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Evaluation of the Compression Behavior of Paracetamol Tablets Produced by Dispersion in β-Cyclodextrin. Part I: Scanning Electron Microscopic Study of Tablets

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Abstract. The compression behaviour of three powder products of Paracetamol–β-cyclodextrin solid dispersions (PAR-β-CD SD) and PAR alone were evaluated using the method of scanning electron microscopy (SEM). The four powder products were: PAR, PAR–β-CD physical mixture, kneaded solid dispersion of PAR–β-CD and spray dried solid dispersion of PAR–β-CD (PAR–β-CD ratio of 1 : 1 w/w). By observing the surface, side and broken surface of each tablet sample under different magnifications the compression behaviour, mechanism of consolidation and deformability of particles were evaluated. PAR alone and the PAR–β-CD physical mixture were compressed by the brittle fracture mechanism; the PAR–β-CD kneaded solid dispersion showed a good plastical deformation. With PAR–β-CD spray dried solid dispersion a good plastic deformation and mechanism of cool sintering were postulated. The influence of β-CD on the compression behavior of the PAR was proved. The results obtained by the SEM method are well correlated with physicopharmaceutical parameters (crushing strength, disintegration time, friability, elastic recovery and tensile strength) of the tablets.

Key words: Paracetamol, β-cyclodextrin, solid dispersions, tablet, scanning electron microscopy, compression behaviour.

1. Introduction

The use of β-cyclodextrin (β-CD) to enhance the solubility and the rate of dissolution of poorly soluble drugs has already been described [1,2]. Some inclusion complexes of Paracetamol (PAR) and β-CD were prepared and the increase of the dissolution rate of PAR from these complexes was evaluated [3]. Instead of PAR/β-CD inclusion complexes (molar ratio 1 : 1), some solid dispersions of PAR/β-CD (weight ratio 1 : 1) were prepared, and enhancement of the solubility and dissolution rate of PAR was reported [4]. The morphological and rheological investigation of

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the particles of PAR/β-CD solid dispersions indicated good possibilities of β-CD as an auxiliary material in drug formulations [5,6]. Besides that, the possibility of using β-CD as a direct compression filler-binder has recently been reported [7–9]. It has been reported in many publications that the compression behavior of PAR was very poor [10,11]. Therefore, it would be interesting to examine the influence of β-CD on the PAR compression behavior. Here we apply the method of scanning electron microscopy (SEM) to PAR/β-CD solid dispersions. This method is well established in investigations of tablet texture, and the structure and consolidation phenomena in many studies of tablet formulations [12,13].

2. Experimental

2.1. Materials

Paracetamol (Ph.Jug.IV grade) was from Vetprom, Belgrade, Yugoslavia; β-CD was obtained from Cyclolab, Budapest, Hungary; Avice® PH 101 (Fluka), Aci-Di-Sol® (FMC Corporation) and Aerosil 200 (Degussa) were from the manufacturers indicated, and magnesium sterate was Ph.Jug.IV grade.

2.2. Preparation of solid dispersions

Four powder products were studied: *paracetamol*; *paracetamol–βCD physical mixture* (w/w 1 : 1 ratio), mixed in a Turbula (W.E. Bachofen, Basel, Switzerland) for 10 min.; *kneaded solid dispersion of paracetamol–βCD* (w/w 1 : 1); the substances were mixed and kneaded with an equal quantity of solvent (water–ethanol 1 : 1) in a mortar with a pestle. The mass was continuously stirred and evaporated under infrared lamps (4 h) and passed through a sieve (1.2 mm), dried overnight at room temperature (21 °C), and sieved again (1.2 mm); *spray dried solid dispersion of paracetamol–βCD* (w/w 1 1) was produced using a Niro minor atomizer (Copenhagen, Denmark); the substances were dissolved in a solvent (water–ethanol 2 : 1) by heating at 40 °C, and mixed to get a clear solution. The powder–solvent ratio was 1 : 5; during the process of spraying the temperature on the inlet air was 105 $\pm$ 5 °C, while on the outlet was 70 $\pm$ 5 °C, and the feed rate was 2000 g h^{-1}.

2.3. Preparation of tablets

The paracetamol powders (plain, physical mixture and two solid dispersions) were used for tabletting. The tablet composition was: Avicel PH 101 (5%),Aerosil 200 (1%), Ac-Di-Sol (1%), magnesium stearate (1%) calculated on 460 mg of solid dispersions or physical mixture (paracetamol–βCD w/w 1 : 1) or paracetamol. The mass was first mixed in a Turbula mixer for 8 min, and then 2 min with magnesium stearate; the mixture was compressed into tablets with a 12 mm diameter plane-faced punch, at a constant compression force of 10 kN, in a Korsch EKO single punch tablet machine (E. Korsch, Berlin, Germany).

