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Letter to the Editor

Microcrystalline Cellulose as a Sponge as an Alternative Concept to the Crystallite-Gel Model for Extrusion and Spheronization

To the Editor:

To explain the process of the production of pellets by extrusion/spheronization, a crystallite gel-model has recently been presented (1). In the model, it is proposed that the microcrystalline cellulose (MCC) particles in the formulation are broken down into smaller particles by shear forces acting on the particles during extrusion. It is suggested that with increasing shear stress the process proceeds so that finally single crystallites of colloidal size occur, and that these in the presence of water form a gel and it is the gel network which aids both extrusion and spheronization. This proposition does not appear to us to be compatible with the known information associated with MCC and the proposal lacks any clear experimental evidence to show that particles of MCC of colloidal dimensions exist. It is essential that colloidal particles exist if the system is to satisfy the classical definition of a gel (2).

There is a wide range of materials which can be described as MCC. Their isolation and separation are described by Battista (3). Those produced for the pharmaceutical industry are clearly aggregates ranging in size from less than 1 to 300 mm (4). Ek *et al.* (5) have clearly shown that it is possible to obtain a consistent particle size from Avicel PH 101 and 102, namely, a median weight diameter of 27 to 29 μm. Thus when Kleinebudde (1) talks about size reduction of MCC, the breaking of aggregates into these individual particles is the first step. This is unlikely to occur by extrusion as the shear forces are relatively low. The individual particles of MCC are very difficult to reduce further in size to colloidal dimensions by mechanical means (3). Evans and Luner (6) have shown that even when fibres of colloidal dimensions can be extracted by extreme conditions, they readily agglomerate to produce aggregates that are 10–20 μm in diameter. Thus, the proposal that MCC is reduced to colloidal dimensions by granulation and extrusion is in our opinion unrealistic and the production of a gel equally unlikely.

Kleinebudde (1) is certainly correct to contend that the saturation model used in granulation is not applicable to extrusion/spheronization. In our opinion, all extrusion/spheronization processes operate at a level of water content at which the pores between the particles are totally filled with water. This value of saturation, however, is not a single value. It is possible to have a range of particle packings which can hold different quantities of water at saturation. Hence some formulations can be made at a range of water levels while some cannot, depending on their ability to significantly alter their arrangements (7).

The suggestion that crystallite-gel-model can answer many of the observations of the processes of extrusion/spheronization does not, however, answer the following observations:

1. It is possible to form pellets from some formulations without any extrusion process simply by adding water, mixing and placing on a spheroniser plate (8). Pellets can be quite round but they would have a wide size range. However, according to the crystallite-gel concept no gel would be formed in such situations.

2. The gel model does nothing to explain the wide range of response that materials have to the process, except, of course, if evidence could be produced to show how materials influence the gel structure. No such evidence is provided by the paper (1). There appears to be relationship between drug solubility and the amount of water required to give a good formulation for a given MCC drug ratio (9) but even here, deviations from the relationship can occur. We know of no relationship which can predict the limit of MCC/drug ratio which can function to produce high quality pellets.

3. Even totally insoluble materials, of approximately the same particle size are not equal in their ability to form spherical pellets with a given grade and quantity of MCC (10). If the process was controlled by a gel structure from the MCC, this would not be the case.

4. If a gel was necessary for the process of extrusion spheronization, one would expect the colloidal grades to be more effective excipients in the process. Kleinebudde (1) dismisses the colloidal grades of MCC as aids to the function of the process. While we would agree with this in general, the formation of MCC with an appropriate form and quantity of an hydrophillic colloid, can improve the function of MCC in terms of requiring a smaller proportion of MCC in the formulation (11). Why this product has an improved performance is not known, but it is a very specific product and not just a simple gel structure.

5. The gel model is considered necessary to account for the high strength of the agglomerates and introduces the need for hydrogen bonding (1). Such a postulation is not, however, necessary. Evans and Luner (6) have shown from coagulation of MCC dispersions that there is clear evidence that the aggregates are held together by van der Waals attraction not hydrogen bonds. There is, however, not universal agreement on this issue, but MCC readily bonds to itself when a wet mix dries.

Thus, we consider that there is no direct scientific evidence for the existence of colloidal particle production from MCC during the process of extrusion and spheronization nor identification of a true gel structure and that at the moment a gel model is unable to answer several of the known features of extrusion and spheronization.

