ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 44 (1997) 169–176

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Comparison between a twin-screw extruder and a rotary ring die press. I. Influence of formulation variables

Christian Schmidt [a], Hans Lindner [b], Peter Kleinebudde [c,*]

[a] Beiersdorf-Lilly GmbH, Hamburg, Germany
[b] Ferring GmbH, Kiel, Germany
[c] Department of Pharmaceutical Technology and Biopharmacy, Christian-Albrecht-University, Kiel, Germany

Received 10 February 1997; received in revised form 5 May 1997; accepted 30 May 1997

Abstract

Pellets were produced on two different types of extruders: a twin-screw extruder and a rotary ring die press. The solubility and the particle size of the excipients were used as formulation variables. All formulations were processed with different moisture content. The power consumption during extrusion, pellet shape and size were selected as yield values. For each formulation and process an optimal moisture content of the extrudate could be determined which resulted in spherical pellets without agglomeration tendency. The optimal moisture content was influenced by both the type of extruder and the selected formulation variables. The optimal moisture content was higher using the twin-screw extruder compared to the ring die press which was explained by the crystallite-gel model. With increasing solubility of the excipient the optimal moisture content was shifted towards lower values. With the ring die press an additional influence of the particle size could be observed: a lower particle size increased the optimal moisture content. The particle size of round pellets depended on the moisture content of the extrudate: due to shrinking during drying extrudates with a high moisture content resulted in the lowest particle size independent of the studied influence variables. © 1997 Elsevier Science B.V.

Keywords: Extrusion/spheronization; Twin-screw extruder; Ring die press; Moisture content; Power consumption; Pellet properties

1. Introduction

Extrusion–spheronization is frequently used for the preparation of pellets in pharmaceutical technology. Extruders can be divided into screw extruders, sieve- or basket-type extruders, ring die press and ram extruders [1]. Other approaches are to classify them according to the die design or the feed mechanism [2]. However, some of this extrusion equipment is already well described in literature [2–11], even by comparison of different extruder types [12–15]. But still there is a deficit in information about a certain type of ring die press, namely, the rotary ring die press or pelletizing press.

The aim of this study was to provide basic knowledge of the rotary ring die press by investigating the influence of formulation variables on the quality of pellets and comparing it to results obtained with a twin-screw extruder. There is information available for the twin-screw extruder used in this study [16–18], but the rotary ring die press is not described in the literature. Therefore, at first the process variables of the pelletizing press (rotation speed and roll gap width) were optimised and standard conditions were established. To allow a better comparison of the two extruders, some

* Corresponding author. Department of Pharmaceutical Technology and Biopharmacy, Christian-Albrecht-University, Gutenbergstr. 76, D-24118 Kiel, Germany; Tel.: +49 431 8801336; e-mail: kleinebudde@pharmazie.uni-kiel.de

0939-6411/97/$17.00 © 1997 Elsevier Science B.V. All rights reserved.
PII S0939-6411(97)00094-5

Table 1
Model drug substances

Model compound	Experiments on			
	Twin-screw extruder		Ring die press	
	Fine	Coarse	Fine	Coarse
Lactose monohydrate (Meggle GmbH, Wasserburg, Germany)	Lactose D80 (particle size: 95% <100 μm)	Lactose D20 (particle size: 6% <100 μm, 98% <300 μm, 100% <600 μm)	Granulac 200 (particle size: 45–75% <32 μm, <10% >100 μm)	Capsulac 60 (particle size: <10% <100 μm, <3% >630 μm)
Dicalcium phosphate dihydrate (Chemische Fabrik Budenheim, Budenheim/ Mainz, Germany)	DI-CAFOS P, C 12-02 (particle size: <5% >45 μm)	DI-CAFOS, C 52-14 (particle size: 3% <45 μm, 50% >150 μm, 1% >300 μm)	DI-CAFOS P, C 52-02 (particle size: <5% >45 μm)	DI-CAFOS, C 52-14 (particle size: 3% <45 μm, 50% >150 μm, 1% >300 μm)
Microcrystalline cellulose (FMC, Cork, Ireland)	Avicel PH 101		Avicel PH 101	

critical process variables have been kept constant throughout this study: the die design [2,5,10], the spheronization time [8,19,20], the spheronization speed [19–22] and the drying conditions [23]. The extrusion behaviour was studied by varying the moisture content of formulations containing ingredients of different particle size and water solubility.

This should lead to a better knowledge of the fundamental differences between the processes and to clarification of the presuppositions for a transfer of formulations later on. According to the recently proposed crystallite-gel model for MCC [24] differences in the performance between the types of extruders can be expected.

