Looking into tablets, Characterization of pore structure in tablets using image analysis
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Chapter 4

The determination of relative path length as a measure for tortuosity in compacts using image analysis

Abstract

Tortuosity is defined as the ratio of the actual path length from start to goal through the pores to the Euclidean distance (shortest linear distance). However, traditional methods to calculate tortuosity, such as the calculation of tortuosity out of the results from dissolution experiments, do not determine path length directly. In this paper we describe the application of image analysis for direct measurement of path length in order to obtain quantitative information on tortuosity.

Several planes in cubic sodium chloride compacts, made by uni-axial compression, were imaged using scanning electron microscopy (SEM). In these images the average path length from top-to-bottom and from left-to-right was calculated, using the grey weighted distance transform (GDT). As the direct, straight forward path was defined as having a length of unity, the relative path length could be taken as a quantitative measure for the tortuosity.

The relative path length through the pores was found to be 1.4-1.6 and the relative path length over the grains was significantly lower (1.0-1.2). In most cases, the relative path length through the pores was significantly higher for the compacts containing small particles than for the compacts made of large particles. The relative path length was also dependent on the direction of the measurement, i.e. in the direction of compression of the compact or perpendicular to it. This indicates anisotropy in structure with the pores preferentially oriented in the direction of compression.

It was concluded that this method is a valuable tool for the determination of path length in compacts as a direct measure for tortuosity. It can also be used to evaluate the anisotropy in structure.

4.1 Introduction

Tortuosity is used to account for the increase in distance a diffusing molecule travels due to bending and branching of pores. A straight channel has a tortuosity of exactly one, while the tortuosity of a channel going through a bead bed of uniformly sized beads lies between 2 and 3 [1]. This can be derived from the definition of tortuosity, which is usually defined as the ratio of the actual path length through the pores to the Euclidean distance:

\[ \tau = \frac{L_{\text{actual}}}{L_{\text{Euclidean}}} \]  

(1)

in which:

- \( \tau \) Tortuosity
- \( L_{\text{actual}} \) Actual path length through the pores
- \( L_{\text{Euclidean}} \) Shortest distance between the start and end points in Euclidean space.

It can readily be seen from equation (1) that the actual path length determines tortuosity. However, to our knowledge, no method is available to determine the actual path length in tablets directly.

A common method to calculate tortuosity is via the results from dissolution measurements. In this indirect method, the tortuosity is calculated from several parameters concerning the dissolution of a drug out of a matrix [2-4]. This is a rather laborious method and the indirect determination of tortuosity sometimes results in unrealistic values of more than one thousand [5] or below one [4]. Tortuosity can also be calculated from the porosity and diffusion coefficients obtained from spin echo NMR measurements. Mercury intrusion porosimetry has been suggested as another method to determine tortuosity. With this method tortuosity is calculated out of the permeability of the sample, the true density of the material and the pore size distribution [6]. Still, all the aforementioned methods do not directly measure path length to determine the tortuosity.

In contrast with the former methods, direct measurement of path length is possible when image analysis is used. So-called distance transforms are available to find optimal paths and measure associated distances in images. Besides the possibility of direct measurement of path length, image analysis has other advantages. One of them is that the tortuosity can be determined at different locations, since it is possible to make images of different sections in the product to be investigated and to analyze them separately. Another advantage is that the
directional sensitivity can be evaluated as well, since the path (length) from left to right and from top to bottom can be determined independently from each other in an image. This can be of importance for a product with an anisotropic pore structure that has a preferential pore direction. In such cases the tortuosity is dependent on the direction in which it is measured. It is impossible to detect this directional component with methods based on mercury porosimetry or dissolution experiments. In addition to these advantages, it is noted that image analysis also permits visualization of the pore structure and the paths found, making the whole concept more tangible.

In this paper we describe a method to find the fastest route through the pores (or over the grains) in images of compacts using an algorithm called ‘grey-weighted distance transform (GDT)’. The GDT determines this fastest path using the principle of wave front propagation with material dependent velocities. Sodium chloride compacts made with uni-axial compression were used as a model system. It will be shown that the GDT’s relative path length can not only be used as a measure of tortuosity but also to detect directional preferences and hence anisotropy in pore space.

4.2 Materials and Methods

4.2.1 Materials
The 45-75 µm sieve fraction and the 212-250 µm sieve fraction of sodium chloride (Chemically pure quality, Akzo Nobel, Hengelo, The Netherlands) were used for the production of compacts. These fractions were obtained by 30 min vibratory sieving (Fritsch analysette 3, Germany) followed by air jet sieving for 12 min over a sieve of 45 µm and 212 µm to remove the fines. The true density of the sodium chloride as measured with helium pycnometry (Quantachrome, Syosset, New York, USA) was 2175 kg/m$^3$.

