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Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion spheronisation

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Summary

Pellets were prepared by extrusion spheronisation using microcrystalline cellulose as pellet forming agent and two drugs with different solubility, theophylline monohydrate and sulfamethoxazole. Different amounts of water were used for the granulation step prior to extrusion spheronisation. The amount of granulating fluid used had an influence on the drug release from the pellets. A slower release rate was observed with increasing amounts of granulating fluid. These differences in the release profiles were correlated with differences in hardness, density and structure of the pellets.

Introduction

Several authors have reported on factors such as Avicel® type, drug concentration, drug solubility and pelletisation technique influencing the drug release rate from pellets (O'Connor et al., 1984; O'Connnor and Schwartz, 1985; Ghali et al., 1989; Millili and Schwartz, 1990; Zhang et al., 1990; Robinson and Hollenbeck, 1991; Zhang et al., 1991). It was previously shown that the amount of granulation liquid had a dramatic effect on the quality of pellets (Baert et al., 1992a,b). The aim of this study is to investigate the influence of the amount of granulation liquid on the drug release rate and some physical characteristics of the pellets.

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Materials and Methods

Materials

Two drugs with different solubility were chosen as model compounds: theophylline monohydrate (Flandria, Zwijnaarde, Belgium) with an aqueous solubility of 8.4 g/l at 25°C and sulfamethoxazole (ACF, Chemiefarma, Maarssen, The Netherlands) with an aqueous solubility of 0.1 g/l at 25°C. Microcrystalline cellulose (Avicel PH 101®, FMC, Wallingstown, Little Island, Cork, Ireland) was used as the filler and pellet forming material and demineralised water was employed as the granulating fluid.

Composition of the mixtures and granulation procedure

Theophylline mixtures Three mixtures, consisting of 150 g theophylline monohydrate and 600 g microcrystalline cellulose each, were dry

blended in a planetary mixer (Kenwood Chef, Hampshire, U.K.) for 10 min at 60 rpm using a K-shaped arm. Next the mixtures were respectively granulated in the planetary mixer for 2 min at 60 rpm with 115% (formulation 1), 95% (formulation 2) and 75% (formulation 3) of water expressed as dry weight.

Sulfamethoxazole mixtures Three mixtures of 75 g sulfamethoxazole and 675 g microcrystalline cellulose each were dry blended in a planetary mixer (Kenwood Chef, Hampshire, U.K.) for 10 min at 60 rpm using a K-shaped arm. The mixtures were subsequently granulated in the planetary mixer for 2 min at 60 rpm with 120% (formulation 1), 100% (formulation 2) and 80% (formulation 3), respectively, of water expressed as dry weight.

Extrusion procedure

After granulation the mixtures were extruded in an instrumented gravity feed extruder (Extruder 40, GB Caleva Ltd, Dorset, U.K.) and extrusion forces were measured as previously described by Baert et al. (1991). The rotational speed of the axes was 30 rpm.

Spheronisation

200 g of the extrudate were spheronised on a friction plate with cross-hatch geometry in a spheroniser (Spheroniser Model 15, Caleva Ltd, Dorset, U.K.) for 10 min at 750 rpm. Next the spheres were dried in a fluidized bed (Aeromatic AG, Basel, Switserland) for 20 min at 50°C.

Determination of pellet hardness

Hardness measurements were performed on a 710–1000 μm sieve fraction with a Zwick tensile tester 1445 (Zwick Gmbh, Willich-Münchheide, Germany) Fitted with a 100 N load cell (type Z6–3). The following parameters were used: a speed to preforce of 1 mm/min, a preforce of 1 mN and a speed of 10 mm/min during the test. Six pellets of each formulation were tested.

Density tests

Density tests were performed on a 710–1 000 μm sieve fraction using a Ultrapycnometer 1000 (Ankersmit, Breda, The Netherlands). The displacement gas used was helium.

Scanning electron microscopy

SEM pictures (sieve fraction 710–1 000 μm) were taken of individual and cross-sectioned pellets using a JEOL JXA-50A SEM (JEOL, Japan).

