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Studies on direct compression of tablets. XI. Characterization of particle fragmentation during compaction by permeametry measurements of tablets *

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Summary

The usefulness of measuring tablet surface areas by a permeametry technique for the characterization of particle fragmentation during compaction was evaluated. Eight materials (sieve fraction 212–250 μm) with varying and documented consolidation behavior were compacted at a series of pressures in the range 20–200 MPa. The permeability of the tablets was measured and the specific surface area of the tablets was calculated.

For all materials, the tablet surface area increased with increased compaction pressure within the pressure range studied. However, the slope of the curves differed between the materials and they could be rank ordered in agreement with earlier experiences of their fragmentation propensity. The permeametry procedure therefore seems acceptable for estimating particle fragmentation during compaction.

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Introduction

The importance of particle fragmentation during compaction of pharmaceutical compounds has been the object of several publications (de Boer et al., 1978; Nyström et al., 1982; Alderborn and Nyström, 1982a and b). The results show that the degree of particle fragmentation is an important factor for the effect of additives (e.g. lubricants and dry binders) and variations in compound particle properties (e.g. size and shape) on the tablet strength. Consequently, methods for estimating the fragmentation propensity of a substance have been discussed (e.g. Duberg and Nyström, 1982; Humbert-Droz et al., 1983). If fragmentation is defined as the formation of smaller, discrete primary particles from an initial grain, an adequate approach for characterizing fragmentation seems to be the measurement of the surface area of a material before and after compaction or the measurement of changes in tablet surface area with compaction pressure (Higuchi et al., 1954; Armstrong and Griffiths, 1970; Hardman and Lilley, 1973; Duberg and Nyström, 1982). In these studies, the surface area of powders and tablets was characterized by gas adsorption techniques. However, several problems seem to be related to the use of such techniques for studying particle fragmentation. The gas adsorption method estimates the total surface area of the specimen (Orr and DallaValle, 1959a) which makes it difficult to establish whether an observed change in surface area is due to particle fragmentation or to other phenomena, such as the formation of cracks or opening of pores. Additionally, a very high initial total surface area due to, e.g., a high intra-particulate porosity may result in a smaller increase in surface area than expected, although extensive fragmentation has taken place.

Since fragmentation here is defined as the formation of a number of smaller, discrete particles from an initial grain, it might be advantageous to use a permeametric method, which measures an external rather than a total surface area of the specimen (Orr and DallaValle, 1959b). A method for estimating the specific surface area of tablets by permeametry has recently been presented (Alderborn et al., 1982c; Alderborn et al., in prep.). The results indicate the possibilities of using such a method for detecting particle fragmentation during compaction. Some disadvantages with the gas adsorption method, as discussed above, might be overcome and additionally, the permeametry method is easier and less time consuming.

The object of this paper was therefore to further study the usefulness of the permeametry method for the characterization of particle fragmentation during compaction.

Materials and Methods

Materials

A number of materials with varying and documented consolidation behavior were chosen as model substances. They could be divided into 3 main categories.

(A) Substances which have been characterized as mainly plastically deforming and consequently show a low degree of fragmentation during compaction: *sodium* *chloride* (cubic crystalline puriss, Kebo-Grave, Sweden) (Hardman and Lilley, 1973; Duberg and Nyström, 1982); *sodium bicarbonate* (crystalline puriss, Kebo-Grave, Sweden) (Duberg and Nyström, in prep.).

(B) Substances which have been characterized as mainly brittle and consequently fragment markedly during compaction: *saccharose* (crystalline, K5, SSA, Sweden) (Hardman and Lilley, 1973; Duberg and Nyström, 1982); *lactose* (α-monohydrate, crystalline, CCF, Friesland, Holland) (Higuchi et al., 1954; Cole et al., 1975); *sodium citrate* (dihydrate, crystalline, ADA, Sweden) (Duberg and Nyström, 1982); *ascorbic acid* (crystalline, Roche, Switzerland) (Nyström et al., 1982); *paracetamol* (crystalline, Bayer, F.R.G.) (Nyström et al., 1982).

(C) Substances which fragment extensively during compaction: *Emcompress* (Edward Mendell, U.S.A.) (de Boer et al., 1978; Duberg and Nyström, 1982).

