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International Journal of Pharmaceutics 147 (1997) 23–30

international journal of pharmaceutics

Influence of processing on the characteristics of matrix pellets based on microcrystalline waxes and starch derivatives

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Received 6 September 1996; accepted 21 October 1996

Abstract

Matrix pellets based on microcrystalline waxes and starch derivatives were manufactured in the different types of high shear granulators with a volume ranging from 2–70 l. Ibuprofen and theophylline were used as model drugs with a loading of 60 and 70% (w/w), respectively. The production process and the formulation of the matrix pellets had to be adapted in function of the high shear granulator used. Processing parameters influenced pellet quality. An increasing mixing time and an increasing mixing speed induced a larger pellet size and a lower porosity. For the ibuprofen pellets the lower porosity correlated well with a decrease in release rate. During production the product temperature had to be controlled within a narrow range. The release kinetics of the wax-starch system was described using the equation $M_t/M_\infty = kt^n$. The drug release mechanism from the ibuprofen pellets is a Fickian diffusion process, while the theophylline pellets were characterized by a non-Fickian release mechanism. © 1997 Elsevier Science B.V.

Keywords: Matrix pellets; Starch; Maltodextrin; Microcrystalline wax; High shear granulator

1. Introduction

The potential of high shear granulators for the production of pellets by means of the melt pelletization technique has already been well documented. Using this technique a binder is added as a melt or as a solid molten during production. Two types of melt pelletization processes were reported. One is based on the melt of hydrophilic binders such as polyethylene glycols for immediate drug release formulations (Schæfer et al., 1992), while the other is based on the use of hydrophobic substances such as glyceryl monostearate, paraffin and microcrystalline waxes, hydrogenated castor oil and stearic acid (Thomsen et al., 1993, 1994; McTaggart et al., 1984).

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PII S0378-5173(96)04786-2

Table 1
High shear granulator specifications

	Gral 10	Vactron 75	LFS granulator	PP1 processor	
				Pelletiser bowl	Granulation bowl
Max. bowl cap. (l)	8	75	2	7.5	3
Batch size (kg)	1	10	0.35	1.5	0.57
Impeller speed (rpm)	430/600	150–440	300–2000	300–1500	300–1500
Chopper speed (rpm)	1500/3000	1500–3000	1200–4500	No chopper	1500/3000
No. of impeller blades	3	3	3	2	3
Impeller geometry	Curved	Curved	Curved	Plain/curved	Plain

The development of sustained release matrix pellets based on microcrystalline waxes and starches and their one step production process was previously described by Zhou et al. (1996). It was demonstrated that the drug release could be adjusted by varying the type and the content of waxes and starches. This work reports on the influence of the granulator type and the processing parameters on the characteristics and the drug release profile from those matrix pellets loaded with a high amount of drug.

2. Materials and methods

2.1. Materials

Micronised ibuprofen (Knoll Pharmaceuticals, Nottingham, UK) and theophylline (Ludeco N.V., Brussels, Belgium) were used as a poorly water soluble and a medium water soluble drug, respectively. Two microcrystalline waxes, Lunacera M® (melting range 68–72°C) and Lunacera P® (melting range 58–62°C) were used as hydrophobic binders (Füller GmbH, Lüneburg, Germany). Waxy maltodextrin (Eridania-Béghin Say-Cerestar, Vilvoorde, Belgium), a partial hydrolysed waxy corn starch (DE = 10) was used as a filler.

2.2. Granulators

Four types of high shear granulators, ranging from a small 2 l labscale granulator to a 75 l granulator, were used to produce the matrix pellets: the Gral 10 (Collette, Wommelgem, Belgium), the Vactron 75 (Collette, Wommelgem, Belgium), the LFS granulator (Fukae Powtec, Kobe, Japan) and the PP1 Processor (Niro-Fielder, Eastleigh, UK). Table 1 presents an overview of the specifications of the different granulators. The PP1 Processor can be equipped with a granulation bowl and with a bowl especially designed for pelletisation. All pelletisers were water jacketed.

