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Research paper

Pore shape in the sodium chloride matrix of tablets after the addition of starch as a second component

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ABSTRACT

The present research aims to test the hypothesis that the addition of a minor component causes a change in pore shape in the matrix of the primary component, causing a decrease in mechanical strength. Tablets made of sodium chloride only and tablets made of a mixture of sodium chloride (97.5% v/v) and starch (2.5% v/v) were compared. Tablets were subjected to a heat treatment to remove the starch. The pore structure was evaluated with mercury porosimetry and image analysis on SEM images. At comparable porosities the tensile strength of the mixture tablets was significantly lower than that of the tablets made of NaCl only. Visual inspection of the images suggested a structure with less connectivity of the grains for the heat treated mixture tablets. This was confirmed by the results of the algorithm calculating the relative path length. Image analysis showed that the pore size distribution shifted towards larger pores after the addition of starch. It was thus concluded that the lower mechanical strength of the tablets made of the binary mixture was caused by the more open pore structure and more larger pores as could be detected with image analysis.

1. Introduction

Tablets that are produced in the pharmaceutical industry usually consist of more than one component. All components in a tablet influence tablet properties, such as mechanical strength or disintegration. It is therefore of great importance to understand the possible interaction between tablet excipients and to investigate how this affects tablet properties. Even in mixtures consisting of only two components, binary mixtures, it is not always easy to predict the properties of the tablets made of a certain composition.

Research on the mechanical strength of tablets consisting of binary mixtures is described in numerous papers [1–9]. These papers generally focus on mixing rules or the percolation theory [10]. It has also been suggested that the shape of the pores is an important factor determining the mechanical strength of tablets. This hypothesis was developed in a research project focusing on tablets made of a binary mixture of sodium chloride and starch [11]. It was found that the addition of small amounts of starch caused a significant decrease in the strength of the sodium chloride matrix. Further measurements on the pore size distribution led to the hypothesis that the addition of the second component caused a change in the shape of the pores, which in turn was the main cause of the decrease in mechanical strength.

It was the aim of the present research to investigate whether the addition of a minor component causes a change in pore shape of a matrix of sodium chloride and how this influences its strength. This was done by comparing two groups of tablets; tablets made with sodium chloride only and tablets produced from a mixture of 97.5% v/v sodium chloride and 2.5% v/v starch. All tablets underwent a heat treatment. In case the tablets contained starch the heat treatment was used to remove the starch. The tablets with only sodium chloride underwent a heat treatment as a control to rule out the possibility that the heat treatment caused a change in mechanical strength of the sodium chloride matrix. The end porosities of all tablets were the same.

2. Materials and methods

2.1. Materials

The particle size fractions of 75–106 μm of potato starch (Paselli MD10, DMV, Veghel, The Netherlands) and the particle size fraction of 106–150 μm of sodium chloride (Chemically pure quality, Akzo Nobel, Hengelo, The Netherlands) were used. The fractions were obtained by 30 min vibratory sieving (Fritsch analysette 3, Germany) and 12 min air jet sieving (Alpine A200, Augsburg,

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Germany) over a sieve of 75 μm or 106 μm to remove the fines. Before use the powder was stored at least three days at a temperature of 20 °C and a relative humidity of 45%. The true density of the sodium chloride as determined with helium pycnometry (Quantachrome, Syosset, New York, USA) was 2175 kg/m^3 and the true density of the starch was found to be 1328 kg/m^3.

2.2. Tablet compaction

A powder mixture of 2.5% v/v starch and 97.5% v/v sodium chloride was made by mixing the appropriate powder quantities in a Turbula mixer (W.A. Bachofen, Basle, Switzerland) at 90 rpm for 15 min. Tablets consisting of 500 mg were made by uni-axial compression (ESH compaction apparatus, Hydro Mooi, Appingedam, The Netherlands) using circular flat faced punches in a round die with a diameter of 13 mm. The lower punch remained stationary and the rate of compaction was 0.1 kN/s. The maximum compression force was about 12–13 kN. Prior to compression the die was lubricated with magnesium stearate using a brush.