Methods

Preparation of powders

For each material, the size fraction 212–250 μm was prepared by dry-sieving. The powders were then stored for not less than 2 days at constant relative humidity (45%) and room temperature.

Compaction and permeability measurement of tablets

A weighed amount of powder was filled into a specially constructed die, sealed on one end by a plate. The die and plate was placed on the table of an instrumented single-punch press (Korsch EK 0, F.R.G.) and the powder was compacted by hand, using flat-faced punches with a diameter of 1.13 cm. The tablet thickness was approximately 0.3 cm and the contact time between powder and upper punch was about 2 s. After compaction, tablet thickness and weight were determined and the die was then connected to a cone-shaped tube with the aid of an O-ring and a clip. The die, with the tablet still stuck inside, could then be fixed to the permeameter by the tube, which fitted the joint on the top of the Blaine-permeameter (Fig. 1). The Blaine-apparatus (Blaine, 1943) is a transient permeameter which measures the time for a constant volume of air to flow through the powder compact. The permeability of the tablet was then measured about 1 min after the compression.

About 15 tablets of each substance were compressed at a series of pressures—one tablet at each pressure—up to 200 MPa (except paracetamol which was not compacted above 100 MPa).

Calculation of tablet surface area

The specific surface area of the tablets was calculated with the Kozeny-Carman permeability equation corrected for slip flow (Wasan et al., 1976). This equation is an additive function with terms for laminar and molecular flow. The function can be solved by firstly calculating the laminar flow term, i.e.:

$$S_K^2 = \frac{2g\zeta t d_t^2 E^3}{5L\eta \ln(h_2/h_1) d_m^2 (1-E)^2} \tag{1}$$

where d_t = cross-sectional diameter of tablet (m); d_m = cross-sectional diameter of manometer arm (m); E = porosity of tablet (−); g = gravitational constant (9.81 $m \cdot s^{-1}$); h_1 = height of stop point at manometer arm (m); h_2 = height of start point at manometer arm (m); L = height of tablet (m); M = molecular mass of air (29 $g \cdot mol^{-1}$); R = universal gas constant (8.315 $J \cdot K^{-1} \cdot mol^{-1}$); S = tablet surface area as given by the laminar flow term (m^{-1}); T = absolute temperature (K); t = time for measurement (s); η = viscosity of air (1.81 10^{-5} $N \cdot s \cdot m^{-2}$); ζ = density of manometer liquid (1045 $kg \cdot m^{-3}$).

Then one should calculate the molecular flow term, i.e.:

$$S_M = \frac{2 g \zeta t d_t^2 E^2}{PL \ln(h_2/h_1) d_m^2 (1 - E)} 0.96 \, (RT/M)^{1/2} \tag{2}$$

where P = atmospheric pressure (1.013 10^5 $N \cdot m^{-2}$); S_M = tablet surface area as given by the slip flow term (m^{-1}).

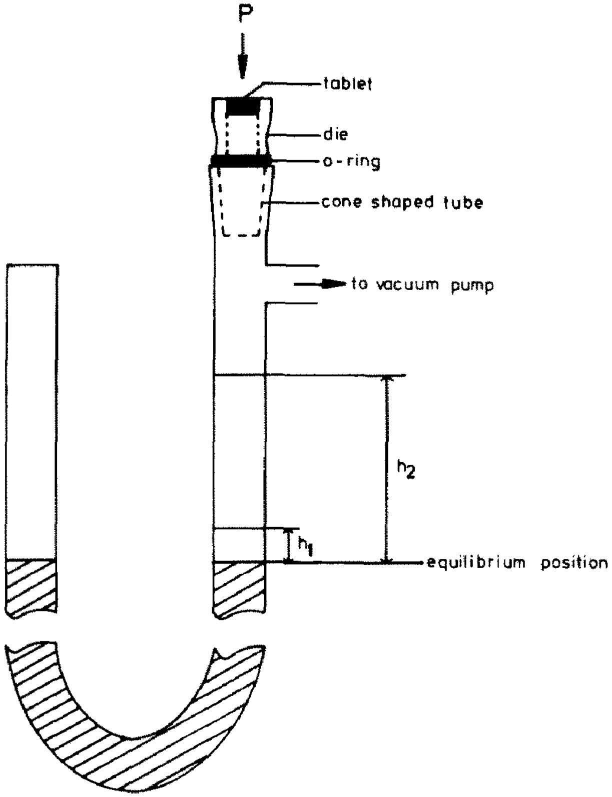

Fig. 1. Line diagram of Blaine permeameter (excluding clip, connecting die with cone-shaped tube).