Cellulose is well known for its ability to hold water, which is considered to occur in two ways. Part of the water is localised within the cellulose fibres in pores and amorphous regions and part is localised between the fibres (12,13). The interaction is complex and subject to much debate. Recently, for example, the crystallinity of MCC was found to increase with the addition of water (14). Using low frequency dielectric spectroscopy, it has been possible to show that the water absorbed in cellulose did not contribute to the magnitude of charge transport, only to the relaxation process, i.e. the water seems to be effectively

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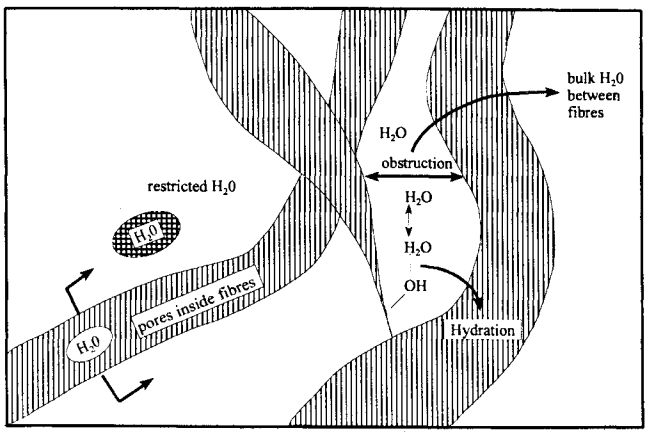

Fig. 1. Schematic illustration of water in the cellulose samples. There are two types of water: bulk water between the fibres with obstruction and hydration interactions with the fibres and restricted water in pores inside fibres. (Taken from Li *et al.* (16), with permission of the copyright holder.)

bound to the cellulose structures (15). A schematic illustration of water cellulose interaction is provided by Li *et al.* (16) and presented in Fig. 1.

Therefore, we think it possible that such interactions can produce the concept of MCC as a "sponge", as suggested by Fielden *et al.* (17) and that such a concept can help to explain the process of extrusion and spheronization. The cellulose particles provide the ability to hold water, as a "sponge". During extrusion, the "sponges" are compressed until water is squeezed out and lubricate the particles flowing through the extruder. This explains why the formulations containing high quantities of cellulose can function in a broader range of water content (7). Variations in the performance of different sources of MCC will be associated with the different interactions between the particular grade of MCC and water due to different pore structures. Variations in water content will be needed for different types of extruders because different shear forces are involved (18). After extrusion, the volume of the "sponges" will increase and the extrudate will be apparently "dry" and brittle, allowing it to be chopped into short lengths in the spheroniser. Subjecting these cylinders to the forces of spheronization again compresses the "sponges" and will allow deformation of the "soft" structures.

The differences which exist between different materials will be associated with the way in which the added ingredients influence the interaction between water and the cellulose fibres. At a bulk level, this can be assessed by detailed rheological evaluation (e.g. 19, 20). At a molecular level, there is need for a more detailed assessment of the influence of drugs on the interaction between water and cellulose. We do believe, however, that the "sponge" model has a greater potential than a gel model to explain the role of MCC in the process of extrusion and spheronization.

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The author replies:

While it is well established that microcrystalline cellulose (MCC) has unique properties as an extrusion aid, there is no model that would sufficiently explain the specific role of MCC and improve our understanding of the process. Therefore, to provide a coherent interpretation of many experimental results in this field, the crystallite-gel model has been proposed recently (1). It was not the purpose of the paper, however, to answer every possible question in wet-granulation, extrusion and spheronization. No direct and definite proof was given to the crystallite-gel model and many important questions cannot be answered at the moment. Therefore, like every model in science it may be subject to revisions whenever new evidence emerges. The letter of Ek & Newton (2) shows that a discussion has started, which may lead us to a higher level of understanding of the process and of the role of MCC in it.

MCC was for the first time described as a sponge in 1988 (3). Based upon this, the sponge model was developed (2). According to the sponge model, each particle of MCC would behave as a porous sponge and each particle would be able to absorb a large quantity of water. Under pressure the water would be partly squeezed out and could be taken up again after releasing the pressure while the volume increases. MCC particles remain intact during the process of wet-granulation, extrusion and spheronization and should be of the same size, shape and volume in the finished product compared to the original MCC powder. In contrast to this, the crystallite-gel model claims that the MCC particles are deformed during the process and that they will gradually lose their original structure (4), resulting in a coherent network of crystallites which is able to immobilize water. The quality and homogeneity of the crystallite-gel depends on the properties of the single crystallites and the conditions during the process.

Cellulose fibres contain elementary fibrils of about 3.5 nm diameter which can aggregate to form microfibrils of varying diameter (10–30 nm). These elementary fibrils are again composed of strands of elementary crystallites, which are held together along the fiber axis by glucan chains linking one crystallite with another. In contrast to this axial linkage, the lateral cohesion between crystallites in the fibril aggregations is mainly due to secondary valence bond (5). Within the crystalline domains the glucan chains are connected by a number of intra- and interchain hydrogen bonds. MCC is produced by partial depolymerization of α-cellulose. The depolymerization takes place in the amorphous domains reaching a level off D.P. of the polymer. The D.P. of MCC is less than 350 (6) which yields a crystallite length of less than 200 nm (7). Particles of MCC are constitued by a porous lattice structure of microcrystals, the crystallites, which are themselves of colloidal dimension. In the production of colloidal grades of MCC the preexisting crystallites are dispersed and covered with sodium carboxymethylcellulose (CMC) as a protecting colloid before spray drying. CMC serves as a peptizing agent for the particles in suspension after redispergation (8).