2.3. Heat treatment

Starch can be removed from a starch/sodium chloride tablet by a heat treatment [12]. A modified version of this method was used to improve the removal of the starch. The modification lies in the fact that the last step involved a higher temperature and that fresh air was led into the oven. The new procedure was as follows. After compaction tablets were stored overnight in a desiccator containing silica at 0% RH. The next morning they were put in a muffle furnace (Naber Industrieofenbau, Bremen, Germany) at 250 °C for 4 h, followed by 4 h at 280 °C, and 60 h at 350 °C. During this procedure, fresh air was led into the oven with an air flow of 150 l/h. After a cool down period of 4 h in the oven (air flow on, no heating), the tablets were stored for at least 16 h at 20 °C/45% RH. Tablet dimensions were then measured with an electronic micrometer (Mitutoyo, Tokyo, Japan) and the weight was determined using an analytical balance (Mettler-Toledo, Greifensee, Switzerland). From these data and the real density of sodium chloride the volume fraction of sodium chloride was calculated. Only tablets with a sodium chloride fraction of 0.8 were used. This fraction of sodium chloride was used because tablets with this fraction had sufficient mechanical strength to withstand the heat treatment and because values in the literature gave reason to believe that the air fraction was above the pore percolation threshold [13,14] so that the (burnt) starch could leave the tablet [12]. The crushing strengths of the tablets were measured with a Schleuniger 6D strength tester (Dr. Schleuniger Productronic, Soloturn, Switzerland). From this value and the tablet dimensions, the tensile strength was calculated according to Fell and Newton [15].

2.4. Analysis of pore structure

The pore size distribution of heat treated tablets was determined with mercury porosimetry (Micromeritics, Model Autopore 9220, Norcross, GA, USA). For the measurement of the pore size distribution three tablets were used. Low pressure measurements were performed from 0 to 0.2 MPa. High pressure measurements were performed from 0.2 to 212 MPa. The surface tension of mercury was assumed to be 480 mN/m and the contact angle of mercury with the sodium chloride was assumed to be 140°.

Image analysis was the second technique used for the characterization of pore structure. For this purpose plan and elevation images were made of the planes depicted in Fig. 1. It is also indicated in Fig. 1 that the direction of compression is named the *z*-direction and that the *x*-direction and the *y*-direction lie perpendicular to this direction. Elevation images contain both the *z*-direction and the *x*-direction. The procedure for obtaining these images was described in earlier work [16]. Five elevation planes and five plan planes were imaged, consisting of eight or nine images, respectively, leading to a total of 40 elevation images and 45 elevation images. In those images several parameters were measured that were calculated according to earlier developed algorithms [16–18]. The calculations were performed using Matlab 7.0.232 R2006a (The MathWorks Inc., Natick, USA) and the DIPimage toolbox version 1.5.3 (Quantitative Imaging Group, Faculty of Applies Sciences, Delft University of Technology, The Netherlands) [19]. One of the parameters that was calculated was the number of transitions. A detailed explanation about this principle can be found in a previous paper [16]. In short the method is as follows. Straight lines are drawn over the images in the *x*-direction and in the *y*-direction (for the plan images) or in the *x*-direction and in the *z*-direction (for the elevation images). Then it is determined how many times each line crosses a transition between the grain phase and the pore phase (=the number of transitions). If the pores are mainly oriented in for instance the *z*-direction, then the number of transitions in the elevation images along the lines in the *z*-direction will be less than the number of transitions along the *x*-direction. Therefore, the quotient of the number of transitions (number of transitions in the *z*-direction divided by the number of transitions in the *x*-direction) will be smaller than one. By comparing the quotient of the number of transitions between the mixture tablets and the pure sodium chloride tablets, it should be possible to detect a possible difference in preferential pore direction between the two groups. The other parameters that were calculated were the relative path length after a morphological closing with an isotropic structuring element [20] of 4 × 4 pixels and further as described earlier [17], and the pore size distribution after the removal of structures smaller than 900 pixels as described earlier [18].

