The Crystallite-Gel-Model for Microcrystalline Cellulose in Wet-Granulation, Extrusion, and Spheronization

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Purpose. A new model for the wet-extrusion/spheronization process with microcrystalline cellulose (MCC) is proposed. The crystallite-gel-model is able to elucidate the unique role of MCC in this process. Many other experimental results, which cannot be explained by the standard model of granulation, the liquid saturation model, give evidence for the crystallite-gel-model.

Methods. Pellets were prepared from different types of MCC. Water content during extrusion, power consumption and aspect ratio were correlated. X-ray diffractograms of MCC powders, extrudates and pellets were taken in order to provide information on changes at the single crystallite level. SEM-photographs and leaching studies gave additional information on changes at the particulate level of MCC.

Results. At the level of MCC powder particles, dramatic changes occurred during extrusion/spheronization. In contrast to this no changes could be observed at the level of individual crystallites.

Conclusions. During granulation and extrusion MCC-particles are thought to be broken down into smaller particles and possibly ultimate single crystallites in the presence of water. The crystallite-gel-model serves as the framework for a new interpretation of the wet-extrusion/spheronization process. Apart from the ability to explain experimental data published previously in the literature it can be used to develop new experimental plans for further research. Consequently, the crystallite-gel-model exhibits explanatory as well as predictive power.

KEY WORDS: microcrystalline cellulose; wet granulation; extrusion/spheronization; crystallite-gel-model; liquid saturation model.

INTRODUCTION

The requirements for a suitable formulation for the wet-extrusion/spheronization process are summarized by Fielden and Newton (1):

> Extrusion mixtures are formulated to produce a cohesive plastic mass which remains homogeneous during extrusion. The mass must possess inherent fluidity, permitting flow during the process and self-lubricating properties as it passes through the die. The resultant extrudate must remain non-adhesive to itself and retain a degree of rigidity so that the shape imposed by the die is retained.
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> The requirements for spheronization of the cylindrical extrudate are as follows:
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> 1. The extrudate must possess sufficient mechanical strength when wet, yet it must be brittle enough to be broken down to short lengths in the spheronizer, but not be so friable that it disintegrates completely. . . .
> 2. The extrudate must be sufficiently plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate in the spheronizer.
> 3. The extrudate must be non-adhesive to itself in order that each spherical granule remains discrete throughout the process (1).

An extrusion aid is essential in obtaining an appropriate result: microcrystalline cellulose (MCC) is the most important extrusion aid (1) and many attempts have been made to explain its unique properties. "The function of MCC is twofold: it controls the movement of water through the wet powder mass during extrusion and modifies the rheological properties of the other ingredients in the mixture, conferring a degree of plasticity which allows to be readily extruded." (1) The rheological properties of wetted masses have been investigated recently in order to establish objective criteria for outlining suitable formulations for extrusion/spheronization (2,3).

The rheological properties of the extrudate and the results after extrusion/spheronization are highly dependent upon the liquid content of the wetted mass (1). Only in a narrow range of liquid content can round pellets of the desired size be produced. Below this specific moisture content range (4,5), plasticity of the extrudate is insufficient; in this case extrusion parameters such as pressure, power consumption or temperature increase. Furthermore, a higher fraction of fines is generated during spheronization and the extrudate does round off. The resulting product is rodlike and anisometric. Exceeding the specific moisture content range results in lower values for the extrusion parameters; the extrudate is soft and easily deformable. As a consequence uncontrolled agglomeration due to coalescence can be observed during spheronization. The resulting particles are large and almost round in shape; the size distribution is broad. These effects are more pronounced with increasing deviation of the liquid content from the specific moisture content range.

Observations in the field of wet granulation are often described based on the strength of mobile liquid bonds in moist agglomerates. These observations led to the model of different states of liquid in moist agglomerates (6,7). However, this standard model has deficits regarding wet extrusion/spheronization with MCC. In the following, a new model providing a better explanation for many experimental results is proposed. Additionally, new experimental data are presented to support the new model.

