J. Pharm. Pharmacol. 1988, 40: 669-673
Received April 29, 1988

Multiple Compression and Plasto-elastic Behaviour of Paracetamol and Microcrystalline Cellulose Mixtures

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Abstract—Radial tensile strength, friability, ER/PC (elastic recovery/plastic compression) ratio and energy ratio analyses were evaluated for various mixtures of paracetamol and microcrystalline cellulose (Avicel). A good correlation occurred between the energy ratio and the other variables. Linear relationships were found between log tensile strength and percentage energy ratio and also between radial tensile strength and stress relaxation energy. Capping occurred when the percentage energy ratio was greater than 15% and the ER/PC ratio greater than 1·5. To produce tablets with acceptable tensile strength and friability, the percentage energy ratio for Avicel/paracetamol should be greater than 10%. The optimal mixture of the two powders, as far as the tensile strength, friability and absence of capping were concerned, was found to be 50% w/w Avicel, 50% w/w paracetamol.

Capping is a common phenomenon in tablet manufacture in which the top of the tablet lops off after compression has taken place. Whilst many workers have attempted to develop methods for quantifying the capping tendency of a formulation, no universally accepted technique has so far been established. Nystrom et al (1977) reported that capping occurred as the axial tensile strength deviated from the radial tensile strength, whilst Malamataris et al (1984) have claimed that the ratio of elastic recovery to the plastic compression (ER/PC) was a useful parameter in measuring capping. These latter workers reported that tablets capped as the ER/PC ratio exceeded 9. Bangudu & Pilpel (1985) investigated the relationship between the effects of moisture, composition and stearic acid on the plasto-elastic properties of paracetamol/Avicel compacts. An inverse relationship was found between the tensile strength and the ER/PC ratio, also a minimum ER/PC value was noted as the moisture content in the compact increased.

The effect of particle size on the ER/PC ratio was studied by Esezobo & Pilpel (1987); they reported the ER/PC ratio decreased with increase in particle size. Further work by Malamataris & Bourdakos (1986) on Avicel/paracetamol tablets, produced a capping index (Ci). They broke the tablets co-directionally (Tc) and vertically (Tv) to the plane of compression. The log ratio of the tensile strength (Tc/Tv) was plotted against Tc and the gradient of this plot was specified as the capping index. They found that capping occurred as the Ci value became negative.

The aim of the present work was to examine the suitability of utilising the ER/PC ratio and energy analysis as a means of measuring capping tendency.

Materials and Methods

Using an Alpine air jet sieve, paracetamol powder BP (Hilton Davies Chemical Ltd, Newcastle-upon-Tyne, UK) and Avicel PH101 (FMC Corp., Philadelphia, USA) were classified into less than 105 μm and 40–105 μm fractions, respectively. The powders were mixed in the proportions shown in Table 1. Powder mixtures were pretreated for 24 h in a vacuum oven at 100°C and then stored under controlled humidity conditions (RH = 40% and 25°C) before compression. True density of each powder mixture was determined using an air comparison pycnometer (Model 930, Beckmann Instruments, UK).

Tablets were prepared using a Universal Testing Machine (Model 1121, Instron Ltd., High Wycombe, UK) fitted with 5/16″ flat faced F-tooling. The compression surfaces were pre-lubricated with 4% w/v magnesium stearate in carbon tetrachloride solution. Sufficient powder was used to produce a compact of 1·83 mm thick at zero theoretical porosity. The crosshead speed used was 50 mm min^{-1} and the minimum punch separation was set to give a peak compression force of 7kN. Compacts were then held under load for 60s; the load was removed and the ejected tablets stored in a desiccator for 24 h before tests for radial tensile strength and friability were performed. Compression data was captured using a computer data logging system which enabled force and punch displacement to be recorded simultaneously using an Apple IIe microcomputer. Corrections were made for tooling distortion and machine effects.

Radial tensile strength of the tablets was evaluated using the Instron machine set at a crosshead speed of 50 mm min^{-1} and friability using a Roche Friabilator; the percentage loss of tablet weight after 100 revolutions being determined. Five

Table 1. The physical and plasto-elastic properties of Avicel/paracetamol tablets.

Mass fraction (Avicel)	Radial tensile strength (MPa)	Friability (% Loss)	PC	ER	ER/PC ratio
0	0	Capped	2·46	4·72	1·92
0·15	0·59	4·05	2·9	4·17	1·44
0·3	1·36	1·63	3·33	4·25	1·28
0·5	2·62	0·64	3·5	3·87	1·11
0·75	5·25	0·4	3·99	3·4	0·852
1·0	6·54	0	4·6	1·4	0·3

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replicate tablets for the tensile test, 10 tablets for the friability test and two tablets from each mixture were subjected to multiple compressions, allowing 5 min intervals between compressions.

The plasto-elastic parameters were calculated (Fig. 1):

$$\text{Plastic compression (PC)} = \frac{\text{Dmax-Dend}}{\text{Dmax}} \times 100 \quad (1)$$

$$\text{Elastic recovery (ER)} = \frac{\text{Dzero-Dend}}{\text{Dend}} \times 100 \quad (2)$$

where Dmax = punch separation at the maximum applied force;
Dend = punch separation at the end of the holding time (60s);
Dzero = punch separation when the applied force returned to zero.

