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Influence of process parameters on sustained-release theophylline pellets coated with aqueous polymer dispersions and organic solvent-based polymer solutions

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Abstract

Multiple-dose units have many kinetic and therapeutic advantages over single-dose sustained-release units. We therefore investigated the influence of pellet core properties and different coating parameters on in vitro theophylline release. Pellet size and pellet surface have a distinct effect on the release behaviour, with the surface morphology also playing a major role. One organic solvent-based and two aqueous dispersion-based polymer systems for sustained-release diffusion membranes were compared with respect to the influence of coating process parameters. The product bed temperature, an important process parameter, proved to be noncritical for the organic solvent-based system within a product bed temperature range of 30–45°C, as was demonstrated by well reproducible release values. Since the release values showed a distinctly higher relative standard deviation at the lower spray rate, probably due to spray losses, the spray rate has to be carefully optimised. With one of the aqueous sustained-release systems, both the product bed temperature and the subsequent curing phase which was carried out at a fixed relative humidity and which needed to be sufficiently long had a decisive effect on the release rate. Modern fluid-bed techniques render anti-adhesives, such as talc, largely superfluous for the aforementioned sustained-release systems. When opting for organic solvent-based sustained-release systems, the technicalities of solvent recovery must be taken into consideration due to legal requirements concerning their emission. Compared with organic solvent-based lacquer systems, aqueous latex systems involve higher development and production costs, as has been demonstrated by the influence of the product bed temperature and the subsequent curing. © 1997 Elsevier Science B.V.

Keywords: Multiple-dose units; Sustained-release; Pellet core properties; Curing; Coating process parameters

1. Introduction

Sustained-release dosage forms based on multiple-dose units have the advantage that they allow a more predictable gastric emptying, with an evacuation through the pylorus spread over a longer period of time and a gastric emptying which is less dependent on the nutritional state since the subunits are sufficiently small to be evacuated through the pylorus during the digestive phase [1].

Pellet cores can be manufactured, among other methods, by extrusion and subsequent rounding [2,3] or by granulation in a high-shear mixer [4]. Most systems use diffusion membranes which are applied to the core by a variety of coating procedures [5–10]. With the same percentage amount of polymer applied, the release rate is directly proportional to the surface of the coated particles [11]. It was demonstrated that various size beads, dispersed in a single bed, display differences in film thickness when coated in a fluidised bed apparatus equipped with a Wurster column [12]. The differences in film thickness were attributed to differences in fluidisation patterns and velocities of the various size beads.

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It was observed that, unlike batches coated in the bottom spray (Wurster) mode, batches coated in the top and tangential spray modes exhibited no trend in film thickness [13]. When polymer from an organic solution is applied to pellet cores, retardation is stronger than when the same percentage amount of polymer from an aqueous dispersion is applied to pellets [14]. The curing of coated beads at elevated temperatures immediately after the coating process significantly changed the drug release pattern of ibuprofen pellets [15]. With propanol pellets, the curing temperature had a more dramatic effect than the curing time [16]. With theophylline pellets, the release rates from pellets coated with Eudragit® RS 30 D were significantly higher when the storage temperature and relative humidity were increased [17]. When Eudragit® RS 30 D and RS 30 L were used for coating theophylline-containing pellets, the theophylline release was very slow and practically parallel to Eudragit® RS 30 D alone, whereas the release was practically unmodified with Eudragit® RL 30 D-coated pellets [18]. For Eudragit® RL/RS 30 D, the minimum film-forming temperature is 20–24°C, depending on the ratio of the two polymers. For the coating of the pellet cores, a product temperature of about 10–20°C above the minimum film-forming temperature is recommended [19]. For aqueous Eudragit® RS 30 D/RL 30 D dispersions, colloidal silica has been found preferable to talc as a separating agent [20].

1.1. Aim of the study

Theophylline was used as active ingredient for studying the effect of the particle size and surface morphology of smooth pellets and rough granules lacquered in the Hüttlin Kugelcoater® on in vitro release. Furthermore, for Eudragit® RL/RS, polymers from organic solvent-based solutions and aqueous dispersions were compared with regard to the application rate, reproducibility and effect of product bed temperature on in vitro release. The effect of dilution and subsequent curing of the applied films on release retardation was investigated for Surelease® X, an aqueous dispersion with a 19% ethyl cellulose content whose minimum film-forming temperature is approximately 30°C [21].

