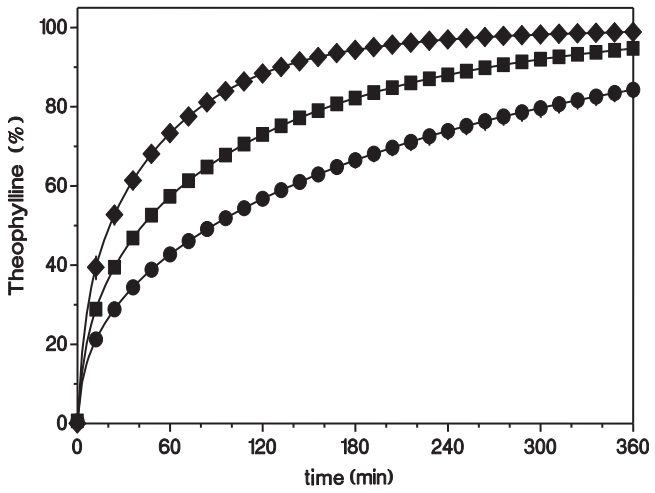

FIGURE 1 **Influence of triacetin on the dissolution rate. Concentration of triacetin in the spraying fluid: ♦ 2%, ■ 1%, and ● 0%. Sieve fraction: 800–1000 μm; Mean ±min/max; n = 3. Composition of pellets: 42% theophylline, 40% polymer (including triacetin), and 18% microcrystalline cellulose; curing conditions: 2 h at 90°C (0% triacetin), 2 h at 70°C (1 and 2% triacetin).**

film-forming only took place to a very limited extent. This can be concluded from the very low MDT_{80} of 22 min.

According to general recommendations for film coating with aqueous polymer dispersions, the PT should be 10–20°C higher than the MFT (Fukumori, 1994; Lippold et al., 1989). For granulation or pelletization processes, this recommendation does not seem to be suitable. Based on our study, the best results for a pelletization process with aqueous dispersion of quaternary poly(meth)acrylates can be achieved with a PT, which is 20°C lower than the MFT. This surprising result may be explained by the considerably higher quantity of free water present in the pellets during the direct pelletization process than on the surface of the pellets during the film-coating process. In our trials, the moisture content of the granules in the fluidized bed varied between 15 and 30%. During the film coating of the pellets in the fluidized bed, much lower levels are assumed (Lippold and Monells Pages 2001). Because water acts as a plasticizer, it seems logical that a reduced plasticizer level is necessary during direct pelletization with an aqueous polymer dispersion. The measurement of the MFT is conducted under starting conditions, which should provide as much free water as the direct pelletization process; so, maybe different drying rates have to be taken into consideration. Once coarse granules or pellets are formed, the drying rate in the inner parts of the pellets decreases significantly. During MFT measurements, a much higher drying rate can be assumed at the surface of the polymer film layer. From this, it becomes clear that the MFT measurement does not reflect the conditions that exist in a growing pellet during direct pelletization with aqueous polymer dispersions. As a consequence, the MFT cannot be used in the same way as for film-coating processes.

Pellet Size, Shape, and Flowability

Table 2 gives an overview of the most relevant pellet properties. It can be clearly seen that all the properties are influenced by triacetin. These results support the hypothesis that controlled pellet growth is prevented after triacetin has been added to the polymer dispersion. Whether this phenomenon is specific for triacetin or a phenomenon common to all plasticizers needs to be further investigated. Preliminary studies show that plasticizers, such as dibutylphatalate or triethylcitrate, cause even more serious sticking and lumping than triacetin at comparable MFTs.

Curing Conditions

Figure 2 shows an overview of the influence of the curing temperature on the MDT_{80}. The optimal curing

TABLE 2 **Influence of Triacetin on Relevant Pellet Properties**

Batch	Triacetin [in polymer dispersion] (%)	$d_{1,3}$ (μm)	Sphericity	Flowability ($g \times min^{-1}$)	Poured density ($g \times mL^{-1}$)	Tapped density ($g \times mL^{-1}$)	Resistance to crushing (kp)
RW2*	2	565 ± 7	4 ± 0.3	634 ± 4	0.54 ± 0.02	0.59 ± 0.01	0.5 ± 0.2
RW1*	1	1023 ± 37	3 ± 0.3	758 ± 7	0.66 ± 0.00	0.68 ± 0.01	0.8 ± 0.2
RW0**	0	1363 ± 73	2 ± 0.3	747 ± 4	0.72 ± 0.01	0.74 ± 0.01	0.8 ± 0.2

Composition of pellets: 42% theophylline, 40% polymer (including triacetin), 18% microcrystalline cellulose.
*Pellets cured for 2 h at 70°C.
**Pellets cured for 2 h at 90°C.

