Influence of Rotational Speed and Surface of Rotating Disc on Pellets Produced by Direct Rotor Pelletization

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Summary

The aim of this research work was to investigate the influence of disc surface and its speed on the direct pelletization with rotor technology. Rotor technology is "single pot" method of pellet production based on fluid bed technology.

Two series of experiments have been carried out on GPCG 1 (Glatt Powder Coater Granulator) fluid bed apparatus. In the first series of the experiments mixture of 350 g of pentoxifylline and 150 g microcrystalline cellulose were used for pellets production. In the second series of experiments, the same amount of ketoprofen was used instead of pentoxifylline. In both series suspension of Eudragit® NE 30 D was used as liquid binder but in each series at different concentration. Within each series of experiments the process variables were kept constant within limitations of the process, except rotational speed of the disc during agglomeration and spheronization step. Additionally, two different rotating disc were used; one with smooth and the other with textured surface.

The results show that both surface and rotational speed of the disc have influence on shape, surface and size of pellets while there is less effect on true density, humidity content and yield of the experiment. Keeping rotational speed of the smooth disc constant during agglomeration of powder particles and increasing rotational speed during spheronization of agglomerates results in more spherical pellets with larger diameters and smoother surfaces. The influence of rotating disc with textured surface is opposite to the previously mentioned influence of smooth disc. Increasing rotational speed during spheronization step at the constant speed during agglomeration step results in smaller and less spherical pellets with rougher surface.

Zusammenfassung

Einfluß der Rotorgeschwindigkeit und der Oberfläche der Rotorscheibe auf durch Rotor-Direktpelletierung hergestellte Pellets

Ziel dieses Forschungsprojektes war, den Einfluß der Rotorgeschwindigkeit und der Charakteristik der Scheibenoberfläche auf die Direktpelletierung in einem Rotorgranulator zu ermitteln.

Die Rotorgranulation ist eine 'Single-Pot'-Methode für die Pelletherstellung in einer Wirbelschichtanlage. Mit einer GPCG-1-Laboranlage (Glatt Powder Coater Granulator) wurden zwei Versuchsreihen durchgeführt. In der ersten Versuchsreihe wurden Pellets aus je 350 g Pentoxifyllin und 150 g mikrokristalliner Zellulose (MCC) hergestellt. In der zweiten Serie wurde Ketoprofen anstelle von Pentoxifyllin verwandt. Als Agglomerationsflüssigkeit diente in beiden Versuchsreihen Eudragit® NE 30D, allerdings in zwei verschiedenen Konzentrationen. Alle Verfahrensparameter wurden gleich gehalten und nur die Scheibenoberfläche (glatt oder strukturiert) und die Rotordrehzahl variiert (Agglomerierphase und Sphäronisierphase).

Die Ergebnisse haben gezeigt, daß sowohl die Scheibenoberfläche wie auch die Rotordrehzahl einen Einfluß auf die Pellet-Form, die Pellet-Oberfläche und die Pellet-Größe ausüben. Der Einfluß auf Dichte, Wassergehalt und Prozeßausbeute ist geringfügig oder nicht signifikant. Bei Verwendung der glatten Rotorscheibe und gleichmäßiger Rotordrehzahl während der Agglomerationsphase und Erhöhung der Drehzahl für die anschließende Ausrundung der Pellets wurden größere Pellets mit glatter Oberfläche hergestellt. Bei Verwendung der strukturierten Rotorscheibe bei gleichen Bedingungen wurden umgekehrte Resultate erzielt: kleine, weniger runde Pellets mit rauher Oberfläche.

Key words Direct rotor pelletization, disc surface, rotational speed · Fluid bed technology · Microcrystalline cellulose · Pellets, single-pot production

1. Introduction

The most widely used pelletization techniques are based on either extrusion and spheronization or layering of pellets. Pelletization by wet granulation is a valuable alternative when used in order to achieve a one-step process [1]. A single-pot method, where pellets are produced, dried and, if desired coated in the same piece of equipment, seems to be promising [2].

In the 90-es some authors have been researching direct pelletization in rotor processing equipment. Vertommen et al. studied the influence of microcrystalline cellulose (MCC) content, water-MCC ratio, rotor speed, spheronization time and water addition rate on the quality of the pellets [2–5]. Holm et al. investigated effect of process and product variables on granule growth, agglomerates shape and porosity, methods of process control and effect of MCC on direct pelletization process [1, 6, 7]. Wan et al. revealed the influence of the liquid spray rate and gap air pressure on the pellet size [8]. The influence of the amount of MCC and the nature of the filler material on several pellet characteristic were studied by Vecchio et al. [9]. Knop et al. investigated the effect of the inlet air temperature, nozzle pressure, liquid spray rate, liquid concentration and the amount of polyvinylpyrrolidone (PVP) in powder on the quality of pellets [10]. Comparison of acetaminophen pellets produced in rotor processor and multiple-step extrusion and spheronization were studied by Robinson et al. [11]. Lipophilic excipients [12] and poly(meth)acrylates [13] were used to modify the dissolution properties of the pellets. Polytetrafluoroethylene (PTFE) coating was used to prevent adhesion of pellets on the rotor insert wall [14, 15].

The aim of this paper is to show the influence of disc surface and its speed on particle size distribution, yield of the process and some other characteristics of pellets (true density, moisture content, shape and surface of the pellets) produced in rotor fluidized bed equipment.