2.3. Methods

2.3.1. Formulation

Ibuprofen and theophylline were used in a concentration of 60 and 70% (w/w), respectively. For the ibuprofen matrix pellets a mixture of Lunacera P® and M® (ratio 3:7; w/w) was used in a concentration of 25% (w/w) for the Gral 10, the Vactron 75 and the pelletiser bowl of the PP1 Processor. The concentration of the hydrophobic binder was 19 and 20% (w/w) for the ibuprofen pellets prepared with the LFS granulator and with the PP1 granulation bowl, respectively. The theophylline matrix pellets contained Lunacera M® as a hydrophobic binder. The concentration of Lunacera M® was 21% (w/w) for the matrix pellets prepared in the PP1 pelletiser bowl and in the Gral 10, while the concentration was set at 19 and 20% (w/w) for the pellets prepared in the LFS granulator and in the PP1 granulation bowl, respectively. The remaining part of the formulation was made up of waxy maltodextrin.

2.3.2. Production of the pellets

Because of the differences in size and geometry between the bowls and the mixing blades of the high shear granulators, the pelletisation process was adjusted for each type of granulator. In the Gral 10 and the LFS granulator the drug and the maltodextrin were blended in the bowl and heated to a preset temperature. The binder was added as a molten phase during slow agitating of the impeller, followed by an additional mixing for 2 min. Next the cooling phase was initiated to a preset temperature, the mass was dispersed into finer particles and mixed at a constant impeller and chopper speed to form the pellets. In the Vactron 75 and the PP1 Processor, the binder was added as a solid phase and blended with the drug and the maltodextrin. Next the mixture was heated and mixed until the binder was melted and homogeneously dispersed throughout the mass, followed by a cooling and pellet forming phase as described previously.

2.3.3. Dissolution testing

A modified paddle method (UP XXII) was used (Zhou et al., 1996). The dissolution test was performed in 900 ml of water and in 900 ml phosphate buffer (pH 7.2) for theophylline and ibuprofen pellets, respectively. The temperature of the medium was kept at 37 ± 0.5°C while the rotational speed of the paddles was set at 100 rpm. 3 ml samples were withdrawn at regular time intervals, replaced by fresh medium and spectrophotometrically determined at 221 and at 274 nm for ibuprofen and theophylline, respectively. All dissolution tests were performed in triplicate.

2.3.4. Analysis of the drug release profile

Under sink conditions the data of drug release up to 80% was characterized by a non-linear regression using the following equation: $M_t/M_\infty = kt^n$. M_t/M_∞ is the fraction of drug released up to time t, k is the kinetic constant, n is the diffusional exponent indicating the mechanism of drug release (Ritger and Peppas, 1987).

2.3.5. Sieve analysis

A 100 g sample was sieved using 2000, 1400, 1250, 1000, 800, 710, 500 and 250 μm sieves, vibrating at an amplitude of 2 mm for 5 min on a Retsch VE1000 shaker (Germany). The fraction remaining on each screen was weighed and expressed as a percentage of the total weight. All results presented are the mean of 3 determinations.

2.3.6. Porosimetric analysis

The pore size distribution of the matrix pellets (1000–1400 μm fraction) was determined using a mercury porosimeter (Autopore III 9420 System, Micromeritics, Norcross, GA, USA).

2.3.7. Scanning electron microscopy

S.E.M. pictures of the pellets were taken using a Siemens K60 analyser (Siemens, Germany).

3. Results and discussion

3.1. Pellet production

Most matrix pellet formulations were successfully processed in the different high shear granulators. As the energy transfer to the mass and the mass movement depended on the shape and the size of the impeller, the chopper and the bowl, the production parameters and even the formulation had to be adjusted in function of the granulator in order to obtain a similar pellet quality. In the case of the Gral 10 and the LFS granulator, the combination of the external heat transfer and a low impeller speed did not allow to melt and homogeneously disperse the solid wax. At a high impeller speed the friction heat was too high when working with the Gral 10 and the process could not be controlled. Too shallow, the bowl of the LFS granulator led to material sticking to the lid when a high impeller speed was used. Therefore the wax had to be added in a molten state when processing in the Gral 10 and the LFS granulator. On the contrary the wax could be added in a solid state using the Vactron 75 and the PP1 Processor as due to the external heat and the friction heat an homogeneous mixture of molten wax, drug and maltodextrin was obtained in a short period of time.

