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COMMUNICATION

Study of the Theophylline Content of Single Coated Particles by Gas Chromatography/Mass Spectrometry

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ABSTRACT

The aim of the present study was to determine by gas chromatography/mass spectrometry (GC/MS) the content uniformity of single theophylline microcapsules of different particle size ranges. Microencapsulation was carried out in a laboratory fluidized bed system using Eudragit L30D aqueous dispersion. Scanning electron microscopy was applied for the characterization of the surface morphology of the prepared theophylline microcapsules of two different particle size ranges. The theophylline content of single particles was determined by GC/MS analysis. It was found that the particle size of microcapsules greatly influenced their theophylline content. The GC/MS analysis was successfully applied to indicate the changes in the content uniformity and thus the interparticular coating distribution of single theophylline microcapsules in the presence of several excipients.

INTRODUCTION

Ever since the pharmacopeia published the ''uniformity of dosage units'' regulation, content uniformity has been considered one of the most important characteristics of solid dosage forms. Some intermediate products, such as single coated particles, used to produce multiple-unit dosage forms were not mentioned in this context. It was generally assumed that good content uniformity of the final dosage form implied satisfactory content uniformity of the intermediate products (1,2). Further expensive and time-consuming investigations concerning the features of the intermediate dosage forms were rarely performed. Since the legal case of the FDA versus Barr Laboratories emphasized the importance of pharmaceutical current good manufacturing practices, the need to control the content uniformity of

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all intermediate products has been urged (3).

Multiparticulate dosage forms are commonly coated in a fluidized bed system. The possible agglomeration of beads during coating could result in nonhomogeneous distribution of coating material on the surface of cores (4,5). Gas chromatography/mass spectrometry (GC/MS) is a sensitive and reliable method for the quantification of a small amount of volatile active ingredient (6–9) of solid particles containing various excipients. Theophylline, widely used in asthmatic preparations, has been assayed by various methods. Spectrophotometric determinations are rapid but nonspecific unless the active ingredients are separated from interfering species adequately (10,11). The GC/MS method demonstrates greater specificity and selectivity in the determination of theophylline due to its thermostable and volatile properties and the selected ion monitoring of mass spectrometry.

The purpose of this study was to determine by GC/MS analysis the theophylline content of single coated particles of different particle size ranges.

EXPERIMENTAL

Materials

Anhydrous theophylline (Ph.Hg. VII, Hungaropharma, Budapest; batch B-16263.95), lactose EP (De Melkindustrie Veghel bv, Holland; batch 640937/5), polyvinylpyrrolidone (Kollidon 30, BASF, Ludwigshafen, Germany; batch 107653), Eudragit L30D aqueous dispersion (Röhm Pharma, Weiterstadt, Germany; batch 1240614138), polyethylene glycol 6000 (Ferax, Berlin, Germany; batch 51359) were used for the experiment.

Preparation of the Cores

Theophylline (200 g) and lactose (200 g) were granulated with 10% (w/w) Kollidon 30 aqueous solution in Aeromatic Strea-1 (Aeromatic AG, Bubendorf, Switzerland) laboratory fluidization equipment. The process parameters were as follows: 400 g base material; top, middle spray atomizing method; 1 bar atomizing pressure; 10 s atomizing; 12.5 ml/min feeding rate of the granulation liquid; 50°C inlet air temperature; 50 s drying time after each atomizing period.

Coating Procedure

Before the coating procedure, the prepared theophylline granules were fractionated. Only the fractions 250–1000 μm were used for coating. The process parameters were as follows: 200 g granules; 1 bar atomizing pressure; 10 s atomizing period; 8.3 ml/min feeding rate of the coating dispersion; 45°C coating temperature; 120 s drying time after each atomizing period. The amount of coating polymer was 10% (w/w).

Particle Size Distribution of Coated Theophylline Particles

The prepared coated particles were fractionated using a vibrating sieve (Retsch AS 200 control, Retsch Verder GmbH, Germany) for 5 min with 2.5-mm amplitude without intervals and sieving aids. The sieve fractions were as follows: 630–1000 μm, 500–630 μm, 250–500 μm, and 250–160 μm.