THEORETICAL BACKGROUND

Liquid Saturation Model

When a liquid is added to a powder, the liquid will cover the void space between the individual particles. The relative amount of liquid in the wetted powder is defined as liquid saturation or voidage saturation, S: the ratio of the volume of liquid to the total volume of pores (8). Different levels of liquid saturation are related to different states of liquid: liquid saturation below 0.25 is associated with the pendular state; values between 0.25 and 0.8 describe the funicular state; and values above 0.8 describe the capillary state. Liquid saturation beyond 1 results in the droplet or suspension state. The tensile

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strength (σ_t) of wet powders can be calculated theoretically as follows:

$$\sigma_t = S \cdot C \cdot \frac{1 - \varepsilon}{\varepsilon} \cdot \frac{\gamma}{d} \cdot \cos \Theta$$

where

C: material constant;
d: diameter of the monosized spheres;
ϵ: interparticulate porosity;
γ: surface tension of the liquid;
cos Θ: contact angle between liquid and solid.

The equation was developed for a liquid saturation above 0.25 and assumes that the tensile strength of the wet mass is based on liquid bridges only. The tensile strength can be related to deformability, which is important in assessing the rheological behavior. The equation demonstrates that increasing liquid saturation results in higher tensile strength of the wet mass if the other values in the equation are held constant. In practice, many deviations are observed, for example, the particles usually exhibit a size distribution and are not spherical. Moreover, porosity may change during the process, the solid may be partially dissolved by the liquid, or the solid is able to swell in the liquid. The tensile strength of wetted powders is additionally affected by particle interactions (8). However, the model of liquid saturation based on liquid bonds is useful and widely accepted in many areas including extrusion/spheronization (4,9). Nevertheless, certain observations relating to extrusion/spheronization cannot be explained sufficiently with this model:

- The first point deals with the special role of MCC. In the standard model all particles are regarded as nonporous, solid spheres and the liquid is distributed in between. If the standard model was applicable it would not become clear why MCC is a superior extrusion aid compared to other excipients.
- A second point relates to the different grades of MCC; MCC is available in various particle size distributions from a number of suppliers. Rowe and Sadeghnejad (9) showed that a change in the particle size of MCC has only a minor effect on the amount of liquid necessary to obtain the maximum in the mean torque curve. On the other hand materials of comparable size but from different suppliers led to distinct changes in liquid content at maximum torque (10). This effect is further supported by a study of Newton et al. (11) where the particle size of MCC was of less importance, with respect to the specific moisture content range, when compared to the source of MCC. The insignificance of particle size on the rheological properties of MCC was also demonstrated (3). On the contrary, the particle size of other ingredients in the powder formulation, e. g. lactose, was found to be critical for the extrusion/spheronization process (12). All these observations are not compatible with the standard model.
- The liquid content required for successful extrusion/spheronization is typically higher than for other wet-granulations (1) and is highly dependent upon the composition of the dry powder blend (13,14). The fraction of MCC in the powder mixture has a particularly strong influence on the specific moisture content range which is reflected in different recommendations for the appropriate moisture content of extrudates based on the fraction of MCC. The optimum ratio of MCC to water varies between 1:1.2 (13) and 1:1.3 (15) corresponding to a water content of 120% and 130% (on dry base).
- Extrusion parameters such as power consumption (16), pressure (17) or extrusion force (13) decrease continuously with increasing amounts of liquid. According to eq. 1, a positive slope for these curves should be expected up to a liquid saturation of 1. This type of curve was identified using mixer torque rheometers (9,10) but not for extruders. Tensile strength measurements exhibited a trend of increasing values with decreasing water-levels, which is contrary to the standard model (2).
- Jerwanska *et al.* (18) recently determined the liquid saturation of extruded cylinders in relation to the water content. Across a broad range of water contents, values for S between 0.9 and 1 were found. From these results, it was concluded that during extrusion a compression stage can be observed at first; the porosity of the wetted mass is reduced until no gas remains in the extrudate and the liquid saturation is close to 1. After compression the extrusion starts. If the amount of liquid is high the distance between the particles is increased. Thereby particle-particle interactions and consequently the extrusion force are reduced. Liquid saturation may thus be less important than considered before.
- Pellets containing MCC tend to shrink during drying (19). While keeping their shape, the size is reduced during oven drying or fluid-bed drying, but not during freeze-drying. The extent of shrinking correlates with the fraction of MCC in the formulation (14). Structural changes of MCC during extrusion, which cannot be explained by the standard model, may be assumed.
- The strength of dry granules and pellets is based on several mechanisms. Most important are the formation of crystalline bridges of dissolved material or viscous bridges of binders between the particles. It is often unnecessary to use additional binders in extrusion/spheronization if the insoluble MCC is included in the formulation. Nevertheless the resulting pellets do not disintegrate. Neither mechanism mentioned above is able to explain the high coherence of dried pellets prepared with MCC.