Table 2
Total yield (expressed as % of pellets smaller than 2.0 mm in comparison to the initial batch size) and 0.7–1.4 mm yield fraction of matrix pellets processed in the different high shear granulators

	Gral 10 $n=2$	Vactron 75 $n=5$	LFS granulator $n=5$	PP1 processor	
				Pelletiser bowl $n=3$	Granulation bowl $n=3$
Ibuprofen pellets					
0.7–1.4 mm yield (%)	74.0	77.0 ± 3.5	79.8 ± 3.5	84.5 ± 0.8	—[a]
Total yield (%)	94.5	93.8 ± 1.7	95.7 ± 0.6	92.5 ± 0.9	92.5 ± 0.8
Theophylline pellets					
0.7–1.4 mm yield (%)	86.2	—[b]	84.4 ± 4.0	85.9 ± 1.3	76.4 ± 2.6
Total yield (%)	93.7	—[b]	91.0 ± 0.7	92.6 ± 0.7	92.4 ± 0.8

The results are listed as mean ± S.D.
[a] Not possible to prepare pellets in the 0.7–1.4 mm fraction.
[b] Not processed.

Following the melting phase the mass was cooled and broken into small particles by means of the chopper as the design of the impeller made it difficult to disperse the mass at a low impeller speed. In case of the PP1 pelletiser bowl, where no chopper is available, the mass was dispersed using a high impeller speed. The PTEF lining of the PP1 pelletizer bowl was efficient in preventing the mass from adhering to the wall in comparison to the metal surfaces. As can be seen from Table 2, an acceptable yield for the pellets containing 60% (w/w) ibuprofen was obtained in the different types of granulators. The preparation of 60% (w/w) ibuprofen pellets sized between 0.7–1.4 mm failed in the PP1 granulation bowl as the growth of the particles stopped at a size range between 0.5–0.7 mm. Increasing the impeller speed and the mixing time did not lead to further particle growth. This might be due to the impeller design equipped with three short and plain blades causing an insufficient mass movement and a too low energy input. Theophylline pellets were successfully manufactured in all granulators tested (Table 2), indicating that the properties of the drug could influence the formation and the growth of the particles. Generally spoken the theophylline pellets were manufactured more easily than the ibuprofen pellets. Fig. 1 shows that substituting ibuprofen with theophylline resulted in a more narrow particle size distribution. In contrast with ibuprofen pellets, theophylline pellets at a drug load of 80% (w/w) were successfully manufactured with a 0.80–1.25 mm yield fraction above 80%. During the process the pellet growth was sensitive to the product temperature which had to be con-

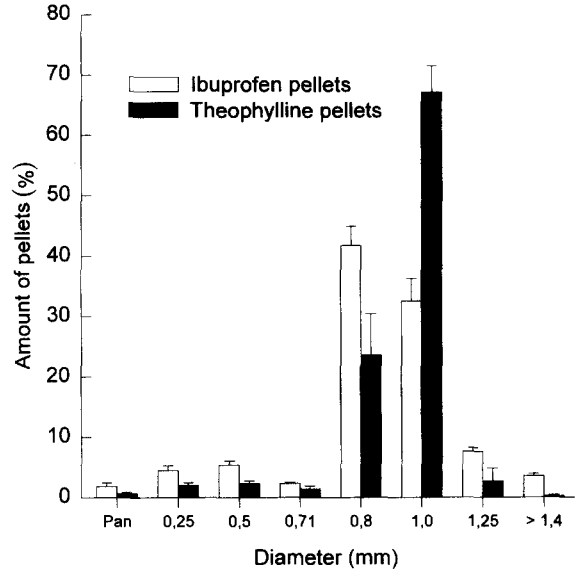

Fig. 1. Effect of the drug on the pellet size distribution ($n=3$). Formulation: drug 60%/wax (M/P-ratio 7:3) 25%/waxy maltodextrin 15%. High shear granulator: PP1 processor with the pelletiser bowl.

