

## PŮVODNÍ PRÁCE

# The influence of the extrusion die on pellet characteristics

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### SUMMARY

#### The influence of the extrusion die on pellet characteristics

Characteristics of pellets (pellet size distribution, their mean diameter, density, hardness, friability, repose angle, Hausner ratio, and drug dissolution profiles) prepared by axial and radial extrusion/spheronization were examined in this experimental study. The formulation consisted of binary mixtures of theophylline, a drug slightly soluble in water, and Avicel® CL 611 as an excipient. Different characteristics were found in the samples prepared using the different extrusion dies: the axially situated extrusion die produces the pellets of higher hardness and density, and slower dissolution profiles. Differences in drug dissolution profiles should be considered, nevertheless they are not significant. All pellet samples showed low friability and excellent flow properties.

**Key words:** pellets – theophylline – Avicel® CL 611 – extrusion/spheronization – axial extrusion – radial extrusion

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### SOUHRN

#### Vliv extruzní přepážky na jakostní parametry pelet

Experimentální studie sledovala vlastnosti pelet (distribuci velikosti částic, průměr pelet, jejich hustotu, pevnost, oděr, sypný úhel, Hausnerův faktor a disoluční profily léčiva) připravených axiální a radiální extruzí/sferonizací. Pelety obsahovaly theofylin jako léčivo těžce rozpustné ve vodě a Avicel® CL 611 ve funkci pomocné látky. Vlastnosti peletových vzorků formovaných rozdílnou extruzní přepážkou byly různé: axiálně situovaná přepážka produkovala pelety s vyšší hustotou a pevností a pomalejšími disolučními profily. Rozdíly v uvolňování léčiva by se neměly opomíjet, přestože nebyly významné. Všechny peletové vzorky vykazovaly nízký oděr a výborné tokové vlastnosti.

**Klíčová slova:** pelety – theofylin – Avicel® CL 611 – extruze/sferonizace – axiální extruze – radiální extruze

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## Introduction

Development of pharmaceutical dosage forms with increasing therapeutic efficacy and safety is a current trend in the pharmaceutical industry. Pellets belong to oral dosage forms providing these advantages. They can be formed using several different techniques. One of the most often used methods in the pharmaceutical industry is extrusion/spheronization<sup>1)</sup>. This process does not require inactive cores as a starting material and pellets containing up to 90 % of the active ingredient can be prepared<sup>2)</sup>. Extrusion/spheronization involves four steps: preparation of the wet mass (granulation), shaping the wet mass into cylinders (extrusion), breaking up the extrudate and rounding of the particles into spheres (spheronization), and finally drying of the formed pellets. All these steps are dependent on each other and are joined by a number of formulation (properties of the active ingredients and the excipients, their concentration in the formulation, properties and amount of the wetting agent) and process variables (method of moisturizing, type of extruder, thickness and type of the extrusion die, speed and time of the spheronization, method of the drying etc.)<sup>3, 4)</sup>. The object of this study was to observe the influence of the axial and radial type of the extrusion die together with the different size of its perforations on the characteristics of theophylline pellets. Theophylline was chosen as a model drug because of its low solubility in water. Microcrystalline cellulose, Avicel<sup>®</sup> CL 611 type, was the second substance in the formulation. Microcrystalline cellulose is an excipient very often used in pellet production because of its lubricant, adsorption, antiadhesive, spheronization-enhancing, and compression properties. Avicel<sup>®</sup> CL 611 contains, besides microcrystalline cellulose, also 15 % of carboxymethylcellulose sodium. Microcrystals of microcrystalline cellulose, insoluble in water, are leashed together with chains of soluble carboxymethylcellulose sodium to form mesh-like powder particles, readily dispersed in water. Due to a small size of the microcrystals (approximately 60 % of the crystallites in dispersion are <0.2 µm), there are a large number of microcrystals packed in each powder particle. These types of Avicel<sup>®</sup> (RC, CL) are reported to slow down the drug release as they form a colloidal thixotropic gel layer controlling the drug dissolution<sup>5)</sup>. Combination of binary mixtures of a slightly soluble drug (8.3 g in 1.0 L of water at 25 °C<sup>6)</sup>) and Avicel<sup>®</sup> CL 611 was considered to decrease the drug release even more, when formed into pellets, to show best the possible changes in theophylline dissolution profiles from prepared samples with expected different characteristics.