4.2.1 Compaction
The preparation of compacts and the subsequent imaging has been described in more detail earlier [7]. In short, cubic compacts of 7x7x7 mm containing 530 mg sodium chloride were made on a hydraulic press (ESH compaction apparatus, Hydro Mooi, Appingedam, The Netherlands) in a square-shaped die. The rate of compaction was 0.5 kN/s and the maximum pressure was maintained for 0.1 s. After compaction the compacts were allowed to equilibrate for at least 24 hours. Compact dimensions were measured with an electronic micrometer (Mitutoyo, Tokyo, Japan) and the weight of the cubes was measured with an analytical balance (Mettler-Toledo, Greifensee, Switzerland). The final porosity calculated out of
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compact weight, its dimensions, and the true density, was 30% (standard deviation of the porosities was 0.3%).

4.2.2 Planes in the compact
After at least 24 hours compacts were embedded with glycolmethacrylate resin. After hardening of the resin, the relevant surfaces were smoothened using a microtome. Several planes in the compact have been imaged using back scattered electron imaging on a JEOL scanning electron microscope (JEOL, type JSM-6301F, Japan). The planes imaged are depicted in figure 1. Two sets of images are defined, the plan and the elevation images. Plan images provide a top view and elevation images provide a side view. Both plan and elevation images were taken of the upper surface at 0 mm from the side. Of each of the planes that were imaged, 9 SEM images were taken covering the whole plane. Figure 1 also clarifies the nomenclature of the different directions. The z-direction is the direction of compression while the x-direction and the y-direction lie perpendicular to this direction. A plan photo shows the x- and y-direction while an elevation photo shows the x- and z-directions.

Figure 1: Figure a shows the locations of the plan images in the cubic compact. Per plane nine images were made. Figure b shows the locations of the elevation images in the cubic compact. Per plane nine images were made.
4.2.3 Preparation of the images
The original SEM images had a size of 2248 x 1836 pixels. For the analysis only the upper left (square) part of each image with a size of 1676 x 1676 pixels was used to avoid bias in the path length measurement. On these original images the following operations were performed using Matlab (Version 7.0.4.356 R14, The Mathworks Inc) and the DIPimage toolbox (Version 1.4.2, Quantitative Imaging Group, Delft University of Technology). Sample preparation and calculation for one image took about 15 seconds with a common PC (with an AMD Athlon™ 64 processor, 3500+, 512 MB).

Firstly, the gray-scale images were made binary with the Isodata threshold algorithm so that each pixel belongs to either the pore or the grain phase. Secondly, small artifacts induced by the use of the microtome were erased. This was done with an operation called ‘closing’ [8]. The process of closing of the grain phase is illustrated in figure 2. This figure shows that the first operation is a dilation of the starting figure with the structuring element, the center of the structuring element, indicated with a black square, is placed in every pixel of the starting figure and the neighbors of this central pixel, indicated with an x, are added to the starting figure. Subsequently, the intermediate figure is eroded with the structuring element. Erosion means that the outside layer of pixels is removed from the figure. Pixels where the structuring element is embedded in the figure are not removed. As can be seen in figure 2 the result of these operations is that the outside border of the starting figure stays the same, but that the small crack separating the two parts of the starting figure is filled. Particles separated by a distance that is larger than the structuring element remain loose particles. Several sizes of the structuring element can be used. For the images with a sodium chloride particle size of 212-250 µm a structuring element of 5 pixels (= 4 µm) was used and for the sodium chloride particle size 45-75 µm a structuring element of 2 pixels (= 1.6 µm) was used, because these sizes gave resulting figures that were most similar to the physical situation as was determined after visual inspection.

![Figure 2: Illustration of the ‘closing’ operation. The starting figure is dilated with the structuring element, followed by erosion of the intermediate figure. Only small cracks are removed. When the opening between two particles is large, the particles stay loose.](image-url)
The porosity was calculated by calculating the percentage of pixels in the pore phase after binarization and after the closing operation. The average porosity calculated out of the 90 images of compacts of large particles was 26.9% (SD 4.2%) and for the 90 images of the compacts of the smaller particles 28.3% (SD 2.2%). The porosity calculated from weight, true density and volume was 30%. So the results coincide reasonably well.