2. Materials and methods

2.1. Materials

Pellets were prepared from binary mixtures of a model compound (70%) (%w/w) and microcrystalline cellulose (30%) which were granulated with demineralized water. Model compounds were lactose monohydrate (water soluble) and dicalcium phosphate dihydrate (DCPD, water insoluble) with a fine and coarse quality, respectively (Table 1). All materials were used as received. The moisture content was calculated by the loss of drying at 105°C for 24 h. DCPD lost the crystal water during drying. The formulations were calculated on dry substances including their crystal water.

2.2. Equipment

2.2.1. Twin-screw extruder

The co-rotating, instrumented twin-screw extruder Berstorff ZE 25 × 18 D (Berstorff GmbH, Hannover, Germany) has been used as described in an earlier study [16]. It should be pointed out that the die plate had 48 cylindrical dies with dimensions of 2.5 mm in length and 1.0 mm in diameter. Spheronization was performed on a Nica S-320 (Nica AG, Mölndal, Sweden) with a friction plate diameter of 320 mm.

2.2.2. Rotary ring die press

The rotary ring die press PP-127 (Schlüter Maschinenfabrik GmbH and Co. KG, Neustadt a. Rbge., Germany) is shown in Fig. 1 in a schematical cross-section. The interchangeable ring die is a rotating hollow

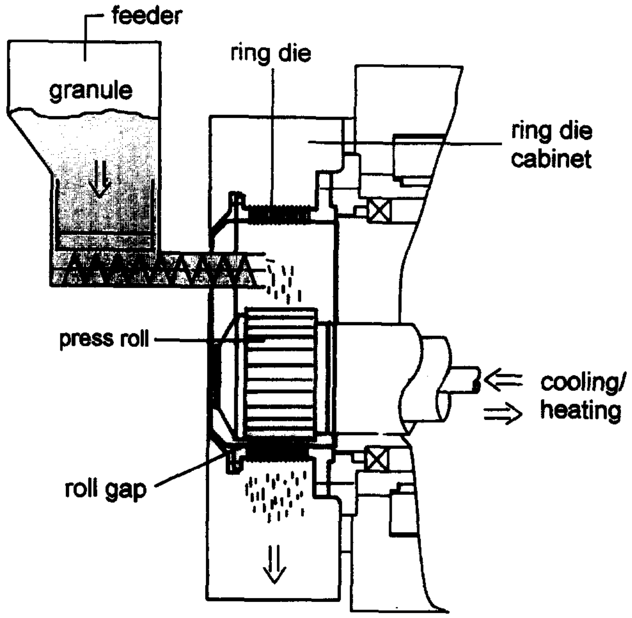

Fig. 1. Schematical cross-section of the ring die press.

roll of 127 mm inner diameter in which the press channels are machined. The diameter of the press channels can range from 0.5 to 4.0 mm. In the present study the ring die exhibited 1750 cylindrical press channels of 2.5 mm in length and 1.0 mm in diameter. The interior of the ring die contains an eccentric press roll of 75 mm diameter, which is also powered and which can be cooled or heated. The number of revolutions of the annular die and the extrusion roller can be continuously varied at a fixed ratio to each other. The speed ratio has been chosen so as to allow the extrusion roller to roll off in the annular die without damaging slip. The roll gap between ring die and press roll is adjustable. The bulk material is fed into the press through a proportioning screw. The bulk material is compressed in the roll gap and rolled into the press channels. Inside the press channels it is compacted to continuous strands. The exiting strands can be cut to a predetermined length by a knife. In order to achieve similar processing conditions to the twin-screw extruder, heating, cooling and a knife were not used for the trials. The PP-127 is connected to an external data acquisition system consisting of a personal computer, a PCL-818HG board (Advantech Co., Ltd., Taipei, Taiwan) and the DASYLab software (Datalog GmbH, Mönchengladbach, Germany). Power consumption and rotational speed of the ring die have been recorded in order to observe the process and detect steady-state conditions.

Extrudates were spheronized on a RM-300 (Schlüter Maschinenfabrik GmbH and Co. KG, Neustadt a. Rbge., Germany) with a diameter of 300 mm.

2.3. Methods

2.3.1. Production of pellets

The twin-screw extruder uses a single-step granulation/extrusion process. So 1500 g of dry powders were blended in a turbula blender (Type T 10 B, Bachofen KG, Basel, Switzerland) for 15 min and poured directly into the powder feeder. Powder feed rate was adjusted to 25 g min^{-1} and screws were rotating at a speed of 60 min^{-1}.