2. Materials and methods

2.1. Materials

2.1.1. Theophylline pellets

The pellets were produced using anhydrous theophylline 200 (Knoll, Ludwigshafen, Germany), povidone 25 (BASF, Ludwigshafen, Germany) and isopropanol (Merck, Darmstadt, Germany).

2.1.2. Microscope

The microscopic evaluation of the pellets was performed using an Olympus SZH 10 microscope (Olympus, Hamburg, Germany).

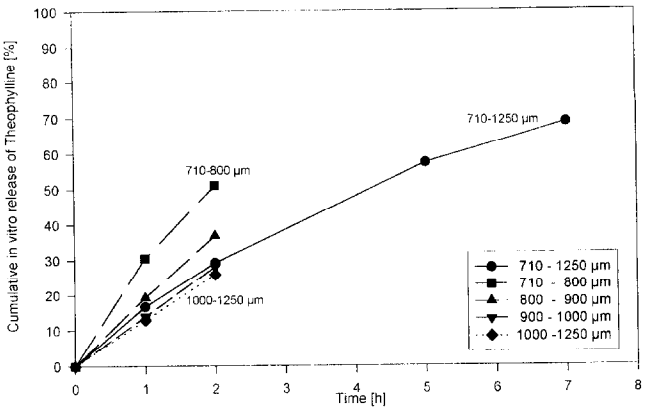

Fig. 1. Influence of pellet size on in vitro release (batch No. 924).

2.1.3. Latex polymer dispersions

Eudragit® RL 30 D and RS 30 D were bought from Röhm Pharma, Weiterstadt, Germany. Before use, dibutyl phthalate (Palatinol® C, BASF, Ludwigshafen, Germany) was added as plasticiser, and Tween 80 (Merck, Darmstadt, Germany) as emulsifier.

Surelease® X was bought from Colorcon, Orpington, Great Britain.

2.1.4. Organic solvent-based polymer solution

Eudragit® RS 100 and RL 100 (Röhm, Darmstadt, Germany) were dissolved with dibutyl phthalate (Palatinol® C, BASF, Ludwigshafen, Germany) as plasticiser in a mixture of isopropanol and acetone (both from Merck, Darmstadt, Germany).

2.1.5. Salt solutions for defined humidities

$MgCl_2$, $NaNO_2$ and NaCl, used to prepare salt solutions, were bought from Merck, Darmstadt, Germany.

2.1.6. Dissolution test

KH_2PO_4 and NaCl were bought from Merck, Darmstadt, Germany.

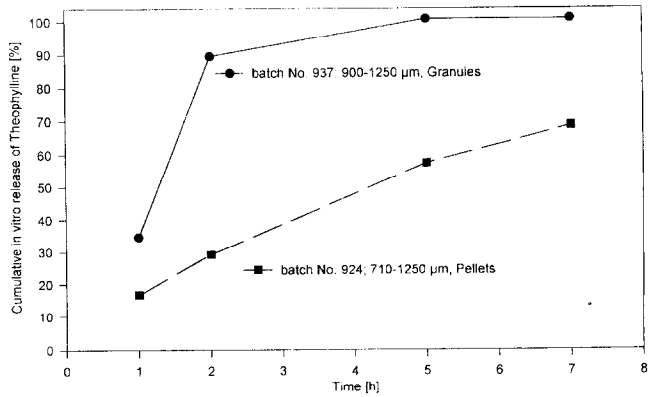

Fig. 2. Influence of particle shape on in vitro release.

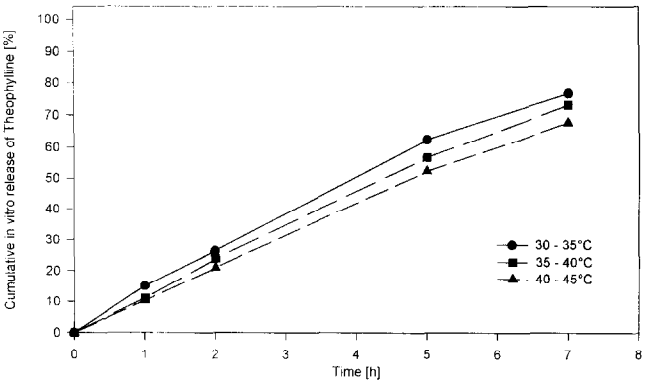

Fig. 3. Influence of product temperature on in vitro release; ammonium methacrylate (organic solution); feed rate 50 g/min.

