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# Characterization of β-cyclodextrin for direct compression tableting

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## Summary

A physically modified β-cyclodextrin (BCD-DC) sample was characterized for direct compression tableting. The compactibility of BCD-DC was compared to a commercial β-cyclodextrin product (Kleptose®) and other commonly used direct compression fillers. Heckel analysis and mercury porosimetry were used to elucidate the primary deformation mechanism of both β-cyclodextrin (BCD) samples. BCD-DC showed superior compactibility compared to Kleptose® and excellent dilution potential. Compactibility and dilution potential of BCD-DC were comparable to microcrystalline cellulose. Lubricant sensitivity of BCD-DC was similar to that of microcrystallline cellulose. Tablet strength was found to increase with decrease in particle size. Heckel analysis and mercury porosimetry revealed that BCD-DC and Kleptose® deform primarily by plastic flow but failed to distinguish between the two samples. Scanning electron photomicrographs and surface area data show that BCD-DC has more irregular and laminated particles than Kleptose®. These differences in the external particle characteristics rather than internal crystal structure are primarily responsible for the greater compactibility of BCD-DC.

## Introduction

The possibility of using β-cyclodextrin (BCD) as a direct compression filler-binder has been recently reported. Shangraw et al. (1992) reported that the compactibility of BCD was higher than all other standard direct compression fillers commonly in use except microcrystalline cellulose. However, the fluidity of the available commercial BCD products was not adequate for direct compression tableting. ElShaboury (1990) studied BCD as a direct compression vehicle used alone or in blends with spray dried lactose for preparing tablets containing sparingly soluble drugs. It was found that BCD and its combinations with spray dried lactose produced tablets with very good mechanical properties and faster dissolution rates. Szabo-Revesz et al. (1989) showed that when a physical mixture of chloramphenicol and BCD was tableted, the rate of dissolution of chloramphenicol was increased. Giordano et al. (1990) reported that moisture plays a very critical role in the compactibility of BCD. It

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is clear from these studies that BCD shows considerable promise as a filler-binder in tablet manufacture. The objective of this study was to characterize a physically modified BCD sample for direct compression tableting and to investigate its primary deformation mechanism.

## Materials and Methods

*Materials*

Two samples of BCD were used. Kleptose® is a commercial BCD product manufactured by Roquette, France. Roquette also supplied a physically modified BCD (BCD-DC). The following other materials were used: Microcrystalline cellulose (MCC) (Avicel® PH102, FMC Corp., U.S.A.), spray dried lactose (SDL) (Fast Flo®, Foremost Whey Products, U.S.A), unmilled dicalcium phosphate (DCP) (Ditab®, Stauffer Chemical Co., U.S.A.), magnesium stearate (2255 Grade, Mallinckrodt Inc., U.S.A.), and ascorbic acid (Roche Vitamins and Fine Chemicals, U.S.A.).

*Methods*

Particle size analysis of the BCD samples was performed using an optical microscope and a microcomputer image analysis system (Bioquant II microcomputer system). This system permits direct measurement of the projected particle diameter (Martin's diameter), represented as the length of the line that bisects the particle image at a constant angle to the microscopic field. Average diameters and standard deviations were calculated for 600 particles of each sample. Moisture content of the samples was determined by noting the loss in weight on drying at 105°C for 3 h under vacuum. Loose and tapped densities for both samples were determined.

Tablets were compressed on an instrumented rotary tablet press (Stokes RB-2, Stokes Engineering, U.S.A.) utilizing 11.1 mm flat faced punches. For tablets made without a lubricant, the punches and die wall were cleaned and lubricated by applying a thin film of a 2% w/v suspension of magnesium stearate in acetone. The die was then filled by hand with 350 mg of powder and the machine was run at a speed setting of 30 rpm and stopped after tablet compression. The angular separation between filling and compression was 180°. Studies conducted by Watt (1983) indicate that a rotary press reaches steady state conditions after little more than a quarter-turn. While tableting, the relative humidity was maintained at 45% (±5%). The crushing strength of the tablets was determined by diametral loading in a standard motorized tester (Key tablet hardness tester, Model NT-300, Key International Inc., U.S.A.) after 24 h storage. Tablet thickness was determined using a dial micrometer (Mitutoyo, Japan). Tablet tensile strength ($\sigma$) was calculated using the equation:

$$\sigma = 2P/\pi Dt$$

where $P$ is the applied load, $D$ denotes the tablet diameter, and $t$ is the tablet thickness (Fell and Newton, 1970). The value used for $P$ was the mean of 10 crushing strength determinations for each tablet sample. Care was taken to ensure that only tablets which failed in tension were counted. This tablet evaluation procedure was followed for all other studies.

The compactibility of the unlubricated BCD samples was compared to SDL, DCP and MCC. At least three compression pressures were used for each material. The compactibilities of sieve fractions of BCD-DC and Kleptose® were also compared.

Lubricant sensitivity of BCD-DC was determined by blending it with either 0.5 or 1.0% magnesium stearate. Blending was performed for 5 min using a 2 quart twin shell blender (Patterson Kelly, U.S.A.). The batch size for both blends was 500 g. Similar blends were prepared with MCC. Tableting equipment was the same as described previously except that prelubrication of the die was not necessary and the rotary press was run continuously with hopper in place. For the dilution potential study, BCD-DC was blended with 10, 25, and 50% ascorbic acid as the diluent. Similar blends were prepared using MCC and SDL instead of BCD-DC. Relative compactibilities of these blends were determined.