2. Materials

Avicel PH 101 (FMC, Philadelphia, PA, USA) as matrix formation agent and binder, Eudragit® NE 30 D (Röhm Pharma, Darmstadt, Germany) as a binder, pentoxifyilline (supplied by Krka d.d. Novo Mesto, Slovenia) and ketoprofen (S.I.M.S., Firence, Italy) were used as model drugs.

3. Methods
3.1. Preparation of the pellets

Pentoxifylline or ketoprofen (350 g) and microcrystalline cellulose (MCC) (150 g) were placed in GPCG 1 (Glatt Powder Coater Granulator, Glatt Systemtechnik, Binzen, Germany) rotor insert. The machine was connected with condensation air dryer unit for the inlet air (KZS-1,5 S, Inštitute Zoran Rant, Škofja Loka, Slovenia). Powders were being dry mixed for approximately 10 min until the temperature in the bed reached a constant value at 35 °C. In the spraying (agglomeration) phase the Eudragit NE 30D suspension (10 % w/w for pentoxifylline, 5 % w/w for ketoprofen mixture) as agglomeration liquid was sprayed on the powdered mass. After determined amount of agglomeration liquid was used, the process ran into 10 min of spheronization phase. The drying phase continued until the pellets reached the temperature of 35 °C. Process phases and some of process variables are shown in Table 1.

3.2. Examination of the particle size of starting material

The average size of starting material was determined with Mastersizer (Malvern Instruments, Malvern, UK).

3.3. Examination of the particle size distribution of pellets

The prepared and dried pellets were fractionated using a vibrating sieve (MLV, Ilmenau, Germany) for 10 min at the highest

Table 1: Process phases and some of its variables for pentoxifylline and ketoprofen pellets.

Process variables	Process phases		
	Agglome-ration	Spheroni-zation	Drying
Inlet air temperature[a] (°C)	24	24	24
Relative humidity of inlet air (%)	40	40	40
Inlet air temperature[b] (°C)	30	30	50
Pellet temperature (°C)	17–18	17–18	35
Nozzle pressure (bar)	2.0	–	–
Position on the pump (rpm)	29	–	–
Air velocity (m/s)	~3	3–4	2.0–3.5
Air flap (%)	~33	30	25–30
Pressure difference – product (kPa)	~1	~1	~1
Pressure difference – filters (kPa)	~0.1	~0.1	~0.1
Time (min)	20/25[c]	10	12–35
Disc speed (rpm)	700-1400	700-1400	400/250[c]
Agglomeration liquid (g)	543/674[c]		
Disc surface	smooth/textured		

[a] After condensation drying.
[b] Inside Powder Coater Granulator.
[c] Ketoprofen mixture.

value of vibration without intervals and sieving aids. The sieves of 100, 250, 500, 800, 1000, 1250 μm (also 1600 and 2000 μm in case PT 10/10) were used.

3.4. Yield of the process

Total yield is defined as the total amount of product recovered as a percentage of the solid starting material. *Usable yield,* which is response variable, is defined as ratio of three continuous largest fractions and solid starting material (with solidified Eudragit), expressed as a percentage of the solid starting material.

3.5. True density

True density was determined with helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, USA) for the pellet fraction between 250–500 μm. For experiment PT 10/10 pellet fraction between 500–800 μm and for experiment KT 7/7 not sifted sample were used.

3.6. Moisture content

The moisture content of samples (~5 g) containing pentoxifylline was determined by loss of drying at 90 °C for 20 min, ketoprofen pellets for 20 min at 80 °C, on the weighing machine with drying unit CP 16/PM 480, Mettler, Greifensee, Switzerland).

3.6.1. Shape and surface of the pellets

The shape and surface of the pellets were determined with SEM (JEOL JSM 5800, Tokyo, Japan) for the same pellet fraction as for determination of true density.

4. Results and discussion
4.1. Pellet production

Direct pelletization in GPCG 1 rotor insert equipement is a single-unit process divided into three phases: agglomeration, spheronization and drying. Usually no preheating phase is necessary because pellets are produced at low temperature. In spite of that fact we dry mixed the powdered mass about 10 min until the temperature in the bed reached a constant value at 35 °C. For all our experiments the inlet air temperature of 24 °C and relative humidity of 40 % (7.5 g H_2O/kg air) were used. The experiments that have been carried out are listed in Table 2.

Table 2: List of experiments.

Batch[a]	Model drug	Disc surface	Disk speed in agglomeration phase (rpm)	Disk speed in spheronization phase (rpm)
PS 7/7	pentoxifylline	smooth	700	700
PS 7/10	pentoxifylline	smooth	700	1000
PS 7/14	pentoxifylline	smooth	700	1400
PS 10/10	pentoxifylline	smooth	1000	1000
PS 10/14	pentoxifylline	smooth	1000	1400
PT 7/7	pentoxifylline	textured	700	700
PT 7/10	pentoxifylline	textured	700	1000
PT 7/14	pentoxifylline	textured	700	1400
PT 10/10	pentoxifylline	textured	1000	1000
PT 10/14	pentoxifylline	textured	1000	1400
KS 7/7	ketoprofen	smooth	700	700
KS 7/10	ketoprofen	smooth	700	1000
KS 7/14	ketoprofen	smooth	700	1400
KS 10/10	ketoprofen	smooth	1000	1000
KS 10/14	ketoprofen	smooth	1000	1400
KT 7/7	ketoprofen	textured	700	700
KT10/10	ketoprofen	textured	1000	1000

[a] P = pentoxifylline. K = ketoprofen. S = smooth. T = textured.