Different amounts of granulation liquid were added by the water pump. After power consumption reached a constant level, 400 g extrudate per batch was collected and spheronized for 5 min at a radial velocity of 13.4 $m \cdot s^{-1}$ (800 min^{-1}). Then, 30 min drying at 50°C in fluid-bed (TR2, Glatt AG, Binzen, Germany) followed. Total water content on dry base (w/w) was determined for three samples per batch. For formulations containing DCPD the fraction of crystal water of DCPD (Eq. (1), M_{CW}) was subtracted from the total water content in order to obtain the water added during granulation/extrusion. For further details about the production process see Ref. [16].

$$M_{CW} = M_{DCPD} - \left(\frac{136}{172} \times M_{DCPD}\right) \quad (1)$$

where M_{DCPD} is fraction of DCPD in the powder mixture

For ring die press experiments 1500 g of dry powders were blended in a planetary mixer (A200, Hobart GmbH, Offenburg, Germany) for 5 min on level 1 (96 min^{-1}). Different amounts of granulation liquid were added within 20–40 s and the powders were granulated for further 5 min on level 2 (176 min^{-1}). The granule was filled in the feeder and extrusion was started after a waiting period of 10 min. The ring die rotated at a speed of 250 min^{-1} and the roll gap was set to 0.33 mm (standard condition). For calculation of net power consumption the empty extruder ran up for 30 min at standard conditions. The mean of power consumption values for the last 5 min was calculated and subtracted from the mean of the values recorded during experimental runs.

Steady-state conditions of the process were monitored by the recorded power consumption. After reaching an equilibrium 500–1000 g of extrudate was collected and spheronized immediately for 5 min at a radial velocity of 13.4 $m \cdot s^{-1}$ (853 min^{-1}). The wet pellets were dried in a fluid-bed drier (TR2, Glatt AG, Binzen, Germany) for 30 min at 50°C. Moisture contents of granules were measured for two samples per batch and calculated as mentioned above with exception of the DCPD formulations. The moisture content (MC) with regard to granulation liquid was calculated from the mixture due to difficulties in recovering the whole moisture content for some batches during drying (Eq. (2)).

$$MC = \frac{M_{MCC} \times MC_{MCC} + M_{Water}}{(M_{MCC} - M_{MCC} \times MC_{MCC}) + (M_{DCPD} - MC_{DCPD} \times M_{DCPD})} \quad (2)$$

where M_{MCC} is fraction of MCC; M_{DCPD} is fraction of DCP including crystal water, $M_{MCC} + M_{DCPD} = 100\%$; M_{Water} is fraction of water (granulation liquid); MC_{MCC} is moisture content of used MCC (4.9%); and MC_{DCPD} is moisture content of used DCPD additional to crystal water (0.0%).

2.3.2. Characterisation of pellets

Pellets were characterised by an image analysis system Leco 2001 (Leco Instruments, St. Joseph, Germany) which has been described previously [25]. Fines (< 500 μm, less than 3% w/w) were removed and the magnification of the system was adjusted to an average diameter of 50–60 pixels per particle. The number of analysed particles depended on their size. In the case of highly agglomerated batches less than 500 particles, but minimal 95, were measured. The following parameters were determined: length L (longest of eight measured feret diameters per particle), breadth B (feret diameter at right angles to length), mean feret D_f (mean of eight measured feret diameters) and projected area A. Aspect ratio AR and equivalent diameter D_{eq} were calculated according to Eqs. (3) and (4).

$$D_{eq} = \sqrt{\frac{4 \times A}{\pi}} \quad (3)$$

$$AR = \frac{L}{B} \quad (4)$$

Pellet quality was mainly rated by aspect ratio. Good pellets should have an AR below 1.1. Furthermore, D_{eq} has been taken into account as a measure of pellet size.

2.3.3. Experimental design

Experiments on twin-screw extruder started on high moisture content level in order to avoid blockades in dies and screws. Liquid amount was decreased gradually until resulting extrudates became too dry for a successful spheronization. Batches that showed agglomeration were rejected.

Experiments on ring die press started with a coarse screening of the moisture content range in which good pellet manufacturing was expected (beginning at low level and increasing moisture content in 5% steps). Afterwards additional trials were performed at levels in between. Moisture content was limited by the feeder unit which only operated sufficiently in a moisture content range of 30–60%.

3. Results

3.1. Power consumption

For all experiments increasing moisture content caused basically decreasing power consumption in a non-linear manner (Figs. 2 and 3). The functional relation between moisture content and power consumption is much stronger for the twin-screw extruder. The results for the ring die press showed more scatter.

The curves (Figs. 2 and 3) differ in dependence on extruder type and model drug substance. On the twin-screw extruder the required moisture content for DCPD formulations was higher than for lactose formulations in order to obtain the same power consumption; particle size of excipients had no influence. The slope was approximately the same for all formulations. On the ring die press the DCPD formulations needed higher moisture content for same power consumption too; but in this case particle size affected the slope. Coarse ingredients resulted in curves with higher slopes than fine ingredients. Comparing batches with similar sized ingredients approximately no differences occurred.