The total surface area can then be calculated by combining Eqns. 1 and 2:

$$S_V = \frac{S_M}{2} + \left(\frac{S_M^2}{4} + S_K^2 \right)^{1/2} \tag{3}$$

S_V = total surface area of tablet (m^{-1}).

Using atmospheric permeameters, as in the present study, correction for slip flow should be used when the mean free path of the flowing molecules is of the same order of magnitude as the diameter of the capillaries in the powder plug. This is probably the situation in a tablet and it has also been pointed out that slip flow correction is necessary for tablet permeability measurements (Gupte, 1976).

The values 5 and 0.96 in Eqns. 1 and 2, respectively, are empirical constants and remain questionable. However, in the absence of better alternatives, these values have been used in this paper.

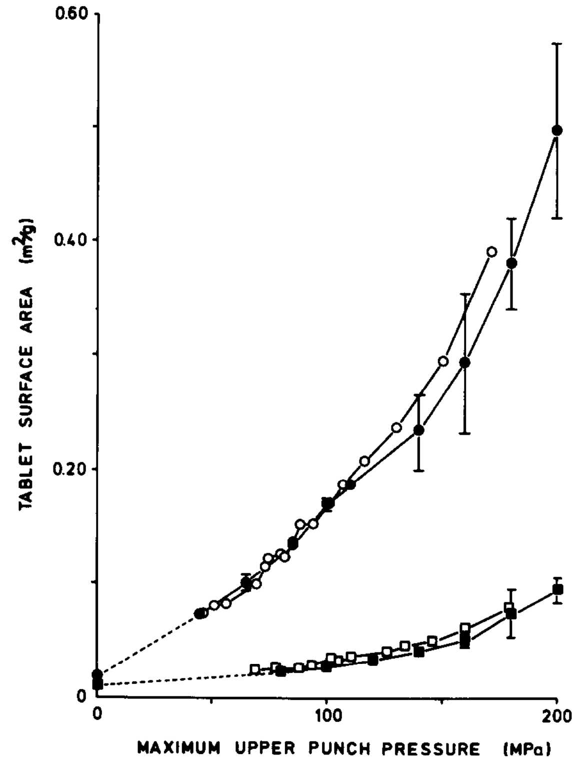

Fig. 2. Specific surface area of sodium chloride (□) and saccharose (○) tablets as a function of compaction pressure. Open symbols represents the result of one tablet and closed symbols the mean of five tablets. Bars represent the 95% confidence limits of the mean of the five measurements (if excluded, they are falling within the symbol).

Results and Discussion

In another study by Alderborn et al. (in prep.), permeametry surface area–pressure curves for sodium chloride and saccharose tablets were presented. In that study, five tablets at each load were compacted and the mean value of their permeametry surface area was calculated and plotted as a function of compaction pressure. In order to evaluate the simplified procedure used in this study (i.e. only one tablet at each pressure), the surface area–pressure curves for sodium chloride and saccharose tablets were compared with the old results (Fig. 2). A good agreement with the earlier data was obtained and it was concluded that the simplified procedure was satisfactorily describing the effect of compaction pressure on tablet permeability surface area within the range of compaction pressures studied.

The effect of compaction pressure on the permeability surface area of the tablets for all materials are presented in Fig. 3.