Compression studies to monitor changes in bed density were carried out using the Smith

Kline Beecham compaction simulator (Celik and Marshall, 1989), fitted with 10 mm flat faced punches. A sawtooth displacement profile was used to control the upper punch while the lower punch was kept stationary. Tablet weight for each material was adjusted to obtain a tablet thickness of 3.0 mm at zero porosity. Six tablets were produced at four compression speeds (10, 50, 100, 200 mm $s^{-1}$) for each sample. The die was prelubricated with 2% w/v of magnesium stearate in acetone before each compression. From the upper and lower punch force and displacement values, it was possible to calculate the thickness of the compact during a single compression event as a function of the punch pressure. From compact weight and true density data the relative density of the tablet during compression was calculated.

The Heckel equation (Heckel, 1961a,b) was used to analyze the relationship between relative density during compaction and the applied pressure:

$$\ln[1/(1-D)] = KP + A$$

where $D$ is the relative density of the compact at pressure $P$, $K$ represents a material constant and is the slope of the straight line portion of the plot. The reciprocal of $K$ is the mean yield pressure of the material ($P_y$). Regression analyses were carried out on the Heckel plots over the range 50–200 MPa for samples of BCD-DC, Kleptose®, MCC and SDL and over the range 100–200 MPa for the DCP sample. These results were then used for the evaluation of the change of $P_y$ with punch velocity. Heckel analysis was also performed on particle size fractions of BCD-DC and Kleptose®. The 125–212 and 38–75 $\mu$m sieve fractions were used. Samples were compressed only at the 100 mm $s^{-1}$ punch speed. Heckel plots and yield pressures of these sieve fractions were compared.

Mercury porosimetry experiments were carried out on tablets compressed from the 90–125 $\mu$m sieve fraction of BCD-DC and Kleptose® using the micromeritics pore sizer (Model 9305, Micromeritics Instrument Corp., U.S.A.). The BCD samples were photographed under a scanning electron microscope (Jeol JSM-T200). Surface area of the BCD samples was determined by the BET method using the micromeritics FlowSorb II 2300 apparatus (Micromeritics Instrument Corp., U.S.A.). Krypton was used as the adsorbate gas (0.1% krypton in helium). All samples were degassed using the krypton-helium mixture for 24 h before measuring their surface area. X-ray diffraction (XRD) studies were performed using a Scintag model XDS 2000 diffractometer (Scintag, U.S.A.) which uses a solid state photon germanium detector.

## Results and Discussion

The relative compactibilities of the two BCD samples compared to other commonly used direct compression fillers are shown in Fig. 1. The compactibility of BCD-DC is significantly superior to that of Kleptose®. Thus, physical modification of BCD has resulted in a significant improvement in its compactibility. At the lower compression pressures, there is almost a linear relationship between tensile strength and compression pressure. However, at higher pressures the tensile strength of BCD-DC does not show an increase with increase in compression pressure. The large confidence interval for tensile strength of BCD-DC at the highest compression pressure suggests incipient lamination (Cole et al., 1975). MCC is reported as the most compactible of all the direct

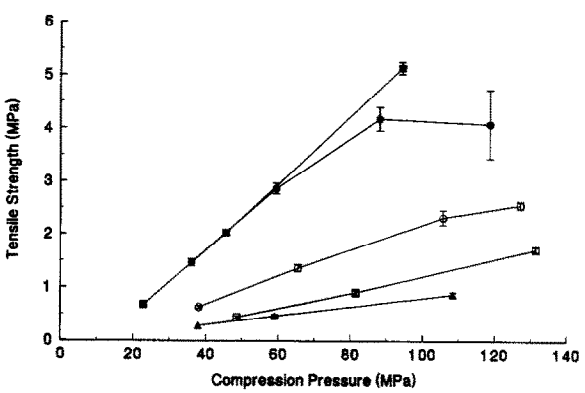


Fig. 1. Compactibility of BCD-DC (●) and Kleptose (○), compared with other fillers: MCC (■), SDL (□) and DCP (▲). No lubricant added. Mean ± 95% confidence interval.

compression fillers (Shangraw, 1989). The compactibility of BCD-DC is comparable to that of MCC and is significantly greater than that of either SDL or DCP.

The effect of lubricant addition on tablet tensile strength has been extensively studied (Lerk et al., 1977; Jarosz and Parrott, 1984). Although magnesium stearate exhibits very good lubricant properties, it can have a negative effect on tablet tensile strength. For BCD-DC tablets, addition of 0.5% magnesium stearate leads to significant softening (Fig. 2). This behavior is similar to that observed for MCC. Addition of 1% magnesium stearate causes further softening for both BCD-DC and MCC tablets. However, a lubricant level of 0.5% magnesium stearate is adequate for BCD-DC. Continuous tableting of BCD-DC with 0.5% magnesium stearate is possible on a rotary press. Tablet weight variation was less than 1.0% indicating good flow. The consolidation characteristics of a filler are known to have considerable influence on its susceptibility to lubrication (De Boer et al., 1978). Materials deforming predominantly by brittle fracture like DCP have been shown to be quite insensitive to magnesium stearate mixing, whereas plastically deforming materials like MCC show a decrease in their binding properties in presence of magnesium stearate. Although lubricant sensitivity alone cannot be used to determine the deformation mechanism, data presented in Fig. 2 indicates that BCD, like MCC, probably deforms by plastic flow.

