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RESEARCH PAPER

Development of Matrix-Based Theophylline Sustained-Release Microtablets

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ABSTRACT

Microtablets containing high theophylline content (from 60% to 80%) based on a Eudragit RS PO matrix were produced on a rotary tablet press. The influence of the compaction pressure, the plasticizer content used for the granulation of theophylline particles, and the amount of theophylline on the drug release were investigated. The effects of surface area and the addition of magnesium stearate as a hydrophobic agent on the drug release were studied. The storage stabilities of the release rate at room temperature and at 50°C were also determined. Dissolution profiles expressed as percentage of theophylline dissolved were obtained over 8 hr in 900 ml of purified water at 37°C and 75 rpm. It was observed that the compaction pressure (from 200 MPa to 250 MPa) had no effect on the theophylline release. The use of triethyl citrate (TEC) as a plasticizer in the granulation of theophylline enhanced the physical properties of the microtablets. Theophylline content in the range 60% to 80% did not affect the drug release. The theophylline release obtained was a function of the quotient surface area/tablet weight and therefore was dependent on the tablet diameter. To reduce the dissolution rates, magnesium stearate was added in a concentration up to 50% of the matrix material. Tablets of this hydrophobic formulation fulfilled the requirements of USP 23 for theophylline sustained-release preparations. Storage at room temperature for 3 months and at 50°C for 2 months showed no significant influence on the theophylline release.

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INTRODUCTION

Multiple-unit dosage forms provide several advantages compared to single-unit ones. Risks such as spontaneous drug release from a single-unit tablet due to damaged coating or its fixation in the stomach or intestine are reduced by the use of multiple-unit forms. Clarke, Newton, and Short found that, with pellets with a density below 2.4 $g.cm^{-3}$, an accumulation in the stomach was avoided (1). Moreover, such pellets enable a more reproducible dispersion throughout the gastrointestinal tract; thus, bioavailability was improved, and variations in drug release were reduced (2).

Multiple-unit dosage forms containing pellets are still produced (3). Nevertheless, microtablets, which are tablets having a diameter of 2 mm or less, represent an interesting alternative to pellets. Since microtablets are produced by compression (4), many steps of pellet production, like moisturizing, extruding, spheronizing, and drying, can be avoided. However, due to the narrow diameter of the die, parameters like particle size and flowability of the granules are critical points for microtableting (5). Although sustained-release tablets containing acrylic resin polymers as a film coating are widely developed, matrix systems appear to be quite attractive and an interesting approach from the economic and the process development points of view. Single-unit matrix tablets have been described by Lehmann (6) and McGinity, Cameron, and Cuff (7). The aim of this study was therefore to develop high-dose theophylline sustained-release microtablets to deliver the drug within 8 hr and with the release controlled by a Eudragit RS PO matrix.

EXPERIMENTAL

Materials

Theophylline (mean particle size 13.7 μm), Eudragit RS PO, Eudragit RS 30D, and triethyl citrate (TEC) were supplied by Röhm GmbH (Darmstadt, Germany). Magnesium stearate and Aerosil 200 were supplied by Bärlocher GmbH (Munich, Germany) and by Degussa AG (Frankfurt/M., Germany), respectively.

Preparation of Theophylline Granules

In a fluidized bed granulator (Uniglatt, Glatt GmbH, Binzen, Germany) equipped with an 0.8-mm nozzle, batches of 400 g powder (Table 1) were granulated by top-spraying 400 g of a 6% solution of Eudragit RS 30D as a binder at an atomizing air rate of 1.2 bar. Inlet air temperature was maintained constant at 60°C, and granulating liquid flow rate was set to 18–20 g/min and controlled by a peristaltic pump (Watson Marlow 505S, Falmouth, England). The granules were then dried in the same apparatus for approximately 15 min at the same temperature. The granules were sieved by hand, and the fraction below 500 μm was used for further preparation of the tablets.

Table 1

Composition and Physical Properties of Granules

	1	2	3	4	5	6	7	8
Theophylline (%)	80	70	60	70	70	70	70	70
Eudragit RS PO (%)	14	24	34	24	24	18	15	12
Magnesium stearate (%)						6	9	12
Eudragit RS 30D (%)	6	6	6					
Eudragit RS 30D + 10% TEC (%)				6		6	6	6
Eudragit RS 30D + 20% TEC (%)					6			
Aerosil 200 (%)[a]	0.5							1.5
Particle size:								
x_{10}	56.27	54.45	66.98	61.92	48.72	55.90	63.43	36.40
x_{50}	126.50	139.24	128.02	115.30	106.79	130.82	162.41	96.70
x_{90}	302.07	299.99	235.83	212.43	247.66	287.09	323.87	254.14
Angle of repose (°)	29.6	29.2	29.0	30.0	32.1	30.2	29.6	36.7

[a] Added after granulation to enhance flow properties.