## EXPERIMENTAL

### Materials

Theophylline monohydrate (Lehmann and Voss, Germany) was the model drug, microcrystalline cellulose Avicel<sup>®</sup> CL 611 (FMC, USA) was the filler and spheroniza-

tion enhancer, and purified water (Ph.B., Ph.Eur.) was the wetting agent.

### Pellet preparation

The powder mixture (250.0 g) was first blended and then gradually wetted with water (115.0 g) in a mixer (Tefal Kaleo, France): 50 ml of water/min. Extrusion was performed on a one-screw axial or radial extruder (Pharmex 35T, Wyss & Probst, Germany). The plastic mass was fed through the hopper on a rotating screw at a standard extruder speed of 110 rpm. The diameter of perforations in the extrusion die was 0.8 mm and 1.0 mm, respectively, its width being 1.0 mm. A 200 g load of the extrudate was placed into a spheronizer (Pharmex 35T, Wyss & Probst, Germany) with a 23 cm diameter serrated plate. The spheronization speed was 640 rpm and spheronization time was 15 minutes. After spheronization, the pellets were dried using a ventilated oven (Hoffman, Type 0488, Germany) at 80 °C for 3 hours.

### Pellet characterization

The size distribution of prepared pellets was determined by sieve analysis, using standard sieves with apertures in a range of 0.25–2.0 mm (Retsch, AS 200, Germany). The pellet mean diameter was calculated from the results of sieve analysis by applying the following formula<sup>7)</sup>:

$$d = \frac{\sum x_i n_i}{100},$$

where "x<sub>i</sub>" is the mean of the upper and lower limits of the sieve fraction and "n<sub>i</sub>" is the percentage of the "i" fraction.

Pellets of sizes from 0.8 mm to 1.25 mm were used for further characterization.

For each sample of pellets, pycnometric density was determined by the gas displacement technique using a helium pycnometer (Pycnomatic – ATC, Porotec GmbH, Germany) and helium as the intrusive gas according to Ph. Eur. 4. The test is intended to determine the volume occupied by a known mass of the powder or particles (7.5–10.5 g depending on the volume; the cell No. 30) by measuring the volume of gas displaced under defined conditions. The sample volume is determined after degassing the examined powder mass or particles and its pressurization using the following formula:

$$V_s = V_c - \frac{V_r}{\frac{P_i - P_r}{P_f - P_r} - 1},$$

where "V<sub>s</sub>" is the sample volume, "V<sub>c</sub>" is the cell volume, "V<sub>r</sub>" is the reference volume, "P<sub>i</sub>" is the initial pressure, "P<sub>r</sub>" is the reference pressure, and "P<sub>f</sub>" is the final pressure. The density of the powder mass "ρ" is given by the equation:

$$\rho = \frac{m}{V_s}.$$

The test was repeated three times.

The pellet hardness was tested in a Tablet Hardness & Compression Tester (Engineering Systems, England) fitted with a C 5 load cell for pellet evaluation. The average hardness of 10 single pellets was calculated<sup>8)</sup>.

The pellet friability was measured in an adapted Roche friabilator (type TAR 10, Erweka GmbH, Germany). 10 g of pellets were rotated in a stainless steel abrasion drum along with 200 pieces of 4-mm glass beads for 10 minutes at 20 rpm. The dust was thereafter removed and pellets were reweighed. The friability, i.e. the weight loss after agitation, was expressed as a percentage<sup>8)</sup>.

The repose angle represented the flowability of produced spheres. 50.0 g of pellet sample was placed in a glass funnel with a stem. The funnel was maintained upright so that the stem terminated 10 cm above a flat solid underlay protected from vibrations. Pellets flowed out of the funnel and formed a cone. Its height "h" and base diameter "d" were measured. The repose angle value "α" was calculated using the following equation<sup>8</sup>:

$$\alpha = \arctg (2 h/d).$$

The friability and repose angle of pellet samples were carried out in triplicate and the results were expressed as an arithmetic mean  $\pm$  standard deviation.

The Hausner ratio<sup>9</sup> was calculated from the pellet tapped and bulk densities according to equation:

$$HR = \frac{\rho_t}{\rho_b},$$

where "HR" is the Hausner ratio, " $\rho_t$ " is the tapped density, and " $\rho_b$ " is the bulk density of the particles.

Dissolution profiles of the drug were determined using the basket dissolution method, 1000 ml of distilled water as the dissolution medium at 37 $\pm$ 0.5 °C, and basket speed 50 rpm (Sotax, AT 7 Smart on-line, Switzerland), and evaluated spectrophotometrically (Perkin Elmer, UV/VIS spectrophotometer, USA) at 273 nm.

