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Note

Influence of the drying technique on theophylline pellets prepared by extrusion–spheronization

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Abstract

Extrusion–spheronization is frequent method for pellet production and especially extrusion stage has been studied for its influence on pellet properties. However, the formation of pellet structure is not finished before drying stage. The possible influence of different drying methods and used temperatures on some properties of pellets, containing theophylline as active ingredient and Avicel® CL-611 as spheronizing agent, is the object of this paper.

Keywords: Pellet; Extrusion; Spheronization; Theophylline; Avicel® CL-611; Drying

The possibility of producing pellets of the required quality by extrusion–spheronization has been reported several times. The pellet quality is mainly based on the determination of their sphericity, size distribution and porosity, and successful values are obtained when all important process parameters are controlled (Rabišková, 1998). This technique has been studied intensively and research is mainly focused on the extrusion stage. This is because at this stage the wet mass is subjected to shaping pressure forces and the final distribution (and quantity) of water in the extrudate has the biggest influence on the final product.

However, the formation of the matrix structure is not completely achieved after spheronization as it has been demonstrated in some of the previous studies (Kleinebudde, 1994). The drying stage can have a strong influence on the final matrix structure, hence drying must not be taken into account only as a secondary process. The drying step could be used as another 'tool' to adjust pellet size, density, hardness etc.

In this study, pellets were prepared using a binary drug–diluent mixture. Theophylline anhydrous was the model drug still studied for its antiasthmatic effects (Bartošíková et al., 2000). Microcrystalline cellulose with sodium carboxymethylcellulose, type Avicel® CL-611, had the function of polymer diluent and spheronizing agent. At the final step of the process the pellets were dried using different techniques—room temperature, ventilated oven, microwave oven,

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Table 1
Pellet formulation

Amount of fluid[a] (%)	Theophylline (% w/w)	Avicel CL-611 (% w/w)
37	75	25

[a] Expressed as percent of the wet weight of the mixture.

fluidized bed and different temperatures. The quality of obtained pellets was determined using physical methods, e.g. particle size analysis, calculated mean diameter (Hasznos et al., 1992), density and hardness.

Pellets were prepared using binary mixtures (Table 1) of theophylline anhydrous (Kulich, Czech Republic, Ph.B., Ph.Eur.) and Avicel® CL-611 (Lehmann and Voss, Germany). Purified water was employed as the granulating liquid. The binary mixtures were pre-blended for 5 min with a mixer (Stephan UM 5, Germany). Then the liquid phase was added in two equal portions over 1.5 min of wet mixing each.

Extrusion was performed on a co-rotating, twin-screw extruder (Fuji Paudal EXDS 60, Collette, Belgium). The wetted material was fed through a hopper onto the counter-rotating screws at standard extruder speed of 32 rpm. The extrudate was placed in a spheronizer (Fuji Paudal Q-400, Collette, Belgium) fitted with a 42 cm diameter serrated plate. The plate was allowed to operate at 880 rpm for 1 min. After spheronization the pellets were dried using different methods until they showed a constant weight. The equipment employed was as follows: a ventilated oven (Hoffmann, Germany), a microwave oven (Tescoma, Czech Republic), and a Multiprocessor MP-1 (Aeromatic AG, Switzerland), Table 2.

The particle size characterization was performed by sieve analysis with sieves of 250, 500, 800, 1000, 1250, 2000 μm apertures. A pycnometer method was chosen for the determination of granule density using ethanol 95% as the immersion fluid. Pellet hardness was measured on a C50 tablet hardness and compression tester (Engineering Systems, Nottingham, UK) fitted with a 5 kg load cell.

Table 2
Pellets' drying

Samples	Method	Temperature (°C)	Time
1	Room temperature	~20	>48 h
2	Ventilated oven	80	3 h
3	Ventilated oven	130	1.5 h
4	Microwave oven	80	10 min
5	Microwave oven	130	10 min
6	Fluidized bed	80	15 min
7	Fluidized bed	130	30 min

Observing the calculated mean diameter (Table 3) of the formulations the higher the temperature employed on drying the smaller is the diameter value indicating a shrinking process. The smallest calculated mean diameters were presented by samples 3 and 7, when pellets were dried at 130 °C. Microwave drying led to a faster and more uniform process. Almost all water content was evaporated in the first minutes of the process and consequently, the matrix structure remained in majority intact. In this case, the shrinking of pellets reached the smallest value (samples 4 and 5). Probably thanks to the particles' movement during fluid-bed drying slightly smaller pellets are obtained when comparing to pellets dried in the ventilated oven (samples 2 and 6, 3 and 7). The diameter findings are supported by the density determinations (Table 3).

When pellets are prepared using excipients able to absorb water, they tend to shrink during drying. During shrinking, the pellet size is reduced and depends on the drying method. The only method, that seems to exclude shrinking, is microwave drying due to immediate general water evaporation.

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Table 3
Characteristic parameters of the different formulations

Sample (800–1250 μm)	Main sieve fraction (%)	Calculated mean diameter (mm)	Granule density ($g\ ml^{-1}$)	Tapped density ($g\ ml^{-1}$)[a]	Hardness (kg)[b]
1	88.00	1.14	1.205	0.813	1.633
2	90.40	1.12	1.283	0.837	1.834
3	92.14	0.96	1.336	0.843	1.893
4	86.54	1.23	1.152	0.798	1.567
5	84.33	1.38	1.184	0.792	1.508
6	91.17	1.06	1.214	0.841	1.887
7	92.74	0.93	1.363	0.844	1.916

[a] Averaged from three determinations.
[b] Averaged from ten determinations.

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