Granule Parameters

Particle size distribution of approximately 20 g of the granules was measured by laser diffraction (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using the gravity-dispersing system GRADIS, a focal length of 500 mm, and a measuring time of 10 s. The mean of three measurements was calculated. Flowability of the granules was determined by the funnel method (DIN 53916). Nonflowing granulations were measured after the addition of colloidal silicon dioxide (Aerosil 200; see Table 1). The angle of repose was measured using 150 cm^3 of granules, and the mean of three samples was determined.

Blending and Tableting

Granules were blended with 2% magnesium stearate for 10 min in a tumbling mixer (Turbula T2C, W. A. Bachofen, Basel, Switzerland). The microtablets were compressed on an instrumented rotary tablet press (Korsch PH 230/17, Korsch Pressen GmbH, Berlin, Germany) using a force feeder and 1 of the 17 punch stations. The punch station was equipped with a punch holder containing 19 small concave punches, each with a diameter of 2 mm. The speed was kept constant at 26 rpm. The band height of the tablet was 0.8 mm, and a compaction pressure of 200 MPa or 250 MPa was employed. Data acquisition and processing were obtained from the Compression Research System (Korsch Pressen GmbH).

Tablets of 6 and 10 mm diameter were compressed on an instrumented single-punch tablet press (EK 0, Korsch Pressen GmbH) at the same compaction pressure. The primary signal from the strain gauges was amplified by a 5-kHz carrier frequency amplifier (Philips PR 9307, Philips GmbH, Kassel, Germany) and was further processed by an analog/digital converter (Spider 8, Spectris Messtechnik GmbH, Darmstadt, Germany). Data acquisition was performed using the software system BEAM (AMS, Flöha, Germany).

Tablet Parameters

The weight (AE 200 balance, Mettler-Toledo GmbH, Gießen, Germany), the thickness (0.01-mm micrometer, Mitutoyo Co., Ltd., Japan), and the crushing strength (model 6D, Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland) of 10 microtablets each were measured. Mean, relative standard deviation, and confidence intervals were calculated.

Dissolution

Drug release profiles were carried out using a paddle apparatus (dissolution-tester, Sotax AT7, Basel, Switzerland). The dissolution medium was 900 ml of purified water maintained at 37°C. Samples of 5-ml aliquots were taken at specified time intervals: 15, 30, 60, 120, 180, 240, 300, 360, 420, and 480 min. The rotational speed of the paddles was 75 rpm. Theophylline content was assayed at 271.4 nm using an ultraviolet (UV) spectrophotometer (Perkin-Elmer 550S, Überlingen, Germany). Each data point represents the mean of measurements of three different samples.

RESULTS AND DISCUSSION

To study the influence of the compaction pressure on the drug release, microtablets containing 70% theophylline, 6% Eudragit RS 30D as a binder, 24% Eudragit RS PO as a matrix-forming polymer, and 10% TEC as a plasticizer (Table 1, granule 4) were compressed at either 200 or 250 MPa. The release profile of theophylline over 8 hr is shown in Fig. 1. The compaction pressure showed no significant effect on the drug release as dissolution rates were quite similar at 200 and 250 MPa. This could be explained by the plastic behavior of the material during compression. Calculation of the tablet porosity revealed a difference of only 0.5% between microtablets compressed at 200 and 250 MPa, for a total porosity of 8.4% (200 MPa).

As the plasticity of the polymers can be enhanced by the addition of a plasticizer, the influence of TEC content on the theophylline release was studied. Microtablets

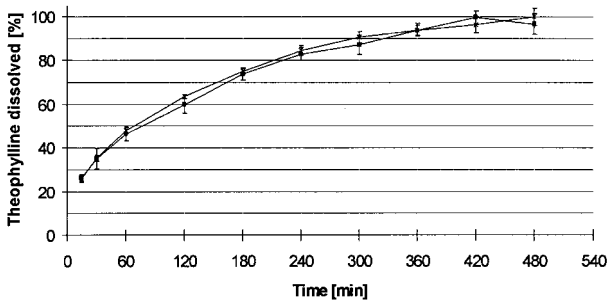

Figure 1. Influence of compaction pressure on the release of theophylline from microtablets ($n = 3$) (Table 1, granule 4). ×, 200 MPa; ■, 250 MPa. Error bars represent the 95% confidence interval.