Morphological Characterization of the Coated Theophylline Particles with Scanning Electron Microscopy

To characterize the morphology of the coated particles of different size ranges, the samples were studied with a scanning electron microscope (Opton DSM 940, Carl Zeiss GmbH, D-7082 Oberkochen, Germany). The specimens were mounted to aluminum stubs with double adhesive tape. To reduce the charging, the specimens were vacuum coated with gold by a Jeol JEE 4B vacuum evaporator. Examination was carried out at 3 kV, 5 kV, or 30 kV accelerating voltage and 500× magnifications were used.

Theophylline Content of Single Coated Particles of Different Size Ranges

The theophylline content of 13 randomly selected coated particles of different size ranges was quantified by GC/MS. Samples were dissolved in methanol. A model GCQ mass spectrometer system (Finnigan Corp., Austin, TX) was used with manual split injection (split: 1/50) and 30QC2/BPX5 (SGE) bonded and cross-linked (5% phenyl) methylpolysiloxane capillary column (30 m × 0.25 mm). The temperature of the injection port was 280°C; the initial temperature of the column was 150°C, and then it was programmed to 233°C at 8.0°C/min. The linear velocity of the

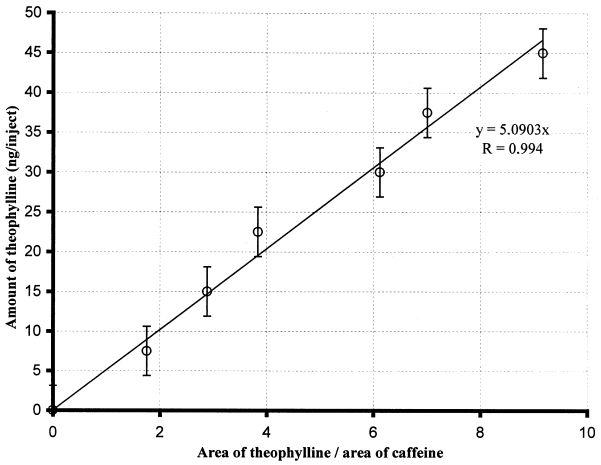

Figure 1. GC/MS calibration curve for determination of anhydrous theophylline in different granules.

helium carrier gas was 40 cm/s. Electron-impact ionization and the selected ion-monitoring software provided by the instrument manufacturer were used for the analysis. Source temperature was 180°C, and the temperature of the transfer line was 270°C.

Calibration curves were constructed by plotting the area ratio of theophylline (m/z 180) and internal caffeine standard (m/z 194) against the amount injected. Figure 1 illustrates six incubated solutions containing theophylline at concentrations of 7.5, 15, 22.5, 30, 37.5, and 45 μg/ml and 2 μg/ml for caffeine were analyzed on the same day using a standard curve to elucidate within-day variability. The between-day coefficient of variation was estimated as the slope of the constructed standard curve on three separate occasions by measuring incubated solutions containing theophylline at the same concentrations of 7–100 μg/ml.

RESULTS AND DISCUSSION

Distribution of the Eudragit polymer in the microcapsules changed according to the particle size, which could affect the characteristics of the drug release (12). The possible explanation for this phenomenon could be that the bigger particles (630–1000 μm) formed aggregates. Figures 2 and 3 show the differences in the surface morphology of theophylline microcapsules. The nonhomogeneous interparticular distribution of the coating polymer resulted in high deviations in the theophylline content. The last was experimentally confirmed;

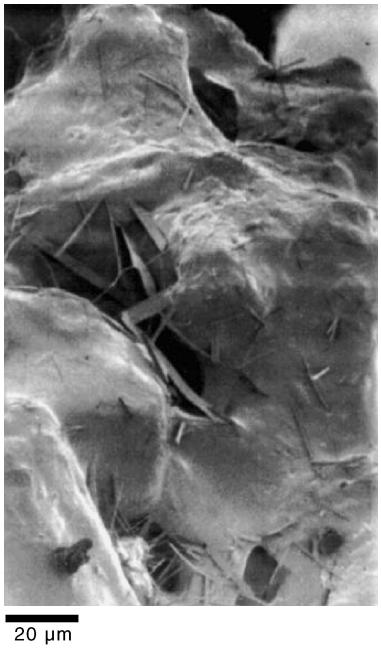

Figure 2. Scanning electron micrograph of theophylline microcapsules in the particle size range of 250–500 μm.