Fig. 1: Area where adhesion of the material usually takes place.

Fig. 2: Size distribution of the batches produced with smooth disc.

The main problem of agglomeration phase is distribution of the agglomeration liquid through the powdered mass. Homogeneous distribution of the liquid assured no adhesion on the insert wall. The optimal distribution is controlled by fluidized air velocity, nozzle pressure, flux of the agglomeration liquid, disc surface, disc speed and also physicochemical properties of the used model drug should be considered. If optimal conditions aren't achieved, adhesion of pellet mass occurred especially on two places (Fig. 1):

In place A, the immersed nozzle causes the local disruption in the flow pattern and therefore the area, where the pellet material can adhere.

On the other hand the higher nozzle pressure assured better liquid distribution, but it enters a local disturbance in the pellet flow pattern in the area B where the agglomeration liquid is sprayed in the bed. Small amounts of the adhered material could be removed by increasing the air velocity. Sticked material on the wall required interruption of the process and its cleaning from the wall, otherwise the adhered pellet mass is lost. Stationary layer usually fall off the wall in the drying phase. Pellets from this mass aren't formed well, their structure is weak. Although the friction in this phase is kept to minimum with low rotor speed, these pellets break down and an increase of powder or very small irregular pellets (< 100 μm) result.

The adhesion of pellet mass on the insert wall (area B) may also occur in the spheronization phase if the removal of the liquid from the pellets inside and its evaporation aren't balanced.

Another specific problem for direct pelletization is the end point detection. Several direct and indirect methods based on particle size and humidity measurement are used for end point detection. In our study we worked with conditioning air, also formulation and process variables were kept constant. An equal amount of water in each experiment was used for the end point detection.

4.2. Pentoxifylline pellets

Fig. 2 shows the size distribution of the pellets produced with smooth disc. A closer look at the results, following the size distributions at the same disc speed in the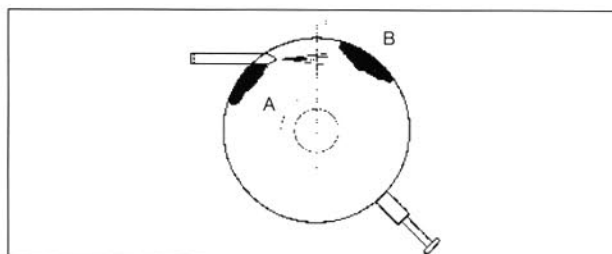 agglomeration phase but different in the spheronization phase, shows that larger pellets are produced at higher rotor speeds in the spheronization phase (Table 3). Obviously the smooth disc doesn't contribute enough mechanical energy for production of spherical pellets at lower speed in spheronization phase (PS 7/7, Fig. 3, 4). Fig. 4 shows the folded surface of a pellet, which transforms to smooth surface, if the disc speed in spheronization phase is increased (Fig. 6). Higher disc speeds in the spheronization phase (PS 7/14) lead to larger and spherical pellets with smoother surface (Fig. 5, Table 3). The size distribution of the pellets produced with smooth disc is narrow, at higher speeds in spheronization phase the main fraction is moved to the higher class (Fig. 2).
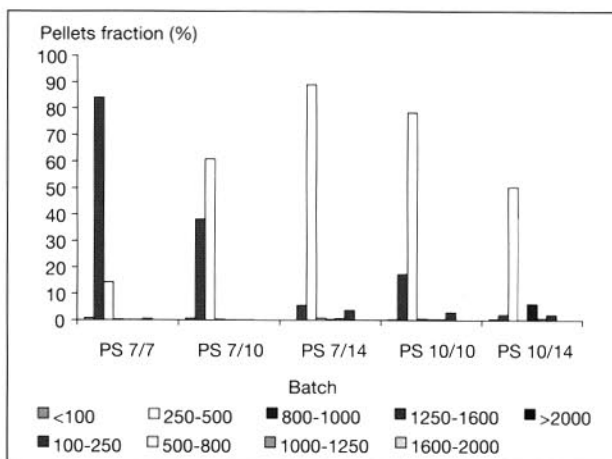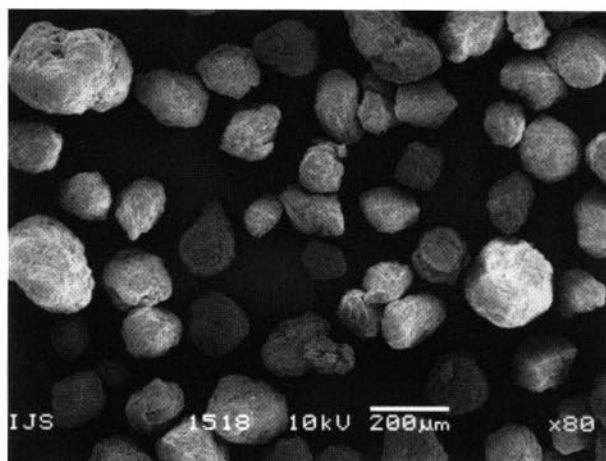

Fig. 3: Batch PS 7/7 (SEM, magnitude 80 ×).

Table 3: Some data of dependent variables (quality) of the pellets.

