J. Pharm. Pharmacol. 1996, 48: 790–797
Received September 9, 1995
Accepted April 24, 1996

Time-dependent Densification Behaviour of Cyclodextrins

ANGEL MUÑOZ-RUIZ*† AND PETTERI PARONEN†

Department of Pharmaceutics, University of Kuopio, P.O. Box 1627, Kuopio 70211 Finland and †Department of Pharmaceutical Technology, Facultad de Farmacia, University of Sevilla, C/Tramontana S/N, Sevilla 41012 Spain

Abstract

Understanding of volume reduction mechanisms is a valuable aid in the development of robust cyclodextrin tablet formulations. The particle and powder properties of α-, β-, γ- and hydroxypropyl (HP) -β-cyclodextrins and their behaviour under compression were examined.

The cyclodextrins studied showed big differences in particle-size distribution and particle shape. The highest densification on tapping was found for cyclodextrins having the smallest particle size. Cyclodextrins were compressed using single-sided saw-tooth displacement-time profiles at rates of 3 and 300 mm s^{-1} with a compaction simulator. The densification of the powders was examined by Heckel treatment, using the tablet-in-die and ejected-tablet methods. The cyclodextrins were denser at the beginning of the tableting process (at low pressures) if high rather than low velocity was used. Ranking according to their tendency toward total deformation and permanent plastic deformation was: HP-β-cyclodextrin > β-cyclodextrin > γ-cyclodextrin > α-cyclodextrin. The ranking order in strain-rate sensitivity (SRS) of total deformation was HP-β-cyclodextrin≫ γ-cyclodextrin ≥ α-cyclodextrin ≥ β-cyclodextrin. On the basis of the yield pressure values and the Heckel plot profiles, all the cyclodextrins were highly prone to plastic deformation. Cyclodextrins showed time-dependent consolidation behaviour manifested as increased yield pressure with decreased contact time.

A ratio was defined between the SRS of fast elastic recovery and total elastic recovery. The two materials with high ratios, HP-β-cyclodextrin and β-cyclodextrin, were especially prone to fast elastic recovery with increasing punch velocities; γ-cyclodextrin and α-cyclodextrin had low values and were less prone. On the basis of this parameter it might be possible to categorize pharmaceutical materials according to capping tendency.

Cyclodextrins are cyclic oligosaccharides produced by enzymatic degradation of starch. Depending on the reaction conditions, cyclodextrins typically contain six, seven or eight glucose units, connected by α-(1,4) bonds; these are known as α-, β- and γ-cyclodextrins, respectively. The resulting ring is very hydrophilic externally and relatively apolar internally. One of the most interesting properties of cyclodextrins is their ability to form inclusion complexes with a wide variety of molecules. The cavity size limits the size of the molecule that can be encapsulated; in this respect β- and γ-cyclodextrins have been the most suitable sizes for pharmaceutical purposes. Numerous derivatives of cyclodextrins have been synthesized, by alkylation or substitution of hydroxyl groups, to modify water solubility (Frömming & Szejtli 1994); hydroxypropyl-β-cyclodextrin is, perhaps, the most utilized derivative. In the field of pharmaceutics, applications of the cyclodextrin drug complexes have been essentially to improve molecular stability and in the improvement of drug bioavailability (Duchêne & Wouessidjewe 1990a, b). Pitha & Pitha (1985) suggested that freeze-drying cyclodextrin complexes of steroids resulted in non-hygroscopic powders that were suitable for direct compression into tablets. In published studies the compression of tablets has been typically performed under only one condition (i.e., constant setting for applied pressure, profile type, compression speed) and in most cases using a hydraulic press (Horiuchi et al 1991) or a single-station, hand-operated unit (Pitha & Pitha 1985).

Correspondence: A. Muñoz-Ruiz, Department of Pharmaceutical Technology, Facultad de Farmacia, C/Tramontana S/N 41012 Seville, Spain.

Little is known about consolidation mechanisms involved in the tablet compression of cyclodextrins. Further understanding of volume reduction mechanisms may be a valuable aid in the development of robust tablet formulations and in improvement of quality and efficacy in manufactured cyclodextrin tablets. The purpose of this work was to study particle and powder properties of α-, β-, and γ-cyclodextrins and hydroxypropyl-β-cyclodextrin, and their effect on the behaviour of cyclodextrins under compression.

Materials and Methods

Materials

The cyclodextrins α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin were manufactured by Cyclolab, Budapest, Hungary, and hydroxypropyl-β-cyclodextrin (Encapsin HPB) was manufactured by Janssen Biotech, Stockholm, Sweden. According to the manufacturer the substitution of hydroxyl groups in HP-β-cyclodextrin was random, the average substitution value being 18·6%. The samples of cyclodextrins were equilibrated over 22% relative humidity at 20°C for 4 days before testing. The water contents, measured by Karl Fisher titrimetry, were 9·6, 13·3, 8·5 and 4·9% for α-, β, and γ-cyclodextrins and HP-β-cyclodextrin, respectively.