During extrusion and spheronization, a high amount of water is present resulting in a liquid saturation of about one (9). Water is thought to act as a lubricant facilitating the slippage and flow of individual microcrystals and their aggregates during processing. It is assumed that during the process some secondary valence bonds are broken due to the shear stress and that new contact points are formed between the crystallites. This allows the crystallite network to rearrange and form a coherent, percolating network structure where the original particles cannot longer be identified. The homogeneity of this resulting crystallite-gel is dependent on the shear stress and the duration of the process. This explains that the quality of the gel can vary in a wide range. Ek & Newton (2) addressed a number of observations which may not be explained by the crystallite-gel model:

1. It is possible to form spheres without any extrusion directly on the spheronizer plate. This is true, but too little is known about the properties of these pellets. The crystallite-gel model was introduced for the process of extrusion and spheronization and does not claim to be applicable for all pelletization processes.
2. The possible interactions of other materials with the crystallite-gel are a broad field which could not be adressed in the paper. A lot of work will be necessary to evaluate interactions which are of importance to the performance of materials.
3. The particle size and solubility of materials are two important parameters regarding their performance in the mentioned process. The wettability of the materials, the apparent density (especially for a formulation based on weight fractions), the porosity of the particles, the fact whether the particles are single crystals or aggregates and other factors may also have an effect on their performance. The sponge model must face the same questions.
4. The addition of hydrocolloids or the use of colloidal grades of MCC was reported to result in less round pellets (e.g. 10, 11). This may be due to the rheological properties of the modified crystallite gel. Other reports, however, show a positive influence of such compounds in pelletization (e.g. 12, 13). The colloidal grades of MCC might illustrate the formation of a crystallite-gel.
5. Ek & Newton (2) are correct that the need for hydrogen bonding to explain the high strength of the pellets has not been demonstrated in the paper (1), although this assumption is in accordance with other papers (14). The hornification theory states the formation of intra- and interfibre secondary valence bonds after drying of wetted cellulose (15).

A number of observations are difficult to explain by the sponge model:

a. The surface of pellets prepared from pure MCC of different particle size (20 to 200 μm) is comparably smooth (1, Fig. 3d-i). According to the sponge model, however, the large particles of Avicel PH200 should result in pellets with a less smooth, raspberry-like surface.

b. If a sponge containing water is subjected to a drying process size, shape and porosity of the sponge will remain the same. A hydrogel on the other hand will shrink during drying and turn into a body of low porosity. Wet pellets obtained by extrusion and spheronization tend to shrink during drying (16). The higher the fraction of MCC in the powder mixture, the higher is the degree of shrinking (17).

c. It is often possible to produce extrudates of good quality in a certain range of moisture content while the moisture range to produce good pellets during spheronization is usually much narrower. According to the sponge model the optimal water content of the extrudate of a certain formulation should only be determined by the forces during spheronization. However, for the same formulation different extrusion processes were found to require different water contents (82% and 122%) for successful spheronization (18). Although the spheronization conditions were not exactly the same in this study this result might not be expected from the sponge model. Other results support this observation (19).

I agree with Ek & Newton that more rheological measurements are necessary to characterize the role of MCC. Based on the differences between the two proposed models experiments that should improve our understanding of the role of MCC can be designed:

- As, according to the sponge model, the granulation step is only necessary to distribute the granulation liquid in the powder, the type of equipment should not influence the result, if an equal distribution is reached. According to the crystallite-gel model, the structure of the resulting gel will depend on the process: different granulation processes may lead to a different quality of the gel requiring a different water content for successful spheronization.
- According to the sponge model the tensile strength of pure MCC-pellets should depend on the particle size of the MCC. A MCC of high particle size should result in a lower tensile strength, because less points of contacts can be formed. The crystallite-gel model predicts a similar tensile strength for all particle sizes of MCC from the same supplier.
- The deformation behaviour of single MCC particles in wet state can be studied; this provides information about the forces necessary to deform the particles. Different expectations for stress-strain curves occur from the two models. The results can be compared to other curves obtained from MCC particles in air and to particles of other materials which are able to absorb a high amount of water.

These are a few examples of experiments that may add further proof to one or the other model. In the end, one model may come out that is superior and able to explain all the observations or different models may turn out to be applicable for different processes.

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