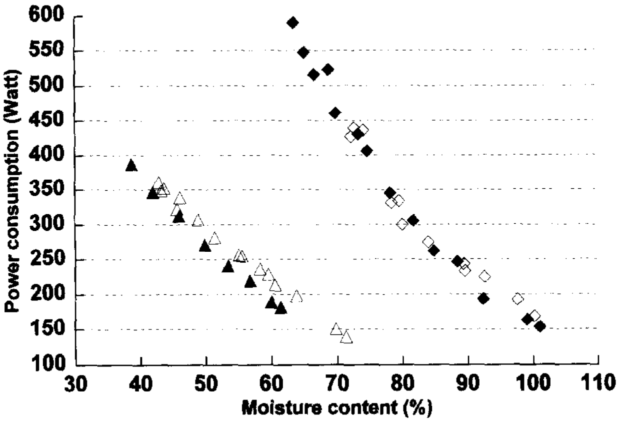

Fig. 2. Relation between power consumption and moisture content of extrudate for the experiments with the twin-screw extruder. ◆: $DCPD_{coarse}$, ◇: $DCPD_{fine}$, ▲: $Lactose_{coarse}$, △: $Lactose_{fine}$.

3.2. Pellet quality

Aspect ratio graphs showed a uniform course too. As moisture content increased AR decreased down to a minimum and rose up slowly afterwards (Figs. 4 and 5). Above that fundamental differences must be noted.

On the ring die press all formulations needed less water than on twin-screw extruder to obtain pellets with a comparable AR. In the case of DCPD the differences were larger compared to lactose. Besides only on ring die press did particle size have an influence on the relation between moisture content and AR. Formulations with coarse ingredients needed about 7.5% less water to form comparable pellets.

According to D_{eq} (Figs. 6 and 7) some additional observations have been made. The extruder type not only affected the required moisture content but also the size of the pellets with the lowest AR. It is interesting to note that for pellets prepared on the twin-screw extruder the minimum for D_{eq} was located at lower

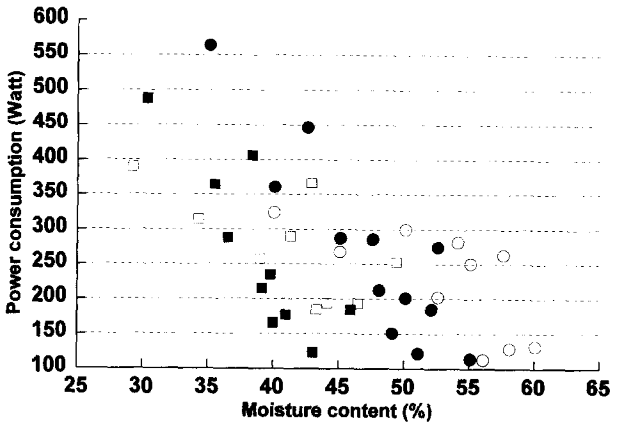

Fig. 3. Relation between net power consumption and moisture content of extrudate for the experiments with the ring die press. ●: $DCPD_{coarse}$, ○: $DCPD_{fine}$, ■: $Lactose_{coarse}$, □: $Lactose_{fine}$.

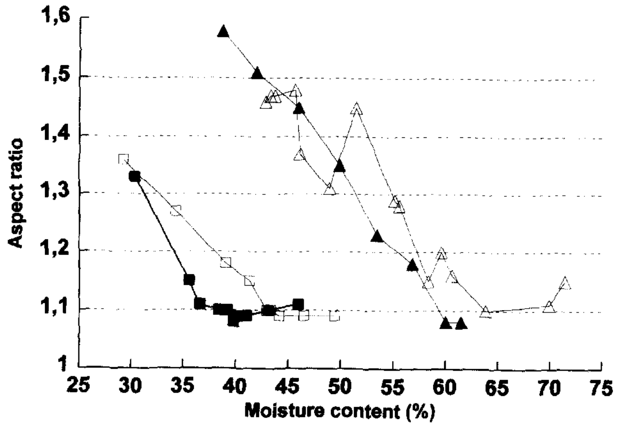

Fig. 4. Dependence of AR on the moisture content of the extrudate for formulations containing lactose. ■□: Ring die press, ▲△: Twin-screw extruder, ■▲: $Lactose_{coarse}$, □△: $Lactose_{fine}$.