Methods

Scanning electron micrographs of the particulate samples, covered with gold, were obtained with a Jeol JSM-35 electron microscope (Jeol, Tokyo, Japan) using an accelerating voltage of 15 keV. The scanning electron micrographs were taken at a magnification appropriate for particle size. The particle-size

distribution of the cyclodextrins was examined using the digitized images of the micrographs where the dimensions that contained approximately four hundred particles were analysed. The equivalent diameter used was the Martin diameter, determined from the chord parallel to the direction of measurements which bisected the projected area (Rumpf 1990). The shape factor, defined as the ratio between equivalent diameters (Rumpf 1990), was calculated as X_a/X_{pe}, where X_a was the equivalent diameter of the sphere having the same area, and X_{pe} the equivalent diameter of the sphere having the same perimeter. The values of the shape factor were larger as the particle shape became more regular. The relationship $X_a \leqslant X_{pe}$ always applied where the equal sign was invalid for spherical particles. The loose and tap densities of the powders were determined by tamping a suitable amount of powder in a 10-mL glass cylinder. After observing the weight and loose volume, the cylinder was mechanically tapped by means of a modified Erweka SVM 2DW (Erweka, Heusenstamm, Germany) motor at 60 rev min^{-1} for 10 min. After tapping, the volume of the powder column was used to calculate the tapped density, measurements being made in triplicate. Compressibility was calculated as: (tapped density-loose density)/loose density, and expressed as a percentage.

The material densities of the powders were determined, in triplicate, by means of an air comparison pycnometer (Quantachrome Multipycnometer, Syosset, NY, USA) using helium as inert gas. The compression was performed using a compaction simulator (Puuman Ltd, Kuopio, Finland). Quantities of powder were manually placed in the die (10 mm diameter) to produce tablets with a theoretical thickness of 1·4 mm at zero porosity. Single-sided saw-tooth profiles, i.e. constant velocity punch movement, were selected. Punch velocities were 3 and 300 mm s^{-1}. At both velocities, flat tablets of cyclodextrins were compressed at 25, 75, 100, 150 and 200 MPa of applied pressure. The tablets in the compaction experiments were made with die-wall lubrication. This was accomplished by manually treating the punch and die wall with a solution of magnesium stearate (5% w/v) in acetone (using a cotton swab) before every test. In every case, four parallel tablets were compressed. During compression, upper and lower punch forces and displacements were monitored. Evaluation of the consolidation mechanism of the powders was made on the basis of the Heckel equation (Heckel 1961a, b):

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

which relates the packing fraction, or relative density, D, (i.e. the ratio between apparent density of a powder bed and the material density) to the applied pressure, P. The slope of the straight line portion, K, was generally expressed as a reciprocal, and was then referred to as the mean yield pressure. Two different methods were used for obtaining data from the Heckel treatment. The first was the tablet-in-die method, in which the applied pressure and packing fractions of the powder column were determined during the loading phase of the compression process (upward part of the Heckel plot). The Heckel plot measured during the upward movement of the punch from the die (downward part of the Heckel plot) was used for describing the fast elastic recovery of the compact during the compression process (Duberg & Nyström 1985).

The second method was the ejected-tablet method in which the packing fractions were determined by measuring the dimensions of the tablets 24 h after ejection from the die. The reciprocal of the difference between the reciprocals of the Heckel upward plot slopes, obtained using the two procedures mentioned above, was used as a parameter to describe the tendency of a material to deform elastically. This consisted of both the fast and slow elastic recoveries of the compact (Paronen & Juslin 1983; Paronen 1992). Time-dependent behaviour of the cyclodextrins under compression was evaluated on the basis of the variation of Heckel plot gradient with different punch velocities. Roberts & Rowe (1985, 1986) defined a strain-rate sensitivity (SRS) index, which is calculated from the equation:

$$(P_{y2} - P_{y1})/P_{y2} \times 100\ (\%) \quad (2)$$

In this study, P_{y1} is the yield pressure at 3 mm s^{-1} (slow speed) and P_{y2} the yield pressure at 300 mm s^{-1} (fast speed).

Results and Discussion

Particle properties

Fig. 1 shows scanning electron micrographs of the cyclodextrins examined. The particle shape of the α-, β- and γ-cyclodextrins was more or less acicular. Large particles of β-cyclodextrin had large cracks. The micrographs of α-cyclodextrin and γ-cyclodextrin showed small particles adhering to the surfaces of larger ones. HP-β-cyclodextrin was a typical spray-dried product, consisting of very small particles generally having a round shape, smooth surfaces and big holes covered by smaller particles. Table 1 shows the mean particle sizes and shape factors of the cyclodextrins. It can be stated, on the basis of the Martin equivalent diameters and size distributions, that γ-cyclodextrin and HP-β-cyclodextrin were materials consisting of very small particles. The particle size distribution was, however, wider for γ-cyclodextrin. β-Cyclodextrin consisted of much larger particles than any of the other cyclodextrins. α-cyclodextrin was intermediate in particle size.

According to the particle shape factor, HP-β-cyclodextrin showed the highest regularity in shape, as expected, because of the spherical form of the particles (Fig. 1). There were, however, no great differences between the shape factors of the other cyclodextrins; the observed ranking order of increasing regularity was α-cyclodextrin < β-cyclodextrin < γ-cyclodextrin. The particles of HP-β-cyclodextrin showed more uniformity in shape than those of the other cyclodextrins. This may also be noticed from the lower value of the standard deviation of particle shape factor in Table 1.