Residual moisture content

Residual moisture contents of pellets (710–1 000 μm sieve fraction) from each formulation were measured using a Mettler LP 16-M Infrared Drying Unit (Mettler Instruments, Greifensee, Switzerland) set at a temperature of 110°C with a drying time of 60 min.

Dissolution tests

Dissolution was performed on a 900 mg sample (theophylline pellets of sieve fraction 710–1 000 μm) or 100 mg sample (sulfamethoxazole pellets of sieve fraction 710–1 000 μm) in 900 ml of distilled water (theophylline pellets) or simulated gastric fluid (USP XXII) (sulfamethoxazole pellets) at 37°C. The paddle method (USP XXII) was used at a rotational speed of 75 rpm. Samples were taken at regular time intervals and extinction was measured at 265 nm (sulfamethoxazole) or 273 nm (theophylline) using a Zeiss PM6-UV spectrophotometer (Zeiss, Oberkochen, Germany).

Results and Discussion

O'Connor et al. (1984, 1985) described the influence of Avicel® type, concentration of drug and drug solubility on the drug release rate from pellets. Ghali et al. (1989) prepared pellets with mixtures of different Avicel® grades (Avicel PH 101® and Avicel RC 581®) and found the release to be dependent on the proportions of the Avicel® types used. With increasing amounts of Avicel RC 581®, containing sodium carboxymethylcellulose, the pellets remained intact in acid but became gelatinous in acid while pure microcrystalline beads remained intact irrespective of the dissolution medium. With increasing Avicel RC 581® content, slower drug release was achieved in

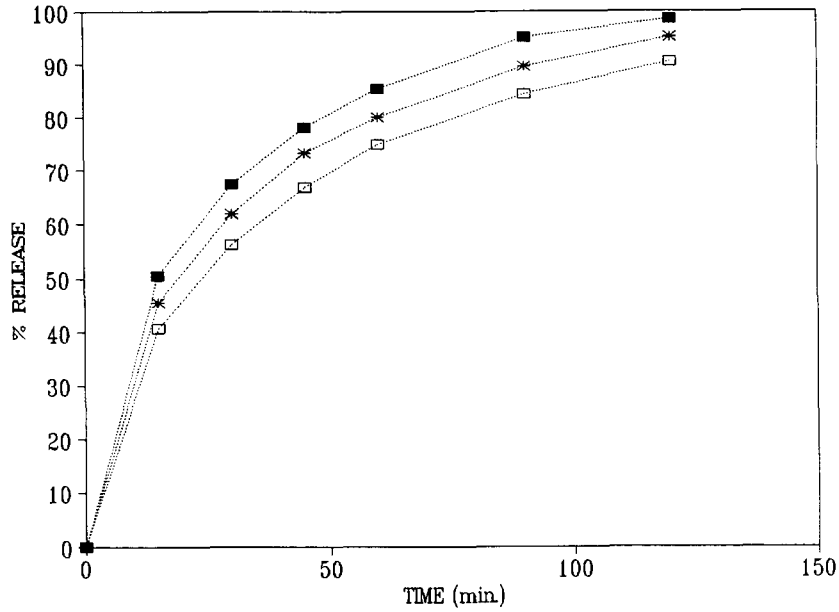

Fig. 1. Dissolution profiles of pellets containing 80% Avicel PH 101®, 20% theophylline monohydrate and granulated with 115% (□), 95% (*) and 75% (■), respectively, of water expressed as dry weight. Each curve is the mean of three experiments. The C.V. was always lower than 2%.

water as as well in acid. Robinson and Hollenbeck (1991) compared spheres prepared using a rotary processor and spheres obtained by extrusion spheronisation and found that the release of rotary processor beads was much faster than those obtained via the latter technique. Zhang et al. (1990, 1991) proved that drug release from pan-made spheres was much more rapid than from spheres made by extrusion spheronisation. In addition, the pan beads disintegrated during dissolution testing while those prepared by extrusion spheronisation remained intact. Millili and Schwartz (1990) found a difference in release rate for pellets prepared with Avicel PH 101® and theophylline and granulated with different proportions of ethanol/water but where the same amount of granulating fluid was used. Pellets prepared with more water showed slower release, lower porosity and greater hardness.