STRUCTURE OF MCC AND INTERACTION WITH WATER

MCC is produced by a partial hydrolysis of cellulose from wood pulp to a level-off D. P. of about 200–300 (20). The resulting suspension of microcrystals or crystallites is spray dried to form powder particles. The properties of the crystallites depend on the source of cellulose and the process of hydrolysis. Powder particle size is determined by spray-drying conditions.

Extensive information is available on the interaction of water with MCC. Water vapor isotherms (21) indicate that MCC can adsorb 16–26% of water based on dry weight. During granulation and extrusion MCC is able to immobilize even more water. Thermal studies showed that 15.4% of water based on dry weight was not freezable in a mixture of MCC and 70% water (on dry base). This water was called structured water.

As the rest of water was only physically retained, MCC was addressed as a 'molecular sponge' (22). The liquid retention potential of MCC was studied by means of a pressure membrane technique (23). Water is retained in a porous material as a result of adsorption and capillary effects. The material was characterized by irreducible saturation, which refers to liquid that remains in a porous bed, regardless of any further increase in pressure applied. For MCC and water, irreducible saturation was 90% while for lactose values of 7.9% and 16.6% were found. This indicates a high extent of solid-liquid interaction for MCC.

It has been shown that powder particles of MCC are broken down into smaller particles during preparation of suspensions (24). The viscosity of the suspension increases with blending time. Due to increasing energy dissipation during the process, the disintegration of the powder particles can be enhanced. Ultimately single crystallites may be obtained.

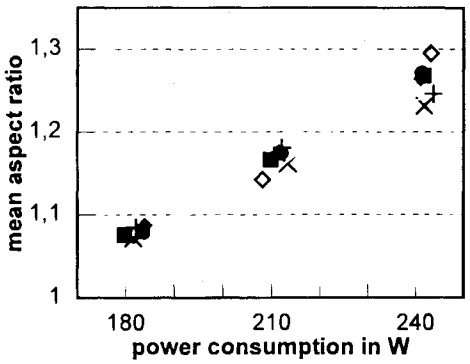

Fig. 1. mean aspect ratio as a result of the power consumption for series two (■: MCC 2, ●: MCC 3, ◆: MCC 4, +: MCC 5, ×: MCC 6, ◇: MCC 7)

CRYSTALLITE-GEL-MODEL

It is proposed that a gel is formed during extrusion with MCC. In the presence of a liquid, especially of water, the MCC particles will break down to smaller subunits due to shear during granulation and extrusion. With increasing shear stress this process will be more or less complete, finally single crystallites of colloidal size may occur. These single particles are able to form a crystallite-gel and immobilize the liquid. The crystallites or their agglomerates can form a framework by crosslinking with hydrogen bonds at the amorphous ends. Single crystallites will result in a delicate network. The viscosity of the gel depends on the particle size of the resulting components and the liquid content. With increasing liquid content the fraction of gelling agent decreases and the deformability increases. This crystallite-gel-model is able to explain the phenomena mentioned above.

The gelling agent is used in a high proportion: a ratio of MCC to water of 1:1.2 corresponds to 45.5% of gelling agent. The unique role of MCC can be explained by the ability of MCC to form a gel with a high amount of gelling agent. The gel is not sticky, because the gelling agent is insoluble in water. The same is known for bentonit and kaolin which have also been suggested as extrusion aids (1).

Extrudates can be produced in a broad range of liquid content. The coherence of the extrudate is determined by the properties of the particular crystallite-gel. The extrudate can only be spheronized successfully, however, if its plasticity and deformability are suitable. The extrudate contains a high percentage of solid material compared to gels prepared with water soluble hydrocolloids. This may be an explanation for the good breaking properties of extrudates containing MCC. The addition of hydrocolloids or the use of colloidal grades of MCC can reduce fragility leading to less isometric particles.

Particle size of the MCC powder is of less importance for the extrudate and pellet properties because the particles are broken down during granulation and extrusion. The properties of the arising crystallites determine the rate of gelling during extrusion. Therefore, MCC from different suppliers will have a high impact on the specific moisture content range if the properties of the crystallites produced are different.

The high water content necessary in extrusion can be explained if the gel-model is used instead of the model of liquid bridges between solid particles. At the same time it becomes evident that the water content is highly dependent on the fraction of MCC in the formulation. Since MCC forms the gel it mainly determines the need of liquid. In most cases, drugs and excipients can be stated as fillers in the gel. However, the presence of other gelling agents in a formulation can interfere with MCC.