Batch	Total yield (ηt (%))	Useful yield[a] ηu (%)	Geometric mean diameter d_g (μm)	True density (g/cm³) (T=26–32 °C)	Humidity content (%)
PS 7/7[b]	86.6	85.2	145	1.41	1.6
PS 7/10	88.5	87.8	170	1.40	1.4
PS 7/14	92.4	88.1	288	1.39	1.6
PS 10/10	91.4	88.0	252	1.39	1.6
PS 10/14	90.7	86.3	332	1.39	1.5
PT 7/7	91.3	82.0	572	1.39	2.0
PT 7/10	91.3	62.9	496	1.39	1.8
PT 7/14	91.4	90.2	240	1.39	1.4
PT 10/10	97.2	62.9	1234	1.38	4.3
PT 10/14	93.3	85.4	354	1.39	2.7
KS 7/7	83.7	81.6	237	1.36	1.2
KS 7/10	93.7	71.4	678	1.35	1.7
KS 7/14	90.0	75.7	339	1.36	1.8
KS 10/10	87.4	80.1	376	1.35	1.6
KS 10/14	89.2	80.8	429	1.35	1.6
KT 7/7	83.4	–	–	1.36	1.5
KT 10/10	84.4	64.4	374	1.35	1.9

[a] Defined as ratio of three consecutive largest fractions and total mass of the starting material.
[b] P = pentoxifylline. K = ketoprofen. S = smooth. T = textured.

The influence of smooth rotating disc in the spheronization phase on size, size distribution and surface of the pellets is correlated with mechanical energy of the disc on the pellets. At higher speeds the friction between pellets, wall and disc surface is high, the surface of pellets is more polish and smooth. The unstable larger pellets fall into smaller particles, which layer other pellets if the humidity content in the insert is high enough. High disc speed contribute high centrifugal force, which accelerates the movement of water from inside to the surface of the pellets. In such conditions layering of pellets with smaller particles is possible.

The most spherical pellets were produced at lower speed and with textured disc (Fig. 7, 9), where the disc contributes just enough mechanical energy to the system. Higher speeds in spheronization phase lead to attrition of the pellets. These pellets are less uniform in shape and with more narrow size distribution with main fraction of smaller pellets (Fig. 8, 10, 11). In this case an excess of mechanical energy is added to the system and the damage of the pellets is unavoidable.

4.3. Ketoprofen pellets

Pellets produced with smooth disc at 1000 rpm in agglomeration phase and different disc speeds in spheronization phase show the same trend as pentoxifyline pellets
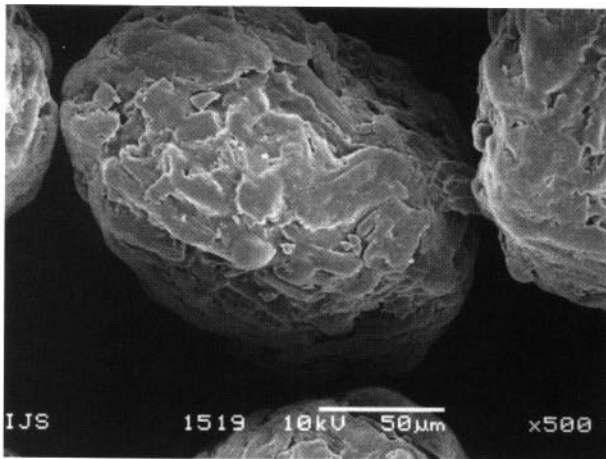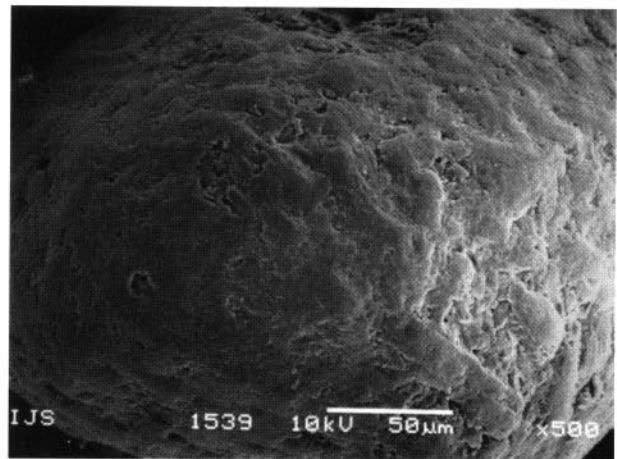

Fig. 4: Batch PS 7/7 (SEM, magnitude 500 ×).

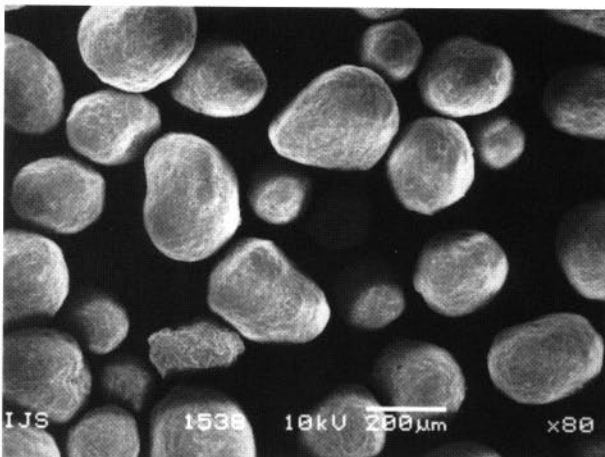*Fig. 6:* Batch PS 7/14 (SEM, magnitude 500 ×).