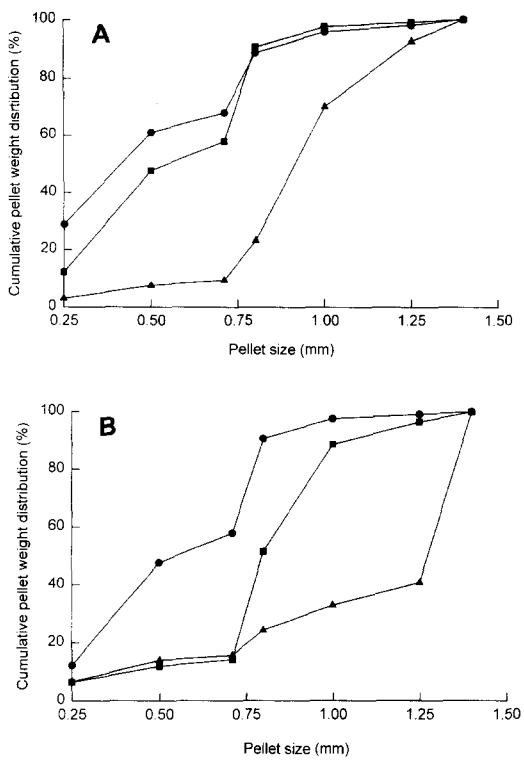

Fig. 2. Effect of the mixing time and the impeller speed on the pellet size growth. Formulation: Ibuprofen 60%/wax (M/P-ratio 7:3) 25%/Waxy maltodextrin 15%. High shear granulator: PP1 processor with the pelletiser bowl. (A) Impeller speed: 550 rpm. Mixing time: ● 20 min; ■ 26 min; ▲ 32 min. (B) Mixing time: 26 min. Impeller speed: ● 550 rpm; ■ 600 rpm; ▲ 650 rpm.

trolled in a narrow range in order to keep the wax in a semi-solid state. At a too high mass temperature a part of the wax remained in a liquid state and induced a quick but uncontrollable pellet growth. In order to control the process, the friction heat should efficiently be removed from the product. Fig. 2A illustrates the influence of the mixing time on the pellets size distribution. After a mixing time of 26 min about 50% of the particles were sized below 500 μm but after 32 min less than 10% fines were present and 80% of the pellets were sized between 710 and 1250 μm. In an initial phase a major part of the fine powder was agglomerated into small granules which then fused into the final pellets as mixing continued. S.E.M. photographs (Fig. 3) show that initially (mixing time: 11 min) the individual particles were still visible but after a longer mixing time (42 min) a smooth pellet was formed due to densification and fusion of the individual particles. The growth rate of the pellets was also function of the mixing speed (Fig. 2B). A too high mixing speed resulted in a continuous and difficult to control increase of the product temperature, while a too low mixing speed resulted in an unacceptable long process time. The product temperature, the mixing time and the mixing speed were also found to be critical parameters of melt pelletization process when formulating pellets based on polyethylene glycol (Schæfer et al., 1992, 1993; Schæfer and Mathiesen, 1996) and on a mixture of microcrystalline wax and glycerolmonostearate (Thomsen et al., 1993).