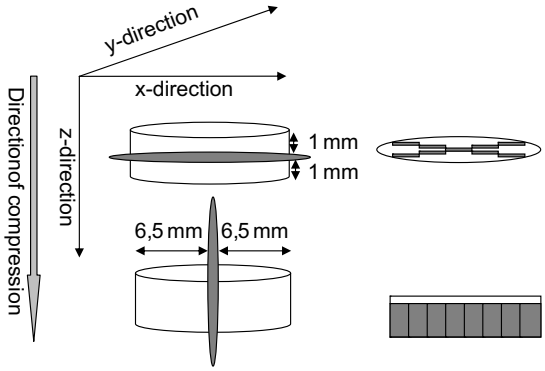

Fig. 1. The location of the images. The location of the plan images is shown above, the location of the elevation images is shown below. The plane that is imaged is shown on the left and the location of the images in this plane are shown on the right.

3. Results and discussion

3.1. Tensile strength

Fig. 2 shows the tensile strength of pure NaCl tablets and mixture tablets before and after heat treatment. There is no significant difference in tensile strength of the NaCl tablets before and after treatment, indicating that the heat treatment does not affect the sodium chloride matrix. The tensile strength of the mixture tablets is also not significantly different before and after the heat treatment, indicating that the tablet strength is entirely determined by the sodium chloride matrix, since the heat treatment removes

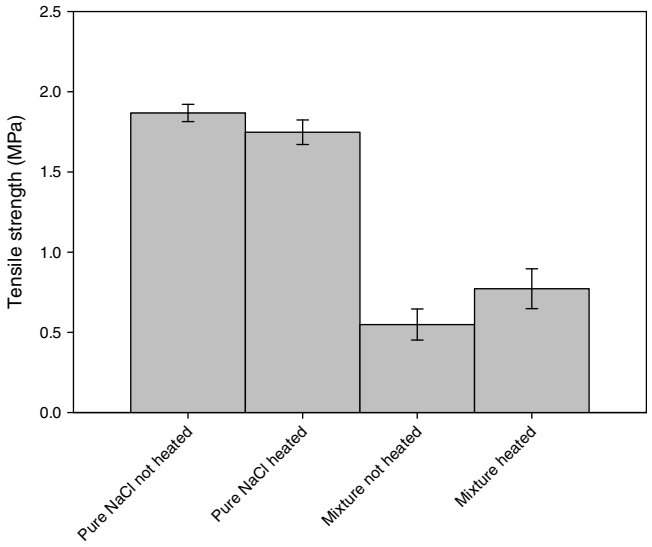

Fig. 2. Tensile strength of pure NaCl tablets and mixture tablets all with a NaCl fraction of 0,8 ($n = 5$). Error bars represent standard error of the mean.

all starch. The finding that the tablet strength of the mixture tablets is entirely determined by the sodium chloride matrix is in concurrence with the percolation theory which states that the tablet properties of a tablet consisting of a binary mixture are determined by the dominating excipient as long as the second component is present in concentrations below the percolation threshold [21]. The used 2.5% v/v concentration of starch is clearly below the percolation threshold of this system. Fig. 2 also shows that the pure NaCl tablets have a higher tensile strength than the mixture tablets. These results are in agreement with the results found by Van Veen [11].

3.2. Image analysis

Fig. 3 shows some examples of original SEM images of heat treated pure sodium chloride tablets and heat treated mixture tablets.

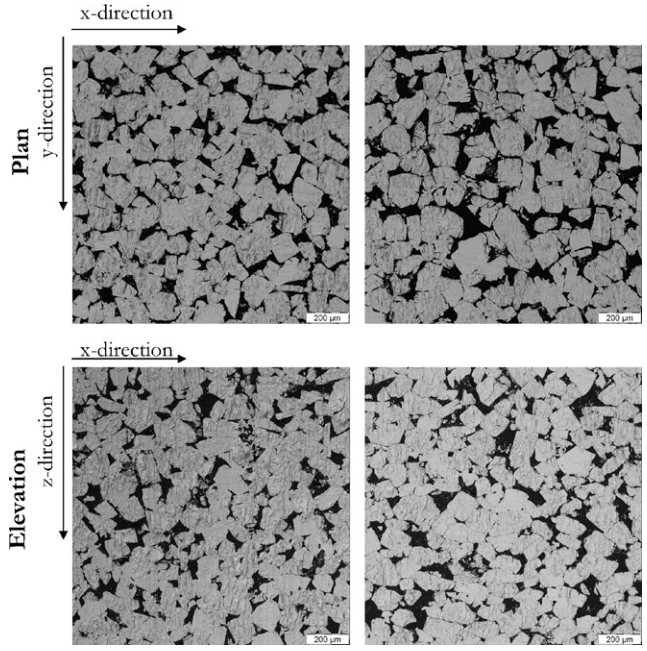

Fig. 3. Original plan and elevation images of heat treated pure NaCl tablets (left) and mixture tablets (right).