Figs 1 and 2 show the dissolution profiles for theophylline and sulfamethoxazole pellets, respectively. In the case of theophylline pellets (for-

TABLE 1

Characteristic parameters of the different formulations

Formulation	Amount of granulation fluid (%) [a]	Extrusion force (N) ($n = 6$, ±SD)	Hardness (N) 710–1 000 ($n = 6$, ±SD)	Density (g/ml)	Moisture content (%)
1	115	785 ± 32	14.1 ± 1.1	1.42201	1.22
2	95	1383 ± 24	11.4 ± 0.9	1.41751	0.87
3	75	2217 ± 16	7.9 ± 1.1	1.39316	2.17
4	120	917 ± 11	10.6 ± 2.8	1.46338	2.32
5	100	1442 ± 13	9.5 ± 1.9	1.43397	2.20
6	80	2340 ± 33	8.0 ± 0.8	1.42130	2.10

[a] Expressed as % of the dry weight of the mixture.

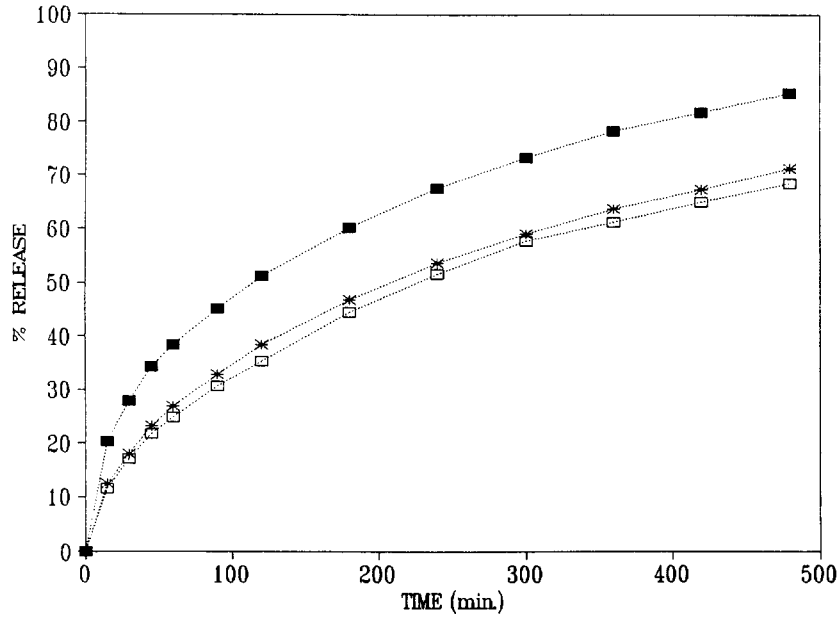

Fig. 2. Dissolution profiles for pellets containing 90% Avicel PH 101®, 10% sulfamethoxazole and granulated with 120% (□), 100% (∗) and 80% (■), respectively, of water expressed as dry weight. Each curve is the mean of three experiments. The C.V. was always lower than 2%.

mulations 1–3), release was slower when more granulation liquid was used. This slower release rate correlated well with an increase in pellet hardness and density (Table 1). Pellets of formulation 1 (115% water expressed as dry weight) where the highest amount of granulating fluid was used showed a hardness of 14.1 N and a density of 1.42201 g/ml, while those of formula-