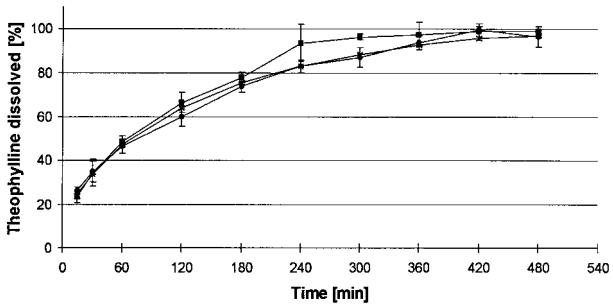

Figure 2. Effect of triethyl citrate concentration on theophylline release from microtablets (n = 3): ■, 0%; ●, 10%; ×, 20% (with 6% Eudragit RS 30D). Error bars represent the 95% confidence interval.

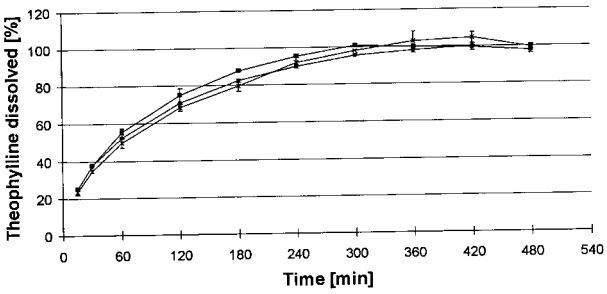

Figure 3. Effect of theophylline content on the dissolution rate of the drug (n = 3): ■, 80%; ●, 70%; ×, 60%. Error bars represent the 95% confidence interval.

containing 70% theophylline and 0%, 10%, or 20% TEC as a plasticizer were compressed at 250 MPa (Table 1, granules 2, 4, 5). The dissolution profiles are shown in Fig. 2. The drug release from microtablets containing TEC showed slightly lower dissolution rates compared to tablets without plasticizer. Nevertheless, no significant difference could be observed between formulations containing 10% and 20% plasticizer. An increase in the content of plasticizer leads to a decrease in the minimum film-forming temperature. Thus, greater elasticity, greater adhesiveness, and better film formation of the polymer were achieved. This is demonstrated in Table 2, in which shows that the physical properties of microtablets containing 20% TEC exhibited a higher crushing strength (Table 2, formulation 5).

The influence of the theophylline content on the drug release is depicted in Fig. 3. Microtablets containing 60% to 80% of theophylline in an Eudragit RS PO matrix were compressed at 200 MPa (Table 1, granules 1–3). The dissolution profiles revealed fast theophylline release. The total amount of theophylline was already dissolved within 5 hr, and the initial release was at least 20% after 15 min for the three different formulations. In the range 60–80% theophylline content, no significant difference in dissolution rate was observed. Cameron and McGinity (8) found a decreasing dissolution rate of theophylline by increasing the total amount of polymer in a matrix tablet. Therefore, by increasing the amount of Eudragit RS PO matrix from 14% to 34%, thus decreasing the content of theophylline, the dissolution rates were expected to be reduced. Surprisingly, it was observed that the theophylline content of microtablets had only a small effect on the drug release. This could be attributed to the effect of the surface area/weight ratio. A strong correlation was therefore expected between the surface area of the tablets and dissolution behavior. Microtablets having a diameter of 2 mm exhibit higher surface area (2.40 mm^2/mg) compared to tablets 6 mm in diameter (surface area 0.99 mm^2/mg) and 10-mm tablets (surface area 0.59 mm^2/mg).

Table 2

*Physical Properties of Microtablets (*n *= 0) Compressed at Compaction Pressures of 200 MPa (Granules 1–3) and 250 MPa (Granules 4–8)*

	1	2	3	4	5	6	7	8
Weight (mg)	6.08 (±0.06)	5.77 (±0.04)	5.70 (±0.06)	6.45 (±0.09)	6.96 (±0.07)	6.92 (±0.06)	6.83 (±0.06)	6.51 (±0.15)
Tablet height (mm)	1.879 (±0.018)	1.864 (±0.022)	1.890 (±0.022)	2.004 (±0.012)	2.143 (±0.009)	2.076 (±0.016)	2.075 (±0.014)	2.018 (±0.018)
Crushing strength (N) (200 MPa/250 MPa)	6.2/— (±0.3/—)	4.1/5.3 (±0.2/0.3)	4.3/5.4 (±0.3/0.4)	6.3/7.4 (±0.3/0.4)	10.3/11.9 (±0.5/0.8)	6.4/7.5 (±0.4/0.4)	6.9/7.5 (±0.4/0.4)	7.5/9.3 (±0.8/0.6)

Figures in parentheses represent the 95% confidence interval.