When comparing the images of the pure NaCl tablet with the images of the heat treated mixture tablets with the naked eye, it is not easy to indicate whether the images of the different tablets show different structures. At the most, the structure in the mixture tablets can be described as having less connectivity of the NaCl grains. If this is the case or if the preferential direction of the pores or the tortuosity is different for both groups, it should be possible to show this with the image analysis parameters.

Fig. 4 shows the quotient number of transitions for the pure NaCl tablets and for the mixture tablets. This parameter can be used to detect a preferential pore direction. However, the quotient of transitions in the images of the pure NaCl tablets and the mixture tablets are not significantly different from each other. This is the case for both the plan images and the elevation images. Hence, this parameter does not point to a difference in preferential pore direction between the two groups.

Fig. 5 shows the relative path lengths through the grains and through the pores for the pure NaCl tablets and for the mixture tablets. The path length through the grains is shorter than the path length through the pores for all directions. This is the case for both the mixture tablets and the pure NaCl tablets and can be explained

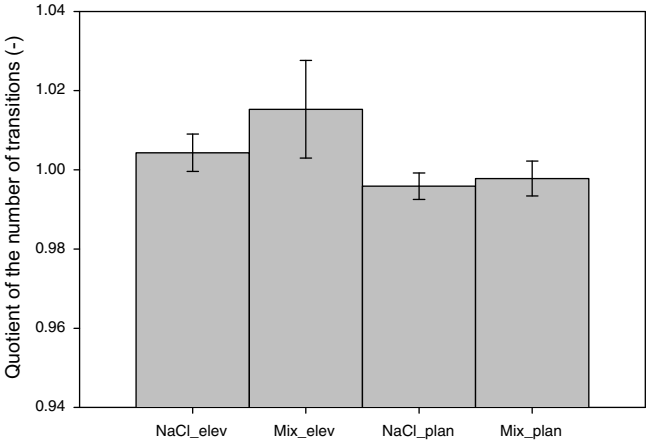

Fig. 4. Quotient number of transitions for the pure NaCl tablets and the mixture tablets with a NaCl fraction of 0,8 after heat treatment. Error bars represent standard error of the mean.

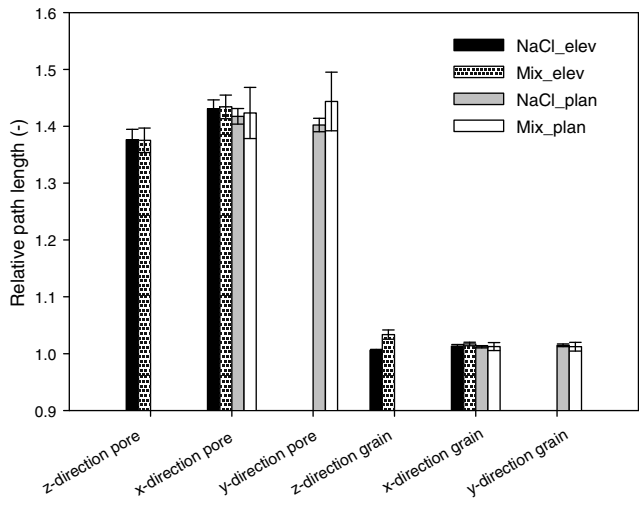

Fig. 5. Relative path length through grains and pores in the different directions for the pure NaCl tablets and the mixture tablets both after heat treatment. Error bars represent standard error of the mean. For the elevation images $n = 40$ and for the plan images $n = 45$.

by the simple fact that in all tablets 80% of the volume is occupied by NaCl and only 20% is occupied by air (pores). Thus, the path length from one end of the image to the other end of the image is much shorter over the grains than over the pores.