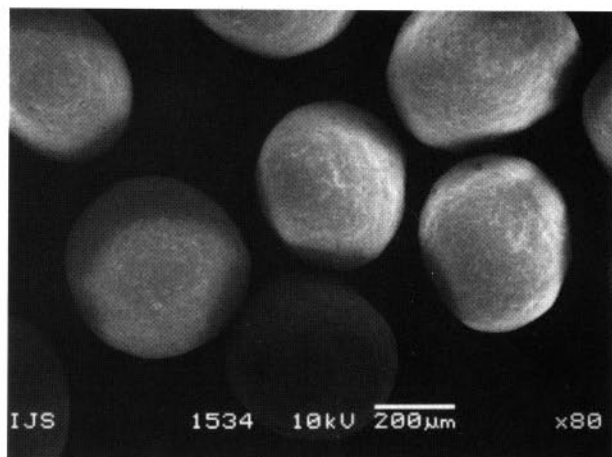*Fig. 5:* Batch PS 7/14 (SEM, magnitude 80 ×).

Fig. 7: Batch PT 7/7 (SEM, magnitude 80 ×).

produced at the same process conditions: more spherical and larger pellets were produced at higher disc speeds in spheronization phase. The differences occurred in batches with disc speed 700 rpm in agglomeration phase, where batch KS 7/10 deviate from this series (Fig. 12).

The batch KS 7/7 expresses the narrowest size distribution and better useful yield, all other pellets produced with smooth disc are more spherical with smoother surface (Fig. 13–20).
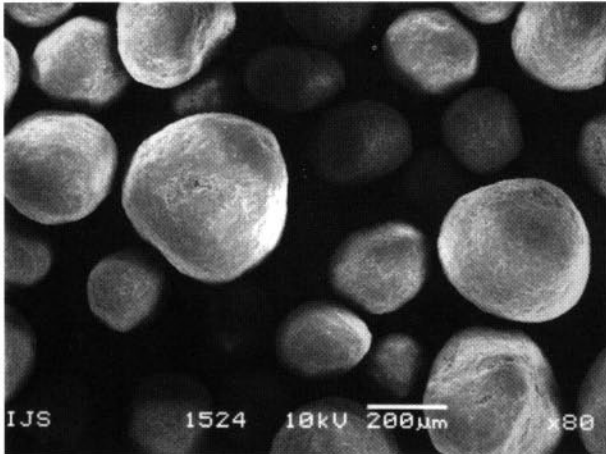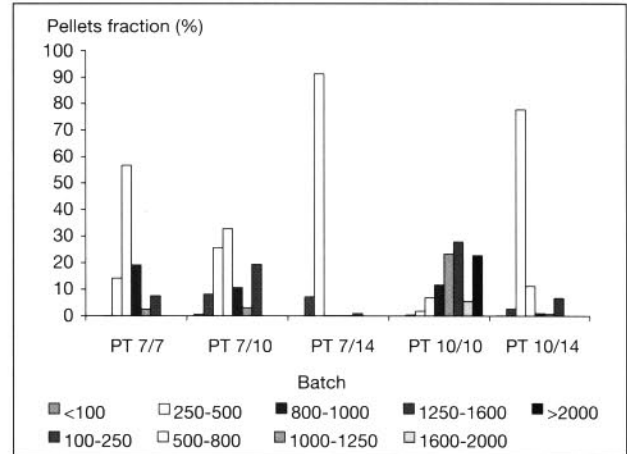

Fig. 8: Batch PT 7/14 (SEM, magnitude 80 ×).