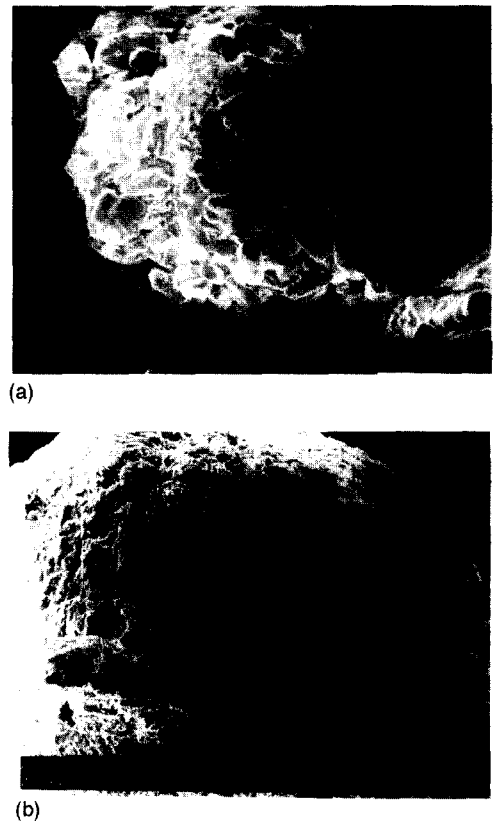

Fig. 3. S.E.M. pictures of pellets at different mixing times. Formulation: Theophylline 70%/Lunacera M® 20%/waxy maltodextrin 10%. High shear granulator: PP1 processor with the pelletiser bowl. Impeller speed: 450 rpm. Mixing time: (A) 11 min; (B) 42 min.

Table 3
Influence of the production parameters and the granulator type on the release characteristics and the porosity of the pellets

Mixer	Impeller speed (rpm)	Mixing time (min)	n	k	Porosity (%)
Ibuprofen pellets					
PP1 pelletiser bowl	550	20	0.39	16.65	22.8
	550	26	0.41	11.50	17.4
	550	32	0.43	7.90	10.3
	600	20	0.35	12.73	15.4
	600	26	0.41	9.18	11.8
	600	32	0.41	8.21	10.9
	625	29	0.54	8.07	14.1
	650	20	0.39	12.54	13.7
Gral 10	430	21	0.47	12.16	11.8
Vactron 75	200	35	0.42	11.12	12.0
Theophylline pellets					
PP1 pelletiser bowl	500	23	0.65	20.85	16.6
	550	18	0.57	22.56	17.6
	550	23	0.64	20.31	13.7
	550	28	0.69	16.90	13.4
	600	23	0.62	20.87	14.1
PP1 granulation bowl	850	20	0.67	18.65	15.2
LFS granulator	430	20	0.72	17.41	13.4

n, diffusional exponent; k, kinetic constant.
r^2 was greater than 0.97 in all cases.

3.2. Dissolution and porosity

The effect of processing parameters on the porosity and the drug release from the pellets was investigated. The final porosity of the ibuprofen and the theophylline pellets was nearly independent of the mixing time and the equipment choice (Table 3). A detailed study of the evolution of the porosity of pellets produced in the Niro PP1 pelletiser bowl revealed a progressive decrease of the porosity of the pellets as a function of the mixing time (Fig. 4). This effect was more pronounced in the case of the ibuprofen pellets and correlated well with a progressive decrease in release rate (Fig. 5). The porosity of the pellets depended also on the impeller speed during the process (Table 3). The release mechanism of the ibuprofen pellets was characterised as a Fickian diffusion ($n \leq 0.43$), whereas a non-Fickian release mechanism was observed in case of the theophylline pellets ($0.43 < n < 1$)(Table 3). Fig. 6 shows that ibuprofen pellets having a similar porosity, but processed in a different granulator had a different release profile. A possible explanation is that the drug release process might be affected by the tortuosity (Ek et al., 1995), especially in a system where the drug release in mainly governed by a diffusion process. The release profiles of the theophylline pellets processed in the

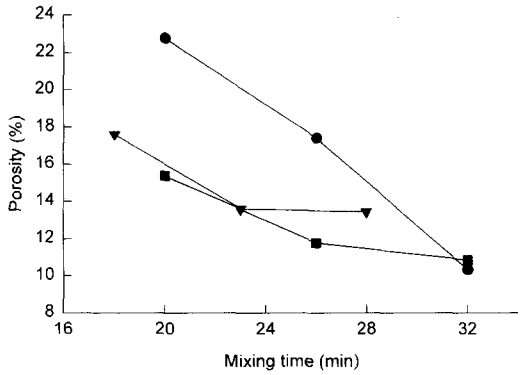

Fig. 4. Effect of the mixing time on the porosity of matrix pellets. Formulation: Ibuprofen 60%/wax (M/P-ratio 7:3) 25%/waxy maltodextrin 15%. High shear granulator: PP1 processor with the pelletiser bowl. Impeller speed: ● 550 rpm, ■ 600 rpm. Formulation: Theophylline 70%/wax (M) 21%/waxy maltodextrin 9%. ▼ Impeller speed: 550 rpm.