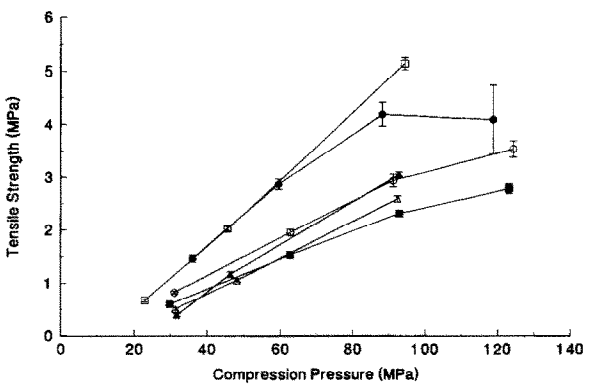


Fig. 2. Sensitivity of BCD-DC and MCC to lubrication with magnesium stearate (Mg. st.). BCD-DC, no Mg. st. (●); BCD-DC, 0.5% Mg. st. (○); BCD-DC 1% Mg. st. (■); MCC, no Mg. st. (□); MCC, 0.5% Mg. st. (▲); MCC, 1% Mg. st. (△). Mean ± 95% confidence interval.

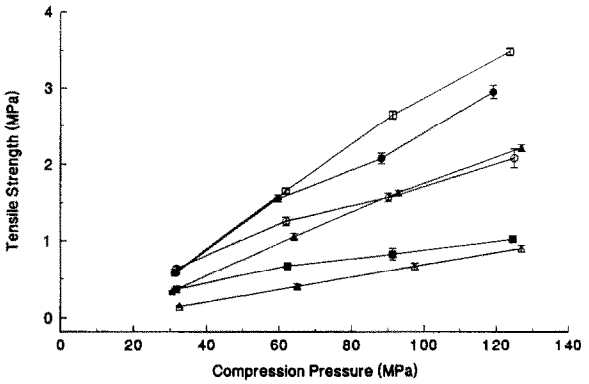


Fig. 3. Dilution potential of BCD-DC compared to MCC; diluent is ascorbic acid (As.). 90% BCD-DC, 10% As. (●); 75% BCD-DC, 25% As. (○); 50% BCD-DC, 50% As. (■); 90% MCC, 10% As. (■); 75% MCC, 25% As. (▲); 50% MCC, 50% As. (△). Mean ± 95% confidence interval.

Dilution potential is a way of measuring the ability of a compressible filler to be diluted with another filler or a drug substance and still maintain its compactibility. For this study, various proportions of ascorbic acid were mixed with BCD-DC and the relative compactibilities of the blends were determined. BCD-DC shows excellent dilution potential. Dilution potential of BCD-DC at the 10% ascorbic acid level is equivalent to MCC at lower compression pressures (Fig. 3). At the 25% ascorbic acid level, compactibility of BCD-DC is better than MCC at lower pressures and equivalent at the higher pressures. At the 50% level, BCD-DC shows superior compactibility at all pressures. BCD-DC shows significantly better compactibility at all ascorbic acid levels as compared to SDL (Fig. 4).

The foregoing discussion clearly indicates that BCD-DC shows considerable promise as a direct compression filler. Further experiments were carried out to explain the differences in the compactibility of BCD-DC and Kleptose® and also to elucidate the deformation mechanism of BCD. Table 1 lists some of the basic powder properties of the two BCD samples. BCD-DC has a slightly higher particle size and lower bulk density. Moisture content of both samples is almost identical.

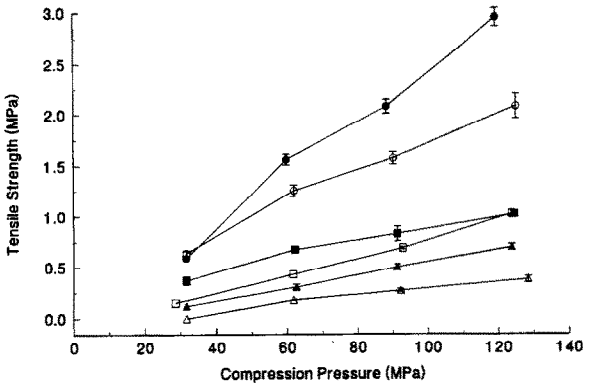


Fig. 4. Dilution potential of BCD-DC compared to SDL; diluent is ascorbic acid (As.). 90% BCD-DC, 10% As. (●); 75% BCD-DC, 25% As. (○); 50% BCD-DC, 50% As. (■); 90% SDL, 10% As. (□); 75% SDL, 25% As. (▲); 50% SDL, 50% As. (△). Mean ± 95% confidence interval.