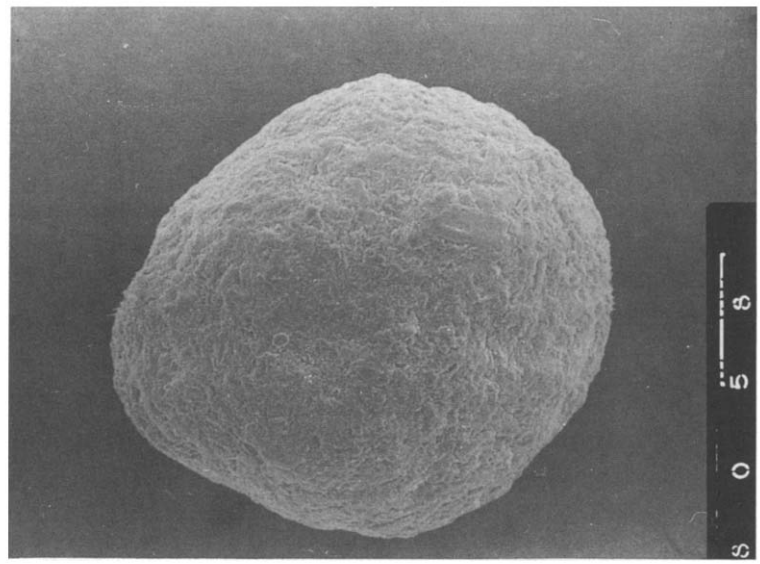

Fig. 3. SEM picture (600×) of a pellet produced using a mixture consisting of 20% theophylline monohydrate and 80% microcrystalline cellulose and granulated with 115% water expressed as dry weight (formulation 1).

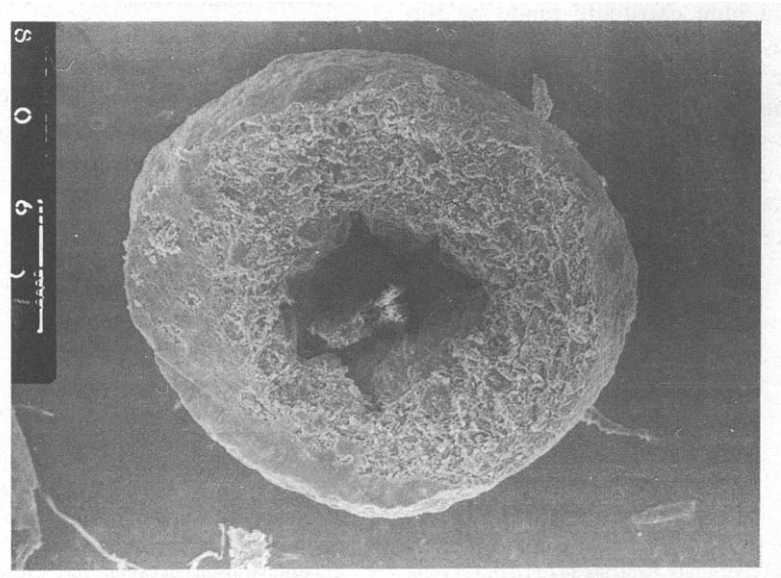

Fig. 4. SEM picture (600 ×) of a pellet produced using a mixture consisting of 20% theophylline monohydrate and 80% microcrystalline cellulose and granulated with 75% water expressed as dry weight (formulation 3).

tion 3 granulated with the lowest amount of water (75% water expressed as dry weight) displaying a hardness of 7.9 N and a density of 1.39316 g/ml. In the case of the sulfamethoxazole pellets (formulations 4–6), differences in release rate for increasing amounts of granulation liquid were also observed (Fig. 2). Hardness and density also increased when more water was used, the hardness and density varying from 10.6 N and 1.46338 g/ml to 8.0 N and 1.42130 g/ ml for formulation