Powder properties

The smaller the compressibility value, the less dense the powder column becomes during tapping and the less sensitive it should be to factors that cause flowability to deteriorate (e.g. induced density differences in the powder column) (Carr 1965). Higher compressibilities were found for HP-β-cyclodextrin and especially for γ-cyclodextrin (Table 2), which were the materials consisting of small particles (Table 1). The lower compressibility of HP-β-cyclodextrin, compared with that of γ-cyclodextrin, may be explained by the more regular particle shape of HP-β-cyclodextrin. The lowest compressibility was found for β-cyclodextrin, which consisted of the largest particles. β-Cyclodextrin reached a relatively dense forceless packing during filling of the cylinder. This is also reflected in

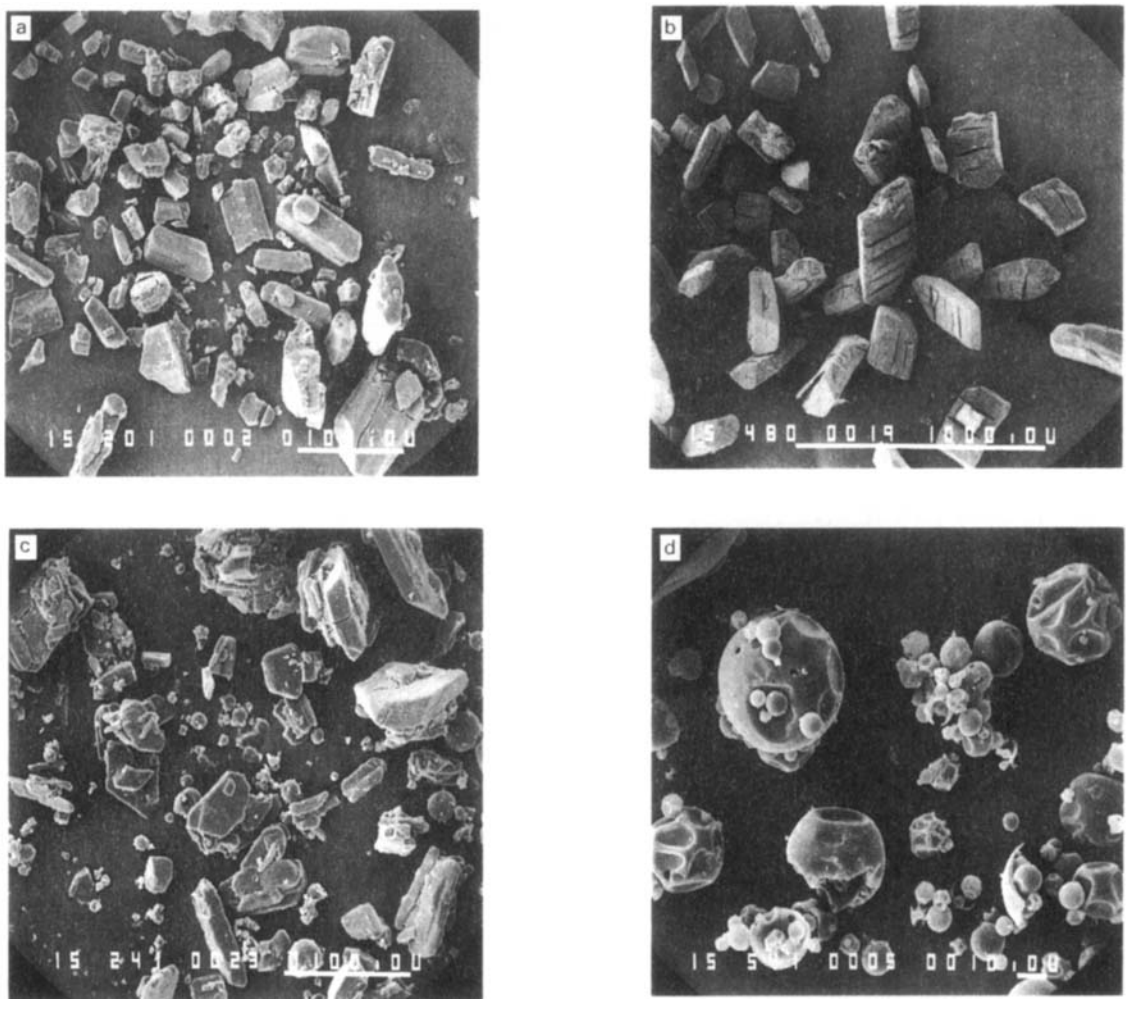

FIG. 1. Scanning electron micrographs of the cyclodextrins: (a) α-cyclodextrin (bar = 100 μm); (b) β-cyclodextrin (bar = 1000 μm); (c) γ-cyclodextrin (bar = 100 μm); (d) HP-β-cyclodextrin (bar = 10 μm).

Table 1. Mean particle size and shape factor (both ± s.d.) of cyclodextrins.

Material	Martin equivalent diameter (μm)	Particle shape factor
α-Cyclodextrin	25·0 ± 20·8	0·874 ± 0·055
β-Cyclodextrin	148·2 ± 83·5	0·892 ± 0·054
γ-Cyclodextrin	11·7 ± 14·4	0·918 ± 0·051
HP-β-cyclodextrin	10·3 ± 7·3	0·951 ± 0·035

its high loose-density value in Table 2. The compressibility value for the β-cyclodextrin from Cyclolab was lower than those obtained by Shangraw et al (1992) for other different available cyclodextrins; these were 20% higher. This different behaviour would be expected because of the difference in particle sizes—that of the β-cyclodextrin from Cyclolab was almost five times greater than those of the others (Shangraw et al 1992).

General shape of Heckel plots

The linear portion of the Heckel plot began after an initial curvature in the pressure range near 100 MPa for the tablet-in-die method (Fig. 2). The least-squares method was used to obtain accurate slope and intercept values.

Table 2. Densities (g mL^{-1} ± s.d.) and compressibility of the cyclodextrins studied.