For the path length over the pores the path length in the mixture tablets is the same as the path length in the pure NaCl tablets. This is the case for all directions. However, for the path length through the grains, the path length in the *z*-direction is longer for the mixture tablets than for the pure NaCl tablets ($p < 0.01$, Mann Whitney *U* test, SPSS 12.0.1 for Windows), indicating that the connectivity of the grains in the *z*-direction is better in the pure NaCl tablets than in the mixture tablets. This is in concurrence with the impression of a structure with less connectivity observed for the mixture tablets in the original SEM images (see Fig. 3). This difference in structure originates from flattening of the starch between the sodium chloride particles during the compression, which explains why the difference mainly exists in the *z*-direction (the direction of compression) and not in the *x*- or *y*-direction. Some elastic relaxation of the starch immediately after compression might also have contributed to the open structure in the mixture tablets. The large standard deviation of the calculated path length in the mixture tablets further suggests that there are differences in structures between the images.

3.3. Pore size distribution

Mercury porosimetry measurements of pure NaCl tablets and mixture tablets, both with a NaCl fraction of 0.8 and after heat treatment, revealed that the pore size distribution was very similar for both kinds of tablets (Fig. 6) with a trend towards larger pores in the heat treated mixture tablets.

The pore size distribution found with image analysis does show a difference in the pore size distribution between the mixture tablets and the pure NaCl tablets as can be seen in Fig. 7. Tablets that contained starch have larger pores. This raises two questions: (1) 'What is the cause of these larger pores?' and (2) 'Why is the difference between the two groups of tablets less pronounced in the mercury porosimetry results?' The answer to the first question can be found in the way the starch grains are distributed between the NaCl grains. Apparently, the flattened starch grains border on the pores, i.e. they are not fully enclosed by the sodium chloride grains, but they are generally present next to the pores. In this way, larger pores are found when the starch grains are burnt after the heat treatment. If this kind of distribution of the second component being present on the borders of the pores is valid for other binary systems, this implicates that the addition of a small quantity of a second component can have a large influence on properties that depend on pore surface such as wetting.

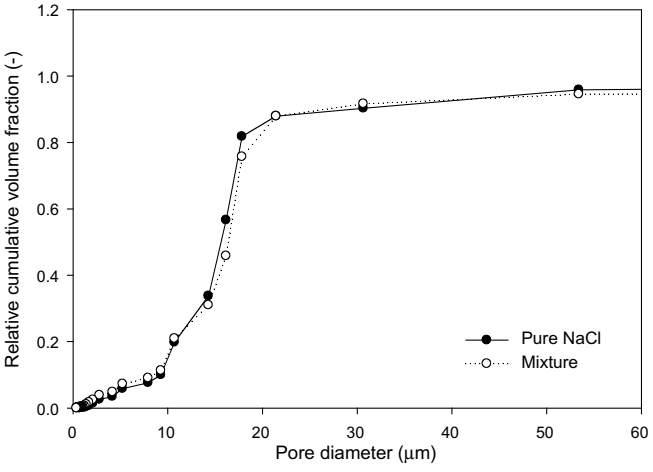

Fig. 6. Mercury porosimetry results for pure NaCl tablets and mixture tablets both after the heat treatment.

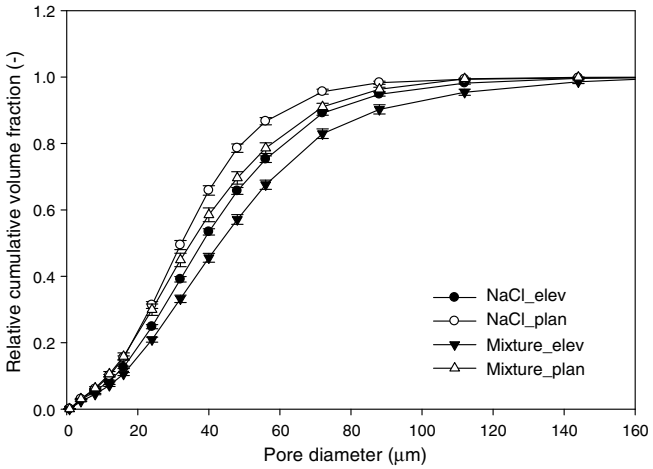

Fig. 7. Pore size distribution determined with image analysis for pure NaCl tablets and mixture tablets both after the heat treatment. Error bars represent standard error of the mean (*n* is at least 31).