Fig. 11: Size distribution of the batches produced with textured disc.
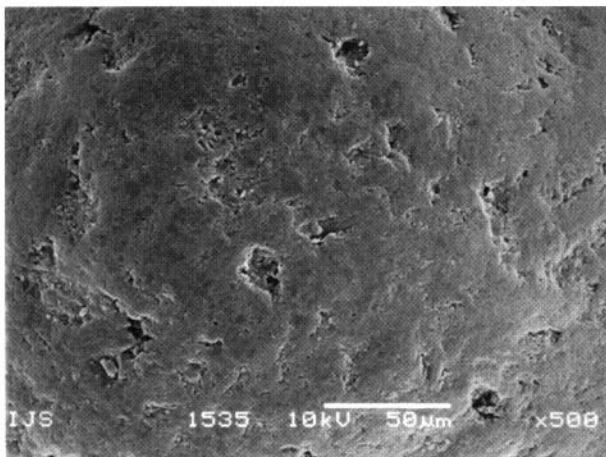
Fig. 9: Batch PT 7/7 (SEM, magnitude 500 ×).
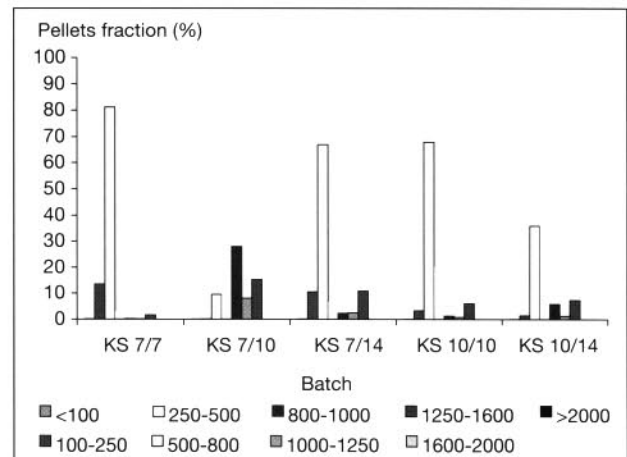
Fig. 12: Size distribution of the batches produced with smooth disc.
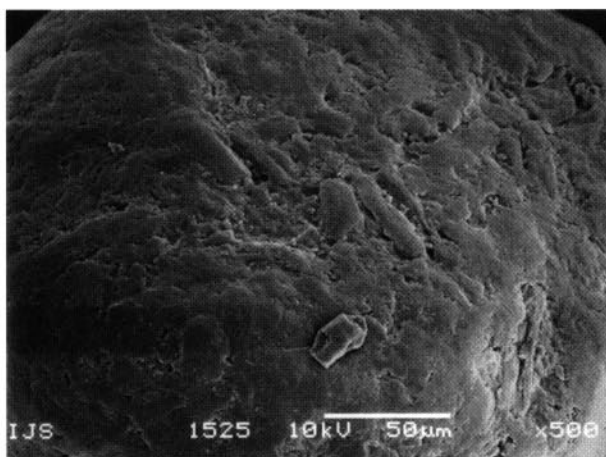
Fig. 10: Batch PT 7/14 (SEM, magnitude 500 ×).
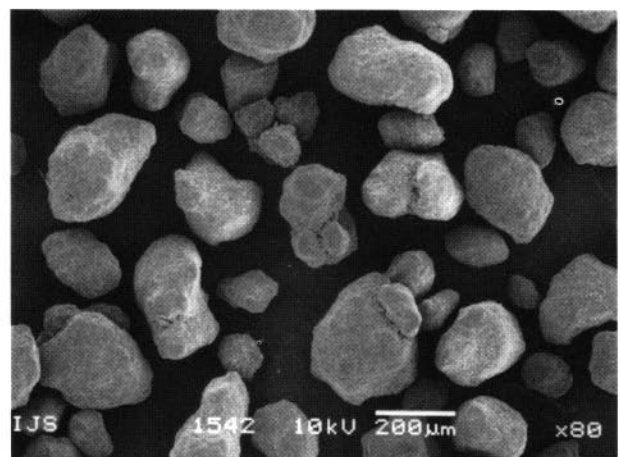
Fig. 13: Batch KS 7/7 (SEM, magnitude 80 ×).

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Useful yield of ketoprofen pellets when smooth disc was used is lower as useful yield of pentoxifylline pellets produced with the same disc (Table 3). The amount of used water is higher in ketoprofen case (Table 1). These show the importance of physical properties of used drugs.

The ketoprofen pellets produced with textured disc didn't give satisfactory results. Ketoprofen particles are small particles with the average diameter of 7 μm and density 1.29 g/cm^3 which is much lower than MCC particles (d=55 μm, ρ=1.55 g/cm^3). The difference in these
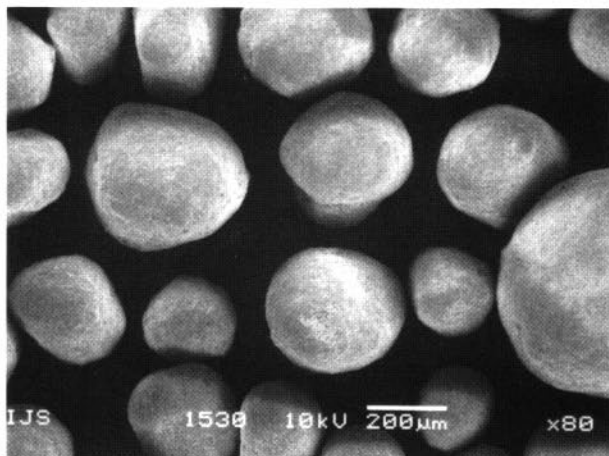
Fig. 14: Batch KS 7/14 (SEM, magnitude 80 ×).
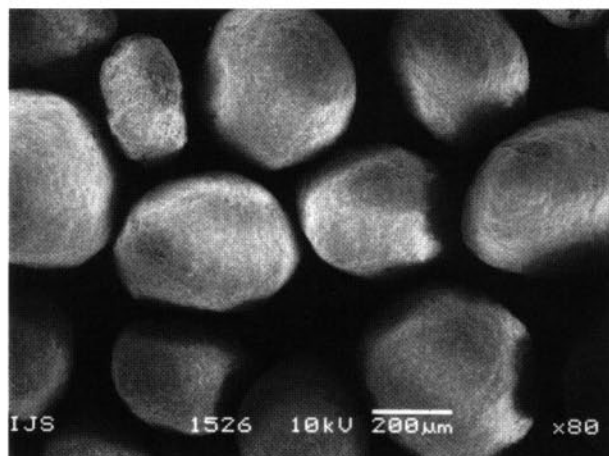
Fig. 17: Batch KS 7/10 (SEM, magnitude 80 ×).
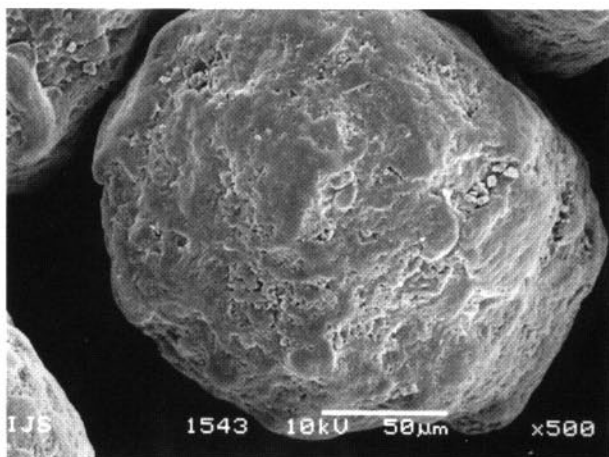
Fig. 15: Batch KS 7/7 (SEM, magnitude 500 ×).
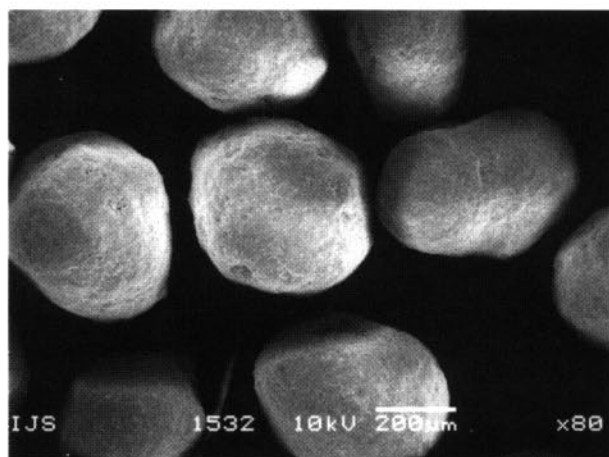
Fig. 18: Batch KS 10/14 (SEM, magnitude 80 ×).