2.2. Methods

2.2.1. Manufacture of theophylline pellets and granules

The powder components, anhydrous theophylline (90%) and povidone 25 (10%), were pelletised in a Henschel FM 10 high-speed mixer (Henschel-Rheinstahl, Kassel, Germany) at 400 rpm with an adequate amount of isopropanol at a spray rate of about 100 ml/min in about 3–5 min. Drying ensued for 20 min at 60°C in a fluid-bed dryer (Aeromatic Strea-1, Niro-Aeromatic, Bubendorf, Switzerland). The particle fraction size between 0.71 mm and 1.25 mm was separated by manual sieving for subsequent use.

For the manufacture of theophylline granules, theophylline pellets were processed in a Frewitt MGL granulator (Frewitt, Fribourg, Switzerland) and hand-sieved (710–1250 μm). This material was then divided by hand-sieving into the 710–800 μm, 800–900 μm, 900–1000 μm and 1000–1250 μm fractions.

2.2.2. Assessment of particle surface morphology

The particle surface morphology was assessed qualitatively by microscopic evaluation. In this study, spherically shaped particles with a smooth surface are defined as smooth pellets, whereas particles with a nonspherical, irregular shape and rough surface are called rough pellets.

2.2.3. Preparation of aqueous polymer dispersions

A mixture of Eudragit® RS 30 D and RL 30 D (350 g) was supplemented with dibutyl phthalate (10.5 g = 10% based on the amount of polymer), Tween 80 (0.105 g), micronised talc (17.5 g) and demineralised water (322 g), and stirred for 1 h (IKA magnetic stirrer, IKA Labortechnik Jahnke and Kunkel, Staufen i. Br., Germany) to ensure an even distribution of the plasticiser. Dibutyl phthalate was predispersed with Tween 80 and a small amount of water using an Ultraturrax (IKA Labortechnik Jahnke and Kunkel, Staufen i. Br., Germany).

Surelease® X (373 g) was mixed with micronised talc (17.5 g), diluted with demineralised water (76 or 1009 g, resulting in a polymer content of 15 or 5%) and stirred for 10 min (IKA magnetic stirrer, IKA Labortechnik Jahnke and Kunkel, Staufen i. Br., Germany).

2.2.4. Preparation of the organic solvent-based polymer solution

Isopropanol (367 g) and acetone (275 g) were put into a vessel and heated to approximately 25°C. A mixture of Eudragit® RS 100 and RL 100 (34.72 g) and dibutyl phthalate (3.5 g) were slowly added by stirring with an Ultraturrax (IKA Labortechnik Jahnke and Kunkel, Staufen i. Br., Germany). The solution was stirred for 1 h until the components were completely dissolved. Afterwards, different amounts of micronised talc (34.75, 17.38, 0 g) were added to three prepared solutions, respectively.

2.2.5. Preparation of salt solutions for defined humidities at 60°C

For a relative humidity of 30%, a saturated $MgCl_2$ solution was prepared, for a relative humidity of 58%, a saturated $NaNO_2$ solution, and for a relative humidity of 75%, a saturated NaCl solution.

2.2.6. Coating of the theophylline pellets

All trials were performed using a Kugelcoater® HKC-5, with a Quattro drive system and a 3-way nozzle system (Hüttlin Coating Technik, Steinen, Germany).