The answer to the second question lies in the different nature of the two methods of analysis [18]. The mercury porosimetry method is based on the fact that mercury is a non-wetting fluid for most substances and that a pressure has to be applied to force mercury into the pores of these substances. By assuming a cylindrical shape of the pores, the height of the exerted pressure can be correlated to the pore diameter. However, closed pores (vacuoles) will never be reached by the mercury. Furthermore, if a large cavity is connected to the outside of the body by pores with a smaller diameter, the volume of the cavity will be ascribed to the diameter of the smaller pore, since mercury enters the cavity through this pore. The results of the mercury porosimetry measurements are thus biased in favor of the smaller pores. In the setting of the heat treated mixture tablets and sodium chloride tablets, some larger pores in the mixture tablets are probably only accessible through pores of a size similar to the sizes of the pores in the sodium chloride tablets. An explanation for this could be that in both cases the minimum size of the percolating pore opening is determined by the structure of the sodium chloride grains formed during the compaction process. Since mercury enters the pores through these openings, differences in pore size between these two kinds of tablets will not be detected. With image analysis there is a chance of making a cross section at a location showing the pore at its smallest diameter. However, it is also possible that the cross section is made at a location showing the pore at a larger or even at its largest diameter. Therefore, this method is less troubled by 'bottleneck pores' and provides a discriminative measurement of the pore size for the setting used here. It can therefore be a valuable technique to measure pore size.

A larger pore size is correlated to a lower tensile strength [22–24] and the differences in tensile strength between the mixture tablets and the pure sodium chloride tablets are thus most probably caused by a difference in pore size.

3.4. Anisotropy in pore size

The pore size in the elevation images is slightly larger than in the plan images for both kinds of tablets (see Fig. 7). The larger pores in the elevation images can be explained by anisotropic stacking of the NaCl particles. When the mixture is poured in the die and subsequently compacted, the particles pile up in tortuous

piles. Between these non-straight piles some relatively large pores, mainly oriented from top to bottom may exist. When a cross section is taken for the plan images, the chances of encountering such a pore at its largest diameter are much smaller than encountering such a pore when making a cross section for the elevation images. This explains the finding of larger pores in the elevation images than in the plan images.

The presence of anisotropy in pore structure is also indicated by a difference in relative path length through the pores in the elevation images between the *z*-direction and the *x*-direction for both the pure NaCl tablets and the mixture tablets. The shorter relative path length in the *z*-direction suggests a better connectivity in the *z*-direction (the direction of compression) for the pores, which corresponds to earlier results found in a cubic NaCl compact [17]. However, the quotient of the number of transitions for the elevation images does not indicate a preferential pore direction (see Fig. 4). Perhaps this discrepancy between the results for the relative path length and the quotient of the number of transitions, lies in the fact that the method with the number of transitions is very suitable to detect a preferential pore direction in ideal pores (ideal meaning non-tortuous pores with smooth borders) but not for very tortuous pores or pores with a lot of protrusions or spikes. When the pores are tortuous it is difficult to detect the preferential pore direction with the number of transitions, since there is not really one direction. When the borders have a lot of small protrusions in a particular direction, these protrusions add considerably to the number of transitions, making the algorithm describe the direction of these protrusions but not of the larger pores. Since the algorithm for the relative path length measures this path length through the whole image, it is less sensitive for these small irregularities.

4. Conclusion

The strength of a tablet made of a mixture of 97.5% v/v NaCl and 2.5% v/v starch is completely determined by the sodium chloride matrix. The strength of this matrix is weakened by the simultaneously compressed starch even after the removal of the starch by a heat treatment compared to a tablet compressed of NaCl only. Mercury porosimetry only showed a trend towards larger pores in the heat treated mixture tablets. However, image analysis detected a lower connectivity of the grains in the mixture tablets and a shift towards larger pores in the heat treated tablets made from the mixture, explaining the difference in tensile strength. The discrepancy in ability to make a distinction between the pore size distribution of the different tablets is caused by the different nature of the mercury porosimetry and the image analysis technique.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2008.05.028.

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