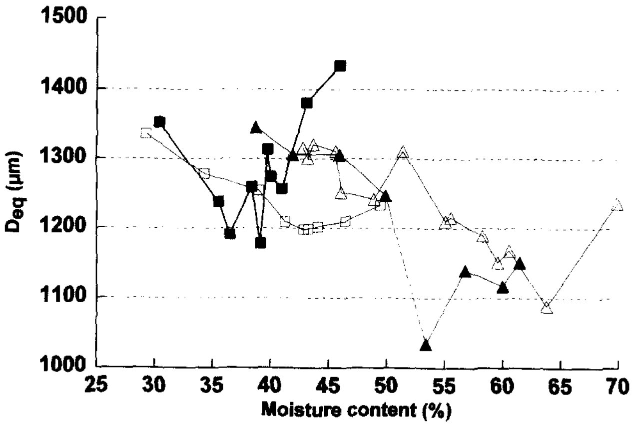

Fig. 6. Dependence of D_{eq} on the moisture content of the extrudate for formulations containing lactose. ■□: Ring die press, ▲△: Twin-screw extruder, ■▲: $Lactose_{coarse}$, □△: $Lactose_{fine}$.

values. Generally D_{eq} values decreased, passed through a minimum then increased for all formulations with an increasing moisture content. The increasing D_{eq} indicated the agglomeration of pellets. This uncontrolled growth during spheronization could be clearly observed for all formulations on the twin-screw extruder and for formulations with coarse ingredients on the ring die press. Again, only on the ring die press was the particle size of the model drug substance of significance. Agglomeration was reduced for formulations with fine ingredients.

4. Discussion

4.1. Power consumption

The twin-screw extruder was superior with respect to the measurement of the power consumption. Two reasons can cause the different quality in the power consumption data. The feeder of the ring die press was not able to ensure a constant feed rate. Due to this the production conditions were less stable compared to the twin-screw extruder resulting in higher variation for power consumption. Furthermore the idle power consumption of the ring die press was not constant throughout the study: values between 1220 and 1331 W were obtained. Since the net power consumption was small compared to the total power consumption any change in the idle power consumption had a strong influence on the net power consumption.

Several authors reported on the influence of moisture content on extrusion parameters, e.g. the extrusion force [3,9,10,12,13,26]. Increasing amounts of water led to better extrusion properties due to a lubrication effect of water on the die wall [27]. The appropriate moisture content range for the production of pellets was shifted towards higher values on the twin-screw extruder for all formulations. This can be explained by the use of the

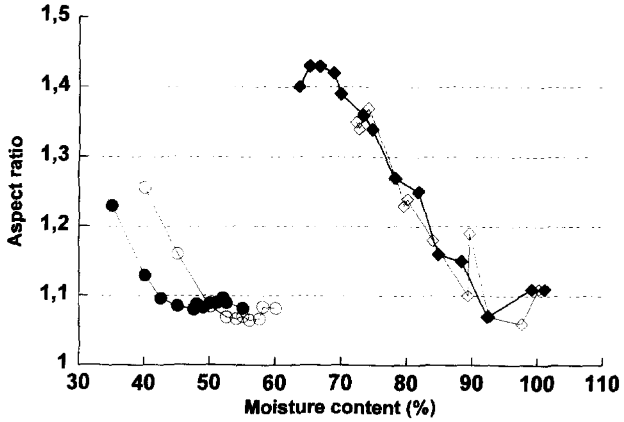

Fig. 5. Dependence of AR on the moisture content of the extrudate for formulations containing DCPD. ●○: Ring die press, ◆◇: Twin-screw extruder, ●◆: $DCPD_{coarse}$, ○◇: $DCPD_{fine}$.

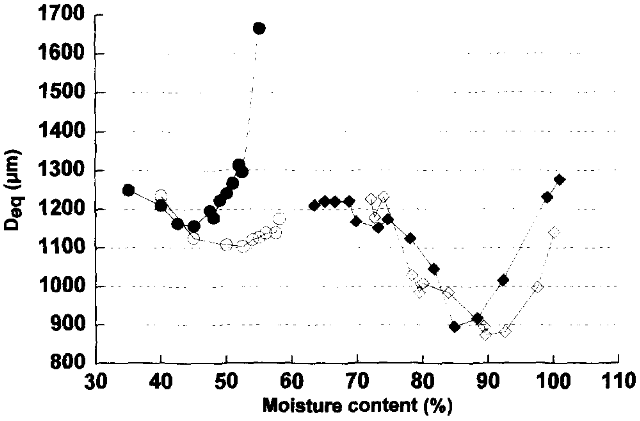

Fig. 7. Dependence of D_{eq} on the moisture content of the extrudate for formulations containing DCPD. ●○: Ring die press, ◆◇: Twin-screw extruder, ●◆: $DCPD_{coarse}$, ○◇: $DCPD_{fine}$.