The following process parameters were kept constant in all trials:

Batch size:	3.5 kg theophylline pellets or granules
Number of spray nozzles:	8
Spray nozzle diameter:	1.0 mm
Spray pressure:	1.5 bar
Flow rate of process air:	340 m^3/h

The following parameters were modified according to the trial design:

	Organic polymer solution:	Aqueous dispersion:
Spray rate:	50 g/min or 100 g/min	30 g/min
Product bed temperature:	30–35°C	23–27°C
	35–40°C	28–32°C
	40–45°C	38–42°C
		48–52°C

Table 1
Cumulative in vitro release of theophylline from pellets coated with organic solvent-based ammonium methacrylate solution at different product bed temperatures

Time [h]	Cumulative in vitro release of theophylline [%]					
	Pt. 30–35°C	SDR [%]	Pt. 35–40°C	SDR [%]	Pt. 40–45°C	SDR [%]
a. Feed rate: 50 g/min ($n = 3$)						
1	15.1	36.4	11.1	13.5	10.3	25.2
2	26.4	14.0	23.8	9.2	20.9	22.5
5	62.5	6.7	56.8	5.8	52.4	15.3
7	76.9	7.8	73.2	4.2	67.8	12.8
b. Feed rate: 100 g/min ($n = 3$)						
1	11.6	10.4	11.4	7.9	10.8	12.0
2	22.0	6.4	21.7	9.8	22.8	7.0
5	51.3	2.0	49.6	6.9	53.5	7.5
7	64.9	2.3	61.6	8.7	65.0	4.8

2.2.7. Curing of the pellets

All pellet samples coated with the aqueous dispersion were subjected to a curing step to allow complete film formation of the applied polymer. This follow-up treatment was performed either in a Petri dish in a dry cabinet (Heraeus, Hanau, Germany) at 60°C for 1 or 24 h or in vials with screw caps over saturated saline solution producing relative humidities of 30, 58 and 75%, at the temperature of 60°C for 1 or 24 h. The humidity calculation was based on DIN 50 008.

2.2.8. Dissolution test

All the samples were subjected to a dissolution test under the following conditions:

Model:	basket, 100 rpm, 37°C, n = 3
Volume:	1000 ml
Change in pH:	
0–2 h:	pH 1.2
2–7 h:	pH 6.8
Dissolution medium at pH 1.2:	according to USP
Dissolution medium at pH 6.8:	according to USP +0.55% (w/v) NaCl

Pellets, 375 mg, were weighed into the basket. After 1, 2, 5 and 7 h, 10 ml of sample were passed through a filter and this volume replaced by the corresponding medium. Determination of the released theophylline was performed photometrically at 271 nm (UV photometer UV-2101PC, Shimadzu, Duisburg, Germany).

3. Results

3.1. Influence of pellet size and surface morphology on in vitro dissolution

Coated pellets taken from a laboratory batch were sieved into four fractions and each fraction was evaluated separately for active ingredient dissolution. Due to the larger surface of an identical mass, the fraction containing smaller pellets showed a faster active ingredient release than the fractions containing larger pellets (Fig. 1). The dissolution curve of the overall batch gave an indication of the relative amount of the four partial fractions contained in this batch.

Rough theophylline granules [900–1250 μm] were coated with ammonium methacrylate (organic solvent-based solution) and subjected to an in vitro dissolution test. Compared with smooth pellets, the coated granules released the active ingredient at an above-average rate from the second hour onwards (Fig. 2).

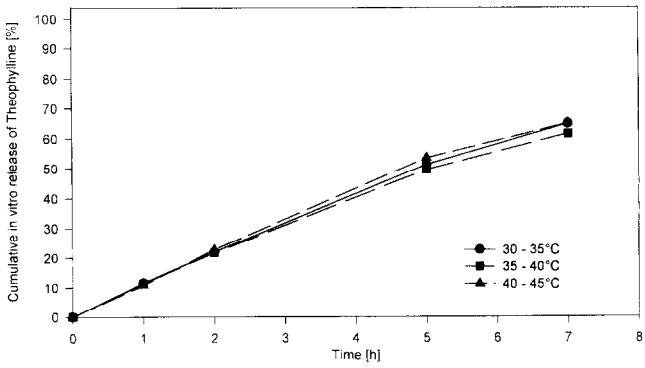

Fig. 4. Influence of product temperature on in vitro release; ammonium methacrylate (organic solution); feed rate 100 g/min.