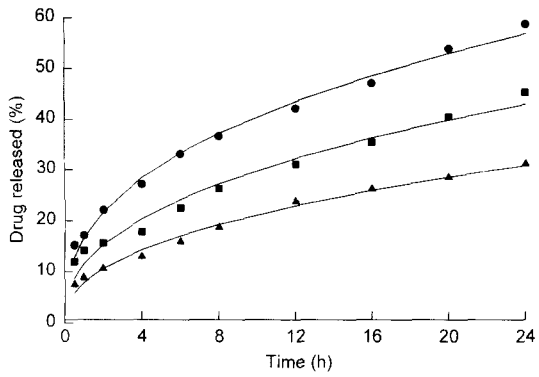

Fig. 5. Effect of the mixing time on the drug release profile of ibuprofen matrix pellets. Formulation: Ibuprofen 60%/wax (*M*/*P*-ratio 7:3) 25%/waxy maltodextrin 15%. High shear granulator: PP1 processor with the pelletiser bowl. Impeller speed: 550 rpm. Mixing time: ● 20 min; ■ 26 min; ▲ 32 min.

different granulators remained unaffected ($t_{50\%}$ = 4 h, releasing 80% of theophylline after 8 h) although the formulation had to be slightly adapted in order to be processed in the different granulators. The difference in release mechanism between ibuprofen and theophylline is probably due to part of the ibuprofen being dissolved in the wax while the remaining part is suspended in the matrix. In the case of theophylline the drug was completely suspended in the matrix. All matrices showed in the beginning a small but limited burst effect depending on the formulation.

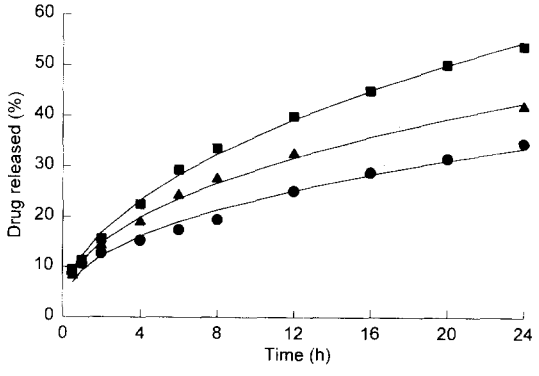

Fig. 6. Effect of the granulator type on the drug release from ibuprofen pellets. Formulation: Ibuprofen 60%/wax (*M*/*P*-ratio 7:3) 25%/waxy maltodextrin 15%. ■ Gral 10 (Mixing time: 21 min/impeller speed: 430 rpm); ▲ Vactron 75 (mixing time: 35 min/impeller speed: 200 rpm); ● PP1 processor with the pelletiser bowl (massing time: 26 min/impeller speed: 600 rpm).

4. Conclusion

Matrix pellets based on maltodextrins and microcrystalline waxes can be manufactured in the different types of high shear granulators. The production process, the formulation and the characteristics of matrix pellets were influenced by the type of the granulator.

Acknowledgements

The authors wish to thank Eridania-Béghin Say-Cerestar (Vilvoorde, Belgium) for the generous supply of the starch derivatives. Special thanks to Niro-Fielder Ltd. (Eastleigh, UK) for providing the PP1 Processor, to Pro-C-epT (Zelzate, Belgium) for providing the LFS granulator and to Collette Ltd (Wommelgem, Belgium) for the use of the Vactron 75 high shear granulator. This project was financially supported by the National Fund of Scientific Research (Brussels, Belgium). C. Vervaet is a research assistant of the National Fund of Scientific Research (Brussels, Belgium).

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