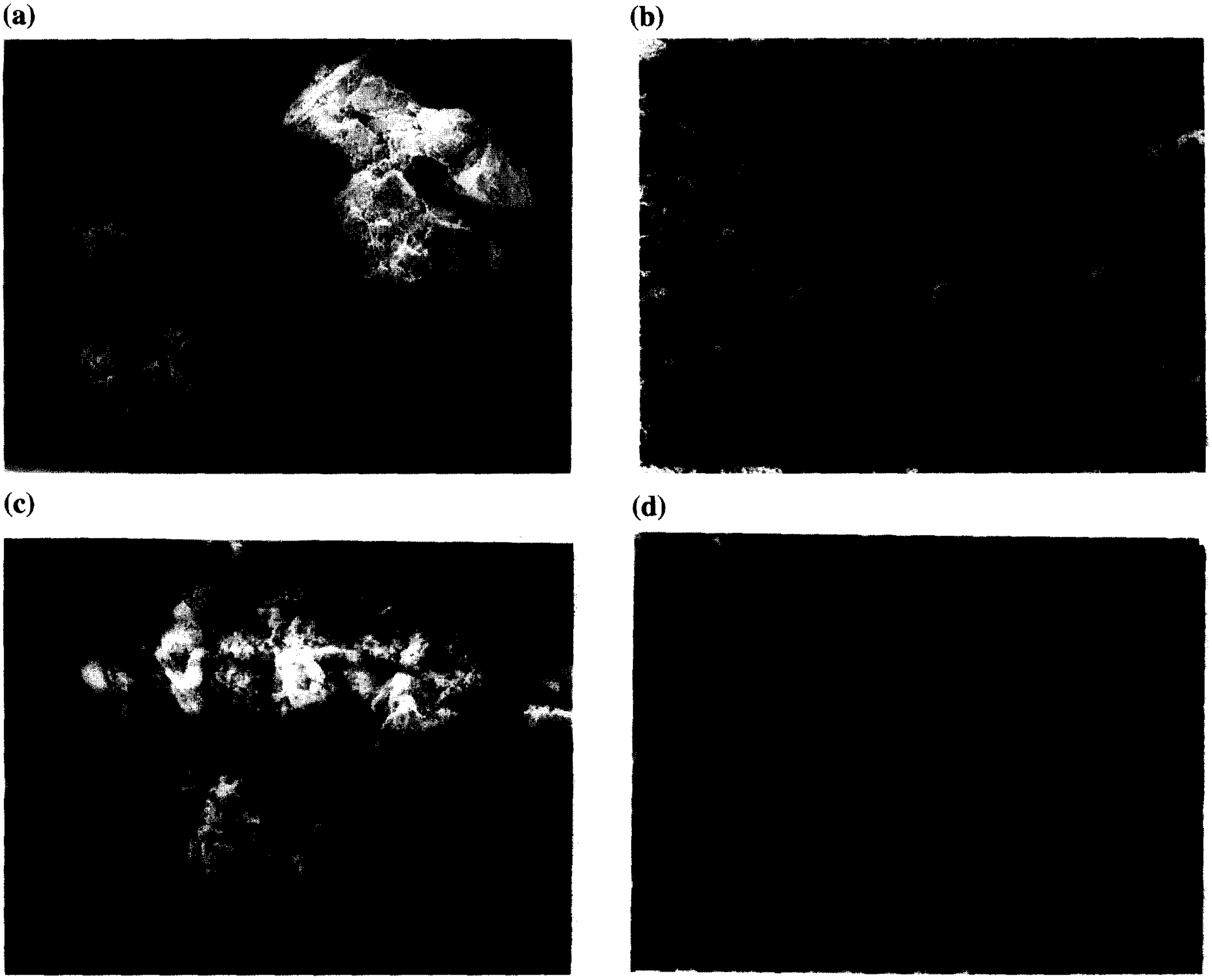

Fig. 8. SEM photographs of (a) $Lactose_{coarse}$ (Capsulac 60), (b) $Lactose_{fine}$ (Granulac 200), (c) $DCPD_{coarse}$ (C 52-14), (d) $DCPD_{fine}$ (C 52-01).

crystallite-gel model [24]. This model proposed the formation of a gel after the reduction of MCC particles to smaller particles down to perhaps ultimately single crystallites. The granulation/ extrusion in the twin-screw extruder is assumed to apply more shear to the wetted mass compared to the planetary mixer and ring die press [1]. With decreasing size of the solid elements in the gel structure more water can be immobilised. Therefore, more water is needed for the same lubricating effect.

On both extruders lactose formulations showed a lower moisture content range compared to DCPD formulations. It is a well-known fact that the influence of solubility of ingredients on the granules extrusion properties is based on the effect on the ratio of solid and liquid phase [3,4]. A drug which dissolves quickly in the granulation liquid like lactose in water is less available in the solid phase and rises the amount of liquid phase. Less liquid is necessary to achieve the same solid/liquid ratio and extrusion properties.

The particle size influenced the relation between power consumption and moisture content only on the ring die press. Other studies with ram extruders revealed high differences between the particle size of lactose on extrusion [28,29]. In this study the particles of the coarse ingredients were in both cases agglomerated from fine particles which can be seen from SEM photographs (Fig. 8). Applying high shear in the twin-screw extruder may induce a reduction of the particle size: consequently the effect of particle size can be neglected. The low shear process in the ring die press did not affect the particle size in the same manner.