Cyclodextrin	Material	Loose	Tap	Compressibility (%)
α-Cyclodextrin	1·517 ± 0·006	0·526 ± 0·021	0·645 ± 0·010	18·4
β-Cyclodextrin	1·470 ± 0·015	0·714 ± 0·038	0·800 ± 0·009	10·7
γ-Cyclodextrin	1·478 ± 0·008	0·417 ± 0·017	0·571 ± 0·012	27·1
HP-β-cyclodextrin	1·398 ± 0·028	0·263 ± 0·022	0·344 ± 0·025	23·7

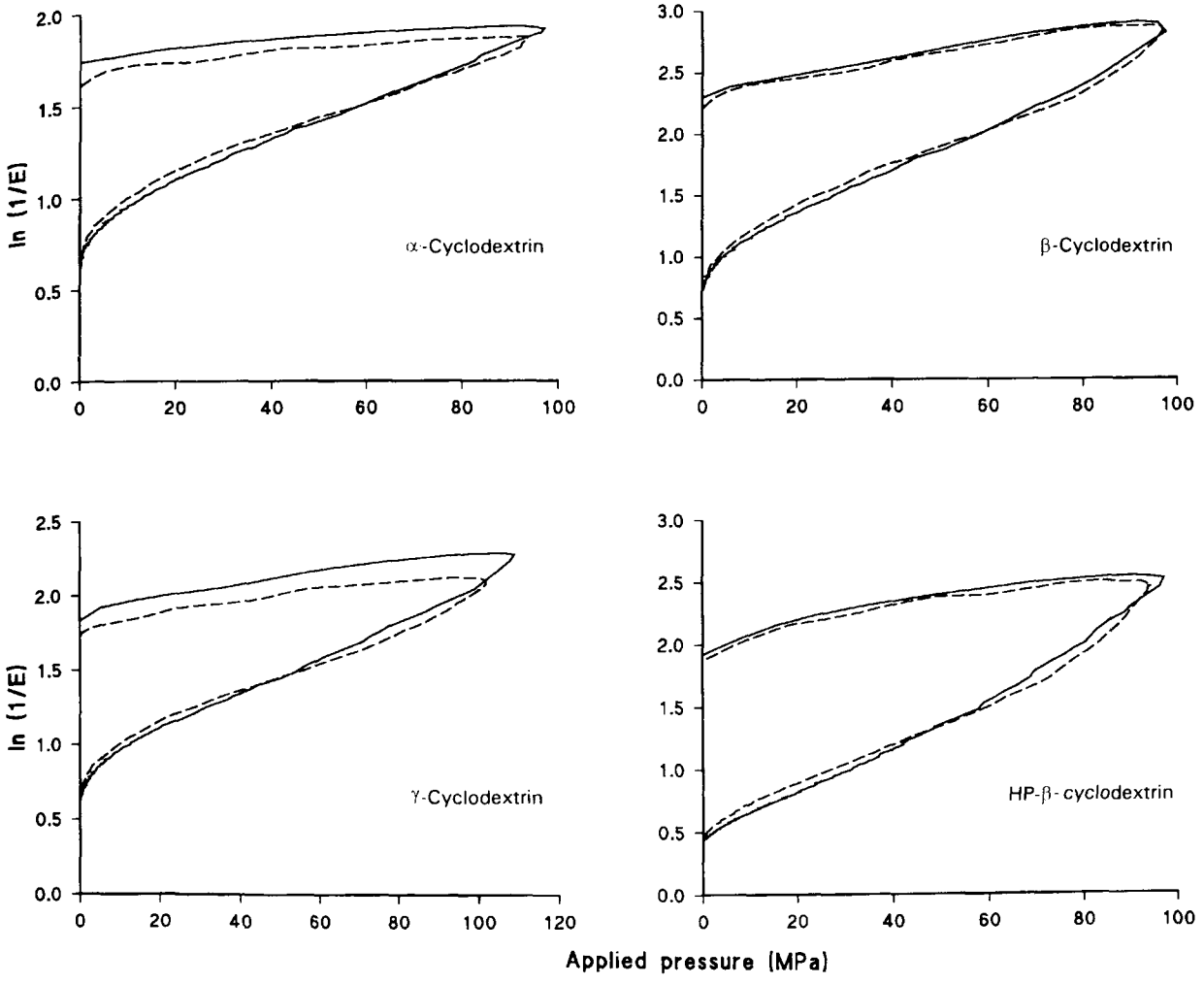

FIG. 2. Typical examples of Heckel tablet-in-die plots for cyclodextrins; the continuous line represents a punch velocity of 3 mm s^{-1} and the discontinuous line one of 300 mm s^{-1}.

The linear portion of the Heckel function was determined on the basis of the best fit to the linear model from consecutive data. The criterion to estimate the fit was obtained from the F ratio between the model and the residual. The linear portion coincided with the group of successive data with the highest F-ratio. The linear portion of the Heckel function was determined separately from the upward and downward parts of all the individual plots. The least-squares method was also employed in the ejected-tablet method, taking into account all measured points within the pressure range 25–200 MPa (Fig. 3). The function values obtained from the dimensions of ejected tablets followed the Heckel equation better than data from the tablet-in-die method.

Heckel plots are strongly curved only at the beginning. The very short initial curvature of the Heckel plot has been related to plastically deforming materials (Doelker 1988). Thus, according to the shape of the tablet-in-die Heckel plots in Fig. 2, all cyclodextrins exhibited a predominant compaction mechanism of plastic deformation. The shortest curvature was found for HP-β-cyclodextrin, which had the smallest and most regular particles.