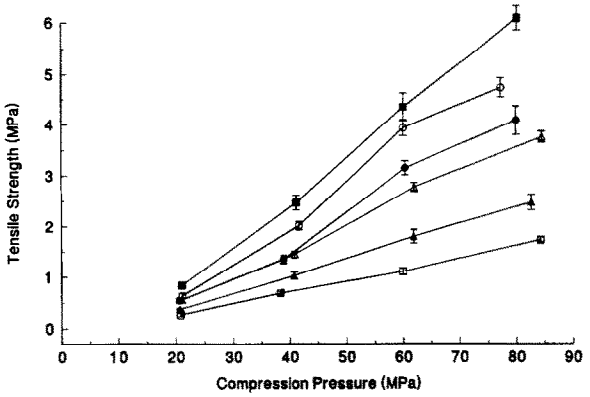


Fig. 5. Effect of particle size on tensile strength of BCD tablets. BCD-DC 212–300 (●); 90–125 (○); 45–75 (■); Kleptose 212–300 (□); 90–125 (▲), 45–75 μm (△). Mean ± 95% confidence interval.

Thus, it is not possible to explain the differences between the two samples based on their particle size or moisture data.

The compactibility of various sieve fractions of BCD-DC and Kleptose® is shown in Fig. 5. A decrease in initial particle size results in an increase in tensile strength of the compacts of both BCD-DC and Kleptose®. This effect is more evident at the higher compression pressures. It should be noted that the difference in compactibility of BCD-DC and Kleptose® is retained through all the sieve fractions. Particle size has been claimed to be one of the most important factors for the strength of compressed tablets. Effect of particle size on the compactibility of various direct compression fillers has been reported in several papers (Alderborn and Nyström, 1982a; Vromans et al., 1985a; De Boer et al., 1986; Alderborn et al., 1988). Both the direction and magnitude of the effect of particle size on tablet strength have been shown to vary between substances, and is related to the fragmentation propensity of the materials studied. For materials which fragment extensively during compression, such as DCP, tablet strength is independent of particle size. On the other hand for materials that fragment to a lesser extent, such as lactose, a significant change in tablet strength due to changes in particle size or shape have been observed. These observations have been explained by noting that with materials that undergo extensive fragmentation, new clean surfaces will be created during the compaction process and therefore the particle size of the original material has a smaller effect compared to those materials that are less prone to fragmentation. The dependence of tablet strength on particle size for both the BCD samples suggests that extensive fragmentation does not occur during compression of BCD. Because of its effect on tablet strength, particle size is an important variable to be monitored with respect to tableting of BCD.

Although several equations have been developed to describe the change in powder density during compression, the Heckel equation is the most widely used. Heckel plots for BCD-DC at various punch speeds are illustrated in Fig. 6. It is obvious from these plots that slopes decrease

TABLE 1

*Basic powder characteristics of BCD samples*

| Sample | Martin's diameter (μm) mean (±95% C.I.) [a] | % moisture (L.O.D) | Loose density (g/cm$^3$) | Tapped density (g/cm$^3$) |
|---|---|---|---|---|
| Kleptose | 39.8 (0.54) | 12.6 | 0.637 | 0.836 |
| BCD-DC | 51.5 (0.59) | 12.8 | 0.495 | 0.676 |

[a] ±95% confidence interval ($n = 400$).

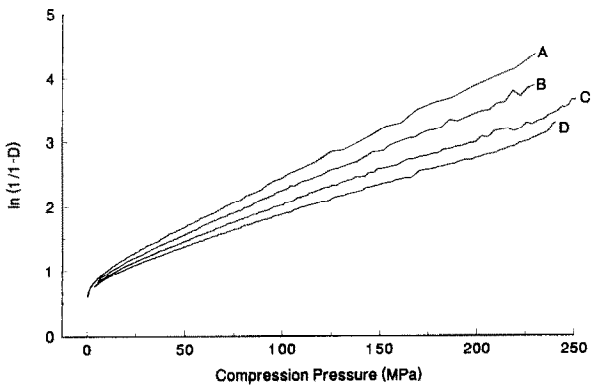


Fig. 6. Heckel plots of BCD-DC at the following punch speeds: A, 10; B, 50; C, 100; D, 200 mm/s.

with increasing punch speed. This will result in an increase in the yield pressure, $P_y$. The effect of punch speed on the $P_y$ of the two BCD samples and other fillers is shown in Fig. 7. BCD-DC has a slightly lower $P_y$ than Kleptose® at all punch speeds, indicating that it deforms more readily. An increase in $P_y$ with punch speed is observed for both BCD samples. A similar increase is observed for MCC. For DCP, when the error of measuring $P_y$ is taken into account, $P_y$ can be assumed to be relatively unchanged. Roberts and Rowe (1985) examined the effect of punch speed on the compaction of a variety of materials using the Heckel equation. For materials known to deform plastically, e.g., MCC, there was an increase in $P_y$ with punch speed. This was

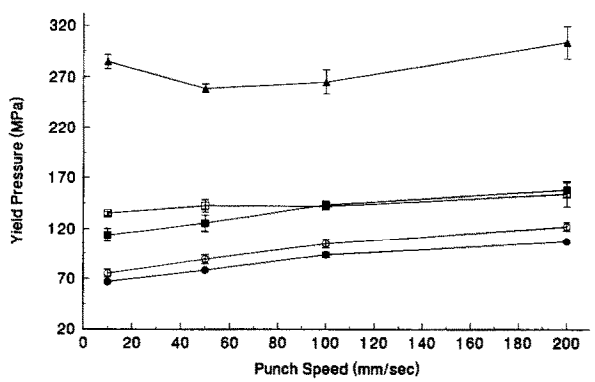


Fig. 7. Yield pressure vs punch speed for: BCD-DC (●); Kleptose (○); MCC (■); SDL (□); DCP (▲). Mean ± 95% confidence interval.