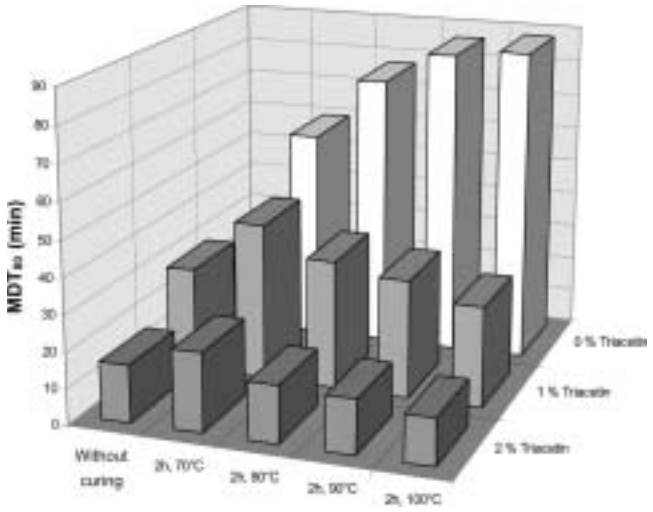

FIGURE 2 **Influence of the curing temperature and concentration of triacetin on the MDT_{80}. Not visible: 0% triacetin, without curing = 15 ± 0.7 min. Sieve fraction: 800–1000 μm; mean; s = 0.6–4.6 min; n = 3. Composition of pellets: 42% theophylline, 40% polymer (including triacetin) and 18% microcrystalline cellulose.**

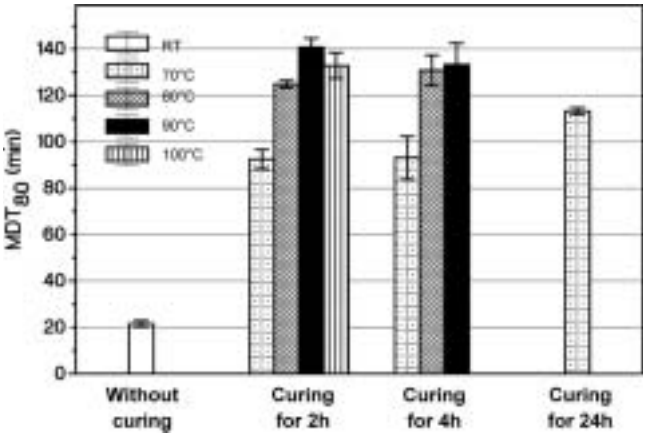

FIGURE 3 **Influence of temperature and duration of curing on the MDT_{80} of plasticizer-free matrix pellets (batch RW0). Sieve fraction: 1000–1250 μm; mean ±s; n = 3. Composition of pellets: 42% theophylline, 40% polymer, and 18% microcrystalline cellulose.**

temperature depends on the quantity of plasticizer. Pellets containing no plasticizer have to be cured at 90°C if a maximum MDT_{80} has to be reached. Pellets that contain 8% or 10% of triacetin seem to have an optimal curing temperature close to 70°C. It is important to note that pellets that contain triacetin generally have lower MDT_{80} levels than triacetin-free pellets. Triacetin seems to impair both pellet growth and matrix-forming during the pelletization process, which cannot be compensated for by subsequent curing at optimal conditions.

Figure 3 shows the influence of curing time on the MDT_{80} of plasticizer-free pellets. After 2 h, pellets cured at 90°C show the highest MDT_{80} values. Curing at 100°C seems to be too aggressive for optimal curing of the pellets. Extended curing (e.g, curing for 4 h or 24 h) does not compensate for lower curing temperatures. The mechanical properties of the pellets such as resistance to attrition or crushing are also improved significantly by curing (Table 3).