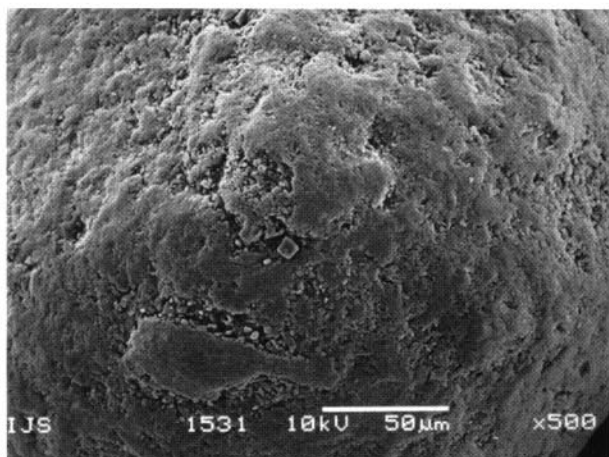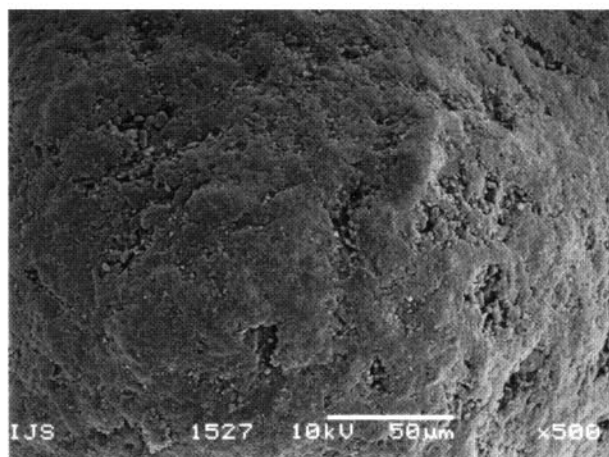*Fig. 16:* Batch KS 7/14 (SEM, magnitude 500 ×).

Fig. 19: Batch KS 7/10 (SEM, magnitude 500 ×).

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physical properties could be the cause why sometimes ketoprofen agglomerates spontaneously already before the agglomeration liquid was added. Ketoprofen is hydrophobic, small particles have large surface area and fluidized air just help them to lower their higher surface free energy by agglomeration (Planinšek et al., in preparation for publication). Small sized drugs such as ketoprofen caused a lot of trouble in fluid bed technology. Therefore it should be kept in mind that extrusion and spheronization is the more appropriate method to produce ketoprofen pellets.

From planned experiments only two were able to be carried out: KT 7/7 and KT 10/10. In both experiments we obtained smaller pellets as expected (Fig. 21–24). Pellet sizes of batch KT 7/7 were too small for size distribution determination.

4.4. Yield of the process, true density and moisture content of the produced pellets

The useful yield varied between 62.9 and 90.2 % for the interval of about 700 µm (Table 3). It must be emphasized that this was just research work on effect of disc speed and its surface on pellets and the optimisation work of pentoxifylline and ketoprofen pellets haven't been done yet.