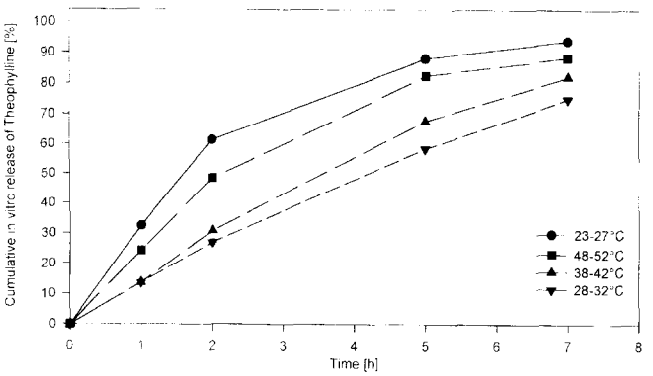

Fig. 5. Influence of product temperature on in vitro release; ammonium methacrylate dispersion (aqueous); feed rate 30 g/min.

3.2. Influence of the coating process on in vitro dissolution

3.2.1. Product bed temperature

3.2.1.1. Organic solvent-based ammonium methacrylate. The evaluation of the influence of the product bed temperature was based on the in vitro dissolution curves and the relative standard deviation (RSD) obtained in three trials of identical design. For good reproducibility, the relative standard deviation of the dissolution should be $\leq 10\%$ (in-house requirement for close dissolution specification ranges).

At a spray rate of 50 g/min, the dissolution curves for the various product bed temperatures were in a relatively close range. However, the RSD values were greater than 10% with few exceptions (Fig. 3, Table 1a).

At a spray rate of 100 g/min, all RSD values were less than 10% from hour two onwards (Fig. 4, Table 1b).

3.2.1.2. Aqueous dispersion-based ammonium methacrylate. With a dispersion containing 15% polymer, applied at a rate of approximately 30 g/min, at product bed temperatures ranging 30–50°C, the release rate became faster as the product bed temperature was increased. However, the fastest release rate was observed for a product bed temperature of about 23–27°C. Compared with the organic solvent-based coating, all four release curves obtained with the aqueous dispersion showed distinctly increased release rates as well as increased relative standard deviations in the release rates (Fig. 5, Table 2).

3.2.1.3. Aqueous dispersion-based ethyl cellulose. The release rate of theophylline pellets coated at different product bed temperatures (40–50°C) was investigated under prolonged curing conditions. With 24 h curing at 60°C, the differences in the release behaviour found between product bed temperatures of 40 and 50°C were within the standard process fluctuation range when a dispersion diluted to 15% polymer was used. With a 5% dispersion, the release curve differed from that of the 15% dispersion from hour five onwards, according to F and t-tests, whereby a product bed temperature of 40°C resulted in a stronger retardation (Fig. 6, Table 3).

3.2.2. Curing conditions

3.2.2.1. Aqueous dispersion based ethyl cellulose. Theophylline pellets were coated with a dispersion diluted to a polymer content of 15% and subsequently cured at 60°C for 1–24 h under different humidity conditions (Fig. 7). Whereas with 1 h curing different relative humidity conditions produced different release curves, 24 h curing resulted in identical curves. By comparison, the in vitro release of a sample cured without controlled humidity conditioning was distinctly faster after 24 h (Fig. 8).

Pellets coated with 0.65% ethyl cellulose from a 5% ethyl cellulose dispersion (instead of the previous 15% dispersion) had the required release rate of 75% within 7 h also after curing (Fig. 9). Curing under controlled humidity conditions for different lengths of time showed that 1 h curing at 60°C/75% RH was insufficient for completing the film-forming process (Fig. 10). Curing for 24 h resulted in the slowest release rate, although longer curing periods did not further prolong the release.

As an alternative to long curing phases, it was investigated whether the film-forming process could be prolonged, and thus completed, already in the coater by spraying in different amounts of water directly after the coating phase. The aim was to add water to the film-forming process and thus, perform a curing step within the coater. However, the release was found to be only slightly slower than that of the untreated sample (Fig. 11).

3.2.3. Addition of talc to the organic solvent-based coating solution and its effect on in vitro release

Pellets from one batch were coated in three assays with an organic solvent-based sustained-release lacquer to which different amounts of talc had been added. The release behaviour of the batch with 50% talc differed only very slightly from the one with 100% talc (as in the original manufacturing instructions). When no talc was added, the release rate was slightly higher. However, this increase appeared to be within the usual batch variability (Fig. 12).

