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RESEARCH PAPER

Manufacture of Slow-Release Matrix Granules by Wet Granulation with an Aqueous Dispersion of Quaternary Poly(meth)acrylates in the Fluidized Bed

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ABSTRACT

Slow-release matrix granules were manufactured in the fluidized bed using an aqueous dispersion of quaternary poly(meth)acrylates (Eudragit® RS 30 D) as binder for granulation. A factorial design was carried out to investigate the influence of the following parameters, spraying rate, applied polymer amount, and inlet air temperature, on various granule properties. Prerequisites for a slow release of the model drug theophylline are high spraying rate, high amount of polymer, and low inlet air temperature. No considerable decrease of the drug release rate can be achieved without a subsequent curing of the dry granules. A clear correlation exists between the moisture content of the fluidized bed, indicated by the terminal moisture content (TMC), and the mean dissolution time for 80% of the drug (MDT_{80}).

Key Words: *Aqueous polymer dispersion; Curing; Fluidized bed granulation; Matrix granules; Slow release*

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INTRODUCTION

Aqueous polymer dispersions were introduced in the pharmaceutical industry more than 25 years ago.[1,2] Up to present, film coating of tablets or pellets is the main application of these dispersions. Their potential for the manufacture of mini-matrices and their use as binder for wet granulation are still rather unknown. Guo and Bodmeier[3] prepared drug containing polymeric microparticles with a particle size in the range of 5 to 20 μm by a spray-drying method. Toms and Goskonda[4–6] describe the manufacture of slow-release matrix pellets by extrusion spheronization with an aqueous polymer dispersion. In both cases, a prerequisite for the achievement of a pronounced slow down of the drug release is the incorporation of additional functional excipients such as hydrocolloids or micro-pH-modulators. From such heterogenous systems it is rather difficult to draw clear conclusions about the amount of polymer and the method of its incorporation, mandatory for the achievement of a reproducible slow drug release. Therefore, and with respect to stability aspects, it is desirable to avoid the incorporation of any ''supportive'' excipient.

OBJECTIVES

The aim of this study is the manufacture of spherical slow-release multiple unit matrices by the use of an aqueous polymer dispersion as binder. The slow release should be related only to the polymer from the aqueous dispersion.

EXPERIMENTAL

In preliminary investigations conventional wet granulation with the commercially available polymer dispersions Eudragit® NE 30 D, Eudragit® RL 30 D/RS 30 D, and Aquacoat® showed the superiority of Eudragit® RS 30 D with respect to manufacturability of granules at room temperature and achievable reduction of the drug release rate. The overall extent of retardation of the drug release was very low (amount of drug released ~80% after 60 min). Increasing the polymer content in the granules from 10% up to 34% (based on the dry mass of the granules) by repeating the granulation procedure after each drying of the granules did show an increase in the dissolution rate instead of a decrease. Thus it was concluded that the polymer dispersion has to be incorporated into the granules in one step. Due to this, and due to the limited polymer concentration of the commercially available polymer dispersions (max. 30%), the fluidized bed granulation seems to be an appropriate agglomeration technique.

Materials

Polymer Dispersion

Aqueous dispersion of quaternary poly(meth)-acrylates (Ammonio Methacrylate Copolymer, Type B USP, Eudragit® RS 30 D, gift from Röhm Pharma, Darmstadt, Germany).

Plasticizer

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

Model Drug

Theophylline anhydrous, fine powder (gift from Knoll AG, Ludwigshafen, Germany); mean particle size $d_{1,3} = 30\,\mu m$ (laser diffraction).

Triacetin was added in order to lower the minimum film-forming temperature (MFT) of the aqueous polymer dispersion below the process temperature during granulation. A level of 10% based on the dry mass of the polymer dispersion lowering the MFT to approximately 15°C was found to be suitable for the granulation process in the fluidized bed at room temperature (21°C).

Methods

Fluidized Bed Granulation

Granulator

Aeromatic Strea 1 (Aeromatic AG Muttenz, Switzerland) fluidized bed granulator fed with air of standardized humidity (40±5% RH at 21±1°C).

Granulation Process

The formulation and operation variables were fixed according to Table 1. The initial raw material for each trial was theophylline powder: 300 g of the powder was fluidized and prewarmed for 3 min; 1500 g of the diluted polymer dispersion (granulation liquid, Table 1), containing 10% triacetin related to the dry mass, was top-sprayed with a constant

Table 1

Factors of the 2^3 Factorial Design

Factor	Low level (−)	High level (+)
Spraying rate (A)	5.5 g min^{-1}	11.0 g min^{-1}
Polymer (B)	11%[a] (≡25% in dry granules)	22%[a] (≡40% in dry granules)
Inlet air temperature (C)	35°C	50°C

[a]Polymer content in granulation liquid.

spraying rate. The granules were dried for 15 min and subsequently cooled for 5 min in the fluidized bed. For each of the process steps, prewarming, spraying, and drying, the inlet air flow was adjusted to an appropriate, constant level in order to provide a fluid bed expansion of approximately 1.5.[7]

Curing

Curing was conducted in an oven for 2 hr at about 70°C.