As the crystallite-gel will be more deformable with an increasing water content and a decreasing fraction of MCC in the extrudate the extrusion parameters will drop continuously. The gel-model is in accordance with the observations that the liquid saturation during extrusion is independent of the water content (18). The crystallite-gel will tend to shrink during drying. The deformability allowing the gel to shrink is due to the capillary pressure. The crystallites will form new hydrogen

Table 1. Types of MCC Used in this Study

Code	Type	Supplier	Mean particle size in μm	Crystallinity index in %
MCC 1	Avicel PH 102	FMC, USA-Philadelphia	100	68
MCC 2	Avicel PH 101	FMC, USA-Philadelphia	50	76
MCC 3	Avicel PH 105	FMC, USA-Philadelphia	20	68
MCC 4	Avicel PH 200	FMC, USA-Philadelphia	200	72
MCC 5	Emcocel 50	Mendell, USA-Patterson	50	73
MCC 6	Vivacel 101	Rettenmaier und Söhne, D-Ellwangen-Holzmühle	50	65
MCC 7	Sanaq 101 L	Pharmatrans Sanaq, CH-Basel	max. 10%>150 min. 35%>50	73

bonds. With increasing fractions of fillers in the formulation the extent of shrinking is reduced (14). It is well known that wet granulation can reduce the compactability of MCC (25). This can now be explained by the formation of a crystallite-gel during wet granulation.

The mechanism of autohesion was also applied to the mechanical properties of pellets (26). Autohesion is defined as the mutual interdiffusion of free polymer chain ends across the particle-particle interface of high molecular weight polymers resulting in a stable link. The formation of hydrogen bonds in the amorphous ends of the crystallites during drying can thus be described as an autohesion effect resulting in a stable matrix. This provides an explanation for the disintegrating (27) and dissolution properties (28) of pellets. Other materials which have been proposed as extrusion aids e. g., bentonit and kaolin, are able to form a gel in the wet state. Since they show no autohesion the coherence of pellets after drying is inferior. Thus MCC is regarded as the most important extrusion aid.

The crystallite-gel-model allows the prediction of a number of pellet properties. With increasing amounts of fillers in the formulation the mechanical strength should decrease. The quality of the crystallite-gel depends on the amount of gelling-agent, the nature of the crystallites, and the preparation of the gel. High shear during granulation and extrusion should result in a more delicate network. This network should require more water to obtain the same plasticity as compared to a coarser network of the gel. Thus, apart from the formulation, the equipment may have an influence on the specific moisture content range, too. The wet-granulation step is especially more important than outlined before now. These predictions will be addressed in future studies.

MATERIALS AND METHODS

Materials

The different types of MCC used are listed in Table 1. Particle size values were taken from the certificates of the suppliers; the crystallinity index was determined as described below. Lactose monohydrate (Lactose D 20, Meggle, Germany) was used as a soluble filler and demineralized water as granulation liquid.

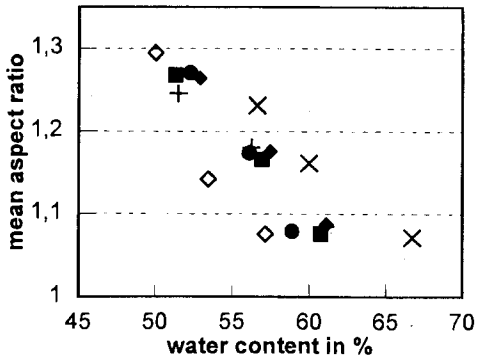

Fig. 2. relation of moisture content of the extrudate and mean aspect ratio for series two (■: MCC 2, ●: MCC 3, ◆: MCC 4, +: MCC 5, ×: MCC 6, ◇: MCC7)

Pellet Preparation

Pellets were prepared using a power-consumption controlled extruder as described earlier (5,14). In a first series, different types of pure MCC were extruded; all types of Avicel (MCC 1 to MCC 4, Table 1) were used. In a second series, blends of 70% (w/w) lactose and 30% MCC were used; all types of MCC with exception of MCC 1 were studied. Settings of the independent variables during extrusion were 180 W for power consumption, 25 g min^{-1} for powder feed rate, and 60 min^{-1} for screw speed. Additionally, pellets were manufactured at power levels of 210 W and 240 W in the second series. Spheronization and drying were carried out as described earlier (5,14). The water content of the extrudate is expressed on dry base.