4. Discussion

4.1. Influence of pellet core characteristics on in vitro release

For good reproducibility of in vitro release, a narrow particle size range and a uniform particle size distribution within this range are required [11,12]. The results

Table 2
Cumulative in vitro release of theophylline from pellets coated with aqueous ammonium methacrylate dispersion at different product bed temperatures

Time [h]	Cumulative in vitro release of theophylline [%]							
	Pt 25°C	SDR [%]	Pt. 30°C	SDR [%]	Pt. 40°C	SDR [%]	Pt. 50°C	SDR [%]
1	32.5	15.4	13.6	22.1	13.6	44.1	24.2	33.1
2	61.4	13.0	27.0	18.5	30.8	35.7	48.5	22.7
5	88.2	6.8	58.5	6.8	67.8	19.2	82.6	7.3
7	94.0	1.1	75.1	9.3	82.2	12.2	88.5	1.1

Feed rate: 30 g/min ($n = 3$).

obtained indicate that the surface morphology of the particles, i.e. particle shape and surface smoothness, is also important for the in vitro release of coated particles. Since the film is thinner at the edges and the coating is likely to break at the edges under strain, both parameters are very likely to have an effect on the thickness of the film and on the stability of the coating. This is supported by the fast in vitro release of the coated granules revealing an irregular shape and a rough surface. Therefore, the conclusion that the release rate is directly proportional to the surface of the coated pellets [11] is valid only for pellets with comparable surface morphology.

4.2. Influence of the coating process on in vitro release

The results indicate that with the system described for the organic solvent-based ammonium methacrylate solution, release values with good reproducibility can be achieved on the laboratory scale in a temperature range of 30–45°C. Compared with the lower spray rate, the higher spray rate produces smaller relative standard deviations of the release values due to reduced spray-drying effects. When organic sustained-release systems are used, it can be assumed that the film-formation process will be completed at the end of the coating process (including follow-up drying) and that the product bed temperature is not a critical parameter over a wide temperature range—at least when this coating technology is used.

The product bed temperature appears to be more important in the case of aqueous sustained-release dispersions: the relatively fast release of the pellets coated at 50°C might be accounted for by higher spray losses and/or increased active ingredient dissolution in the coating [5,15]. At 25°C, the rapid release may be attributable to the fact that this temperature is below the minimum film-forming temperature. Additionally, the relative standard deviations of the release values were distinctly above 10% at all product bed temperatures. This may be because the trials were not performed under controlled humidity conditions (which may in fact be necessary) [22] and because the film formation was not completed during the short curing phase (1 h at 60°C). It appears that with aqueous sustained-release dispersions, the product bed temperature must be viewed in connection with the follow-up treatment of

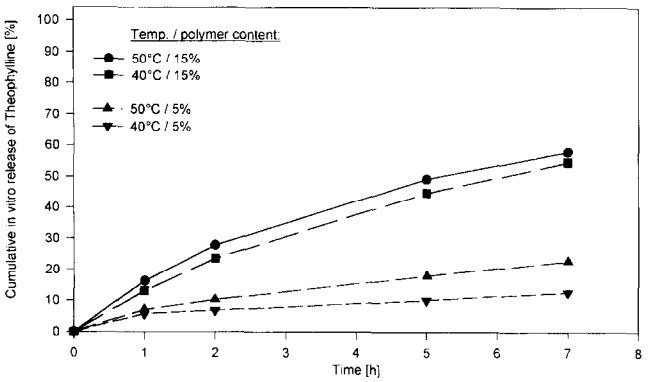

Fig. 6. Influence of product temperature and dispersion dilution on in vitro release; Ethyl cellulose (aqueous; 2% polymer per pellet); feed rate 30 g/min; curing: 24 h/60°C; no controlled humidity; $n = 3$.

Table 3
Cumulative in vitro release of theophylline from pellets coated with aqueous ethyl cellulose dispersion at different product bed temperatures and subjected to prolonged curing (5% dispersion, $n = 3$)

Time [h]	Test value PF	F test ($n = 3$)	Test value Tau	t-test ($n = 3$)
1	0.65	$F(95) = 19.0$	0.38	$F(95) = 2.78$
2	1.55	$F(99) = 99.0$	1.33	$F(99) = 4.60$
5	6.26	$F(99.9) = 999.0$	3.24	$F(99.9) = 8.61$
7	25.56		3.90	

Results of F and t-tests.