The powder column of cyclodextrins became more dense in the beginning of tableting process (at low pressures) at high velocity rather than low velocity. This kind of behaviour has seldom been reported. Maganti & Celik (1993) observed similar behaviour, however, for pellets containing 80% microcrystalline cellulose. The same tendency was observed for all the cyclodextrins in this study, and the results obtained from the ejected-tablet method (Fig. 3) support this observation. To achieve close packing, considerable slippage and rearrangement of the particles of materials such as maize starch would occur before the onset of plastic deformation (Roberts & Rowe 1986). In this sense photomicrographs presented by Down (1983) over the pressure range 0–35 MPa have shown considerable movement of the particles. The non-specific intermolecular forces between adjacent particles is one of the dominating types of bond causing adherence of particles in compressed powders (Hiestand & Smith 1984). This is especially true for dry binders, such as microcrystalline cellulose, modified starches and lactose (Nyström et al 1993). These forces could be facilitated by the rapid movement of particles during fast compression. Although the induced stress

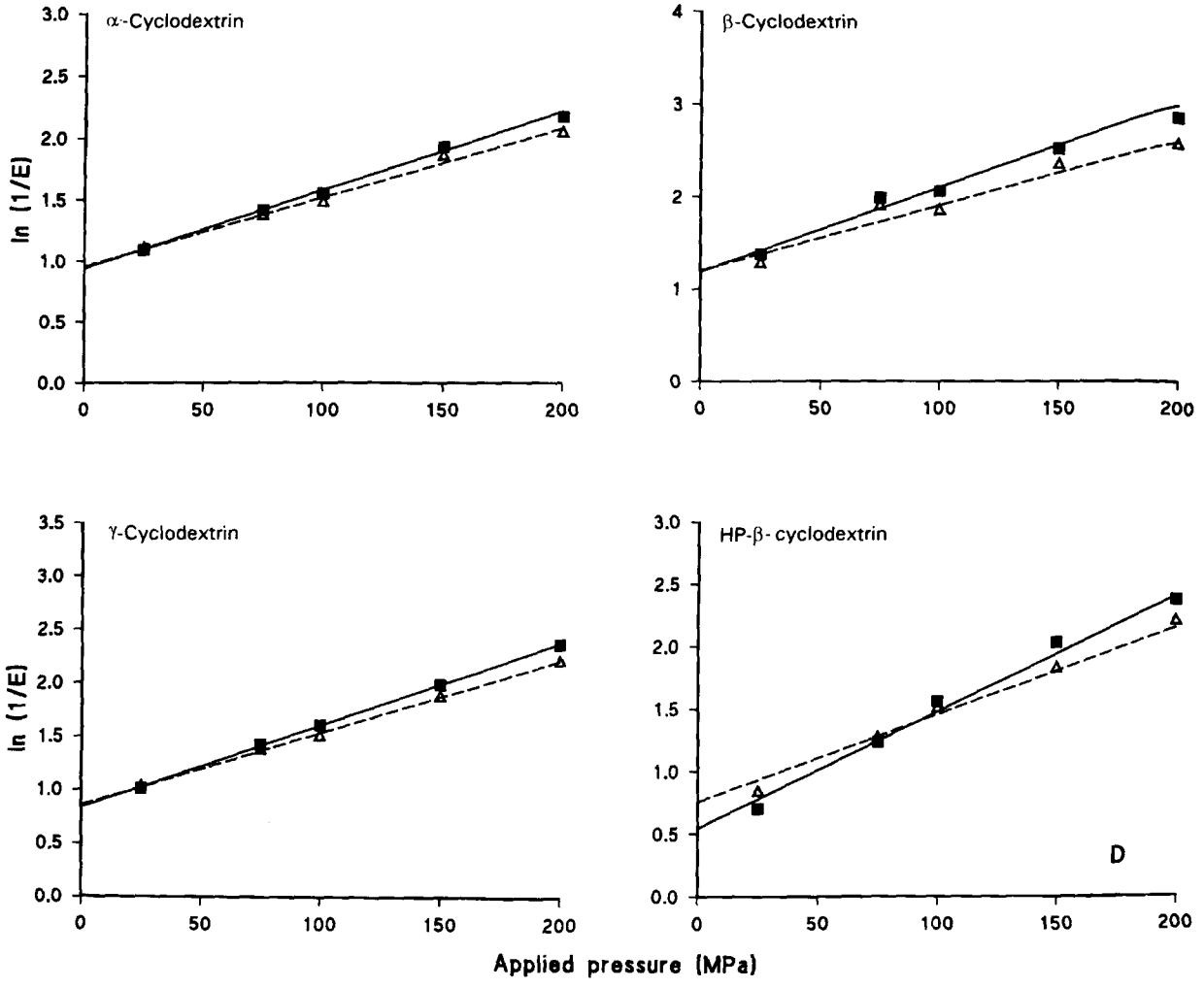

FIG. 3. Heckel ejected-tablet plot for cyclodextrins; the continuous line represents a punch velocity of 3 mm s^{-1} and the discontinuous line one of 300 mm s^{-1}.

level in the whole compact is low, the multiplier effect, because of the viscoelasticity of the materials at a high compression speed on inter-particle attraction, might be sufficient to cause isthmus formation (Hiestand 1991). Thus, besides effective rearrangement of particles, localized plastic deformation on particle surfaces might also enhance densification at high speed compression. This phenomenon is perhaps possible only with easily deforming materials like cyclodextrins.