Moisture Content

Application of Different Terminal Moisture Contents (TMC)

As already mentioned, the MDT_{80} of matrix granules manufactured by conventional fluidized bed granulation with an aqueous polymer dispersion strongly depends on the TMC: the higher the TMC, the higher the MDT_{80} of the matrix granules (Radtke et al., 2002). The same dependency should be observed with pellets, which are manufactured in the rotary fluidized bed. The higher densification of the matrix granules (pellets), brought about by rotational agitation, should result in an overall higher level of the MDT_{80} than the conventional fluidized bed. It is surprising that, transferring the parameter settings of the conventional fluidized bed process to the rotary fluidized bed causes process failures. Reducing the inlet air humidity from 40 to 10% RH was found to be a suitable method to render the process feasible. However, independent of the TMC level, no pronounced retardation was achieved. In the range tested (21–31%), the maximum MDT_{80} did not exceed 20 min. Based on these results, processability of the rotary fluidized bed seems to be more sensitive to triacetin than the conventional fluidized bed at given inlet air conditions. Application of moisture plateaus and premoisturizing of the fluidized bed were identified as possible methods to overcome the lack of retardation efficiency.

Application of Moisture Plateaus

The main intention of the moisture plateau was to increase the MDT_{80}. From a theoretical point of view, it was assumed that by keeping the pellets moistened for a longer period of time, thus decreasing the drying rate down to zero, matrix-forming conditions should be improved significantly. In addition, synergistic

TABLE 3 **Influence of Curing on the Mechanical Properties of Triacetin-Free Pellets**

	Resistance to crushing (kp)		Attrition (%)	
Batch	Without curing	With curing	Without curing	With curing
RW0	0.78 ± 0.199	0.90 ± 0.286	21 ± 0.7	16 ± 0.9
RR1	0.66 ± 0.247	0.86 ± 0.172	18 ± 0.5	15 ± 1.9
RR2	0.75 ± 0.215	0.90 ± 0.235	19 ± 0.5	15 ± 0.6
RR3	0.74 ± 0.275	0.91 ± 0.233	18 ± 0.2	15 ± 0.6

Composition of pellets: 42% theophylline, 40% polymer, 18% microcrystalline cellulose; curing conditions: 2 h at 90°C.

TABLE 4 **Influence of Moisture Plateaus on Relevant Pellet Properties**

Batch	Spraying fluid	Moisture content (%)	MDT_{80} (min)	n_f	$d_{1,3}$ (μm)	Sphericity	Flowability ($g \times min^{-1}$)	Poured density ($g \times mL^{-1}$)	Tapped density ($g \times mL^{-1}$)
RS 6									
RM1	Polymer dispersion	27 (TMC)	16 ± 1.5	0.46 ± 0,03	772 ± 66	3.0 ± 0.0	652 ± 14	0.59 ± 0.01	0.64 ± 0.01
RM2									
RP1	Water	24 (Plateau)	18	0,41	422	3.0	n.d.	n.d.	n.d.
RP2									
RP3	Water	27 (Plateau)	22 ± 2.5	0.45 ± 0,01	916 ± 56	1.0 ± 0.0	782 ± 24	0.69 ± 0.01	0.74 ± 0.02
RP4									
RP5									
RP6	Polymer dispersion	27 (Plateau)	30 ± 6.9	0.56 ± 0,07	798 ± 44	1.3 ± 0.2	756 ± 24	0.63 ± 0.02	0.68 ± 0.01
RP7									

Composition of pellets: 42% theophylline, 40% polymer (including 10% triacetin), 18% microcrystalline cellulose; curing conditions: 2 h at 70°C; n.d. = not determined.

effects were expected because of the densification of the pellet matrix through the high-speed rotation of the rotating disk. Moisture plateaus on a lower level should allow for more stable processes with moderate retardation efficiency. Lower absolute levels of moisture should also allow the incorporation of triacetin without sticking and lumping. Higher moisture levels should allow the optimization of shape and surface of the pellets and should provide significantly higher MDT_{80} levels. Table 4 summarizes the main findings.