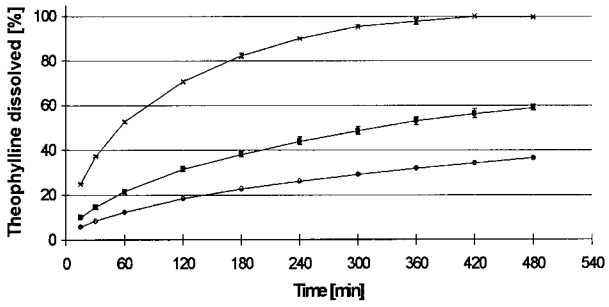

Figure 4. Release of theophylline from tablets ($n = 3$) of different diameters: ×, 2 mm; ■, 6 mm; and ○, 10 mm. Error bars represent the 95% confidence interval.

Release of a drug is a function of the quotient surface area/tablet weight. To verify this, tablets 2, 6, and 10 mm in diameter containing 70% theophylline and 24% Eudragit RS PO (Table 1, granule 2) were compressed at 200 MPa. The liberation of theophylline depended on tablet surface area (Fig. 4). Compared to 2-mm cores, drug release was slower with 6-mm tablets and much slower with 10-mm tablets. Consequently, tablets with a low quotient surface area/tablet weight lead to slower release.

As it is not possible to modify the quotient surface area/tablet weight of the microtablets, it was necessary to change the composition of the inert matrix by replacing part of the Eudragit RS PO with a hydrophobic substance to decrease wettability and hence the dissolution rate of the active ingredient. Magnesium stearate was chosen and added at different concentrations. Tablets composed of 70% theophylline, 24% matrix (comprised of Eudragit RS PO and magnesium stearate), and 6% Eudragit RS

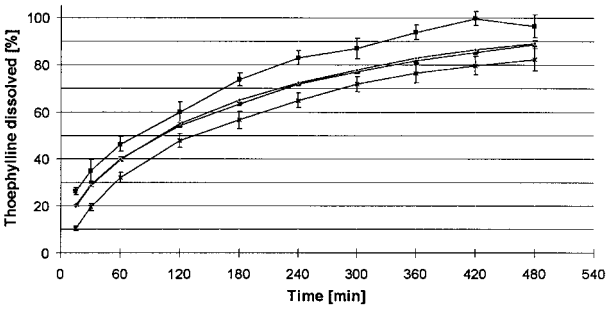

Figure 5. Release of theophylline from microtablets ($n = 3$) containing a matrix composed of Eudragit RS PO and magnesium stearate at different levels: ■, 0%; ▲, 6%; ◆, 9%; and ×, 12%. Error bars represent the 95% confidence interval.

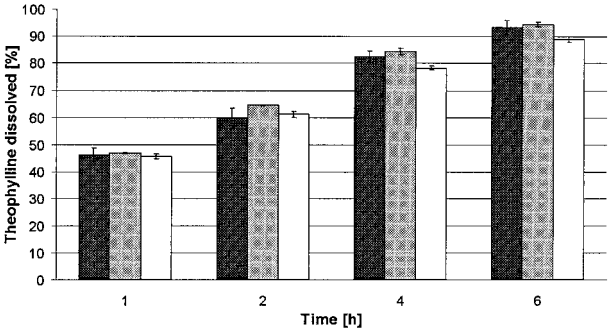

Figure 6. Influence of storage time on the theophylline release from microtablets ($n = 3$): ■, freshly prepared; ■, 3 months at room temperature; □, 2 months at 50°C. Error bars represent the 95% confidence interval.

30D plus 10% TEC as a binder (Table 1, granules 4, 6–8) were compressed at 250 MPa. The cumulative percentage of theophylline release is shown in Fig. 5. Obviously, slower dissolution profiles were obtained when magnesium stearate in the range 6–12% was present in the matrix. However, only a slight difference could be observed between 6% and 9% of magnesium stearate, but at a concentration of 12%, which is 50% of the total matrix weight, the release was significantly slower.

To investigate the storage stability of the theophylline release, microtablets (Table 1, granule 4) were stored at room temperature for 3 months and at 50°C for 2 months. Dissolution rates were determined and compared to the initial ones to see if there were deviations. The data obtained after 1, 2, 4, and 6 hr of dissolution testing are depicted in Fig. 6. As can be seen in the figure, the dissolution rates of the stored microtablets are quite similar to those of the freshly prepared ones, indicating that microtablets are quite stable at both elevated temperatures and room temperature.

CONCLUSIONS

Based on the findings of this study, the following conclusions may be drawn regarding matrix microtablets:

- Matrix microtablets can be used as subunits to prepare multiple-unit dosage forms.
- Microtablets provide high reproducibility with respect to weight uniformity, hardness, and dissolution rate.
- Drug release from microtablets is independent of the theophylline content in the range 60–80% and the compaction pressure.

- Addition of hydrophobic substances reduces dissolution rates, and this may satisfy the USP 23 requirements.
- Microtablets are quite stable at both elevated temperatures and room temperature.

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