Table I. The physicopharmaceutical characteristics of tablets made by PAR/β-CD solid dispersions.

Samples	Weight (g) r.s.d. (%)	Crushing strength (kp)	Disint. time (s)	Friability (%)	Elastic recovery (%)	Tensile strength (MN m^{-1})
PAR–β physical mixture	0.519 1.691	9.00	27	1.868	0.0550	1.1076
PAR–βCD kneaded solid dispersion	0.524 0.858	17.00	52	1.353	0.0316	2.2688
PAR–βCD spray dried solid dispersion	0.524 1.068	>20.00	896	1.906	0.0852	2.5466

2.4. TESTING OF TABLETS

Weight uniformity was determined according to Ph.Jug.IV. The *crushing strength* of the tablet was determined using a Heberlein tester (Heberlein WTP 3, Zurich, Switzerland). The results quoted are the average values of 10 determinations. The tablet thickness was determined using a micrometer (Somet, Czechoslovakia). The *tensile strength* (σ) was calculated using the equation:

$$\sigma = \frac{2P}{\pi D t} \tag{1}$$

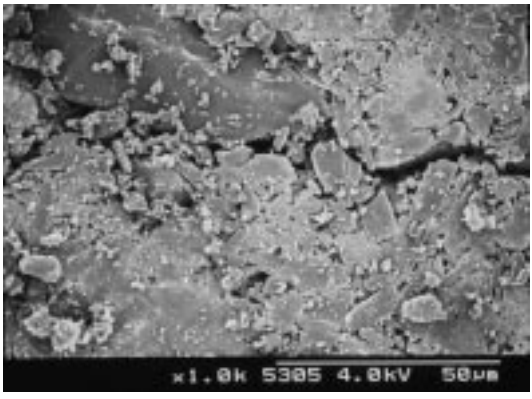
where P is the crushing strength (kp) after 24 h, D is the diameter of tablets (mm), t is the thickness of the tablet after 24 h (mm) [14]. The *elastic recovery* was calculated using the equation:

$$K_R = \frac{H_e - H_c}{H_c} \cdot 100 \tag{2}$$

where H_e is the thickness of the tablet after 24 h (mm), and H_c is the thickness of the tablet immediately after production [15]. The *friability* of the tablet was measured using a Roche friabiliator (10 tablets, 5 min.). The results quoted are the average values of two determinations. The *disintegration time* was determined on each batch of the tablets by the Ph.Jug.IV method using an Erweka disintegration test unit (Disintegration tester ZT3, Erweka, Heusenstamm, Germany). Each tablet formulation was examined by SEM in three positions: the surface, side and broken surfaces under different magnifications. A Tesla BS 300 SEM was used for the study of the tablet texture, with 20 kV accelerating voltage. The surfaces of the sample for electron microscopy were previously made electrically conductive in a sputtering apparatus (Polaron Equipment Ltd,UK) by evaporation of gold.

3. Results

The physicopharmaceutical characteristics of the tablets are presented in Table I. The weight variations of all samples were below 2% and acceptable for conventional



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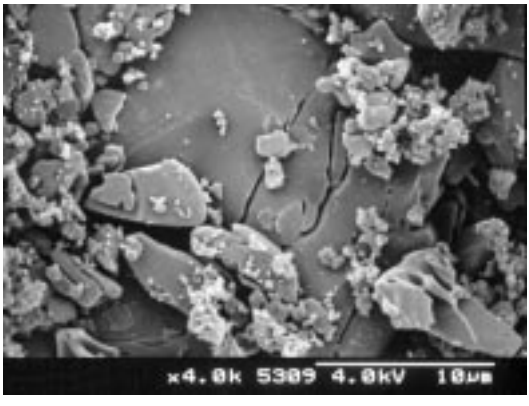
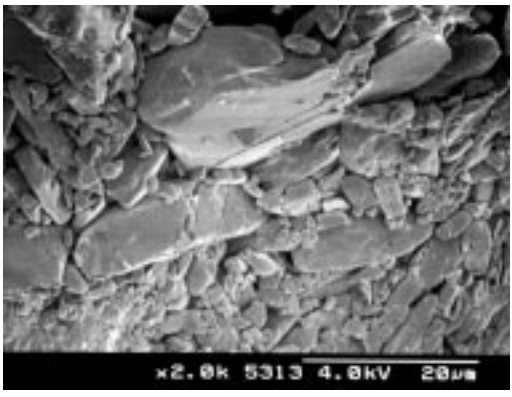


(b)

(c)

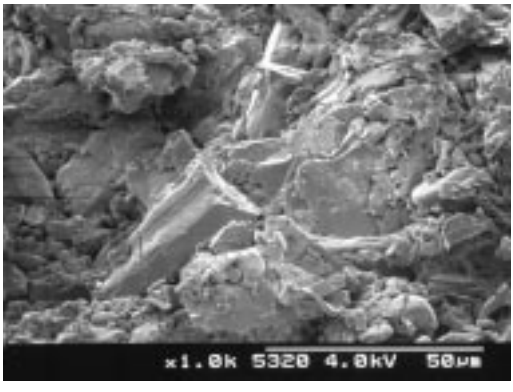
Figures 1a–c.