Particle Size

Sieve analysis (Vibro, Retsch, Haan, Germany): 100 g of each granule was sieved for 10 min at 1 mm amplitude (n=4; standard error=0.5%). Mean granule diameter d_m was calculated according to Eq. (1):

$$d_m = \sum_{i=1}^{n} \frac{x_i m_i}{e} \ (\mu m) \tag{1}$$

where:

n = no. of fractions
x_i = mean granule diameter of fraction i (μm)
m_i = mass of fraction i (g)
e = total mass (g)

Bulk/Tapped Density

Bulk and tapped density was measured according to EP method 2.9.15 (n=3; standard error = 0.002 g mL^{-1}).

Angle of Repose

Measurement was conducted in accordance with DIN 53916 (Deutsche Industrie Norm, German Industry Standard) (n=3; standard error=0.5°).

Moisture Content

Weight loss in percent after drying with P_2O_5 under vacuum (n=3; standard error=0.2%).

Drug Dissolution/MDT_{80}

Dissolution Apparatus DT6 (Erweka, Heusenstamm, Germany), baskets, rotating speed 100 min^{-1}, 0.1 N HCl as dissolution medium at 37±0.5°C, selected wavelength for continuous UV-detection of dissolved theophylline: 243 nm, flow-through cells.

The mean dissolution time up to a dissolution extent of 80% (MDT_{80}) was calculated according to Eq. (2) as a parameter for the release rate of different formulations, n=3–6:

$$MDT_{80} = \sum_{i=1}^{n} \bar{t}_i \bar{Q}_i / Q_{80} \tag{2}$$

where:

$\overline{Q_i}$ = fraction released in time $\overline{t_i}$ [= $(t_i + t_{i-1})/2$]
Q_{80} = 80% fraction released

Factorial Design

A 2^3 factorial design was carried out and evaluated using the scheme of Yates. Homogeneity of variances was proven by repetition of one trial (n=3).

The spraying rate, added amount of polymer, and inlet air temperature of the fluidized bed granulator were supposed to be the most promising release rate-affecting variables (factors). The factor levels were defined in accordance with findings from preliminary investigations (Table 1).

Negligible dependence of the viscosity of the granulation liquid on its polymer content was achieved by diluting the polymer dispersion before use as a granulation liquid. Polymer contents lower

or equal to 22% result in a viscosity up to 5 mPas at maximum.[8] Attempts to compensate different viscosities of the granulation liquid by adding further excipients revealed the incompatibility of the polymer dispersion with various commonly used types of hydrocolloids.[8,9]

The spraying rate of each granulation fluid was adjusted in order to provide equal water feeding rates. Using preconditioned inlet air humidity and defined inlet air volume, comparable moisture contents of the wet granules at the end of the granulation process (terminal moisture content, TMC), independent from the polymer content of the granulation liquids, were achieved.

Curing of the Matrix Granules

Curing is a prerequisite for the forming of coherent non-porous film coatings.[10] Although wet granulation is a completely different process compared to film coating, a presumable influence of the curing on the coherence of the polymer matrix and therefore on the drug release of the granules was expected.

Selected sieve fractions of the granules obtained from the factorial design were cured for 2 hr at 70°C. The drug dissolution rate (MDT_{80}) was determined and compared to the non-cured granules.

Variation of the TMC

Based on the results of the factorial design, a series of granules were manufactured using the high polymer level (40% of the dry granule) and TMC values between 3% and 23%. Different TMCs were achieved by applying different spraying rates. Reproducibility was tested using a constant spraying rate of 11 g min^{-1} in four trials.

RESULTS AND DISCUSSION

Factorial Design

Table 2 gives an overview of the results obtained. Table 3 summarizes the effects and interactions. Increasing the concentration of the polymer (B) leads to an increase of the mean granule diameter d_m. Therefore, granule growth is mainly determined by the presence of the polymer, which acts, even being dispersed in the granulation fluid, like a typical (dissolved) binder. Its binding capacity is influenced by the temperature in a positive sense (BC), by the spraying rate in a negative sense (AB).

Flowability and sphericity, indicated by all other target parameters, are found to be on a low level. Improvement was achieved mainly by increasing the spraying rate (A), which is in accordance with general findings in fluidized bed granulation technology.[11–13] The achievement of satisfying sphericity, however, turned out to be impossible with conventional fluidized bed granulation technology.