4.2.4 Calculation of relative path length in the images
The path length was determined using the binary images, since it was believed that a two phase-system resembles the physical structure, consisting of either pores or grains, better than a gray scale image. The path length was determined using the ‘grey weighted distance transform’ [9]. This algorithm calculates the path that results in the shortest traveling time when going from a set of predefined starting points to any other point in the image. This path is found using the principle of wave front propagation. From each starting point a wave front is initiated and from each point that is reached by the wave front, a new wave front is started. The propagation speed depends on the gray values of the pixels it crosses, i.e. gray value ten causes the wave to propagate ten times faster than gray value one. In our first experiment, the pixels of one phase were given the minimum propagation speed of 1 pixel/time unit, while the propagation speed in the other phase was varied between 1 and a pre-defined maximum. This was done to investigate the influence of the ratio of the two propagation speeds on the resulting path length. In the subsequent path length determinations a propagation speed of 1 pixel/time unit for one phase and a propagation speed of 1676 pixels/time unit for the other phase were chosen, since the size of the images was 1676 x 1676 pixels, and since it was found that raising the propagation speed any further did not affect the path found, as will be discussed later. By setting the propagation speed through the pores faster in one run and setting the propagation speed over the grains faster in another run, the fastest path through the pores and the fastest path over the grains could both be calculated.

All the pixels in one extremity of the image (either the top or the left side of the image) were taken as starting points for the paths and all the pixels on the opposite side of the image were defined as the end points. For each image, this resulted in 1676 path lengths from top-to-bottom and the same number of path lengths from left-to-right. From these path lengths the relative path length from top- to-bottom and from left-to-right was calculated for each image, according to:
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\[ L_R = \frac{\bar{L}_{\text{path}}}{L_{\text{image}}} \]  \hspace{1cm} (2)

In which:
\( L_R \) Relative path length (-),
\( \bar{L}_{\text{path}} \) Average path length of the path in one direction (in pixels),
\( L_{\text{image}} \) Length/width of the image (in pixels) corresponds to the minimal length in the chosen direction.

This was done for both the elevation images and the plan images. In the plan images the path length from top-to-bottom and from left-to-right corresponds to the path length in the x- and y- direction. For the elevation images the corresponding directions are the x- and z-directions.

The principle of wave front propagation at different propagation speeds and the resulting path length is illustrated in figure 3. Figure 3a shows the difference in propagation speed of wave front propagation in the two phases. For visualization purposes, the propagation speed in the pore phase was set to 4 pixels/time unit, while the propagation speed in the grains is set to 1 pixel/time unit. As can be seen in figure 3a the wave fronts are much more closely packed in the grains than in the pores, depicting the lower propagation speed in the grains.

![Figure 3a and 3b: Wave front propagation in an elevation image. The wave progresses 4 times as fast in the pores than in the grains. Figure b shows the paths that have been followed to reach some end points at the bottom of the image. Red lines represent parts of the paths that go through the pores, yellow lines represent parts that go over the grains. The wave progresses 4 times as fast in the pores than in the grains.](image-url)
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After the fastest path to all pixels in the image had been determined by the principle of wave front propagation, the length of each path was calculated. This fastest path can be retrieved by tracing the path of steepest descend starting at an end point until a start point is found. As a consequence, we move perpendicular to the wave fronts and various paths may merge as illustrated in figure 3b. In this figure the red lines represent parts of the path that go through the pores and the yellow lines represent parts of the path that need to go over the grain.

By taking all the path lengths needed to reach the endpoints and by averaging them, the average path through the image is found. Dividing this average path length by the length of the image results in the relative path length. This was done for each image in both directions.

4. 3 Results and discussion

4.3.1 Influence of difference in propagation speed on the fastest path

The influence of the difference in propagation speed between the two phases on the measured relative path length is shown in figure 4. For this experiment the propagation speed in the grain phase stays at one pixel/time unit, while the propagation speed in the pore phase is varied. Figure 4 shows the relative path length in the z-direction as a function of the propagation speed in the pore phase for elevation images made of compacts of the larger particle size. The correlation between propagation speed and relative path length is similar for the other direction and for the other planes (data not shown). The same applies to the smaller particle size. Figure 4 shows that the relative path length increases with increasing propagation speed difference until a certain maximum is reached. This can be explained as follows. When the difference in propagation speed for the two phases is small, the punishment in arrival for passing through the other phase (i.e. crossing a grain) remains small. Therefore, the fastest path stays rather straight and the relative path length is only marginally higher than 1. However, when the difference in propagation speed is larger, it is faster to make a detour via the pores in order to avoid crossing a grain. This increases the (relative) path length as is illustrated in figure 5a and 5b.
The difference in propagation speed can thus be used to punish going over one of the phases. By increasing the propagation speed in one phase, it becomes less and less attractive to cross the other phase. Above a certain propagation speed the fastest path remains the same and therefore the relative path length reaches an asymptotic value, as can be seen in figure 4. This means that the number of pixels of the 'slow' phase cannot be reduced any further to find a path that arrives at the other side of the image.