At higher pressures, however, higher densification of cyclodextrins occurs during slow compression, firstly, because of the predominance of frictional and cohesive forces between particles during fast compression and secondly, owing to the reduced volume which restricts the freedom of particle movement in the powder bed. The most remarkable difference in Heckel plots with slow and fast compression was noticed with HP-β-cyclodextrin. This material consisted of the smallest particles with a high inter-particle area of contact. Thus, the friction effect might be more prominent in this material than in the other cyclodextrins studied.

The downward portion of tablet-in-die Heckel plot (Fig. 2) illustrates the volume expansion of cyclodextrins. Because of the wide densification scale of the whole compression process, it is not possible to see clearly the differences in the gradient of volume expansion during decompression. Some differences were, however, obtained by calculation methods.

Packing fractions in the bulk stage

The packing fractions are given in Table 3. The packing fraction of a powder, D_0, is the relative density of the powder bed at the point where a measurable force of 10 N appears. The tendency of the materials toward densification at the very beginning of the compression process was the same as that observed for the loose and tap densities; i.e. as particle size decreased the number of contact points increased. This resulted in higher inter-particle cohesive forces that would tend to oppose dense packing conditions (Fell & Newton 1971; York 1978; Paronen & Juslin 1983; Roberts & Rowe 1985). Thus, β-cyclodextrin becomes more dense in the pre-compression phase, particularly during die filling, and also in the early stages of downward movement of the upper punch into the die. Large particles of β-cyclodextrin were free-flowing, and obviously rather uncohesive. The small particles of HP-β-cyclodextrin, forming a more cohesive powder column, however, showed the opposite behaviour. α-Cyclodextrin and γ-cyclodextrin were intermediate materials both in particle size and in behaviour during the early stages of the compression

Table 3. Packing fractions obtained from Heckel plots using different methods (fast 300 mm s^{-1}, slow = 3 mm s^{-1}).

Material	Compression speed	Compression phase				
		Tablet-in-die method			Ejected-tablet method	
		D_0	D_A	D_B	D_A	D_B
α-Cyclodextrin	Slow	0·486	0·604	0·118	0·609	0·123
	Fast	0·446	0·636	0·190	0·615	0·169
β-Cyclodextrin	Slow	0·541	0·662	0·121	0·695	0·154
	Fast	0·515	0·689	0·174	0·699	0·184
γ-Cyclodextrin	Slow	0·476	0·596	0·120	0·565	0·089
	Fast	0·437	0·639	0·202	0·574	0·137
HP-β-cyclodextrin	Slow	0·342	0·372	0·029	0·420	0·077
	Fast	0·325	0·452	0·127	0·531	0·206

process when compared with β-cyclodextrin and HP-β-cyclodextrin. For all the cyclodextrins, D_0 values tended to decrease slightly with increasing punch velocity, as shown in Table 3. This observation supports the finding by Roberts & Rowe (1985, 1986) for numerous pharmaceutical materials.

Packing fractions in the compression stage

D_A values describe the portion of densification which results from die filling and particle rearrangement. The extent of this phase for the different cyclodextrins showed the same trend as packing fractions in the bulk stage. Here, the lowest value for D_A was from HP-β-cyclodextrin, the highest from β-cyclodextrin, and intermediate values from α-cyclodextrin and γ-cyclodextrin. The differences in particle size of the cyclodextrins studied, and hence the differences in area for contact between particles, explains the different resistance of particles to particle movement. D_A tended to increase with punch velocity, both in the tablet-in-die (compression phase) and ejected-tablet methods, as can be seen in Table 3 and Figs 2 and 3. The increase in D_A with punch velocity in this study was, however, in agreement with the results of Rees & Rue (1978) who used the ejected-tablet method for maize starch, and of Roberts & Rowe (1985) who used the tablet-in-die method for the same material. The cyclodextrins in this study and the starch are both ductile, soft and plastically deforming materials. It seems realistic to suppose that the enhanced densification at the beginning of compression process, under high velocity, is a real phenomenon.

D_B is obtained from the difference between D_A and D_0 and represents the densification obtained as a result of particle rearrangement. Low D_B values are typical of plastic materials (Doelker 1988; Nyström et al 1993). According to this, HP-β-cyclodextrin showed the highest plasticity, which was also supported by the shape difference of the Heckel plots in Fig. 2. The more spherical shape of the particles of HP-β-cyclodextrin, however, also tended to reduce this value (York 1978). D_B tended to increase with punch velocity. This could be because of the subsequent transition of the theoretical point of densification, at which the deformation of the particles begins in fast compression, with regard to slow compression.

No differences of note were found between the use of the tablet-in-die and ejected-tablet methods for determining the packing fraction by means of the Heckel equation; these results support the findings of Paronen & Juslin (1983) and Humbert-Droz et al (1982).

The constants of deformation

The tendency of the materials to deform, both plastically and elastically, is shown by the reciprocal of the slope obtained from the upward portion of the Heckel plot when using the tablet-in-die method (K_d values in Table 4). The ranking of the materials, according to their tendency toward total deformation

Table 4. Yield pressure (MPa) and correlation coefficient from the Heckel plots (fast 300 mm s^{-1}, slow = 3 mm s^{-1}).

