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RESEARCH PAPER

Evaluation of Compression Behavior of Paracetamol Tablets Produced with β-Cyclodextrin Dispersions. Part II: Energy Distribution Study of Tablets

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ABSTRACT

The compression behavior of three paracetamol/β-cyclodextrin solid dispersions (PAR/β-CD, ratio 1:1 w/w), which differ in particle size, shape, and crystallinity, were studied using force-displacement measurements (F-D plots). The measured parameters included: effective work, expansion work, friction work, useful work, and plasticity derived from F-D plots at the tableting stage. The PAR/β-CD spray-dried solid dispersion has the best compressional behavior, compared to other dispersions (PAR/β-CD physical mixture and PAR/β-CD kneaded solid dispersion) and PAR alone. Energy distribution study also showed that β-CD has positive influence on the PAR compression characteristics.

INTRODUCTION

Compression behavior of Paracetamol (PAR) is well known to be relatively poor (1,2). One of the reason for this is the crystal habit of PAR (3–5). Morphological changes of PAR particles are possible by using different procedures (granulation, spray-drying) and different auxiliary materials (mannitol, β-cyclodextrin, etc.) (6,7). A recent publication (8) has pointed out a new way to exceed the poor compression ability of PAR. The authors prepared a new pure PAR (form II, which crystallizes in the orthorhombic system) for direct compression. The modification of the crystal habit of PAR was possible with agar, gelatin, polyvinylpyrrolidone, and hydroxypropylmethylcellulose (9).

β-cyclodextrin (β-CD) is used in drug formulation to improve solubility, dissolution, or stability of drug materials (10,11). The possibility of using β-CD as a filler-binder in tablet formulations has been reported (12–15).

In our research about PAR/β-CD solid dispersion, we evaluated the important morphological characteristics of PAR/β-CD particles (7). Certain rheological behavior of these dispersion powders has been studied (16). This investigation showed that PAR/β-CD solid dispersion powders prepared by different processes (kneading and spray-drying) had better packing density, the smallest cohesion, and faster flow than the PAR alone. All of these rheological characteristics of examined powders were of great importance for the tableting ability.

Using scanning electron microscopy (SEM), we established the tablet texture, structure, and consolidation phenomena of PAR/β-CD tablet formulations (17). Another common method for the assessment of the compaction behavior of materials is the use of compression force versus punch displacement profiles.

The aim of this work was to evaluated the compression behavior of PAR/β-CD solid dispersions compared to PAR, using force displacement measurements. We also made some assessment of the ability of β-CD to achieve improvement of the PAR compressional characteristics.

EXPERIMENTAL

Materials

PAR (Ph. Jug. IV grade) was obtained from Vetprom (Belgrade, Yugoslavia); β-CD was obtained from Chinoin (Budapest, Hungary); Aerosil 200 was from Degussa; and magnesium stearate was used. (Ph. Jug. IV grade).

Preparation of Solid Dispersions

Four powder products were included in the experiment as follows: *paracetamol; paracetamol/β-CD physical mixture* (w/w 1:1, molar ratio 7.5:1) mixed in a Turbula mixer (W. E. Bachofen, Basel, Switzerland) for 10 min.; *kneaded solid dispersion of paracetamol/β-CD* (w/w 1:1); and *spray-dried solid dispersion paracetamol/β-CD* (w/w 1:1). Preparation of kneaded product: the substances were mixed and kneaded with an equal quantity of solvent (water:ethanol 1:1) with a mortar and pestle. The mass was continuously stirred and evaporated under infrared lamps (4 hr), passed through a sieve (1.2 mm), dried overnight at room temperature (21°C), and sieved again (1.2 mm). The spray-dried solid dispersion PAR/β-CD (w/w 1:1) was produced using a Niro minor atomizer (Copenhagen, Denmark); the substances were dissolved in solvent (water-ethanol 2:1) by heating at 40°C and mixed to a clear solution. The powder:solvent ratio was 1:5; during the spray process the rotation rate on the inlet air was 105 ± 5°C, the outlet was 70 ± 5°C, and the feed rate was 2000 g hr^{-1}.

Compression Procedures

All powders were lubricated with 1% Aerosil and 1% magnesium stearate (mixed in a Turbula mixer for 5 and 2 min). The powders were compressed with a 10 mm diameter plane-faced punch (average tablet weight 500 mg) on an instrumented single-punch tablet machine (Erweka, Korsch, Berlin) at three different compression forces between 5 and 13 kN. The compression force of the upper and lower punch and the load and displacement were recorded. Data were analyzed by using an IBM-compatible microcomputer. Ten tablets were made at each compression pressure. The lots with relative standard deviation not exceeding 5% were accepted.