Figure 1. SEM photos of the surfaces (of the cap a, b and under the cap c, d) of original PAR tablet: (a) magnification 1000; (b) magnification 4000; (c) magnification 1000; (d) magnification 2000.



(d)

Figure 1d.



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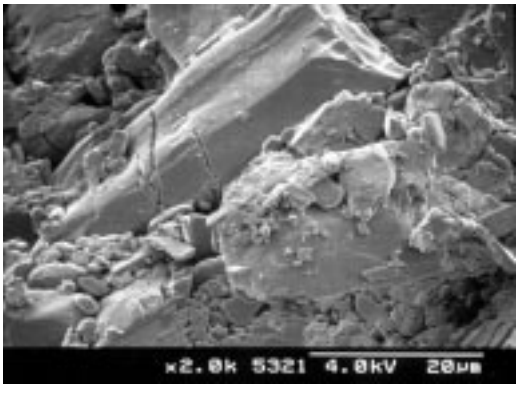


(b)

Figure 2. SEM photos of the broken surface of original PAR tablets: (a) magnification 1000; (b) magnification 2000.

tablet formulation. The crushing strength of the tablets ranged between 9 kp and 20 kp. The friability of all samples was below 2%. The disintegration time for

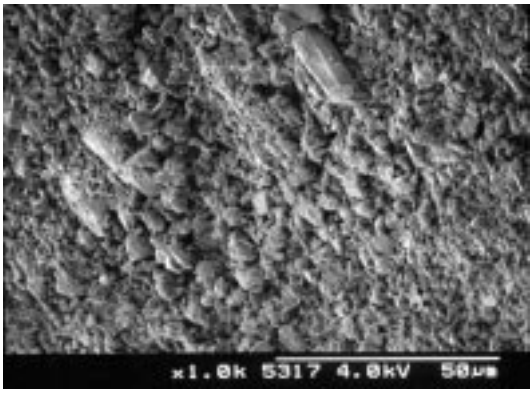


Figure 3. SEM photo of the side of original PAR tablet (magnification 1000)

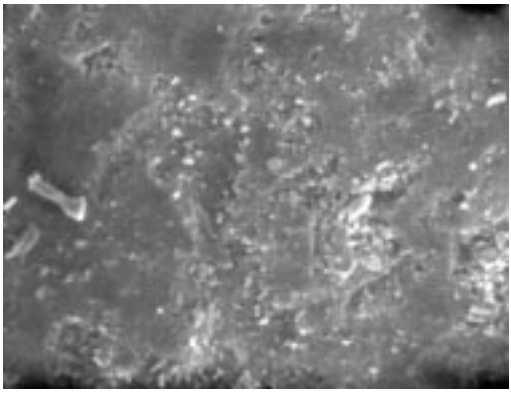
all samples ranged between 27 and 896 s which is acceptable according to the Ph.Jug.IV regulation (900 s for the conventional tablet).

Each tablet sample was viewed microscopically on the surface, the side and the broken surface, using several magnifications. In this way we had the possibility to study the compression behavior, deformability, mechanism of consolidation, inter- or intraparticular bonding, and behavior under decompression, of the different powder materials.

Figure 1 shows the surface of the PAR plain tablet formulation. This composition showed a capping after compression. We investigated the surface of the cap (Figure 1a–b). Secunder cracking can be seen on the surface. It may be a longer slit, but smaller individual particles can be observed (Figure 1a).The plastic deformation of MCC particles can also be seen in some places in the texture at higher magnification. In the SEM picture (Figure 1b) the elastic behavior of the active crystal agent is very clear. We can observe individual particles with irregular form, and a bigger paracetamol crystal with an elastic slit in it. It can be seen that the surface under the cap is very uneven (Figure 1c–d). The big PAR crystals rise from the texture and deeper areas with smaller deformed particles appear among these crystals. The texture is rather loose because of the pores. The deformation of MCC particles, deep pores and slits can be observed in the breaking surface of the PAR tablet (Figure 2a–b).The side of the PAR tablet is also uneven (Figure 3).Small recrystallized crystals can be seen on it.