No slow drug release was achieved and no significant effect on the MDT_{80} was observed by variation of the factors A, B, and C in the selected range.

Table 2

Results of the 2^3 Factorial Design

Trial	Factor level A	B	C	MDT_{80}[a] (min)	Mean Granule Diameter d_m (μm)	Angle of Repose α[b] (°)	Bulk Density ρ_{bulk}[b] (g mL^{-1})	Tapped Density ρ_{tapped}[b] (g mL^{-1})
(1)	−	−	−	5	353	36.9	0.29	0.35
a	+	−	−	7	557	34.4	0.35	0.41
b	−	+	−	6	469	52.5	0.27	0.32
ab	+	+	−	32	672	34.5	0.39	0.46
c	−	−	+	8	346	38.2	0.28	0.33
ac	+	−	+	5	317	36.9	0.28	0.33
bc	−	+	+	6	757	39.9	0.28	0.32
abc	+	+	+	11	513	36.4	0.32	0.37

[a]Granule fraction: 630–800 μm.
[b]Granule fraction: 400–630 μm.

Table 3

Effects, Interactions and Significance Values for the 2^3 Factorial Design

Factor/Interaction	MDT_{80} (min)	Mean Granule Diameter d_m (μm)	Angle of Repose α (°)	Bulk Density ρ_{bulk} ($g\,mL^{-1}$)	Tapped Density ρ_{tapped} ($g\,mL^{-1}$)
A	3.8	14.5	−3.2***	0.03***	0.03**
B	3.8	102.4***	2.1**	0.01*	0.01
AB	4.0	−29.5*	−2.2**	0.01*	0.02*
C	−2.5	−12.3	−0.9*	−0.02**	−0.02*
AC	−3.3	−82.7**	2.0**	−0.02**	−0.02*
BC	−2.8	49.4**	−1.8**	0.00	−0.00
ABC	−2.0	−24.5	1.7**	0.00	−0.00

*Significant, p=0.1.
**Significant, p=0.05.
***Significant, p=0.01.

Even a high level of factor B, corresponding to a polymer load of 40% in the granules, did not cause a pronounced increase of the MDT_{80}. Obviously, in spite of the one-step incorporation of this high polymer amount, no coherent polymer matrix was built during the fluidized bed granulation.

Curing of the Matrix Granules

The influence of curing on the drug release rate is shown in Figs. 1 and 2. There is a tremendous decrease of the drug release rate from granules ab. No effect of the curing can be observed on the low polymer level [granules (1), a, c, ac]. A polymer load of 25% seems to be insufficient for the formation of a coherent matrix in the granules.

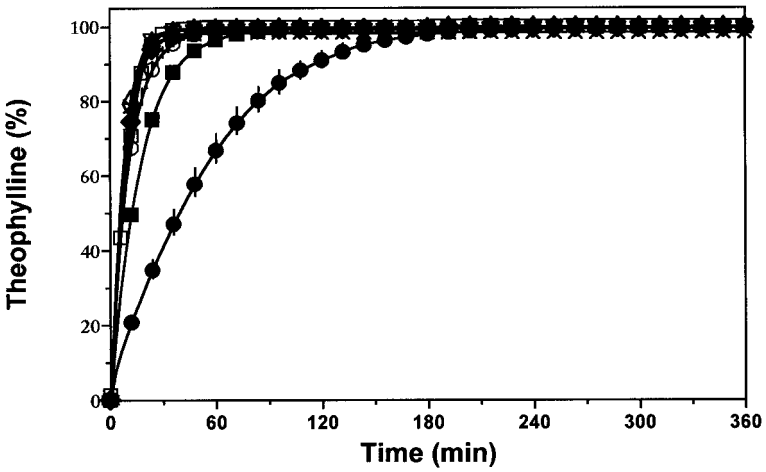
On the high polymer level, improvement of the effect of curing is achievable by an increase of the spraying rate (A). Increasing the inlet air temperature (C) obviously compensates this effect. This is indicated by the only slight increase of the MDT_{80} for granules abc (vs. granules bc) compared to the much more pronounced increase for granules ab (vs. granules b).

Variation of the TMC

Both an increase of the spraying rate (A) and a decrease of the inlet air temperature (C) cause an increase of the TMC. Figure 3 summarizes the results about the influence of the TMC on the MDT_{80}. According to the findings of the factorial design, no slow drug release was observed if the fluidized bed was rather dry, indicated by a low and almost constant MDT_{80} for TMC values below 12%. Exceeding this value, the MDT_{80} increases exponentially with increasing TMC, leading to a reasonable decrease of the release rate. The adjustment of the fluidized bed to a TMC of 21% allowed a satisfactory reproducibility of the MDT_{80}. On the 23% level, however, reproduction of the MDT_{80} was not possible. Considering that both TMCs (21% and 23%) were achieved in spite of applying the same spraying rate ($11\,g\,min^{-1}$), it becomes evident that other parameters of the granulation process must have varied to an unacceptable extent. On-line measurement of the moisture content of the fluidized bed, e.g., via near infrared (NIR) spectroscopy, seems to be necessary. First preliminary studies look promising and will be reported soon.