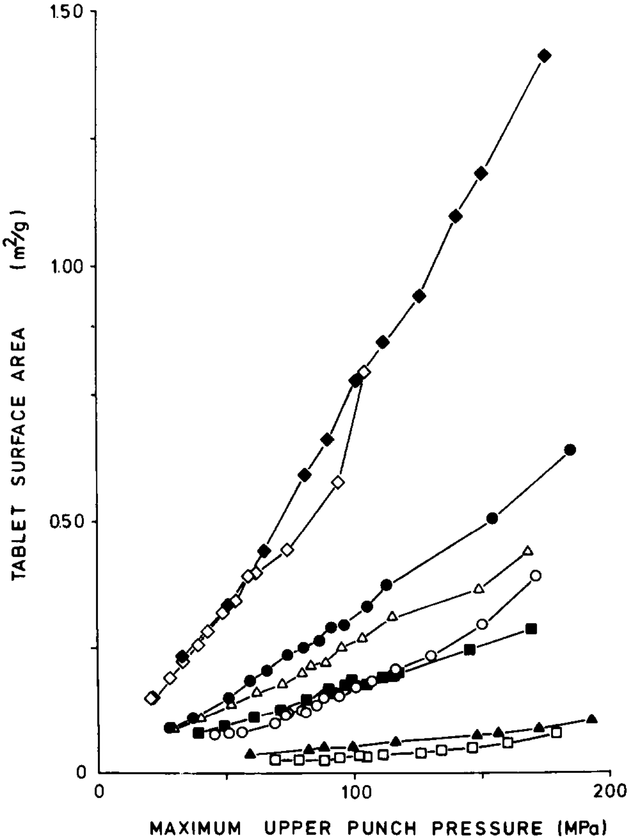

Fig. 3. Specific surface area of sodium chloride (□), sodium bicarbonate (▲), saccharose (○), lactose (●), sodium citrate (■), ascorbic acid (△), paracetamol (◇) and Emcompress (◆) tablets as a function of compaction pressure.

The results show an increasing surface area with pressure for all materials, which indicates fragmentation of particles during compaction. However, the slopes of the curves differ markedly, indicating varying degrees of fragmentation between the materials. The substances can roughly be divided into three groups with respect to the changes in surface area with compaction pressure.

Sodium chloride and sodium bicarbonate both show a comparatively small change in tablet surface area with pressure. This confirms the documented tendency of these materials to consolidate mainly by plastic deformation. However, some fragmentation probably occurs, as demonstrated by the increased surface area with pressure. A slight fragmentation of sodium chloride has also been observed from gas adsorption measurements of sodium chloride tablets (Hardman and Lilley, 1973; Alderborn et al., in prep.).

Emcompress shows a dramatic increase in surface area with pressure. This suggests that Emcompress fragments extensively during compaction. This substance consists of aggregates of small primary particles and it is probable that these aggregates fragment during the consolidation which will explain the marked change in surface area with pressure. Also paracetamol seems to fragment markedly during the compaction, as seen from the similar surface area–pressure curve compared to Emcompress. In this case, tablets could not be compacted above 100 MPa because the tablets tended to cap at higher pressures. This illustrates one of the limitations with the permeametry method. If a substance gives laminated or capped tablets the reliability of the results could be questioned.

The rest of the materials forms a group between these extremes and can be characterized as intermediates concerning the degree of fragmentation during compaction. Lactose, saccharose and sodium citrate have earlier been described as such intermediate materials (Duberg and Nyström, 1982) and the results in this study confirm this and indicate also that ascorbic acid belongs to this group of materials.

As seen from the results (Figs. 2 and 3) the surface area–pressure curves are increasing continuously over the whole pressure range studied. This type of surface area–pressure curve differs from the results obtained with gas adsorption measurements where a plateu or even a fall in surface area at higher pressures is observed (e.g. Higuchi et al., 1954; Alderborn et al., in prep.). It also seems theoretically probable that a curve with a plateau should be obtained. These deviations at higher pressures are probably an error with the permeability method as discussed earlier (Alderborn et al., in prep.) but it does not affect a qualitative estimation of the tendency of a material to fragment during compaction.

To summarize, the results in this study indicate that the measurement of permeametry surface areas as a function of compaction pressure is useful for the characterization of particle fragmentation during compaction. Advantages with the permeametry technique, compared to other useful methods are, firstly, that an estimation of changes in tablet surface area with pressure is obtained, which is a direct way of describing the degree of fragmentation during compaction. Secondly, the experimental procedure is rapid and simple and the equipment needed is comparatively cheap. Finally, materials with rather poor binding ability, e.g. sodium bicarbonate and ascorbic acid, can be characterized with the permeametry method.

The main limitations seem to be firstly, coherent compacts without the addition of binders must be formed which means that the material must have at least some binding ability. Secondly, if the compaction results in capping or lamination of the tablets, the reliability of the results may be questioned.

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