Force Displacement Measurements

The following energy values were calculated from the force displacement plots (Fig. 1).

W_{eff} = effective work (E_2); W_{exp} = expansion work (E_3); W_f = work of friction, and W_{use} = useful work.

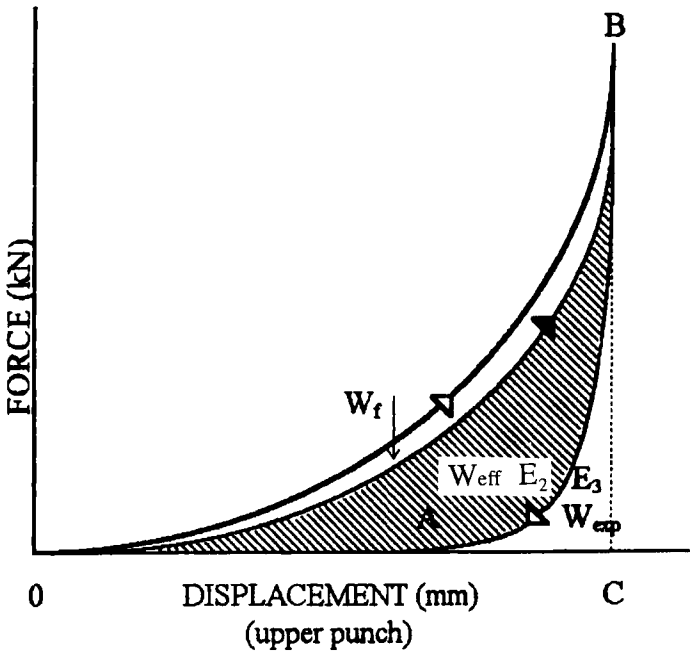

Figure 1. Force vs. displacement profiles: a diagramatic representation (according Ref. 23).

The calculations for E_2 and E_3 are from the plots following the procedure described by Wenzel and Kala (18). The work of friction is calculated according to Järvinen and Juslin (19). The useful work is calculated using the equation

$$W_{use} = W_{eff} - W_f \quad (1)$$

Plasticity

Plasticity (PL) values calculated from the F-D diagram (Fig. 1) according to the equation (20)

$$PL = \frac{100 \cdot E_2}{E_2 + E_3} \quad (2)$$

The parameter PL was processed by one-way analysis of variance to evaluate the homogeneity between the samples compared to compression forces (Statigraphics). In this manner, it was possible to establish the significance of this parameter and characterize the compression behavior of PAR solid dispersion powders.

RESULTS

Table 1 presents the results of compressional parameters from F-D plots (effective work, expansion work, work of friction, and useful work) of examined PAR/β-CD products. The values of plasticity (PL) and the homogenity of results ($p < 0.05$) are presented in Table 1 as well.

The experiment included the four different PAR powder products: PAR, physical mixture, kneaded solid dispersion, and spray-dried solid dispersion (the last three have a PAR/β-CD ratio 1:1 w/w), which were compressed under the three different compression forces (upper punch force between 5.68 and 13.49 kN). The results obtained showed great differences.

The effective work was increased with an increase in and compression force with all samples. The tablet produced by spray-dried solid dispersion of PAR/β-CD showed the highest value of the effective work, followed by the tablets made by kneaded solid dispersion, and then the tablet made by physical mixture of PAR/β-CD. The lowest value of effective work was found with tablets made by PAR alone.

The expansion work increased with an increase of pressure force with all samples, except the PAR. With this sample, the values of expansion work were nearly the same at all applied compression forces.

The friction work showed the dependence of applied compression force with all samples. But, the highest values of work of friction were observed in the samples of physical mixture PAR/β-CD.

Observing the results of useful work, we could see the following: all samples showed the direct dependence from applied compression force; and the four observed samples showed big differences. A comparison of PAR

Table 1

Compression Parameters from F-D Plots of Examined PAR/β-CD Powders[a]