## RESULTS AND DISCUSSION

Four batches of pellets containing 75 % of theophylline monohydrate and 25 % of Avicel<sup>®</sup> CL 611 were prepared by extrusion/spheronization: sample 1 using an extrusion die of 0.8 mm perforations diameter, sample 2 with an extrusion die of 1.0 mm perforations diameter,

both in the axial position; samples 3 and 4 with extrusion dies of 0.8 and 1.0 mm perforations diameters, respectively, in a radial extruder. The smaller diameter of the extrusion screen perforations produced, according to our expectation, pellets of a smaller mean diameter of 0.95 mm (sample 1) and 0.94 mm (sample 3) in comparison to 1.14 mm and 1.13 mm mean diameter of samples 2 and 4 (Table 1). The yield of the pellets was high, in between 82.7 and 98.2 %, as well as the yield of the requested size fraction (within the range from 0.80 mm to 1.25 mm) above 76.7 % (Table 1).

Pellets prepared using the axial extrusion die showed higher hardness values of 10.67 and 11.18 N vs. 8.06 and 8.54 N in the case of the radial die position (Table 2, Figure 1). Also the pellet density was higher in the samples prepared through the axially situated die compared to the pellets formed with the radial extrusion die (Table 2). Higher values of these parameters are caused by generating a higher pressure on the plastic mass during axial extrusion<sup>2</sup>. Pellet hardness and density values also differ depending on extrusion die perforations (Table 2,

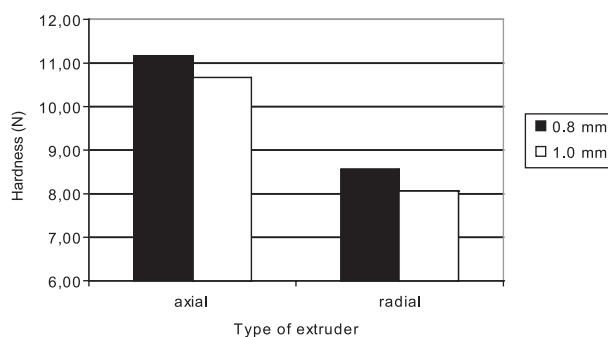


Figure 1. Influence of the extrusion screen on pellet hardness

Table 1. Pellet size distribution

Sample	Size distribution (mm)						Mean diameter (mm)
	<0.25 (%)	0.25–0.50 (%)	0.50–0.80 (%)	0.80–1.0 (%)	1.0–1.25 (%)	>1.25 (%)	
1	0.5	3.9	15.6	37.5	39.2	3.3	0.95
2	0.0	0.9	4.9	20.1	56.8	17.3	1.14
3	0.2	1.0	15.1	52.2	29.7	1.8	0.94
4	0.5	1.1	2.6	11.5	73.3	11.0	1.13

Table 2. Pellet physical properties

Sample	Pycnometric density* (g/cm <sup>3</sup> )	Hardness** (N)	Friability* (%)	Repose angle* (°)	Hausner ratio
1	1.342 $\pm$ 0.014	11.18 $\pm$ 1.26	0.10 $\pm$ 0.02	25.40 $\pm$ 0.55	1.03
2	1.337 $\pm$ 0.007	10.67 $\pm$ 1.13	0.07 $\pm$ 0.02	26.30 $\pm$ 0.21	1.01
3	1.332 $\pm$ 0.008	8.54 $\pm$ 1.68	0.05 $\pm$ 0.02	23.12 $\pm$ 0.94	1.02
4	1.329 $\pm$ 0.018	8.06 $\pm$ 2.55	0.08 $\pm$ 0.01	22.50 $\pm$ 0.53	1.03

\* average from three measurements

\*\* average from ten measurements

Table 3. Theophylline dissolution profiles

Sample	Amount of released theophylline (%)					
	15 min	30 min	45 min	60 min	75 min	90 min
1	37.16 ±0.13	67.85 ±0.21	82.00 ±0.16	88.66 ±0.26	92.79 ±0.14	95.40 ±0.24
2	32.65 ±0.20	64.49 ±0.10	81.59 ±0.24	89.27 ±0.09	93.00 ±0.19	95.19 ±0.17
3	45.26 ±0.21	80.77 ±0.13	94.38 ±0.18	98.88 ±0.17	99.85 ±0.28	99.87 ±0.15
4	32.21 ±0.12	65.95 ±0.17	85.38 ±0.22	94.18 ±0.23	98.55 ±0.15	99.54 ±0.28