The surface of the tablet made from the PAR–βCD physical mixture is presented in Figure 4. The texture of this tablet was unhomogenous with the parts of porous compressed β-CD crystals. We can also clearly recognize the particles of fragmented PAR crystals in Figure 4b. The fragments of the PAR crystals and porous compressed tablet surface, can be seen more clearly under higher magnification in the same photo (Figure 4c).

The surface of the broken tablet made from the PAR–βCD physical mixture is presented in Figure 5. The surface has an unpleasant look (Figure 5a). Under



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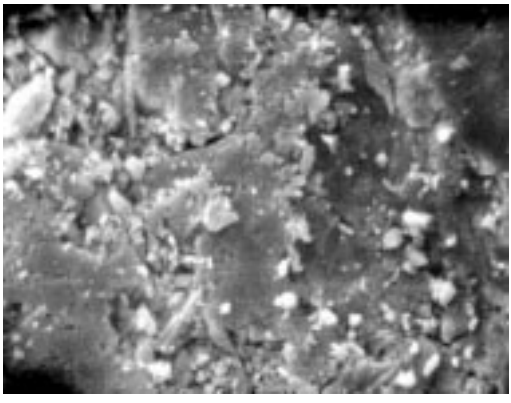

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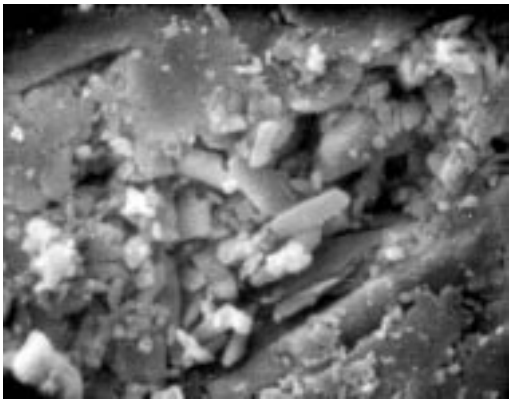
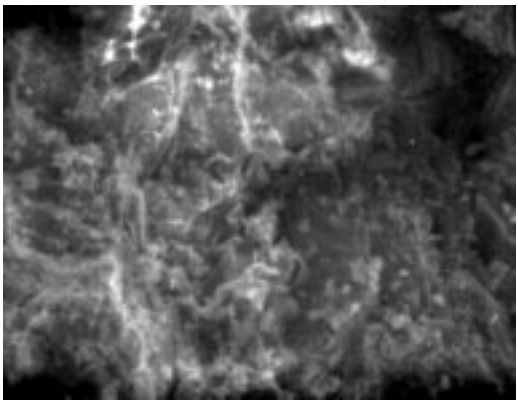


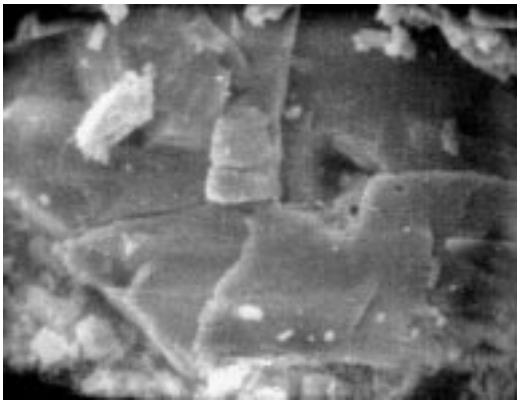
(c)

Figure 4. SEM photos of the surface of original PAR–βCD physical mixture tablet: (a) magnification 400; (b) magnification 1000; (c) magnification 2000.

higher magnification, smooth crystalline surfaces of β-CD were observed (Figure 5b). Beside these crystals there were no connected bridges.



(a)



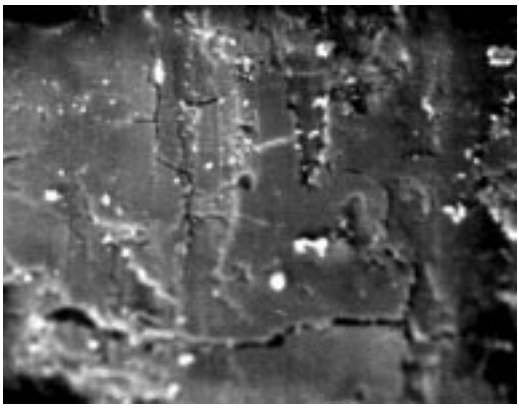
(b)

Figure 5. SEM photos of the broken surface of original PAR–βCD physical mixture tablet: (a) magnification 400; (b) magnification 1000.