Material	Compression speed	Tablet-in-die				Ejected-tablet (plastic deformation)		Combined (elastic deformation)
		Compression phase (total deformation)		Decompression phase (fast elastic deformation)				K_{et}
		K_d	r	K_{ef}	r	K_P	r	
α-Cyclodextrin	Slow	106·8	0·9991	1493·2	0·9469	158·7	0·9976	326·6
	Fast	128·9	0·9988	1224·4	0·9634	179·8	0·9943	455·3
β-Cyclodextrin	Slow	65·2	0·9991	455·9	0·9672	108·9	0·9974	162·5
	Fast	77·2	0·9981	419·3	0·8064	141·0	0·9998	170·5
γ-Cyclodextrin	Slow	96·2	0·9996	651·2	0·9403	128·7	0·9998	380·9
	Fast	119·2	0·9972	576·8	0·9514	147·6	0·9993	619·5
HP-β-cyclodextrin	Slow	46·7	0·9993	310·1	0·9429	107·3	0·988	482·7
	Fast	69·1	0·9997	250·3	0·8981	143·1	0·9887	133·6

Table 5. Strain rate sensitivity.

Material	Tablet-in-die method		Ejected-tablet method	Combined method
	Compression phase Total deformation	Decompression phase Fast elastic deformation	Plastic deformation	Total elastic deformation
α-Cyclodextrin	17·1	−18·0	11·7	28·3
β-Cyclodextrin	15·5	−8·0	22·8	4·4
γ-Cyclodextrin	19·3	−11·4	12·8	62·6
HP-β-cyclodextrin	32·4	−19·2	25·0	8·1

was: HP-β-cyclodextrin > β-cyclodextrin > γ-cyclodextrin > α-cyclodextrin. The values of K_d are of the same magnitude as those in the studies of Muñoz-Ruiz et al (1993) and Mollan & Celik (1993). These studies used the tablet-in-die method for directly compressible maltodextrins. The K_d found by Shangraw et al (1992) for β-cyclodextrin using an instrumented single-punch tablet press (68·4 MPa) was between the values found in this study at slow speed (65·2 MPa) and fast speed (77·2 MPa).

The tendency of a material to deform plastically is shown by the reciprocal of the Heckel plot slope (Fig. 3), obtained using the ejected-tablet method (K_p values in Table 4). The practical importance of K_p is that it gives an impression of the ease of plastic deformation and of the softness of the material. A lower value of K_p tends to favour plastic deformation. The order of the materials, according to this permanent densification tendency, was the same as mentioned above for K_d. On this basis, HP-β-cyclodextrin and β-cyclodextrin were the softest materials. The behaviour of HP-β-cyclodextrin and β-cyclodextrin was, however, even more similar when plastic deformation was considered. The differences obtained by these two methods indicate that great differences exist in the tendencies of these materials to recover elastically.

The reciprocal of the difference between reciprocals of the Heckel upward plot slopes, obtained from the two methods mentioned above, has been used as a parameter to describe the tendency of a material to deform elastically (K_{et} values in Table 4). According to this parameter, HP-β-cyclodextrin in particular, but also β-cyclodextrin, were clearly more susceptible to elastic recovery than α-cyclodextrin and γ-cyclodextrin. The tendency of the material to immediate elasticity is shown by the reciprocal of the downward part of the Heckel plot using the tablet-in-die method (K_{ef} values in Table 4). According to these results, rapid elastic recovery during the compression process seemed to be a particular characteristic of HP-β-cyclodextrin. The elasticity of α-cyclodextrin seemed to be negligible during this phase. The behaviour of β-cyclodextrin and γ-cyclodextrin during the decompression phase of the compaction process was intermediate between those of α-cyclodextrin and HP-β-cyclodextrin.

Strain rate sensitivity

Some indication of the time-dependent behaviour of materials under compression can be obtained by using the strain-rate sensitivity (SRS) equation (Roberts & Rowe 1985). This equation had only been used for the slope of the upward part of the Heckel plot with the tablet-in-die method. In this paper, we used this equation for the different Heckel methods previously described. The calculated SRS values for the cyclodextrins under study are given in Table 5. The materials with high SRS values were those materials that deform plastically (Rees & Rue 1978). The order of ranking in SRS of total deformation was HP-β-cyclodextrin ≫ γ-cyclodextrin ≥ α-cyclodextrin ≥ β-cyclodextrin. With the exception of β-cyclodextrin, this order compares well with the order of ranking of increasing yield pressures of total deformation. When only plastic deformation is taken into account, however, the result showed that β-cyclodextrin was more sensitive to strain rate than α-cyclodextrin and γ-cyclodextrin, with the yield pressure of plastic deformation also being lower than those for α-cyclodextrin and γ-cyclodextrin.

The SRS values of fast elastic recovery in Table 5 are not related to the yield pressures of fast elastic recovery in Table 4. The negative SRS values are indicative of more pronounced elastic recovery of the compact in the die during slow compression than during fast compression. The lowest sensitivity of fast elastic recovery to punch velocity was found for β-cyclodextrin and γ-cyclodextrin. The SRS of total elastic deformation were positive values, indicating a more pronounced total elasticity of the cyclodextrin compacts after slow compression than after fast compression. The velocity-dependence seemed to be higher for materials having a higher yield pressure of elastic deformation (i.e., materials with a lower tendency toward elastic deformation). Thus, γ-cyclodextrin and α-cyclodextrin had the highest SRS indices and the highest yield pressures, whereas HP-β-cyclodextrin and β-cyclodextrin had the lowest SRS indices and the lowest yield pressures.