No.	Sample	Displ. (mm)	u.f. (kN)	l.f. (kN)	W_{eff} (J)	W_{exp} (J)	W_f (J)	W_{use} (J)	PL (%)	Homo.
1	PAR	2.69	5.68	3.73	2.92	0.69	1.98	0.94	87.50	a
		2.74	8.32	5.40	4.53	0.66	2.64	1.89	87.23	a
		2.92	10.51	6.86	5.55	0.82	3.16	2.39	87.19	a
2	PAR/β-CD	3.18	6.90	4.75	4.87	0.21	2.62	2.25	95.07	a
	physical mixture	3.78	11.73	8.68	8.26	0.57	3.38	4.88	93.57	a
		5.38	12.76	9.47	9.20	0.74	3.84	5.36	92.58	a
3	PAR/β-CD	3.49	5.86	4.37	5.15	0.21	1.90	3.25	96.58	a
	kneaded solid dispersion	3.93	10.13	7.81	9.15	0.58	2.98	6.17	94.27	a
		4.48	13.49	10.77	12.03	0.92	3.55	8.84	92.85	a
4	PAR/β-CD	4.17	6.37	5.31	5.37	0.19	2.16	3.21	96.60	a
	spray-dried solid dispersion	4.36	9.99	8.34	11.83	0.79	2.54	9.29	93.68	a
		4.53	12.31	10.11	14.32	1.02	3.05	11.27	92.69	a

[a]SD below 5%.

Symbols: displ. = displacement; u.f. = upper force; l.f. = lower force; W_{eff} = effective work; W_{exp} = expansion work; W_f = friction work; W_{use} = useful work; PL = plasticity; homo. = homogenity.

to the useful work values of physical mixture PAR/β-CD, showed that the tablet had more than double the value, with the kneaded solid dispersion PAR/β-CD sample nearly three times higher, and with spray-dried solid dispersion, PAR/β-CD tablets had almost a five times higher value.

DISCUSSION

The importance of understanding the consolidation behavior of the materials is twofold: technological (tendency for laminations and capping, problems on ejection, effect of lubricant on tablet strength, etc.) and biopharmaceutical (effect of pressure or lubrication on the dissolution rate and hence on drug absorption). Doekler (21) observed the consolidation mechanism and postulated two general lines: bulk deformation and particle deformation. Consequently, different techniques and methods for the first and the second line of observation have been developed (22). The SEM method was valuable for compression study for investigation of the tablet texture, structure, and particularly for particle deformation. In our previous study, we used SEM for evaluation of the compression behavior of PAR/β dispersions and particle deformation (17). The calculations of the work (energy) of compaction from the F-D diagrams are currently in use for bulk deformation. Energy that machines such as punches deliver to powder mass was used for particle rearrangement, elastic-plastic deformation, and/or brittle fracture materials, and the bonds in material. The use of F-D curves (compression force vs. punch displacement profile) allows the calculation of the work involved during the tablet compaction. The methods of obtaining F-D curves, the definition of the areas under the curves plotted, and the interpretation of the energies calculated varies in the literature (23). In our study we used the following energy data: effective work (W_{eff}), expansion work (W_{exp}), friction work (W_f) and useful work (W_{use}). Effective work (usually called formulation energy of the compact) includes the energy consumed by plastic flow and/or fragmentation of the particles. The expansion work or elastic recovery energy is a measure of the work which a tablet does by expansion, when the upper punch has passed the lower point and its direction of movement has changed. The value of expansion work depends on the rate of elastic deformation processes and the whole deformation of the particles.

Elastic recovery is not an absolute value, since its magnitude is greatly influenced by the tablet speed. Friction work comes from the friction in the die and the presence of lubricants influenced this parameter. The same quantity of lubricant (magnesium stearate) was used for all tested samples in this study. Thus, the marked W_f values originated from the powder characteristics themselves. Since a large part of the energy is lost by processes such as friction, we included the parameter useful work (W_{use}) [see Eq. (1)]. In this manner the more valuable energy data were evaluated. Hiestand and Smith (24) remarked that the ability of formulated powders to form satisfactory tablets depends on their plastic deformation during compression and on their elastic recovery during decompression.

In our study the PAR alone and the three PAR/β-CD powder products were observed. The morphology, the particle size, and the crystallinity of these three PAR/β-CD dispersion powders (physical mixture, kneaded, and spray-dried solid dispersion) were different, and certainly influenced compression behavior and energy distribution. Generally, the three different compression forces applied in the experiment had influence on quantity of energy, which would be absorbed in the tablet mass. But, at the same compression force (e.g., ~10 kN) we could see the distinct difference of network parameters between the samples. These four powders showed different compaction properties and consolidation mechanisms.

The highest energy parameters were apparent in the sample PAR/β-CD spray-dried solid dispersion, compared to other dispersions and PAR. The effective work value of this sample was double compared to PAR. In the case of spray-dried product, we had the small spherical particles (mean diameter 75 μm) with smooth surfaces (7,16) and the energy spent on the phase particle rearrangements was minor. This dispersion powder has an amorphous structure (25) and this is important for compactibility. The great part of energy was absorbed by powders during compression and used for density consolidation, particle deformation, and bonding formation. In the SEM photo, we can see that in this sample the particle deformation level was not as high (17). Most of the energy was preserved in the tablet by means of interparticular connection which was formed during the consolidation of tablets. By the expansion work measurements during compression and by tensile strength measurements after compression (17), we proved that these bound particles survived the decompression phase in tableting.