TABLE 2

*Strain rate sensitivity of fillers*

| Filler | Strain rate sensitivity (%) |
|---|---|
| Kleptose | 38.5 |
| BCD-DC | 37.6 |
| MCC | 28.0 |
| SDL | 12.2 |
| DCP | – |

attributed to either a change from plastic to brittle behavior or a reduction in the amount of plastic deformation due to the time dependent nature of plastic flow. For materials known to consolidate by fragmentation, e.g., DCP, there was no change in $P_y$ with punch speed. Thus, the change in $P_y$ for BCD samples indicates that they deform primarily by plastic flow.

Roberts and Rowe (1985) also presented an equation to determine the strain rate sensitivity (SRS) of the various materials tested:

$$\text{SRS} = (P_{y_2} - P_{y_1})/P_{y_2} \times 100$$

For the present study, $P_{y_1}$ = the yield pressure at 10 mm $s^{-1}$ and $P_{y_2}$ = the yield pressure at 200 mm $s^{-1}$. The SRS values are shown in Table 2. The SRS value of DCP could not be calculated. Both the BCD samples have higher SRS values than MCC. Heckel plots of two particle size fractions of both BCD samples are presented in Fig. 8. From this plot it is seen that the slopes of the Heckel plots and consequently the yield pressures are independent of particle size. This would be expected since, as reported by Roberts and Rowe (1986), yield pressures are independent of particle size for plastically deforming materials such as MCC. On the other hand for lactose, a material known to deform by a mixed mechanism of particle fracture and plastic deformation the yield pressure was shown to increase as particle size decreased. Another point to be noted from the Heckel study is that the deformation mechanism for both BCD-DC and Kleptose® is similar. Thus, although the Heckel study clearly indicates that plastic flow is the primary deformation mecha-

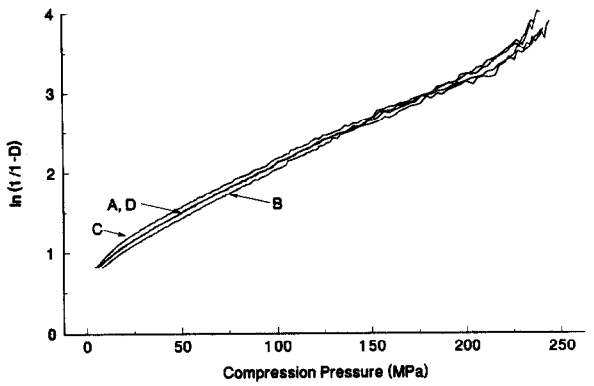


Fig. 8. Heckel plots for sieve fractions of BCD-DC and Kleptose: A, BCD-DC 125–212; B, BCD-DC 38–75; C, Kleptose 125–212; D, Kleptose 38–75 $\mu$m.

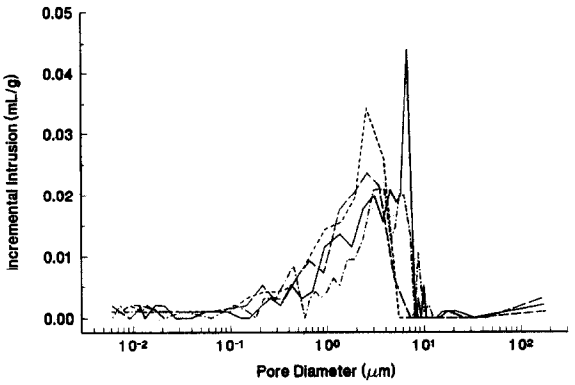


Fig. 9. Incremental intrusion volume vs pore diameter: BCD-DC 40 MPa tablets (solid line); Kleptose 40 MPa tablets (dot and dash); BCD-DC 80 MPa tablets (short dash); Kleptose 80 MPa tablets (long dash).

nism for BCD, it fails to provide an explanation for the differences in tablet strength for BCD-DC and Kleptose®. This is not unexpected since Heckel analysis applies only to the volume reduction properties of materials and not to the process of bond formation.

Mercury porosimetry studies can be used to examine pore volume distributions of tablets made from BCD-DC and Kleptose®. For this study, tablets of both BCD-DC and Kleptose® were compressed at 40 and 80 MPa. The incremental volume distributions for the BCD-DC and Kleptose® tablets are similar (Fig. 9). The distributions are also independent of compression pressure. This behavior is similar to that seen with MCC (Vromans et al., 1985b). With MCC no new particles are created as compression pressure is increased and so there are no major changes in the pore volume distribution. With lactose, with increasing compaction load there is a shift of the total pore volume distribution towards smaller pores. This is because lactose fragments during compaction, resulting in an increase in the number of small particles and consequently a new pore volume distribution. Table 3 lists the median pore diameter, pore surface area, and tablet porosity calculated from the porosimetry data. Both samples result in tablets with similar porosity. Even though, an increase in compression pressure leads to an increase in tablet strength, the pore surface area does not increase. This has also been observed with MCC (Vromans et al., 1985b). This is in contrast to the data for lactose where a linear relationship was found to exist between tablet strength and pore surface area. Thus, the increase in tablet strength is coupled with an increase in specific area for a fragmenting material, but no change is observed for a plastically deforming substance. Thus, the mercury porosimetry data also shows that plastic flow rather than fragmentation is the predominant deformation mechanism for BCD.