The relative increase of elasticity during decompression (fast elastic recovery) with increasing punch velocity appeared to be an important factor for the capping tendency of compacts (Garr & Rubinstein 1991). We have defined a ratio of the SRS for fast elastic recovery to that for total elastic recovery, with the intention of describing the sensitivity of the compact to fast elastic recovery during decompression when compared with total recovery both during and after compression. The ratios calculated for α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and HP-β-cyclodextrin were 0·636, 1·818, 0·182 and 2·370, respectively. It was possible to categorize the materials on the basis of this parameter. Fast elastic recovery with increasing punch velocities was a particular characteristic of materials with high values, i.e. HP-β-cyclodextrin and β-cyclodextrin, whereas fast elastic recovery was less likely for materials with low values, i.e. γ-cyclodextrin and α-cyclodextrin, although with these elastic recovery was still possible after the compression process with increasing velocities. γ-cyclodextrin and α-cyclodextrin could not be related by capping tendency. This,

at least, correlates well with the capping tendency observed in this study. The utility of this novel parameter needs further experimentation.

Acknowledgements

The authors thank the Ministerio de Educación y Ciencia, Spain for the mobility grant, the Technology Development Centre of Finland (TeKes) and the Research and Science Foundation of Farmos, Finland for financial support, and Ms M. Simonen and Ms M de la Matta (University of Kuopio, Finland) for skilful experimental assistance.

References

Carr, R. L. (1965) Classifying flow properties of solids. Chem. Eng. 72: 69–72

Doelker, E. (1988) Recent advances in tableting science. Boll. Chim. Pharm. 127: 37–49

Down, G. R. B. (1983) Localized particle fracture during compression of materials expected to undergo plastic deformation. Powder Technol. 35: 167–169

Duberg, M., Nystrom, C. (1985) 8 Nordiska Symposiet für Farmaciläjrare, Turku, Finland, 11–12 June 1985, Abstract No. 26

Duchêne, D., Wouessidjewe, D. (1990a) Physicochemical characteristics and pharmaceutical uses of cyclodextrin derivatives, part I. Pharm. Technol. Int. 2 (June): 21–29

Duchêne, D., Wouessidjewe, D. (1990b) Physicochemical characteristics and pharmaceutical uses of cyclodextrin derivatives, part II. Pharm. Technol. Int. 2 (August): 22–30

Fell, J. T., Newton, J. M. (1971) Effect of particle size and speed of compaction on density changes in tablets of crystalline and spray-dried lactose. J. Pharm. Sci. 60: 1866–1869

Frömming, K. H., Szejtli, J. (1994) Cyclodextrin derivatives. In: Frömming, K. H., Szejtli, J. (eds) Cyclodextrins in Pharmacy. Kluwer Academic, Dordrecht, pp 19–32

Garr, J. S. M., Rubinstein, M. H. (1991) An investigation into capping tendency of paracetamol at increasing speed of compression. Int. J. Pharm. 72: 117–122

Heckel, R. W. (1961a) Density-pressure relationship in powder compaction. Trans. Metall. Soc. AIME 221: 671–675

Heckel, R. W. (1961b) An analysis of powder compaction phenomena. Trans. Metall. Soc. AIME 221: 1001–1008

Hiestand, E. N. (1991) Tablet bond. 1. A theoretical model. Int. J. Pharm. 67: 217–229

Hiestand, E. N., Smith, D. P. (1984) Indices of tableting performance. Powder Technol. 38: 145–159

Horiuchi, Y., Abe, K., Hirayama, F., Uekama, K. (1991) Release control of theophylline by cyclodextrin derivatives: hybridizing effect of hydrophilic, hydrophobic and ionizable cyclodextrin complexes. J. Control. Release 15: 177–183

Humbert-Droz, P., Mordier, D., Doelker, E. (1982) Méthode rapide de détermination du comportement; à la compression pour des études de préformulation. Pharm. Acta Helv. 57: 136–143

Maganti, L., Celik, M. (1993) Compaction studies on pellets. I uncoated pellets. Int. J. Pharm. 95: 29–42

Mollan, M. J., Celik, M. (1993) Characterization of directly compressible maltodextrins manufactured by three different processes. Drug Dev. Ind. Pharm. 19: 2335–2358

Muñoz-Ruiz, A., Monedero, M. C., Velasco, M. V., Jiménez-Castellanos, M. R. (1993) Physical and rheological properties of raw materials. S. T. P. Pharm. Sci. 3: 307–312

Nyström, G., Alderborn, G., Duberg, M., Karehill, P. G. (1993) Bonding surface area and bonding mechanisms—two important factors for the understanding of powder compactability. Drug Dev. Ind. Pharm. 19: 2143–2196

Paronen, P. (1992) Heckel plots as indicators of elastic properties. In: Rubinstein, M. (ed.) Tablet Technology, vol. 1, Ellis Horwood, Chichester, pp 139–144

Paronen, P., Juslin, M. (1983) Compressional characteristics of four starches. J. Pharm. Pharmacol. 35: 627–635

Pitha, J., Pitha, J., (1985) Amorphous water-soluble derivatives of cyclodextrin: nontoxic dissolution enhancing excipients. J. Pharm. Sci. 74: 987–990

Reer, D. E., Rue, P. J. (1978) Time-dependent deformation of some direct compression excipients. J. Pharm. Pharmacol. 30: 601–607

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

Roberts, R. J., Rowe, R. C. (1986) 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: 567–571

Rumpf, H. (1990) The characteristics of system and their changes of state. In: Scarlett, B. (ed.) Particle Technology. Chapman and Hall, London, pp 14–15

Shangraw, R. F., Pande, G. S., Gala, P. (1992) Characterization of the tableting properties of cyclodextrin and the effect of the processing variables on inclusion complex formation, compactability and dissolution. Drug Dev. Ind. Pharm. 18: 1831–1851

York, P. (1978) Particle slippage and rearrangement during compression of pharmaceutical powders. J. Pharm. Pharmacol. 30: 6–10.