The lowest value of all energy parameters was measured in PAR. It is well known and has been evaluated (3–5) that the PAR particles are needle-shaped crystals,

and a lot of energy is probably used for particle rearrangement and for brittle fracture. Intensive particle fragmentation occurred during compression, and it was well evaluated by expansion work and friction work data. Almost the same expansion work value was observed with different applied compression forces (0.69 J, 0.66 J, and 0.82 J, respectively, 5.68 kN, 8.32 kN, and 10.51 kN). That means that this parameter does not depend on compression force. The brittle fracture which occurred during compression produced almost the same size, shape, and mass of the particles of the sample, and the same expansion work, too. The main part of formulation energy was spent for friction (about 50–60%). Thus, the rest of the energy that accumulated in the tablet (useful work) was at a low level (about 30–40% of the effective work).

In the case of PAR/β-CD physical mixture, the energy parameters were higher comparing to PAR, but lower regarding other dispersion powders. This dispersion was a simple physical mixture of two powders (PAR and β-CD) with different particle morphology (a needle crystal and a cubic crystal) (7) and degree of crystallinity (25). The PAR was compressed by brittle fracture mechanism (1), and the β-CD by plastic flow (14). Thus, the β-CD had influence on compression characteristics of this sample, as we can see from the energy parameters. With this sample we can observe the highest values of friction work, compared to other samples. In all four samples the same concentration of excipients (Aerosil and magnesium stearate) was used, and the differences found conformed on individual behavior of dispersion powders during compression and ejection of tablet. The particle shape and the powder interparticular connections in the compact were important factors of friction work. The friction was the consequence of intensive fragmentation of PAR and the presence of many new broken particles of PAR, which were not bounded enough with β-CD. The acoustic emission during compression of this sample was remarkable. The traces of cut tablet surfaces on the back side of the tablet were evaluated by SEM (17). These findings indicate that β-CD has influence on compression of PAR and it was useful like a filler in direct compression, but these binder properties were not confirmed. This is in disagreement with some publications about the use of β-CD as a tablet filler–binder (13,14).

The compression behavior of PAR/β-CD kneaded solid dispersions was better, according to compressional data, than the PAR and PAR/β-CD physical mixture, but was not better in comparison with PAR/β-CD spray-dried solid dispersion. Kneaded solid dispersions have classical granular form (mean particle diameter is 500 μm) (7,16) and have their own crystalline structure (25). Observing the energy parameters of this sample, some similarity to the PAR/β-CD physical mixture data was evident. But the effective work values were higher, the friction work values were lower, and the expansion work was nearly the same as the PAR/β-CD physical mixture. This could be due to the peculiar crystallinity of the PAR/β-CD kneaded solid dispersions.

In general, the energy data are not considered separately from each other, and often are used to calculate the plasticity. The plasticity describes the ratio between the reversible and irreversible deformation processes during tableting. According to Stamm and Mathis (20), the higher value of plasticity was indicated on good plastic-forming materials. The best results of plasticity were found with the PAR/β-CD spray-dried solid dispersion. The plasticity values of other dispersion products were similar. The plasticity values of the PAR are the lowest compared to all dispersion products. All three dispersion products showed an inverse correlation between the plasticity and the applied pressure forces, while the PAR did not show such dependence. By the one-way analysis of variance, we found the significant differences (unhomogenity) of plasticity with PAR/β-CD spray-dried solid dispersion and PAR/β-CD kneaded solid dispersions, regarding compression forces. With PAR and PAR/β-CD physical mixture, the plasticity values were homogeneous. This means that the same mechanism of compression (plastic flow) was evaluated for the former group of samples and the same mechanism of compression (brittle fracture) for the latter group of samples.

CONCLUSION

From this study, it can be concluded that the compression behavior of PAR and PAR/β-CD solid dispersions are different. Compressional parameters from F-D plots (energy data) show that the PAR/β-CD spray-dried solid dispersion has the best compressional behavior, compared to other dispersions (PAR/β-CD physical mixture and PAR/β-CD kneaded solid dispersions), and PAR alone. The energy parameters and plasticity data attend to brittle fracture mechanism of compression with PAR/β-CD physical mixture, while the PAR/β-CD kneaded solid dispersions and PAR/β-CD spray-dried solid dispersion are compressed by plastic flow. The study also showed that the β-CD is a good partner for improvement of PAR compression charac-

teristics. The F-D curve model was proved to be very sensitive at detecting different behavior in the compression process.

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