TABLE 3

*Mercury porosimetry of BCD tablets*

| | BCD-DC 40 MPa tablets | Kleptose 40 MPa tablets | BCD-DC 80 MPa tablets | Kleptose 80 MPa tablets |
|---|---|---|---|---|
| Total pore area ($m^2/g$) | $12.7 \pm 0.1$ | $13.1 \pm 3.1$ | $12.9 \pm 3.6$ | $13.7 \pm 1.9$ |
| Median pore diameter ($\mu$m) | $3.7 \pm 0.7$ | $3.6 \pm 0.3$ | $1.6 \pm 0.2$ | $1.4 \pm 0.6$ |
| % porosity | $29.8 \pm 3.5$ | $28.8 \pm 2.8$ | $20.2 \pm 1.7$ | $21.1 \pm 2.4$ |

NB: All values reported are mean $\pm$ 95% confidence interval ($n = 3$).

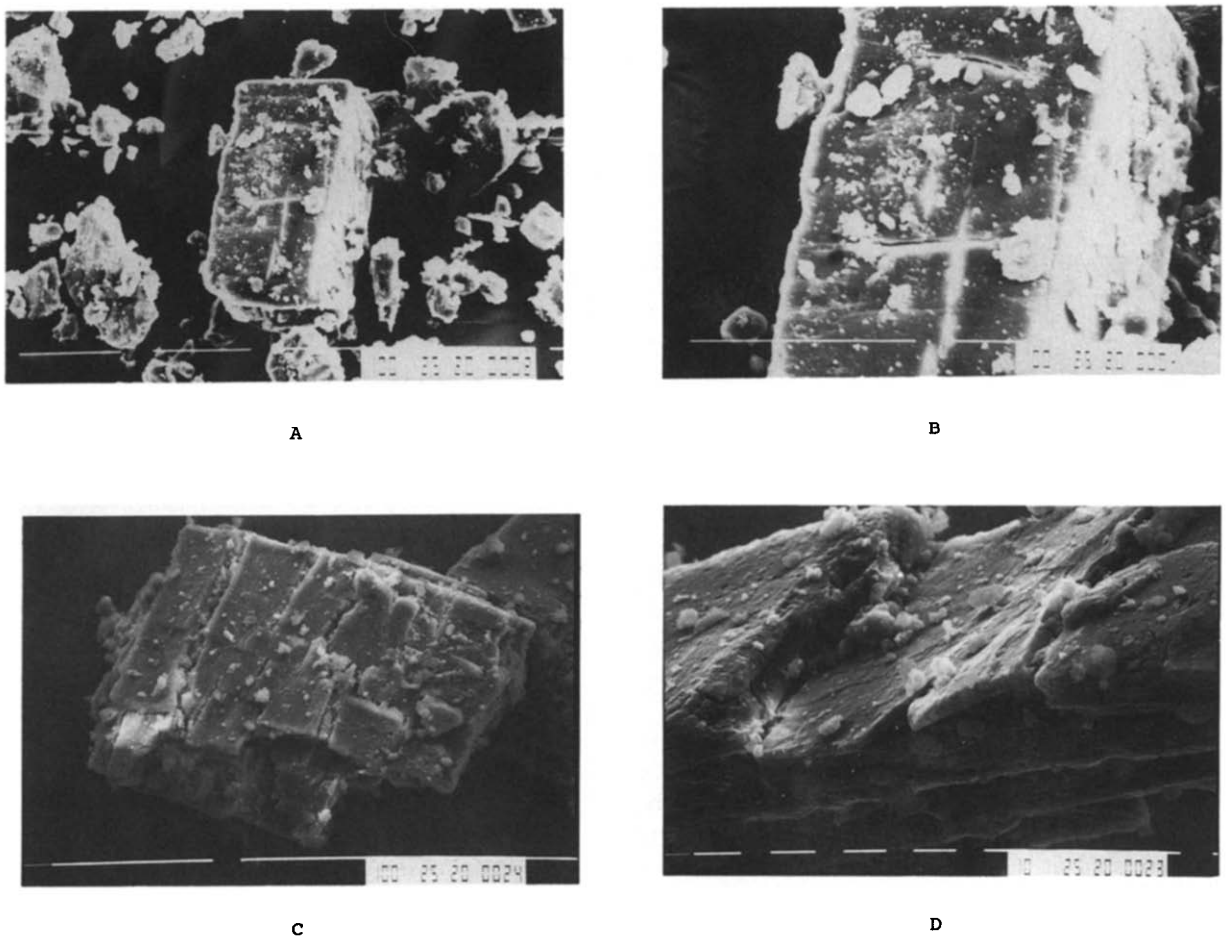

Fig. 10. Scanning elecron micrographs: A, Kleptose, magnification 200 ×; B, Kleptose, magnification 500 ×; C, BCD-DC, magnification 350 ×; D, BCD-DC, magnification 1000 ×.