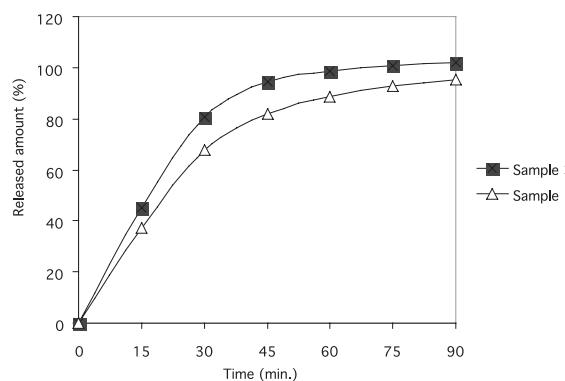


Figure 2. Theophylline dissolution profiles from samples 1 and 3 (die openings diameter 0.8 mm)

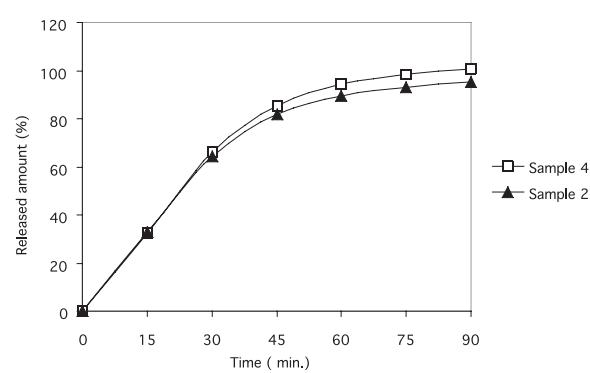


Figure 3. Theophylline dissolution profiles from the samples 2 and 4 (die openings diameter 1.0 mm)

Figure 1). Pellets of higher hardness and density were manufactured by forcing the extrudate through the extrusion screen with 0.8 mm perforations. The reason is greater densification of the material caused by a higher pressure during extrusion through the smaller die openings. All samples of the formulated pellets had very low friability below 0.10 % (Table 2) proving their appropriate mechanical properties and good ability for further processes (e.g. coating, filling, compression, and transportation).

Hausner ratio with a value close to 1.0 (advent to small differences between bulk and tapped densities) guarantees trouble-free capsule filling of pellets into hard gelatine capsules, and good achievement of required weight uniformity. Good flow properties of pellets are confirmed also by the low values of the repose angle, below 26° 20' (Table 2).

Drug dissolution profiles showed that theophylline was released more slowly from pellets prepared by axial extrusion (Table 3, Figures 2 and 3). These results indicate that slower drug release could be achieved from more "compact" pellets with higher hardness and density values. However, the found differences, especially in samples 2 and 4 (Figure 3), are small. Theophylline was completely released from all samples within 90 minutes.

We can conclude that the axially situated extrusion die produces pellets of better physical properties (hardness, density). The differences in drug dissolution profiles

should be considered, nevertheless they are not significant.

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## REFERENCES

1. **Ghandi, R., Lal Kaul, Ch., Panchagnula, R.:** Pharm. Sc.i Technol. Today, 1999; 2, 160-170.
2. **Ghebre-Sellassie, I.:** Pharmaceutical Pelletization Technology. New York and Basel, Marcel Dekker, 1989, 274 s.
3. **Vervaet, Ch., Baert, L., Remon, J. P.:** Int. J. Pharm., 1995; 116, 131-146.
4. **Peréz J-P., Rabišková M.:** Int. J. Pharm. 2002; 242, 349-351.
5. <http://www.fmcbiopolymers.com> 16.11.2006
6. **Kim, H.; Fassihi, R.:** J. Pharm. Sci. 1997; 86, 323-328.
7. **Hasznos, L., Langer, I., Gyarmathy, M.:** Drug Dev. Ind. Pharm., 1992; 18, 409-437.
8. **Krejčová, K., Rabišková, M., Vetchý, D. et al.:** Drug Dev. Ind. Pharm., 2006; 32, 585-593.
9. **Swarbrick, J., Boylan, J. C.:** Encyclopedia of Pharmaceutical Technology, Volume 6. New York and Basel, Marcel Dekker Inc., 1996, 489 s.