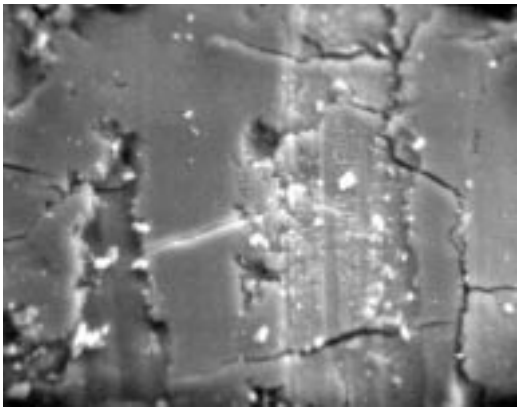
The photos of the side of the tablet made from the PAR–βCD physical mixture show the consequences of the friction work, which had to be done during the ejection of the tablet through the die (Figure 6). There was a rupture at the side of the tablet, caused by the tablet's decompression (Figure 6b).

The surface of the tablet made by the PAR–βCD kneaded solid dispersion is presented in Figure 7. The texture of the tablet indicated the plastic deformation and sintering of the coarse materials (aggregates), with strong and deep splits-narrows. These show a high elastic recovery in the die immediately after the compression.These narrows were longer and deeper than the similar ones noticeable in the photo of the tablet surfaces of PAR plain formulation (see Figure 1a).

Distinctly plastically deformed aggregates can be seen in pictures of the surface of a broken tablet made from the PAR–βCD kneaded solid dispersion (Figure 8).The breaking of the tablet usually happened exactly through the splits noticable on the tablet surfaces.



(a)



(b)

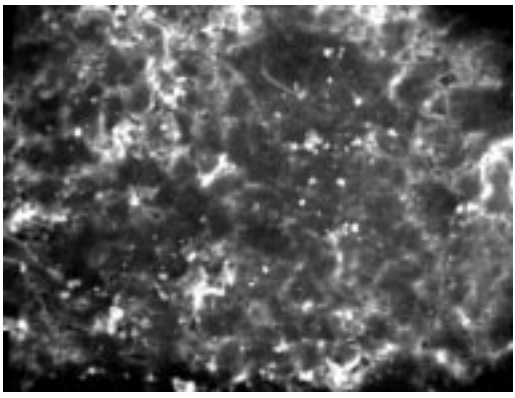
Figure 6. SEM photos of the side of original PAR–βCD physical mixture tablet: (a) magnification 400; (b) magnification 1000.

Figure 9 shows the SEM photographs of the side of a tablet made from the PAR–βCD kneaded solid dispersion. The plastically deformed surfaces of the compressed dispersion powder can be seen in Figure 9, together with a slight but noticable trace of the friction of the tablet (Figure 9a).

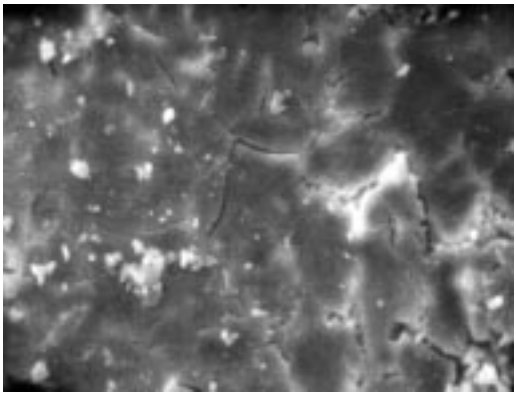
The big aggregates of particles, with thick secondary splits-cracks, and the spray dried solid dispersion of PAR–βCD from which the tablets were made, can be seen in Figure 10. These pictures present the surface of the tablet mentioned above. Under higher magnification, it can be seen that aggregates contained many individual spherical particles with solid bridges (Figure 10b).

In the pictures of the broken tablet surface (Figure 11), we recognized the spray dried PAR–βCD particles with their original morphology [5]; there were many porous, and small but strong solid bridges.

The side of the tablet made from the spray dried solid dispersion of PAR–βCD is shown in Figure 12. We can see: the big sintered surface and the big friction at the side of the tablet (Figure 12a); and the long horizontal crack-split as well



(a)



(b)

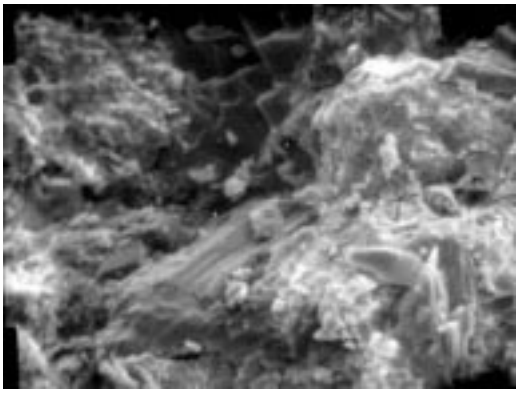
Figure 7. SEM photos of the surface of original PAR–βCD kneaded solid dispersion tablet: (a) magnification 400; (b) magnification 1000.