Moisture plateaus seem to have little effect on the MDT_{80} (at least in the presence of triacetin). Densification of the pellets can be achieved. Moisture plateaus on lower moisture levels (24%) seem to have no beneficial effects. Triacetin can be incorporated without sticking and lumping, but without any retardation being achieved. Moisture plateaus on high moisture levels (27%) achieve better sphericity of the pellets. Figures 4 and 5 show that densification seems to take place mainly at the outer parts of the pellets. Pellet growth has evidently almost been completed before moisture plateaus are applied, which might explain why the impact on the density and homogeneity of the polymer matrix in the pellets is only low.

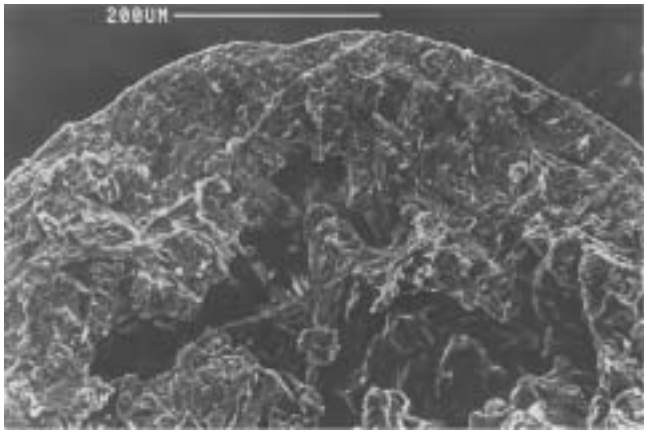

FIGURE 4 **REM picture of the cross section of a pellet manufactured with moisture plateau before dissolution (Batch RP2).**

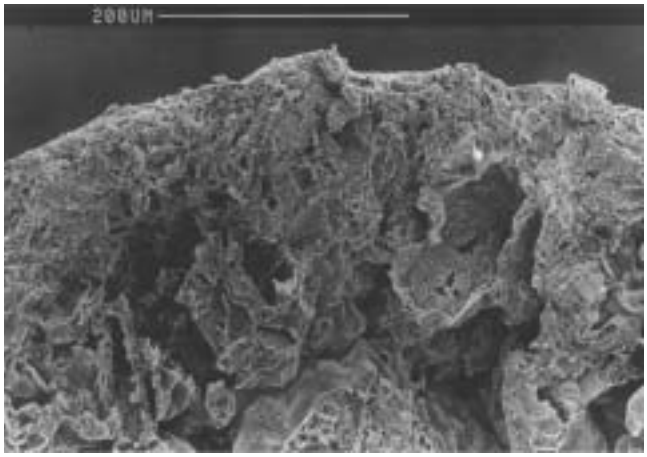

FIGURE 5 **REM picture of the cross section of a pellet manufactured with moisture plateau after complete dissolution (Batch RP2).**

Figure 6 illustrates how shape and surface characteristics of pellets can be improved by the application of moisture plateaus. It can be concluded that moisture plateaus might be an effective tool for improving sphericity and surface characteristics of pellets, which have to be manufactured out of suboptimal pellet formulations in general. This seems to be of relevance especially for high drug-loaded pellets.

Premoisturizing of the fluidized bed

The theoretical principle of premoisturizing is to optimize the film-forming conditions via prewetting dry surfaces of the fluidized bed and hence increasing the amount of free water in the initial phase of the direct pelletization process. Premoisturizing was achieved by spraying purified water into the fluidized bed before the polymer dispersion was added. Table 5 and Fig. 7 illustrate that premoisturizing is an effective tool for increasing the MDT_{80}. From this it can be concluded that the matrix-forming conditions during pellet growth are improved significantly by premoisturizing. The fact that only little effect on the mean pellet diameter $d_{1,3}$ is observed proves that almost no pellet growth occurs during the premoisturizing phase. Only slight modifications toward even lower n_f values show that no partial coating of already formed agglomerates (during the premoisturizing phase) is responsible for the increased retardation efficiency.

Premoisturizing allows reduced amounts of polymer dispersion without encountering a decrease of the MDT_{80}. Therefore, it serves as an effective tool for increasing the retardation efficiency of a direct pelletization process in the rotary fluidized bed with aqueous polymer dispersions.