4.2. Pellet quality

The aim of pellet production usually is to obtain round particles which have no tendency to agglomerate. For the assessment of the roundness aspect ratio is

Table 2
Parameters for pellets with optimal AR

Formulation	Extruder type							
	Ring die press				Twin-screw extruder			
	AR_{op}	MC_{sp} (%)	D_{sp} (μm)	PC_{sp} (W)	AR_{op}	MC_{sp} (%)	D_{sp} (μm)	PC_{sp} (W)
$Lactose_{coarse}$	1.08	39.8	1313	235	1.08	60.0	1151	189
$Lactose_{fine}$	1.09	44.1	1209	194	1.10	63.8	1088	198
$DCPD_{coarse}$	1.08	47.6	1196	286	1.07	92.3	1016	193
$DCPD_{fine}$	1.07	56.1	1138	113	1.06	97.6	997	192

commonly used. Plotting AR as function of moisture content led to curves shown and described above (Figs. 4 and 5). It is notable that all curves pass through a minimum. It appears useful to describe the position of this point. It indicates the lowest AR that can be achieved for a certain formulation under constant conditions by varying the moisture content. Therefore, this AR value is defined as optimum AR (AR_{op}) and the corresponding moisture content level as specific moisture content (MC_{sp}, Table 2).

Looking at the plot below and above the AR_{op} different courses must be noticed (Figs. 4 and 5). Lower moisture content led to clearly increasing AR values indicating poor spheronizing properties. Higher moisture content had no remarkable effect on the curve. Even agglomeration could not be detected reliably. For this purpose, D_{eq} is appropriate (Figs. 6 and 7): even a slight overwetting of the extrudate resulted in a remarkable increase of D_{eq}.

Following the prior procedure the D_{eq} and power consumption at the specific moisture content were defined as specific D_{eq} (D_{sp}) and specific power consumption (PC_{sp}, Table 2). Plotting the equivalent diameter versus moisture (Figs. 6 and 7) content revealed that the minimum D_{eq} corresponded in most cases with the D_{sp}. This means that for each formulation and process an optimal moisture content can be identified resulting in nearly spherical pellets without any agglomeration. At the optimal moisture content the values for power consumption (PC_{sp}) were nearly constant for all formulations using the twin-screw extruder. The pellet quality is strongly related to the level of power consumption during extrusion. These results support the concept of the power-consumption controlled extruder which was published earlier [17,18]. A higher scatter for PC_{sp} using the ring die press was not unexpected with regard to the high variation on power consumption measurements described above.

The optimal moisture content depended on the type of extruder, the type of excipient and in some cases on the particle size of the excipient. The influence of the different parameters was already discussed with respect to the power consumption. Differences in optimal moisture content can be related to the structure of the crystallite-gel and to the solubility as well as the final particle size of the excipients.

It was obvious that for each formulation the D_{sp} was lower for the twin-screw extruder compared to the ring die press. This can be related to the specific moisture content of the extrudate: a higher moisture content resulted in a lower D_{sp} ($r = -0.941$, $p < 0.001$). This is caused by shrinking phenomena during drying which are more pronounced with increasing initial moisture content [18].

5. Conclusions

The study showed important differences in the optimal moisture content between the two different types of extruders. However, some factors were not kept constant during the comparison of the extruders: the type of spheronizer (diameter and geometry of friction plate) and the spheronizer load were different for the twin-screw extruder compared to the ring die press. In order to investigate the influence of these process variables further experiments will be described in the second part of the paper.

Acknowledgements

The authors would like to thank Dr F.W. Obereichholz-Bangert, Dr H.J. Lange, Dr W.C. Vladuchick and Mr G. Denney for helpful discussions, financial and material support.

References

[1] D.C. Hicks, H.L. Freese, Extrusion and spheronizing equipment, in: I. Ghebre-Sellassie (Ed.), Pharmaceutical Pelletization Technology, Marcel Dekker, New York, 1989, pp. 71–84.

[2] K.E. Fielden, J.M. Newton, Extrusion and extruders, in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopaedia of Pharmaceutical Technology 5, Marcel Dekker, New York, 1992, pp. 422–431.