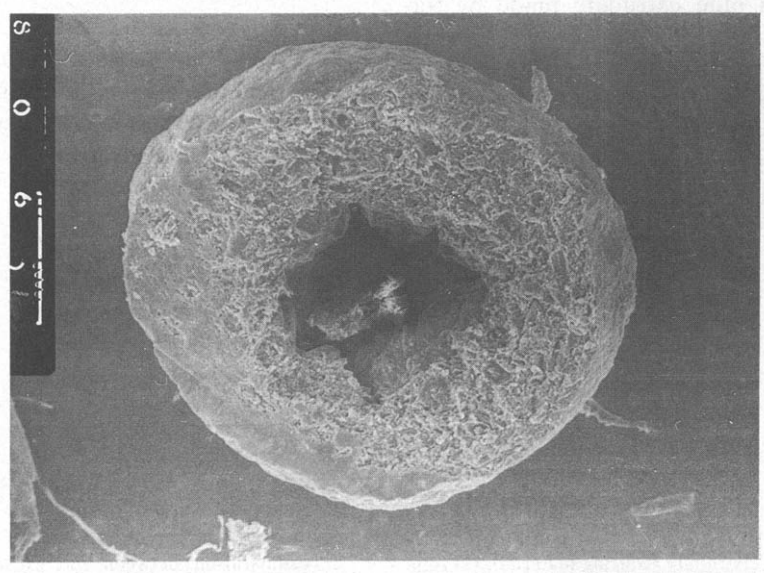

Fig. 5. SEM picture (600 ×) of a cross-section of a pellet produced using a mixture consisting of 20% theophylline monohydrate and 80% microcrystalline cellulose and granulated with 95% water expressed as dry weight (formulation 2).

4 (120% water expressed as dry weight) and formulation 6 (80% water expressed as dry weight), respectively.

The above results are in accordance with data reported by Millili et al. (1990) where a greater amount of water in a water/ethanol mixture resulted in slower release and greater hardness of the pellets. Fig. 3 shows a SEM picture of a pellet made of 80% microcrystalline cellulose and 20% theophylline monohydrate and granulated with the highest amount of water (115% water expressed as dry weight). A round sphere with a smooth surface was obtained. Fig. 4 shows a SEM picture of theophylline pellets made with the lowest amount of water (75% water expressed as dry weight); the sphere is not round and a kind of folding occurred during the spheronisation step, indicating that mechanisms of pellet formation other than those described by Rowe (1985) might exist. Rowe mentioned that the extrudate breaks on the spheroniser and forms cylinders with rounded ends before forming dumb-bells, ellipses and finally spheres. Cross-sections of the spheres (Fig. 5) show the spheres to possess a cavity in the middle which might be an additional indication that some type of folding might occur. To demonstrate that the cavities were not formed by aggregation of small particles during the spheronisation process, a blue extrudate made by the addition of methylene blue to the granulation liquid and a white extrudate, both of formulation 3, were fed together in the spheroniser for 10 min at 750 rpm. Cross-sections of the pellets obtained clearly show that no formation of aggregates of small particles occurred.

In order to ascertain possible mechanisms for the formation of a cavity during extrusion and spheronisation, an extrudate (2 cm long and 1 cm diameter) was made with plasticine. Next this extrudate was spheronised (Spheroniser, Caleva Model 15, Caleva Ltd, Dorset, U.K.) for 10, 15, 25 and 60 s at 750 rpm. Fig. 6 shows how spheres were formed from the plasticine extrudate. In the first step, rope-folding (2) of the extrudate (1) occurred followed by twisting, resulting in the formation of a kind of dumb-bell (3). A further twist resulted in the breaking of the dumb-bell into two parts with a central cavity (4). Finally, this cavity closed and spheres were formed (5).

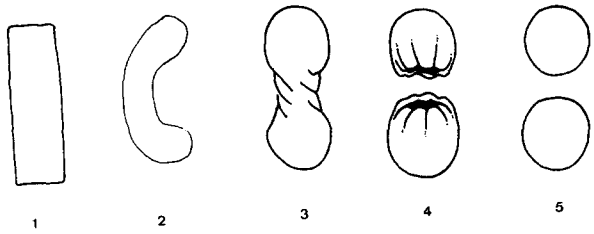

Fig. 6. Model of sphere forming mechanism using plasticine as a model compound. (1) Extrudate (starting material); (2) rope (after 10 s); (3) 'dumb-bell (after 15 s); (4) sphere with a cavity outside (after 25 s); (5) sphere (after 1 min).

Conclusions

It might be concluded that changes in the amount of granulating fluid during production might influence drug release and that the differences in release rate can be correlated with pellet hardness and pellet density. Furthermore, some indications were found that pellet formation might occur through different mechanisms of extrudate deformation and breaking.

Acknowledgements

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