Reproducibility

Table 6 shows the properties of pellets of four different direct pelletization batches. The pelletization process was stopped at a TMC of 28%. No plasticizer, moisture plateaus, or premoisturizing were applied. The overall reproducibility is considered to be very good. The standard deviation of all the relevant parameters is rather low and should be acceptable for commercial production. The fact that the first batch is

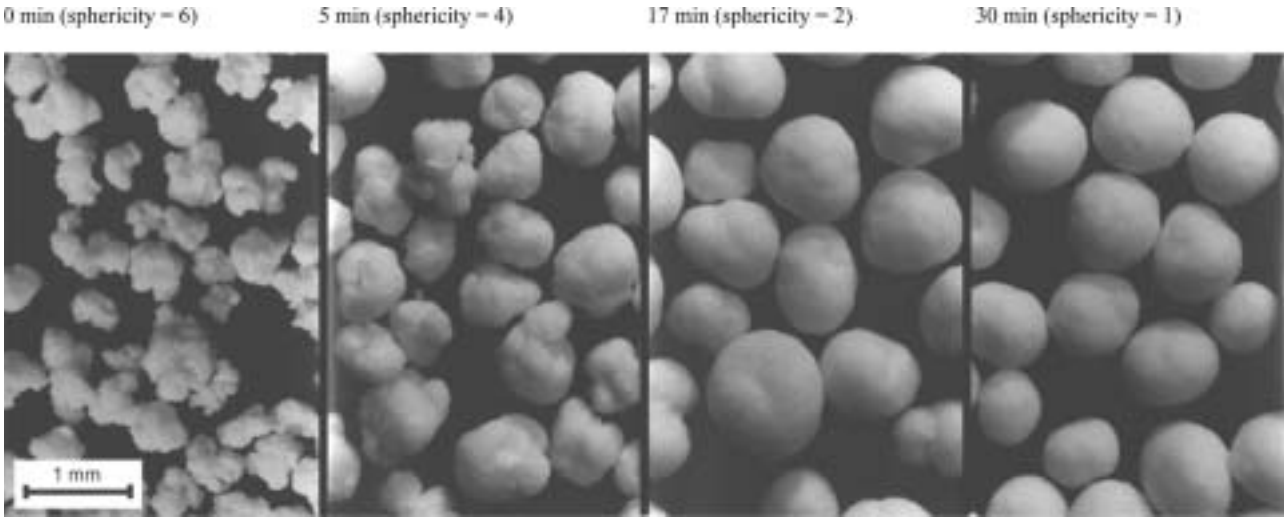

FIGURE 6 **Application of a moisture plateau; pellet growth and optimization of sphericity (Batch RP2).**

TABLE 5 **Influence of Premoisturizing on Relevant Pellet Properties**

Batch	Pre-moisturizing (min)	Concentration of dispersion (%)	Content of polymer in pellet matrix (%)	MDT_{80} (min)	n_f	$d_{1,3}$ (μm)	Pellet properties Sphericity	Flowability ($g \times min^{-1}$)	Poured density ($g \times mL^{-1}$)	Tapped density ($g \times mL^{-1}$)
RR1*	—	22	40	109 ± 2	0.41 ± 0.01	1064 ± 54	3 ± 0.0	700 ± 4	0.64 ± 0.01	0.68 ± 0.00
RV1*	5	22	40	226 ± 12	0.41 ± 0.01	1070 ± 118	3 ± 0.3	712 ± 1	0.62 ± 0.00	0.68 ± 0.00
RV2**	—	22	30	52 ± 5	0.55 ± 0.06	922 ± 88	2 ± 0.5	710 ± 11	0.63 ± 0.00	0.67 ± 0.01
RV3**	5	22	30	77 ± 2	0.53 ± 0.02	1153 ± 41	2 ± 0.3	738 ± 15	0.69 ± 0.00	0.76 ± 0.01
RV4**	10	22	30	65 ± 4	0.50 ± 0.02	1221 ± 48	2 ± 0.5	735 ± 10	0.66 ± 0.04	0.74 ± 0.01
RV5**	—	30	30	41 ± 2	0.54 ± 0.01	1244 ± 112	3 ± 0.5	697 ± 5	0.60 ± 0.00	0.67 ± 0.01
RV6**	10	30	30	54 ± 2	0.51 ± 0.00	1350 ± 74	3 ± 0.3	767 ± 5	0.67 ± 0.00	0.76 ± 0.00
RV7**	10	30	30	56 ± 1	0.51 ± 0.03	1320 ± 91	2 ± 0.5	789 ± 10	0.69 ± 0.00	0.77 ± 0.00

*Composition of pellets: 42% theophylline, 40% polymer, 18% microcrystalline cellulose; TMC: 25–27%; curing conditions: 2 h at 90°C.
**Composition of pellets: 49% theophylline, 30% polymer, 21% microcrystalline cellulose; TMC: 25–27%; curing conditions: 2 h at 90°C.