There were no differences in true density of pellets, the exception is batch PT 10/10 where also the higher percentage of humidity content was obtained. These pellets are larger and drying conditions weren't sufficient to remove the water from pellets.
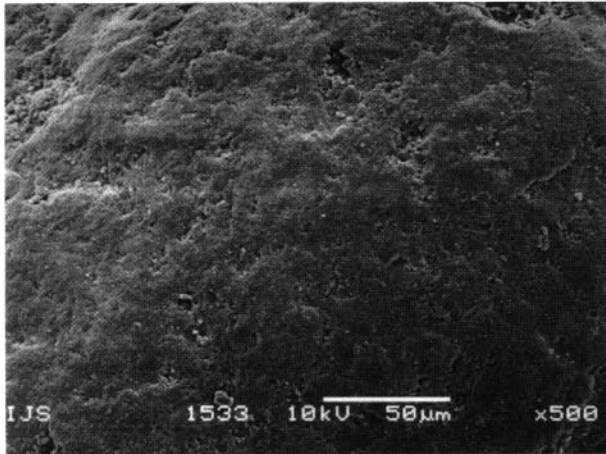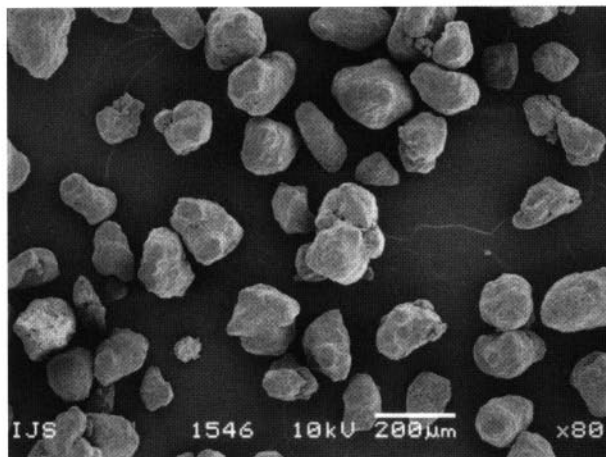

Fig. 20: Batch KS 10/14 (SEM, magnitude 500 ×).
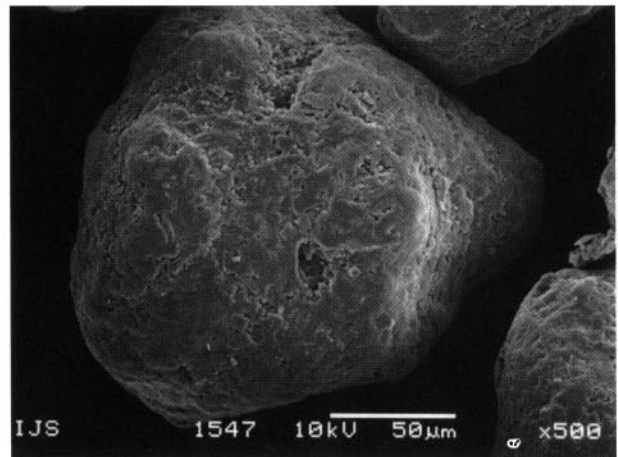

Fig. 21: Batch KT 7/7 (SEM, magnitude 80 ×).

Fig. 23: Batch KT 7/7 (SEM, magnitude 500 ×).

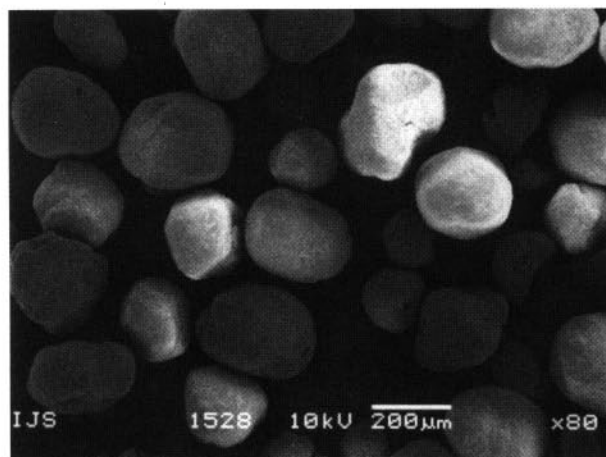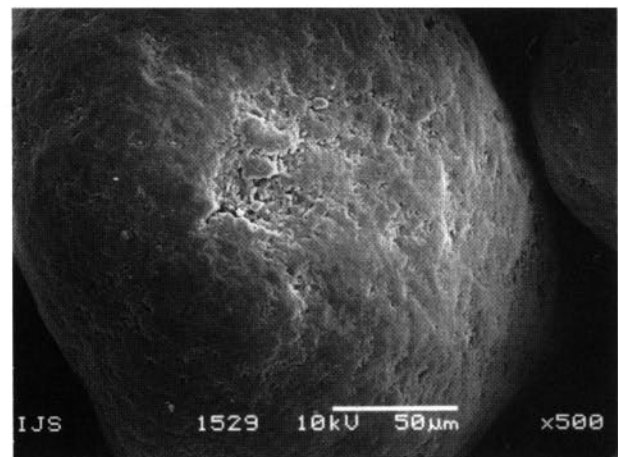*Fig. 22:* Batch KT 10/10 (SEM, magnitude 80 ×).

Fig. 24: Batch KT 10/10 (SEM, magnitude 500 ×).

5. Conclusion

The results show that both surface and rotational speed of the disc have significant influence on the shape, surface, size and size distribution of the pellets. Keeping rotational speed of the smooth disc constant during agglomeration phase and increasing rotational speed during spheronization of agglomerates results in more spherical pellets with larger diameters and smoother surfaces. Increasing rotational speed during spheronization step at the constant speed during agglomeration step with textured disc results in smaller and less spherical pellets with rougher surface.

The quality of pentoxifylline pellets produced with textured disc were better than those produced with smooth disc. On the other hand, for the ketoprofen pellets, better results with smooth disc were obtained.

It can be stated that direct pelletization is a complex process. Although the MCC amount of 30 % makes direct pelletization generally possible, the optimisation of process variables is not enough to produce high loaded quality pellets. The formulation variables, especially physicochemical properties of drugs should be considered very seriously.

6. Literature

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