CONCLUSIONS

Slow-release matrix granules can be manufactured by fluidized bed granulation of theophylline powder with an aqueous polymer dispersion. For the achievement of slow release of the model drug there is no need for further excipients besides the polymer (dispersion) itself. Curing of the matrix granules after the manufacturing procedure is a prerequisite for a slow release. The release rate of the cured granules is predetermined by the moisture content of



Symbol	Granule	MDT_{80} (min) uncured	cured
X	(1)	5	6
O	a	7	7
◆	b	6	9
●	ab	32	*178*
∇	c	8	13
Δ	ac	5	6
□	bc	6	15
■	abc	11	21

Figure 1. Release of theophylline from uncured matrix granules. Polymer load 40%, fraction 630–800 μm, mean, min/max, n=3.

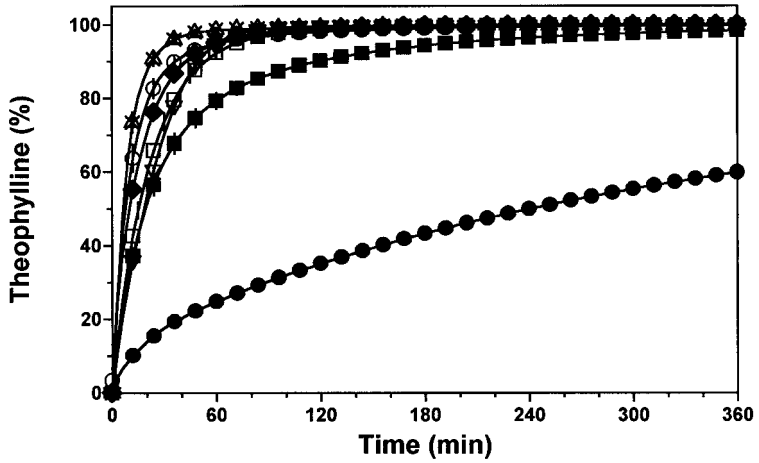
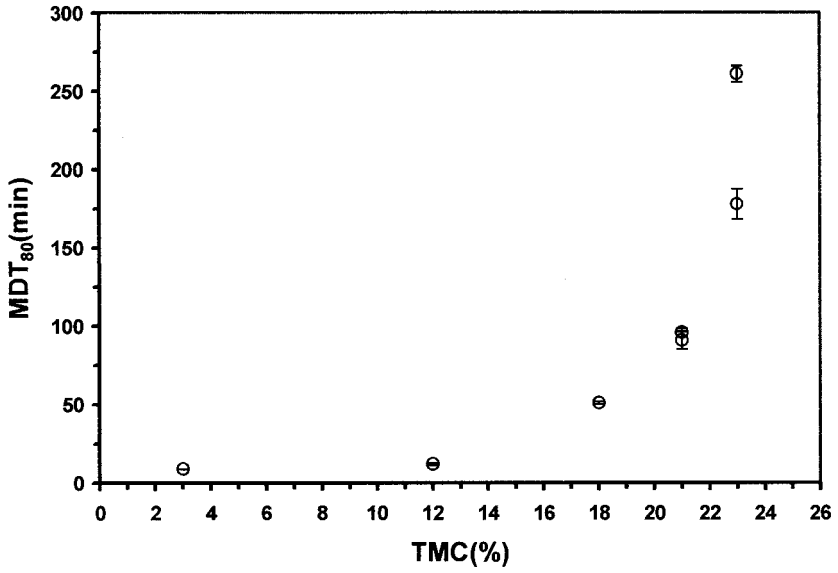


Figure 2. Release of theophylline from cured matrix granules. Polymer load 40%, curing 2 hr at 70°C, fraction 630–800 μm, mean, min/max, n=3. Symbols as in Fig. 1.



Applied spraying rate ($g \cdot min^{-1}$)	TMC (%)
5.5	3
9.5	12
10.5	18
11.0	21; 23

Figure 3. Influence of the TMC on the MDT_{80} of cured matrix granules. Polymer load 40%, fraction 400–630 μm, curing 2 hr at 70°C, Mean±RSD, n=3.

the fluidized bed at the end of the granulation process (TMC): the higher the moisture content, the lower the release rate (within a certain range). The reproducibility of the manufacturing of the slow-release matrix granules is suboptimal. Further improvement may be possible by the on-line measurement of the moisture content of the fluidized bed, e.g., via NIR and the respective adjustment during the complete granulation process.

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