Image Analysis

Image analysis was performed as described before (29). Sphericity was assessed by the mean aspect ratio.

Crystallinity Index and X-Ray Diffractometry

The crystallinity index of MCC was calculated from X-ray diffractograms according to Knolle and Jayme (30). X-ray diffractograms were taken using equipment with a rotating anode (Stoe & Cie, D-Darmstadt). All measurements were carried out with a voltage of 40 kV and a current of about 200 mA. The sample was fixed in a holder between two films. A range for 2θ between 5 and 50° was scanned in 45 steps of 10 s using a position sensitive detector. The signals were stored on a MicroVAX II (Digital Equipment, USA-Maynard) and evaluated with the appropriate software. X-ray diffractograms were prepared for all types of MCC (Table 1) and for extrudate and pellets made from MCC 1. Two samples of each product were measured.

SEM-Photographs

For MCC 2 to MCC 4 the powders and the pellets of the first series were analyzed without any further treatment. Pellets of the second series were treated with water in order to dissolve lactose. 100 ml of water were added to about 200 mg of pellets. The suspension was shaken for 24 h and subsequently washed at least 5 times with water. The eluted, wet pellets were frozen at −18° C and freeze-dried (Lyovac GT 3, Leybold-Heraeus, D-Köln).

The dried pellets were coated with a gold layer using a sputter (SCD 005, Bal-Tec AG, Fürstentum-Liechtenstein) with 50 mA for 180 s. Subsequently, SEM-photographs were taken with a scanning electron microscope (XL 20, Philips, NL-Eindhoven).

RESULTS AND DISCUSSION

The surface morphology of the resulting pellets should be different from that of the powder particles. For pellets containing a soluble filler, MCC should form a coherent network after dissolution of the filler. These points should be evaluated in order to confirm the crystallite-gel-model.

The crystallinity index for pellets prepared from MCC 1 was 67–68%. The corresponding extrudate exhibited a crys-