(Figures 12a and b). Into one of the cracks we clearly see the individual spherical particles which are sligthly sintered (Figure 12c).

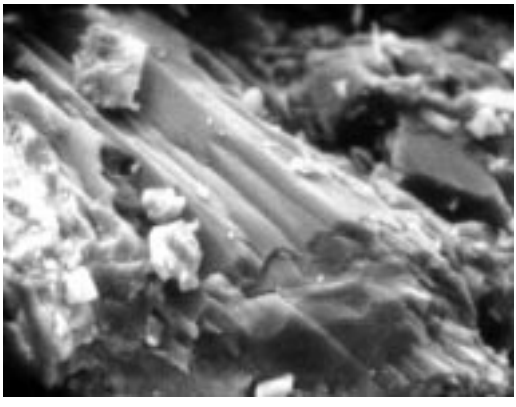
4. Discussion

The compression behavior of the powder depends on particle size, shape, nature of materials, etc. The ability of the formulated powders to form satisfactory tablets depends on their plastic deformation during compression and on their elastic recovery during decompression [16]. In our case, we have four PAR tablet formulations with a wide range of particle sizes and shapes [5].

The direct compression of PAR crystals is not possible despite the presence of MCC. The very high elastic behavior of the PAR crystal was checked by microscopic investigation and the fracture of the PAR crystal during the compression and decompression phase of consolidation (see Figure 1).The presence of MCC in this sample did not reduce the natural behavior of the PAR crystal [17]. The SEM



(a)



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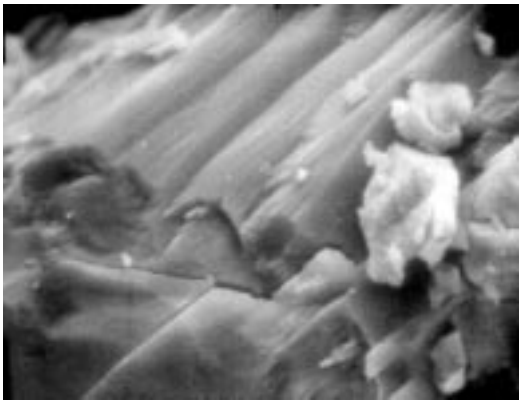
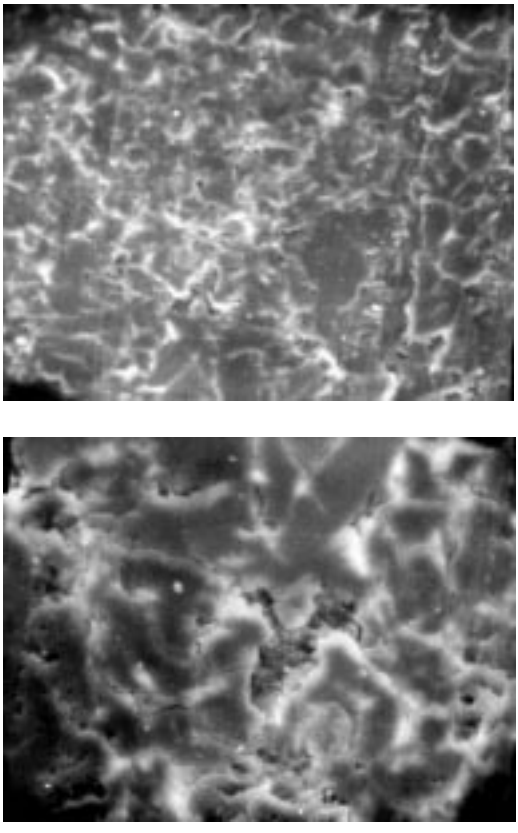


(c)

Figure 8. SEM photos of the broken surface of original PAR–βCD kneaded solid dispersion tablet: (a) magnification 400; (b) magnification 1000; (c) magnification 2000.

investigation of the PAR plain tablet showed that the PAR is compressed by brittle fracture and the MCC by the mechanism of plastic deformation.