The plastic compression value (PC) is an indication of the amount of plastic deformation of the material, whilst the elastic recovery (ER) value gives an indication of the amount of elastic expansion. Therefore the proportion of both quantities can be described by the ratio of ER/PC.

For energy analysis, the area of the force-displacement curve (Fig. 1) was computed and the compression portion was designated as the gross compaction energy (region 1). The mean of the fourth, fifth and the sixth compaction energy was calculated as the elastic energy of the compact. The stress relaxation energy (region 2) was also calculated thus enabling the net elastic energy to be determined. The energy ratio of the compact was, therefore, defined as

$$\text{Eelastic} = \text{Mean compaction energy of the 4th, 5th \& 6th recompression} \quad (3)$$

$$\text{Ebonding} = (\text{1st compression energy} + \text{relaxation energy}) - \text{mean recompression energy} \quad (4)$$

$$\text{Energy ratio} = \frac{\text{Eelastic} - \text{Erelax}}{\text{Ebonding}} \quad (5)$$

where Eelastic = elastic energy (J),
Ebonding = bonding energy (J),
Erelax = stress relaxation energy (J), i.e. the energy converted from elastic to bonding energy.

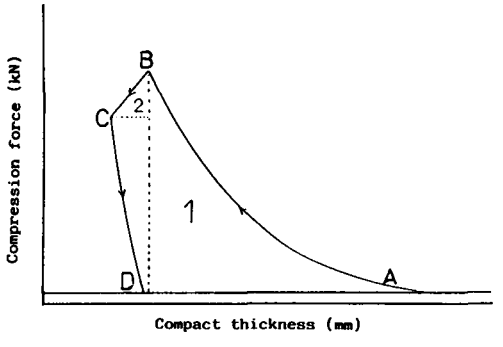

FIG. 1. Schematic diagram of force-displacement curve. A = Thickness at the beginning of compression. B = Thickness at max. load. C = Thickness at the end of holding period. D = Thickness at the end of decompression. Region 1 = Compression energy. Region 2 = Stress relaxation energy.

Results and Discussion

Tensile strength provides a method of estimating internal particle bonding and indicates regions of weakness by the fashion of the tablet breakage, whereas friability determines the toughness and the cohesiveness of a tablet. Fig. 2 shows the relationship between these two properties as the amount of Avicel in the tablets is varied. As the content of Avicel is reduced, the tensile strength decreases and the percentage friability increases. It is well known that Avicel is able to undergo plastic flow when subjected to external load, thus enabling particles to achieve a more intimate contact with each other, so that hydrogen bonding can take place. Paracetamol, on the other hand, exhibits marked brittle fracture during compression, which generates new surface area for particle-particle bonding. The strength of the latter is considerably weaker than that due to hydrogen bonding; which explains the much lower tensile strength and friability of tablets made from 100% paracetamol compared with 100% Avicel (Fig. 2).

Malamataris et al (1984) reported that capping occurred when the amount of Avicel fell below 25% w/w. In the present study, intact tablets were produced with as little as 15% w/w Avicel in paracetamol. However, the friability results from tablets with less than 50% w/w of Avicel were outside the acceptable limit of less than 1% weight loss. It is therefore suggested that equal proportion of Avicel and paracetamol produces the most pharmaceutically acceptable tablets.

Despite the fact that radial tensile strength and friability were used for testing the mechanical strength of the finished compacts, these measurements reveal very little about the underlying bonding mechanisms. Moreover, they cannot be used to test capped tablets or those tablets with a very weak structure.

The other parameter studied was ER/PC ratio, which can be used as an index for comparing the elastic and plastic properties during the post compression phase. Since plasticity is known to promote good bond formation, whereas elasticity weakens bonding, hence, a high ER/PC ratio would indicate weak tablets and probably capping. Fig. 3 exhibited a non-linear relationship between the ER/PC ratio and the amount of Avicel in the tablets. Pure paracetamol tablets capped with an ER/PC ratio of about 2 (Table 1); and was found to exhibit more elastic recovery than plastic deformation, approximately twice as much. On the other hand, pure

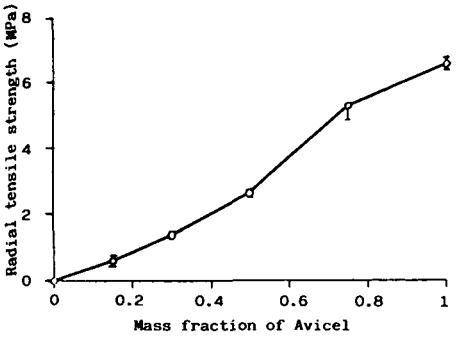

FIG. 2. The relationship between the radial tensile strength and the mass fraction of Avicel in the mixture.