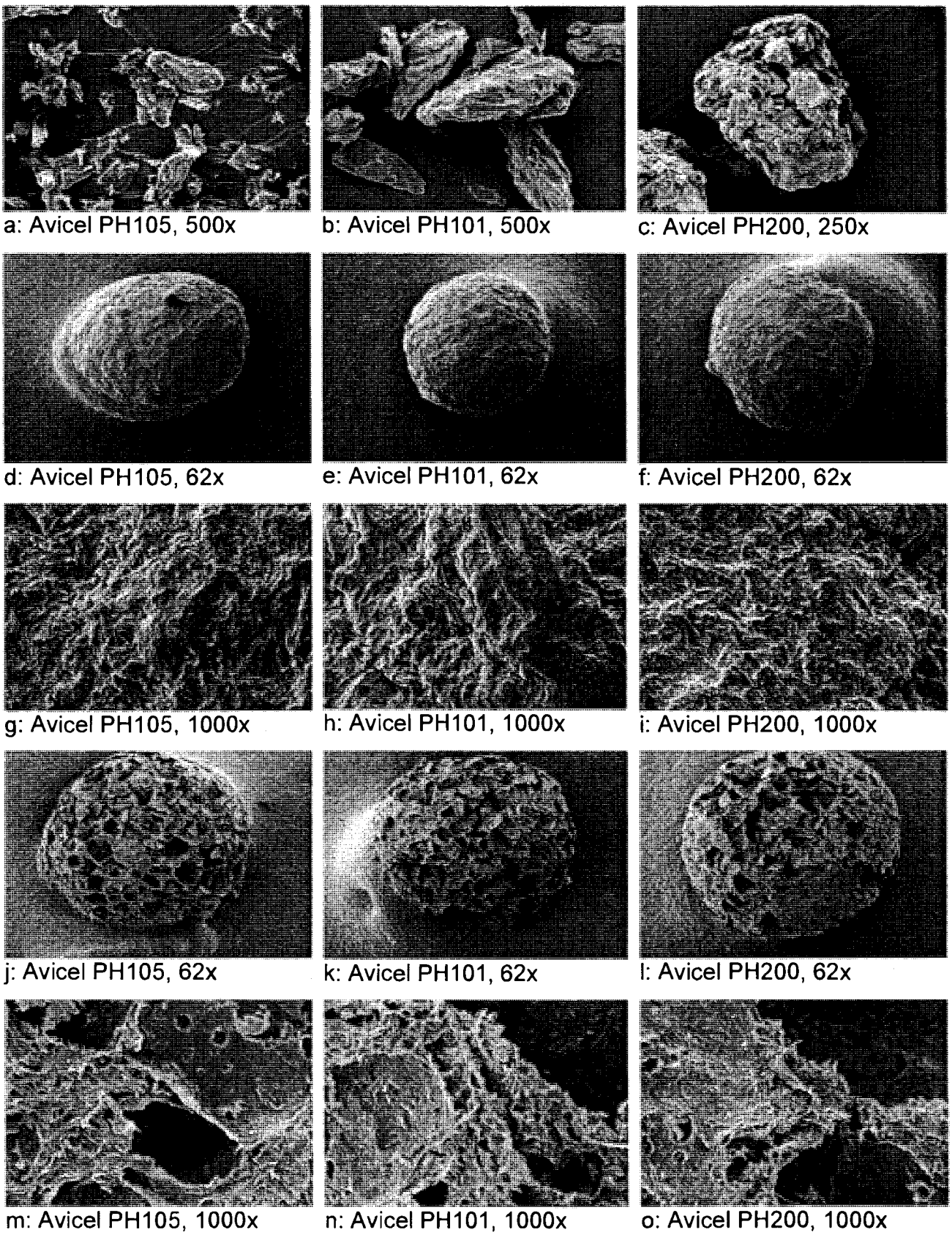

Fig. 3. SEM-photographs of different pellets and MCC powders 3a–c: MCC powders 3d–f: overview of pellets from series one (100% MCC) 3g–i: surface details of pellets from series one 3j–l: overview of eluted pellets from series two (30% MCC) 3m–o: surface details of pellets from series two.

tallinity index of 67%. Values of 66% and 70% were obtained for the powder. Thus, no detectable change in the crystallinity index of MCC during extrusion and spheronization had occurred. All changes in the structure of the MCC particles left the individual crystallites unaffected.

Figure 1 shows the influence of power consumption during extrusion on the mean aspect ratio of the pellets from the second series. Regardless of the type of MCC a power consumption of 180 W resulted in almost round pellets with a mean aspect ratio below 1.1. This relation was observed and explained earlier (5,14). However, a change in the type of MCC may lead to a different moisture content necessary to obtain round pellets from the extrudate. Figure 2 shows the relation of moisture content and mean aspect ratio of the resulting pellets. At a constant moisture level, e.g., 57%, different mean aspect ratios can be observed. On the other hand different moisture contents result in pellets with a mean aspect ratio below 1.1. It is interesting to note that while the three types of Avicel (MCC 2 to MCC 4) show a very similar behavior, a similar particle size of MCC can lead to a different need in moisture required for successful extrusion (MCC 2 and MCC 5 to MCC 7). As described above the particle size of the initial powder is less important when compared to the source of the crystallite material. If pellets are produced at a fixed level of moisture, it is not possible to substitute MCC without affecting pellet properties such as shape. The results indicate that power consumption may be related to the rheological properties of the crystallite-gel in the extrudate; extrudates produced at the same level of power consumption perform similarly during spheronization.

It was possible to dissolve the lactose monohydrate in the pellets without disintegration of the pellets. Additionally, pellets of series one survived a disintegration test. MCC forms a coherent matrix without any additional binder in the granulation liquid or in the powder formulation necessary. This supports the crystallite-gel-model.

SEM-photographs should provide further details of the pellet structure. Therefore pellets prepared from different types of Avicel (MCC 2 to MCC 4) have been studied. Figure 3 shows SEM-photographs of MCC powders and of pellets of both series: each batch is characterized in an overview and a detailed close-up of the surface structure. The different initial particle size of the MCC powders can easily be seen on Figure 3a–c. Pellets of series one show a smooth surface without pores (Figure 3d–f). In the detailed view no differences can be seen between the three batches (Figure 3g–i). Regardless of the particle size of the starting material, the resulting surface appears to be the same. The pellets in the second series have a rough and porous structure due to the leaching of lactose (Figure 3j–l). Nevertheless the surface structure is very similar again and can be described as a filigreed sponge-like structure (Figure 3m–o). The structure of the original powder particles disappeared completely and turned into a coherent network.

These observations substantiate the crystallite-gel-model. During extrusion the MCC powder particles were destroyed and rearranged to form the solid structure of a gel. During drying the structure is able to form a solid matrix due to 'autohesion' phenomena. The stable matrix will not disintegrate after coming into contact with water again.

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