The scanning electron micrographs show significant differences in the surface characteristics of the two BCD samples (Fig. 10). The BCD-DC particles show cracks and laminations as compared to the more solid crystals of Kleptose®. The surface area results support this observation (Fig 11). The surface area of BCD-DC is almost twice that of Kleptose®. When similar sieve fractions are compared, the difference in surface area is still apparent. The 212–300 $\mu$m sieve fraction shows the maximum difference in surface area, but even in the smallest sieve fraction (45–75 $\mu$m) the difference is quite significant. This indicates that the differences in surface area are not

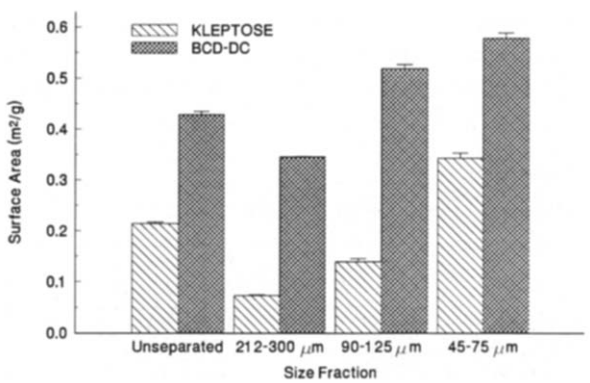


Fig. 11. Surface area of BCD-DC and Kleptose. Error bars indicate 95% confidence interval.

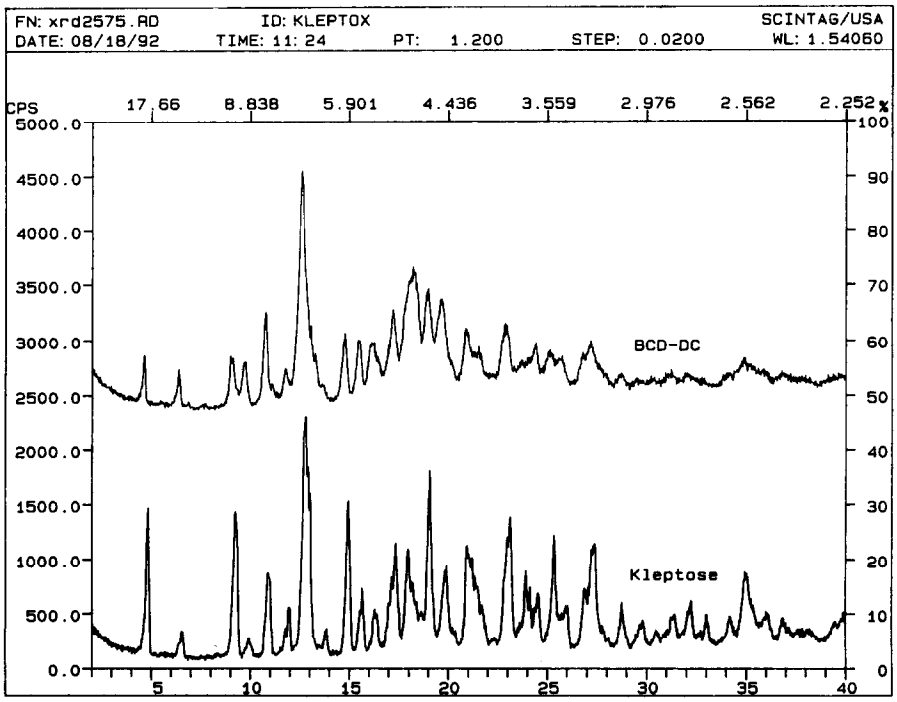


Fig. 12. X-ray diffraction patterns of BCD-DC and Kleptose.

as a result of differences in particle size, but rather cracks and/or laminations. Both particle size and shape have been shown to be important for plastically deforming materials (Alderborn and Nyström, 1982b; Alderborn et al., 1988). The cracks and/or laminations could serve as slip planes to facilitate plastic deformation ultimately resulting in stronger tablets. The lower yield pressures for BCD-DC compared to Kleptose® at all punch speeds support this observation.

The XRD patterns of the two BCD samples were examined (Fig. 12). The spectra are equivalent except that for the BCD-DC sample some of the peaks show slightly lower intensity, probably indicating less crystal perfection. These differences in realtive peak intensities between the two BCD samples may be also due to preferred orientation. In an earlier study, Nakai et al. (1985) had reported that decreasing the crystallinity of BCD resulted in stronger tablets. Although BCD-DC probably has slightly higher amorphous content, the scanning electron photomicrographs and surface area data clearly indicate that it is the differences in external particle characteristics rather than crystallinity which is primarily responsible for producing stronger tablets. Crystalline disorder throughout the crystal is readily recognized by XRD but this technique does not readily identify changes that take place for only a few nanometers into the particle surface (Hersey and Kryser, 1980).

## Conclusion

It is clear from the results of this study that physical modification of BCD resulted in a considerable improvement in its properties as a direct compression filler-binder. The compactibility of the BCD-DC sample is significantly superior to the Kleptose® sample. Both compactibility and and dilution potential of BCD-DC is comparable to that of MCC. Also, unlike some of the previously tested BCD samples, BCD-DC possesses adequate flow for direct compression using a rotary press. The deformation mechanism of BCD

was found to be similar to MCC, i.e., plastic flow. Consequently, some of the processing effects are similar to MCC, e.g., lubricant softening. Scanning electron photomicrographs of BCD-DC show the presence of cracks and laminations which explain the higher surface area of BCD-DC. These differences in the external particle characteristics rather than internal crystal structure are primarily responsible for the greater compactibility of BCD-DC. Thus, BCD-DC shows promise as a direct compression filler, warranting further investigation.