In order to minimize the path length through one of the phases, the propagation speed has been set to 1676 pixels/time unit for one phase and to 1 pixel/time unit for the other phase throughout the remainder of this paper.

### 4.3.2 Relative path lengths through grains and over pores

Figure 6 shows the measured relative path lengths through the pores as well as over the grains for the different particle sizes. In each figure the relative path length through the pores is depicted by the four bars on the right side of the figure and the relative path length through the grains is depicted by the four bars on the left part of the figure.

Comparison of the four bars on the right side with the bars on the left side of figure 6a and 6b, shows that the relative path length through the grains is shorter than the relative path length through the pores for both particle sizes. For the smaller particle size the average relative path length through the grains lies around 1.0-1.1 and the relative path length through the pores lies around 1.5-1.6. The same
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pattern can be seen for the larger particle size (1.1-1.2 versus 1.4-1.5). It will be obvious from figure 6a and figure 6b that these differences are significant. The difference is easily explainable since the porosity of the compacts is 30%, meaning that a larger volume percentage, 70%, of the compact is occupied with grains. Therefore, it should be easier to cross the images when traveling over the grains than when traveling through the pores.

Figure 5a and 5b: Some paths that have been retrieved by starting at an end point and moving backwards, perpendicular to the direction of the wave propagation. Red lines represent parts of the paths that go through the pores, yellow lines represent parts that go over the grains. In figure a the wave progresses 4 times as fast through the pores than through the grains and in figure b the wave progresses 1676 times as fast through the pores.

4.3.3 Influence of particle size on the relative path length
Comparison of figure 6a with figure 6b shows that there is an influence of particle size on relative path length. The relative path length through the pores in the x-direction and in the y-direction in the plan images is higher for the compacts containing small particles than for the compact made of large particles. The same applies to the relative path lengths through the pores in the z-direction in the elevation images (see table 1). This can be explained as follows. Since sodium chloride does not fragment to a large extent, the pores in the compacts made of the particle size 212-250 µm are larger in size than the pores in the compacts of the smaller particle size. Therefore, when traveling through the pores of the compacts made of the larger particle size it is easier to cut a corner, reducing the distances traveled. The pores between the particles of 45-75 µm are much smaller, leaving hardly any room for cutting corners. This is illustrated in figure 7.
Table 1: Significance level obtained with the two-tailed Students t-test (SPSS 12.0.1 for Windows, SPSS Inc.) when comparing the relative path length through the pores of the compacts made of the small particle size (45-75 µm) with the relative path length through the pores of the compacts made of the large particle size (212-250 µm). ns stands for not significant.

<table>
<thead>
<tr>
<th>Plan Elevation</th>
<th>x-direction</th>
<th>y-direction</th>
<th>x-direction</th>
<th>z-direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path length through pores</td>
<td>45-75 µm vs. 212-250 µm</td>
<td>p ≤ 0.01</td>
<td>p ≤ 0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Path length through grains</td>
<td>45-75 µm vs. 212-250 µm</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
</tr>
</tbody>
</table>

Figure 6: Relative path length through grains and through the pores for the particle sizes 45-75 µm (figure a) and 212-250 µm (figure b).
Contrary to the relative path lengths of the pores, the relative path lengths for the grains are smaller for the particle size 45-75 µm than for the particle size 212-250 µm. This difference is significant for the relative path lengths in the plan and the elevation images in both directions when each of the four groups of 45-75 µm is compared with the corresponding group of the larger particle size as can be seen in table 1. The difference in relative path length is probably caused by a difference in angles in the paths; the angles in the paths over the smaller particles are probably smaller than the angles in the paths over the larger particles, hence the lower relative path length of the paths over the smaller grains.

4.3.4 Relative path length as measure for structural anisotropy

Figure 8 shows a typical example of an elevation image and a plan image. Both images are taken from the outside surface of a compact made of the particle size fraction 212-250 µm. Visual observation of this figure reveals a difference in structure between the plan and the elevation image. In the plan image there does not seem to be a preferred orientation of either pores or particles while this does seem to be the case in the elevation image. This is in concurrence with results found by other authors who observed anisotropy in structure in scanning electron microscopic images of cross sections of tablets made with uni-axial compression [10, 11]. They also investigated the anisotropy in strength, but did not report a method of quantifying anisotropy in structure.