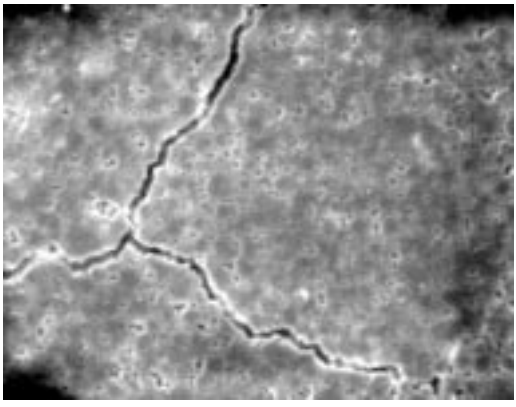


(a)

(b)

Figure 9. SEM photos of the side of original PAR–βCD kneaded solid dispersion tablet: (a) magnification 400; (b) magnification 1000.

The next three samples of the PAR tablet contained 50% of β-CD in different dispersion forms. Our aim was to see whether or not the β-CD had some influence on the compression behavior of PAR. As is well known, the PAR was deformed by brittle fracture [10, 11]. In the tablet made from the PAR–βCD physical mixture, the same brittle fracture compression mechanism was checked by the SEM study. As the SEM photos showed, the interparticular connection in this sample was negligible (see Figure 5a–c). The connection between particles made during compression was very slight, and did not survive the decompression phase of material consolidation. Therefore, the value of the tensile strength and the crushing strength of this PAR tablet samples was very low. As a consequence, a rapid disintegration of tablets (26 s) occurred. The deformation of a granule of the PAR–βCD kneaded dispersion is a clear type of plastic deformation; crystal deformation is known to involve twin formation and multiple twin formation [18]. This type of plastic deformation happened with rapid crystal deformation. Führer explained this phenomenon in terms of the model of a pile of cards. The parallel sliding planes were



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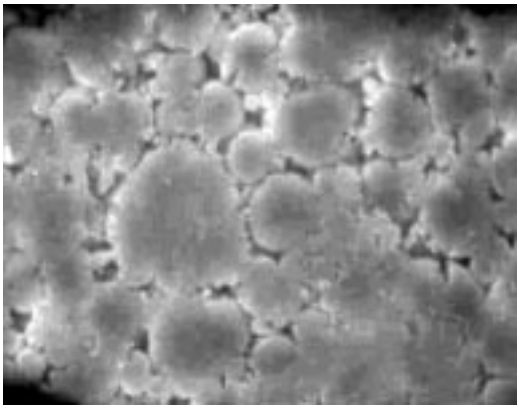
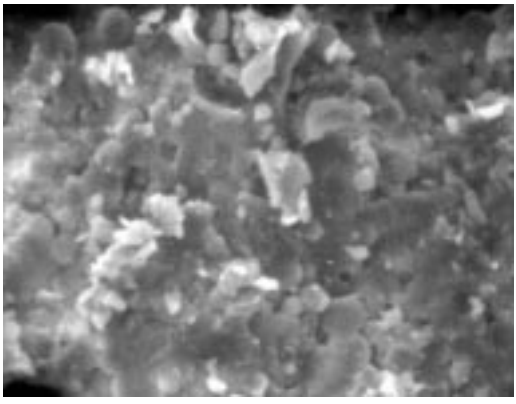


(b)

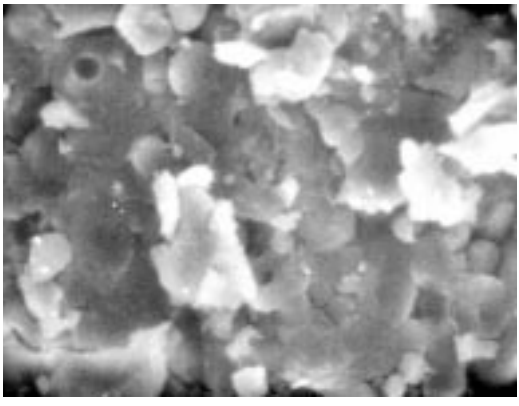
Figure 10. SEM photos of the surface of original PAR–βCD spray dried solid dispersion tablet: (a) magnification 400; (b) magnification 2000.

displaced against each other over a definite distance. The resultant crystal deformed to a twin has a void shape around a symmetrical plane [18]. Sometimes, the crystals formed zigzag forms, as in our case (Figures 8b–c), because of the multiple twin deformation. This dispersion was deformed plastically. Recently published results showed that the mechanism of β-CD deformation was plastic flow [7–9]. Thus, in the case of the kneaded dispersion of PAR–βCD, the β-CD had an important role in the consolidation, changing it from brittle fracture to plastic flow. The results of measurements of tensile strength and elastic recovery (see Table I) can support the previous conclusions. The low value of elastic recovery (0.0316%) correlated with low decompression of the tablet, and was also indicative of good plastic deforming materials [15].