TABLE 6 **Reproducibility**

Batch	MDT_{80} (min)	n_f	$d_{1,3}$ (μm)	Yield 1000–1250 μm (%)	Yield 500–1600 μm (%)	Flowability ($g \times min^{-1}$)	Poured density ($g \times mL^{-1}$)	Tapped density ($g \times mL^{-1}$)	Sphericity
RW0*	141	0.43	1363	25	75	747	0.72	0.74	2
RR1*	109	0.42	1064	20	84	700	0.64	0.68	3
RR2*	116	0.41	982	18	84	682	0.61	0.65	3
RR3*	110	0.41	1012	21	88	718	0.67	0.69	3
Mean	119 ± 14	0.42 ± 0.01	1105 ± 165	21 ± 2.8	84 ± 5	712 ± 25	0.66 ± 0.04	0.69 ± 0.04	2.8 ± 0.5

Composition of pellets: 42% theophylline, 40% polymer, 18% microcrystalline cellulose; TMC: 28% ± 0.5%; curing conditions: 2 h at 90°C.

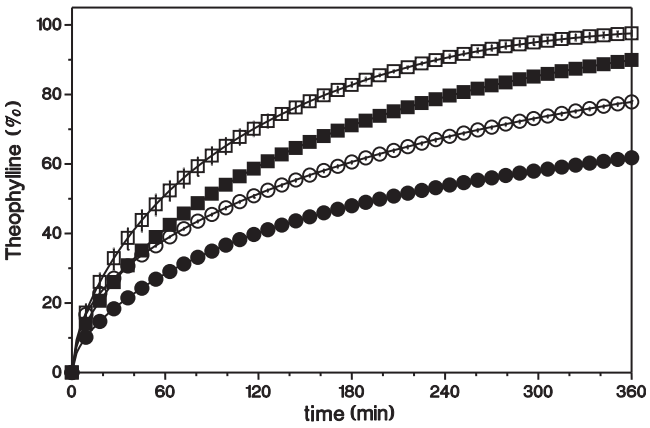

FIGURE 7 Influence of premoisturizing on the dissolution rate. Empty symbols: without premoisturizing; filled symbols: with premoisturizing; Polymer content (pellets): □ (RV2), ■ (RV3): 30%; ○(RR1), ●(RV1): 40%. Sieve fraction: 1000–1250 μm; Mean ±min/max; n = 3; curing conditions: 2 h at 90°C.

somewhat different from the following batches is not considered problematic but might be further investigated. The authors assume that by applying moisture plateaus (without triacetin) and/or further refining the NIR in-process control of the TMC, a further improved process might be achievable for routine production.

CONCLUSIONS

1. It is possible to reproducibly manufacture slow-release multiple-unit matrices (matrix pellets) by wet granulation with an aqueous dispersion of quaternary poly(meth)acrylates in the rotary fluidized bed.
2. Several ways to optimize the manufacture of slow-release matrix pellets by direct pelletization in the rotary fluidized bed with an aqueous polymer dispersion have been identified.
3. Premoisturizing economizes the direct pelletization processes with aqueous polymer dispersion by improving the retardation efficiency (less polymer for the same slow-release profile).
4. Application of moisture plateaus can be an effective tool for optimizing important pellet properties such as sphericity and surface roughness.
5. In contrast to film-coating processes, an MFT of 10–20°C higher than the process temperature cannot be recommended for granulation or pelletization processes with aqueous polymer dispersions.
6. Adding a plasticizer such as triacetin to the polymer dispersion is not suitable for improving the shape or the slow-release characteristics of pellets manufactured by direct pelletization with aqueous polymer dispersions.

ACKNOWLEDGMENTS

The authors thank the companies Glatt AG and Optan AG for providing equipment and software.

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