## Acknowledgments

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## References

Alderborn., G., Börjesson, E., Glazer, M. and Nyström, C., Studies on direct compression of tablets: 19. The effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets. *Acta Pharm. Suec.*, 25 (1988) 31–40.

Alderborn, G. and Nyström, C., Studies on direct compression of tablets: 4. The effect of particle size on the mechanical strength of tablets. *Acta Pharm. Suec.*, 19 (1982a) 381–390.

Alderborn, G. and Nyström, C., Studies on direct compression of tablets: 3. The effect on tablet strength of changes in particle shape and texture obtained by milling. *Acta Pharm. Suec.*, 19 (1982b) 147–156.

Celik, M. and Marshall, K., Use of a compaction simulator system in tableting research. *Drug Dev. Ind. Pharm.*, 15 (1989) 759–800.

Cole, E.T., Rees, G.E. and Hersey, J.A., Relations between compaction of some data for some crystalline pharmaceutical materials. *Pharm. Acta Helv.*, 50 (1975) 28–32.

De Boer, A.H., Bolhuis, G.K.. and Lerk, C.F., Bonding characteristics by scanning electron microscopy of powders mixed with magnesium stearate. *Powder Technol.*, 20 (1978) 75–82.

De Boer, A.H., Vromans, H., Lerk, C.F., Bolhuis, G.K.. Kussendrager, K.D. and Bosch, H., Studies on tableting properties of lactose: 3. The consolidation behavior of sieve fractions of crystalline $\alpha$-lactose monohydrate. *Pharm. Weekbl. Sci.*, 8 (1986) 145–150.

ElShaboury, M.H., Physical properties and dissolution profiles of tablets directly compressed with $\beta$-cyclodextrin. *Int. J. Pharm.*, 63 (1990) 95–100.

Fell, J.T. and Newton, J.M., Determination of tablet strength by the diametral-compression test. *J. Pharm. Sci.*, 59 (1970) 688–691.

Giordano, F., Gazzaniga, A., Bettinetti, G.P. and La Manna, A., The influence of water content on the binding capacity of $\beta$-cyclodextrin. *Int. J. Pharm.*, 63 (1990) 153–156.

Heckel, R.W., Density-pressure relationships in powder compaction. *Trans. Metall. Soc. A.I.M.E.*, 221 (1961a) 671–675.

Heckel, R.W., An analysis of powder compaction phenomena. *Trans. Metall. Soc. A.I.M.E.*, 221 (1961b) 1001–1008.

Hersey, J.A. and Kryser, A., Biopharmaceutical implications of technological change. *Int. J. Pharm. Tech. Prod. Manuf.*, 1 (1980) 18–21.

Jarosz, P.J. and Parrott, E.L., Effect of lubricants on tensile strength of tablets. *Drug Dev. Ind. Pharm.*, 10 (1984) 259–273.

Lerk, C.F., Bolhuis, G.K.. and Smedema, S.S., Interaction of lubricants and colloidal silica during mixing with excipients. *Pharm. Acta Helv.*, 52 (1977) 33–39.

Nakai, Y.. Yamamoto, K., Terada K. and Kajiyama, A., Relationships between crystallinity of $\beta$-cyclodextrin and tablet characteristics. *Chem. Pharm. Bull.*, 33 (1985) 5110–5112.

Roberts, R.J. and Rowe, R.C., The effect of punch velocity on the compaction of a variety of materials. *J. Pharm. Pharmacol.*, 37 (1985) 377–384.

Roberts, R.J. and Rowe, R.C., The effect of the relationship between punch velocity and particle size on the compaction behaviour of materials with varying deformation mechanisms. *J. Pharm. Pharmacol.*, 38 (1986) 567–571.

Shangraw, R.F., Pande, G.S. and Gala, P., Characterization of the tableting properties of $\beta$-cyclodextrin and the effects of processing variables on inclusion complex formation, compactibility and dissolution. *Drug Dev. Ind. Pharm.*, 18 (1992) 1831–1851.

Shangraw, R.F., Compressed tablets by direct compression. In Lieberman, H.B., Lachman, L. and Schwartz, J.B. (Eds), *Pharmaceutical Dosage Forms, Tablets, Vol. 1,* Dekker, New York, 1989, pp. 195–246.

Szabo-Revesz, P., Pintye-Hodi, K., Miseta, M. and Selmeczi B., Untersuchung des physikalischen Gemishes von Chloramphenicol-$\beta$-Cyclodextrin. *Pharm. Ind.*, 51 (1989) 94–97.

Vromans, H., De Boer, A.H., Bolhuis, G.K.. and Lerk, C.F., Studies on tableting properties of lactose: 1. The effect of initial particle size on binding properties and dehydration characteristics of lactose. *Acta Pharm. Suec.*, 22 (1985a) 163–172.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H., Studies on tableting properties of lactose: 2. Consolidation and compaction of different types of crystalline lactose. *Pharm. Weebkl. Sci.*, 7 (1985b) 186–193.

Watt, P.R., Measurement of acceleration in a rotary tablet machine. *J. Pharm. Pharmacol.*, 35 (1983) 746.