SEM pictures of the surface, the side and the broken surface of the tablet made by the spray dried PAR–βCD dispersion showed that individual deformations of particles were poor and slight (see Figure 10b). The presence of the strong interparticular connections was also marked. The three hole points in Figures 11a–



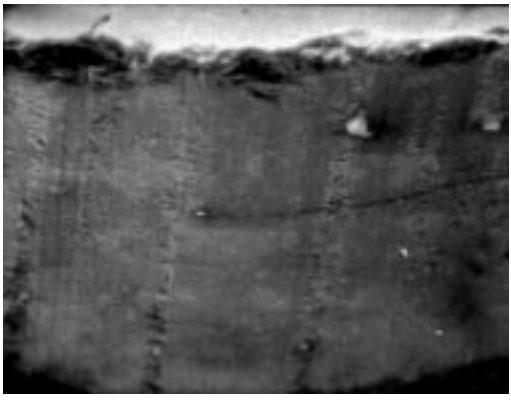
(a)



(b)

Figure 11. SEM photos of the broken surface of original PAR–βCD spray dried solid dispersion tablet: (a) magnification 1000; (b) magnification 2000.

b represent the broken interparticular bonds. These bonds were very strong. Of course, in an SEM photo we could not measure the interparticular bonds, but we can assume that if the deformation of particles occurs without any cracking and slits, then the bonds must be strong. The sintered particles that were observed in this sample testified to the effect of the cool sintering as the mechanism of consolidation. Besides this, the value of the tensile strength of this sample was comparable with that of other samples. The value of the elastic recovery is the highest (Table I) and it can be well seen in the SEM photos Figure 12b–c as a long horizontal crack-split. The crack is a consequence of the decompression of the tablet. The disintegration time of this sample was very long (896 s) because of the original consolidated material structure. In this case the disintegration proceeded by the process of dissolution.



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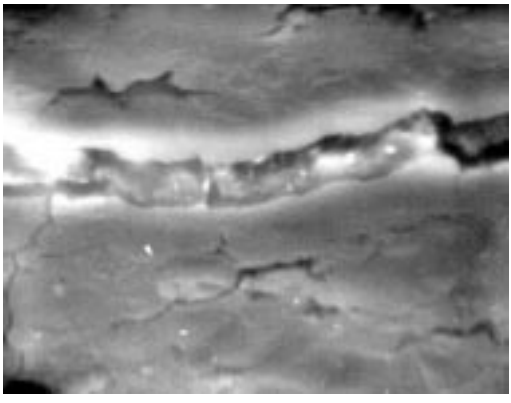

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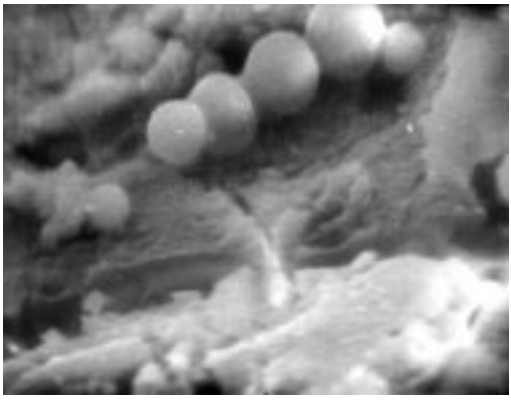

(c)

Figure 12. SEM photos of the side of original PAR–βCD spray dried solid dispersion tablet: (a) magnification 100; (b) magnification 4000; (c) magnification 4000.

5. Conclusion

Using the SEM method the texture, structure, compactibility and consolidation phenomenon of three PAR–βCD dispersion powders (physical mixture, kneaded

solid dispersion and spray dried solid dispersion) were studied. For comparison, plain PAR was used. The results obtained showed that β-CD influenced the compression behavior of the PAR. The different methods for preparation of dispersions produced powdered samples with a wide range of particle sizes, shapes, crystalline structures and rheological behaviors [4–6]. In these circumstances, the compression properties and mechanism of consolidation of the samples examined were different from these of PAR alone.

In the PAR–βCD physical mixture tablet, the brittle fractures of the PAR particles happened as usual. The PAR–βCD kneaded solid dispersion showed a good plastic deformation, with strong cohesion and small elasticity of particles. With the PAR–βCD spray dried solid dispersion the good plastic deformation and mechanism of cool sintering was postulated. The influence of β-CD on the compression behavior of the PAR was proved. The SEM method was shown to be valuable for compression investigation. This method of investigation is very useful for studying the compactibility of powders and the deformatibility of particles during compression and is well correlated with the postcompressional parameters of tablets (crushing strength, disintegration time, friability, elastic recovery, tensile strength). The evaluation of the compression behavior of PAR–βCD solid dispersions by study of the energy parameters is in preparation.

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