[3] L. Baert, D. Fanara, P. De Baets, J.P. Remon, Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces, J. Pharm. Pharmacol. 43 (1991) 745–749.
[4] L. Baert, D. Fanara, J.P. Remon, D. Massart, Correlation of extrusion forces, raw materials and sphere characteristics, J. Pharm. Pharmacol. 44 (1992) 676–678.
[5] P.J. Harrison, J.M. Newton, R.C. Rowe, Flow defects in wet powder mass extrusion, J. Pharm. Pharmacol. 37 (1985) 81–83.
[6] L. Hellén, M. Ritala, J. Yliruusi, P. Palmroos, E. Kristoffersson, Process variables of the radial screen extruder. Part I, Pharm. Tech. Int. 4 (1992) 50–60.
[7] L. Hellén, J. Yliruusi, E. Muttonen, E. Kristoffersson, Process variables of the radial screen extruder. Part II. Size and size distribution, Pharm. Tech. Int. 5 (1993) 44–53.
[8] G.A. Hileman, S.R. Goskoda, A.J. Spalitto, S.M. Upadrashta, A factorial approach to high dose product development by an extrusion/spheronization process, Drug Dev. Ind. Pharm. 19 (1993) 483–491.
[9] R.D. Shah, M. Kabadi, D.G. Pope, L.L. Augsburger, Physicomechanical characterization of the extrusion-spheronization process. I. Instrumentation of the extruder, Pharm. Res. II (1994) 355–360.
[10] C. Vervaet, L. Baert, P.A. Risha, J.P. Remon, The influence of the extrusion screen on pellet quality using an instrumented basket extruder, Int. J. Pharm. 107 (1994) 29–39.
[11] C. Vervaet, J.P. Remon, Influence of impeller design, method of screen perforation and perforation geometry on the quality of pellets made by extrusion–spheronization, Int. J. Pharm. 133 (1996) 29–37.
[12] K.E. Fielden, J.M. Newton, R.C. Rowe, A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and a cylinder extruder, Int. J. Pharm. 81 (1992) 225–233.
[13] L. Baert, J.P. Remon, P. Knight, J.M. Newton, A comparison between extrusion forces and sphere quality of a gravity feed extruder and a ram extruder, Int. J. Pharm. 86 (1992) 187–192.
[14] L. Baert, J.P. Remon, J.A.C. Elbers, E.M.G. Van Bommel, Comparison between a gravity feed extruder and a twin screw extruder, Int. J. Pharm. 99 (1993) 7–12.
[15] E. Le Doeuff, M. Vanhoeve, A.T. Gayot, P. Becourt, An approach of extrusion and spheronization, comparison of two extruders by means of experimental designs, Proc. 6th Int. Conf. Pharm. Technol. (APGI) 6 (3) (1992) 207–215.
[16] P. Kleinebudde, H. Lindner, Experiments with an instrumented twin-screw extruder using a single-step granulation/extrusion process, Int. J. Pharm. 94 (1993) 49–58.
[17] P. Kleinebudde, Use of a power-consumption-controlled extruder in the development of formulations, J. Pharm. Sci. 84 (1995) 1259–1264.
[18] P. Kleinebudde, A.J. Sølvberg, H. Lindner, The power-consumption-controlled extruder: A tool for pellet production, J. Pharm. Pharmacol. 46 (1994) 542–546.
[19] L. Baert, H. Vermeersch, J.P. Remon, J. Smeyers-Verbeke, D.L. Massart, Study of parameters important in the spheronisation process, Int. J. Pharm. 96 (1993) 225–229.
[20] C.W. Woodruff, N.O. Nuessle, Effect of processing variables on particles obtained by extrusion-spheronization, J. Pharm. Sci. 61 (1972) 787–790.
[21] M. Chariot, J. Francès, G.A. Lewis, D. Mathieu, R. Phan Tan Luu, H.N.E. Stevens, A factorial approach to process variables of extrusion-spheronization of the wet powder mass, Drug Dev. Ind. Pharm. 13 (1987) 1639–1649.
[22] H.J. Malinowski, W.E. Smith, Use of factorial design to evaluate granulations prepared by spheronization, J. Pharm. Sci. 64 (1975) 1688–1692.
[23] B. Bataille, K. Ligarski, M. Jakob, C. Thomas, Study of the spheronization and drying conditions on the physical and mechanical properties of neutral spheroids containing Avicel PH 101 and lactose, Drug Dev. Ind. Pharm. 19 (1993) 653–671.
[24] P. Kleinebudde, The crystallite-gel-model for microcrystalline cellulose in wet-granulation, extrusion and spheronization, Pharm. Res. 14 (1997) 808–813.
[25] H. Lindner, P. Kleinebudde, Characterization of pellets by means of automatic image analysis (in German), Pharm. Ind. 55 (1993) 694–701.
[26] D. Bains, S.L. Boutell, J.M. Newton, The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose, Int. J. Pharm. 69 (1991) 233–237.
[27] J.F. Pinto, G. Buckton, J.M. Newton, The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronization, Int. J. Pharm. 83 (1992) 187–196.
[28] K.E. Fielden, J.M. Newton, R.C. Rowe, The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures, J. Pharm. Pharmacol. 41 (1991) 217–221.
[29] K.E. Fielden, J.M. Newton, R.C. Rowe, The influence of lactose particle size on spheronization of extrudate processed by a ram extruder, Int. J. Pharm. 81 (1992) 205–224.