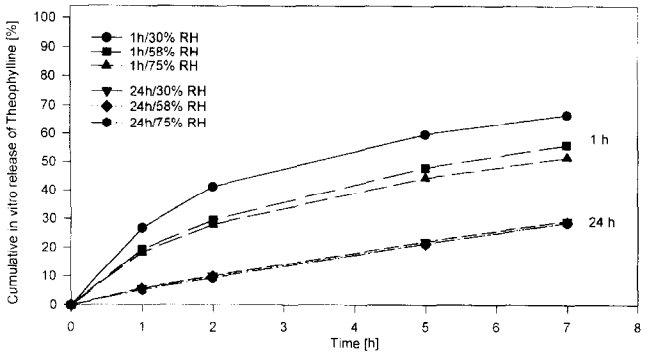

Fig. 7. Influence of duration and humidity during curing at 60°C on in vitro release; ethyl cellulose (2% per pellet; aqueous dispersion diluted to 15% polymer content; product temperature 40°C; $n = 1$).

the coated pellets, and product bed temperature and tempering conditions must be optimised jointly [23].

Curing trials performed with pellets coated with ethyl cellulose under various relative humidity conditions demonstrated that as from a curing period of 24 h, the film-forming process can be considered complete. After this curing period, the absolute value of the relative humidity in the range of 30–75% no longer seems to be decisive. However, the results of the curing trials without controlled humidity also show that only curing under controlled humidity conditions will result in the complete film coating by the latex particles. This is confirmed by results from Amighi and Moës who investigated Eudragit® RS 30 D [17].

Although water can act as a plasticiser during the film-forming process, spraying water immediately after the coating process does not provide an alternative to curing since the release is only slightly slower than that of the untreated sample.

Trials aimed at optimising the polymer amount showed that, for ethyl cellulose, the amount of polymer required for the release of at least 75% of the theophylline active ingredient within 7 h is very small, so that—under actual production conditions—fluctuations in the surface properties and in the particle size

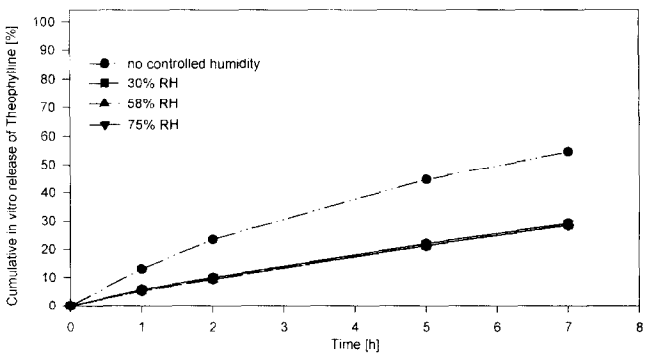

Fig. 8. Influence of humidity during curing for 24 h at 60°C on in vitro release; ethyl cellulose (2% per pellet; aqueous dispersion diluted to 15% polymer content; product temperature 40°C; $n = 1$).

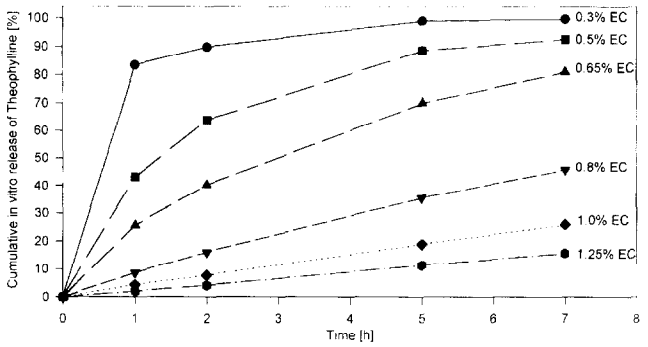

Fig. 9. Influence of polymer amount on in vitro release; ethyl cellulose dispersion (aqueous dispersion diluted to 5% polymer content) curing conditions: 24 h/60°C per 75% RH.

distribution of the pellet cores alone are likely to result in poor reproducibility. It is therefore advisable to process ethyl cellulose together with pore formers, as described in the literature [24–27].