The relative path length provides a method of analyzing anisotropy in structure, since the anisotropy in structure shows that the relative path length through the pores in the x-direction is different from the relative path length in the z-direction, the direction of compression. Indeed, the relative path length, measured in the elevation images, is significantly shorter in the z-direction than in the x-direction when it is measured through the pores (see table 2). This is found for both particle sizes, suggesting that the relative path length through the pores provides a useful tool in assessing the anisotropy in structure.
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Figure 8a and 8b: Figure 8a shows an elevation image taken from the outer surface of a compact made of the particle size 212-250 µm. Figure 8b shows a plan image taken from the outer surface of a compact made of the particle size 212-250 µm.

Table 2: Significance level obtained with the two-tailed Students t-test (SPSS 12.0.1 for Windows, SPSS Inc.) when comparing the relative path length in the x-direction with the relative path length in the z-direction in the elevation photos. This is done for the path length through the pores as well as for the path length through the grains, ns stands for not significant.

<table>
<thead>
<tr>
<th>Path length through pores (in elevation images)</th>
<th>x – direction vs. z-direction</th>
<th>45-75 µm</th>
<th>212-250 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-direction</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>z-direction</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.5 Relative path length as measure for tortuosity

The relative path length strongly resembles the tortuosity, since tortuosity is defined as the ratio of the actual path length through the pores and the Euclidean distance (equation 1), while the relative path length is defined as the ratio of the average path length through one phase across the image (horizontally or vertically) and the size (width or height) of the image (equation 2). It is clear that both
parameters are calculated out of a path length through the pores and the Euclidean distance and consequently are quite similar.

However, tortuosity and relative path length are not completely the same. The difference between the two parameters lies in the fact that tortuosity does not allow transport through the grains, while the relative path length is the mean of a series of path lengths that may contain a number of paths that go over (part of) a grain. This can be minimized by maximizing the difference in propagation speed through the two phases as can be seen in figure 4. However, crossing a grain is sometimes unavoidable. For instance when a grain is blocking the pathway through the pores and no detour is available that goes through the pores only. In such cases the algorithm chooses the path that crosses the smallest number of grain pixels. Sometimes paths are even started on grains if grains are present on the predefined starting points along the image border. However, paths started on grains hardly every reach the other side of the image and are therefore not used to calculate the average path length. This is because the propagation speed through the grains is so slow that it is much faster to take a path that is started in a pore. This can be seen in figure 3a at the top of the image. Here paths are started in the grains, but before these paths reach the other side of the grain paths started in the pore next to the grain have already reached the other side of the grain. Therefore, although paths are started in grains, these paths do not contribute to the average path length through the pores. The case is different for the endpoint in the grains. This is because the algorithm only stops when all endpoints are reached i.e. also those that lie on a grain. Therefore, paths that end on a grain do contribute to the average path length.

This might not be a problem when comparing the tortuosity with the relative path length as it should be kept in mind that an image is two-dimensional, while a real compact is three-dimensional. This means that while it is necessary in the two-dimensional image to cross a grain, this might not be necessary in the real compact where a path through the pores over or under the grain is possible.

However, even in a three-dimensional situation the porous structure does not always form a continuous network. Following the theory of percolation, the pores will exist as isolated entities below a certain threshold value (the site percolation threshold). This implies that in such cases the concept of tortuosity depends on the scale of scrutiny of the determination. On the scale of one pore, tortuosity can have a finite value. In contrast, tortuosity is not defined on the scale of an entire compact, because it is impossible to cross the entire compact via pores. However, even when the pores do not form a percolating system, path length
calculations have the capability to determine a measure for tortuosity (the extra distance that has to be covered due to curvature of the pores).

The aforementioned arguments also hold when the algorithm is set up in such a way that the propagation speed through the grains is higher. In that case the relative path length reflects the tortuosity of the solid phase. This can be considered as an advantage of the method, since a measure of the tortuosity for both the pores and the particles can be obtained.

4.4 Conclusion

The method presented in this paper offers the possibility to measure path length in images of a compact as a measure for tortuosity. Because of the possibility to cross a grain and the fact that the solution is restricted to a two-dimensional cross-section, the relative path length is not exactly the same as the tortuosity. However, a relative path length can be calculated even when the porous structure does not form a continuous network in the SEM images. In those cases, the path only goes over a grain when it is absolutely necessary, thus giving only small deviations from the definition of tortuosity. The relative path length therefore provides a direct measure for the tortuosity in a compact. Furthermore, with this method an influence of particle size could be detected and anisotropy in structure could be shown. Therefore, this method is a valuable tool to characterize (images of) porous structures and to assess tortuosity in compacts.

4.5 References