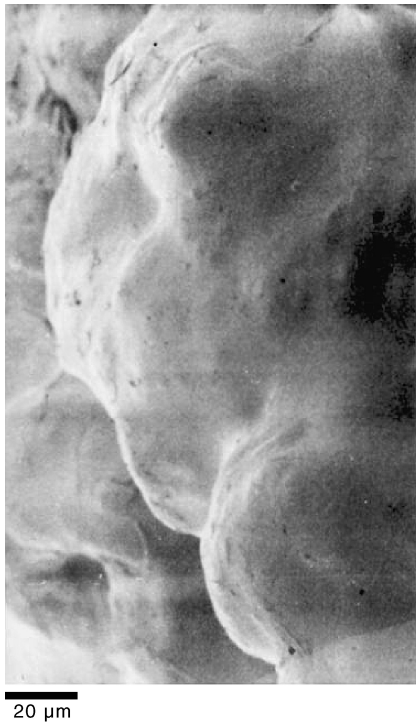

Figure 3. Scanning electron micrograph of theophylline microcapsules in the particle size range of 500–800 μm.

Table 1

Theophylline Contents (μg) of Microcapsules of Different Particle Size Ranges

	Particle Size (μm) Uncoated		Particle Size (μm) Coated	
Sample	250–500	630–1000	250–500	630–1000
1	8.80	3.09	13.75	17.26
2	6.35	5.24	17.98	5.93
3	6.21	10.80	18.05	6.21
4	9.23	9.81	14.26	26.95
5	8.85	5.35	17.96	24.83
6	11.26	13.42	18.08	34.96
7	8.70	6.97	17.89	12.83
8	7.65	9.87	18.12	22.64
9	9.45	20.74	17.86	23.98
10	8.63	9.56	17.94	11.73
11	6.48	7.76	13.68	13.50
12	8.73	7.53	18.29	42.18
13	10.56	16.67	19.25	15.19
Average theophylline content (μg)	8.53	9.75	17.16	19.86
Standard deviation	1.54	4.86	1.90	10.77

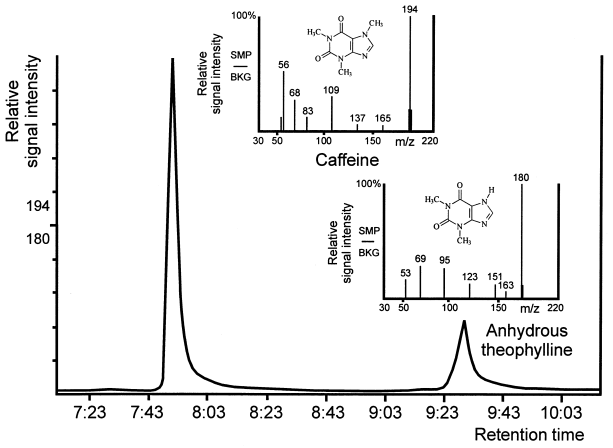

Figure 4. Selected ion monitoring of m/z 194 for caffeine and m/z 180 for anhydrous theophylline.

the theophylline content of uncoated and coated particles of different size ranges are summarized in Table 1. Figure 4 illustrates the chromatogram obtained by selected ion monitoring and the ionization spectra of theophylline and that of the caffeine applied as an internal standard. There was no significant difference between the deviations of the theophylline content of uncoated particles (cores) according to their particle size (Kruskal-Wallis test, $P = .1$). Along with the increase of the particle size of the prepared microcapsules, the deviation between the theophylline content of individual particles was increased.

CONCLUSIONS

GC/MS analysis offers a very sensitive and specific method for the analysis of the content uniformity and for the interparticular coating distribution of microcapsules containing a volatile active substance like theophylline in the presence of several additives. In the case of theophylline, it also offers a very sensitive tool for the analysis of the possible decomposition products of the active ingredient in the course of formulation and storage.

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