4.3. Addition of talc to the organic solvent-based coating solution and its effect on in vitro release

The results indicate that with modern coating techniques such as using the Hüttlin Kugelcoater®, the amount of anti-adhesive in the lacquer solution can be distinctly reduced or even dispensed with when using several spray zones and the same time effective drying can be achieved within one spraying cycle (period from the first spray jet passage of the pellets to the second). With the three-way spray nozzle system, problems like blocking of the piping and the spraying system do not occur, as is observed with two-way spray nozzle systems [20].

4.4. Fluidisation characteristics of the Hüttlin® Kugelcoater

Wesdyk et al. concluded that batches coated either in the top or the tangential spray mode do not show any

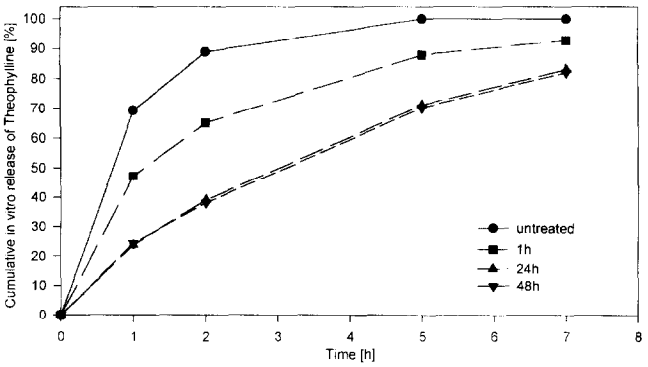

Fig. 10. Influence of the curing period with controlled humidity (60°C/75% RH) on in vitro release; ethyl cellulose (0.65% polymer per pellet; aqueous dispersion diluted to 5% polymer content).

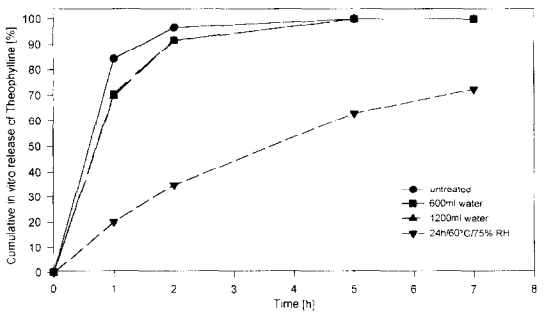

Fig. 11. Influence of the spraying of water after coating on in vitro release; ethyl cellulose (0.65%; aqueous dispersion diluted to 5% polymer content).

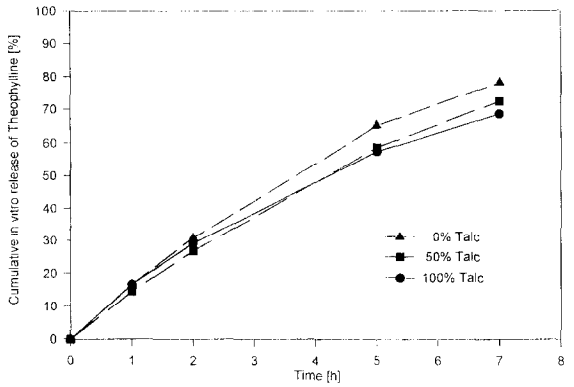

Fig. 12. Influence of talc on in vitro release.

differences in film thickness for different pellet fractions, in contrast to the same pellets coated using the Wurster column [13] where the differences were due to different fluidisation patterns and velocities of varying sizes beads. Since the dissolution curve of the overall batch is a composition of the four partial fractions investigated here, differences with regard to the fluidisation pattern and velocities of various size beads do not seem to exist for the Hüttlin Kugelcoater®.

5. Conclusion

Modern coating technologies allow the efficient and reproducible coating of pellets with organic solvent-based sustained-release systems. When aqueous sustained-release lacquer dispersions are used, curing of the coated pellets under controlled temperature and humidity conditions appears to be indispensable for obtaining reproducible release results.

Same amounts of sustained-release polymer coated onto pellet cores reveal stronger retardation of the release behaviour when organic solvent-based polymers are used. Compared with aqueous-based dispersions, organic solvent-based polymers allow a three times faster spray rate for the same amount of polymer.

For the production scale, the efforts required for solvent recovery when organic solvent-based systems are used must be fully assessed. Compared with organic solvent-based systems, aqueous systems require higher expenditure for process optimisation and process validation.

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