Avicel had an ER/PC value of 0·3, indicating that this excipient deforms predominantly by plastic flow. No capping occurred when Avicel was incorporated into the mixture at a concentration of more than 15% w/w. In order to prevent capping in a formulation, it would appear that the elastic recovery (ER) value should not exceed the plastic compression (PC) value by more than 1·5 times; that is the ER/PC ratio should not be greater than 1·5. Although in practice, tablets with a ER/PC ratio close to 1·5 did not cap, they still exhibited low tensile strengths and poor friability, which would not be acceptable in normal handling. Thus, it was found that the ER/PC ratio had to be significantly less than the proposed 1·5 value, and the best results were achieved with a 50% w/w mixture of Avicel/paracetamol which had a ER/PC value of 1·11. It has been reported by Malamatarius (1984) that all tablets capped when the ER/PC ratio was greater than 9, however, in our study, a significantly smaller ratio was sufficient to signify capping in tablets. One possible explanation of this discrepancy between our results and those of Malamatarius et al (1984) could be the inclusion of the correction factor in the present study for tooling distortion which was not mentioned in the earlier work.

Plotting log radial tensile strength against the ER/PC ratio (Fig. 4) revealed a non-linear relationship between these two parameters, as found by Malamatarius et al (1984). The increase of the log tensile strength with the decrease of the ER/PC ratio can simply be explained by the greater plasticity in the compact with higher proportions of Avicel.

De Blaey & Polderman (1970) were the first workers to evaluate compression energy using a double compression technique. They assumed that plastic flow was complete after the first compression and that the energy for the second compression was solely expended as elastic deformation. However, Patel et al (1985) have reported that the recompression energy of Encompress remains constant only after the 19th compression, whilst Avicel was constant after the 2nd compression. The stage of elastic deformation should, therefore only be considered when the recompression energy remains constant.

In the present work, all compacts were subjected to a 60s holding period under stress. During the holding interval, no external work had been put into the system, because the position of the crosshead was kept stationary. The shrinkage of the compacts was therefore, considered to be the effect of internal energy conversion, that is, the stored energy was converted into deformation energy and utilized for bond formation.

The effect of the amount of Avicel in the compacts on the percentage energy ratio is shown in Fig. 3. For pure

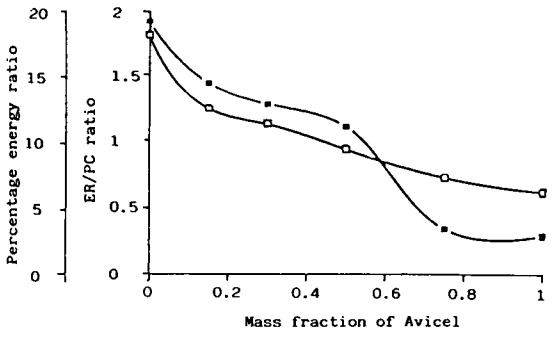

FIG. 3. The ER/PC ratio and the percentage energy ratio versus the mass fraction of Avicel in the mixture. ■ ER/PC ratio. □ Energy ratio %.

paracetamol, the value of the percentage energy ratio was 18·12 compared with 6·35 for Avicel (Table 2). The proportion of elastic energy was significantly higher for paracetamol, which explains the high capping tendency of this material. The shape of the curve was similar to that of the ER/PC versus mass fraction graph. This is not surprising, because both measurements were based on the same principle. There was a very good correlation between the logarithm of the tensile strength and the percentage energy ratio. It can be described by the equation:

$$\log T = A(Er\%) + B$$

where T = radial tensile strength (MPa),
Er% = percentage energy ratio,
A and B = constant.

Thus, by extrapolating from the equation for T = 0, the Er% value for capped tablet would be about 15%. Thus, tablets with a Er% value greater than 15% would be susceptible to capping.

In the case of pure paracetamol, it was found that the first compression energy was low compared with pure Avicel. Increasing the ratio of Avicel to paracetamol, it would be expected that a gradual increase in the first compression energy would occur due to the increase in the plasticity of the material. In this study, the result confirmed this expectation (Fig. 5). It is believed that the reason Avicel requires more compression energy and exhibits a higher stress relaxation energy than paracetamol powder is due to their different structures. Avicel is known to be a fibrous material and thus when a force is applied, Avicel behaves like a sponge and accommodates internal rearrangement and deformation which in the process utilises a great deal of energy. Paracetamol on the other hand is a brittle material and does not easily

Table 2. Energy analysis of Avicel/paracetamol tablets.

Mass fraction (Avicel)	1st compression energy $(J\ g)^{-1}$	Relaxation energy $(XE\text{-}1\ J\ g)^{-1}$	Mean recompression energy $(J\ g)^{-1}$	Net bonding energy $(J\ g)^{-1}$	Net elastic energy $(J\ g)^{-1}$	% Energy ratio
0	10·8	0·433	1·699	9·144	1·656	18·12
0·15	12·79	0·924	1·508	11·37	1·416	12·45
0·3	15·53	1·311	1·703	13·96	1·572	11·26
0·5	18·52	1·574	1·724	16·64	1·567	9·42
0·75	22·33	2·093	1·718	20·4	1·509	7·4
1·0	31·03	2·863	2·14	29·18	1·854	6·35

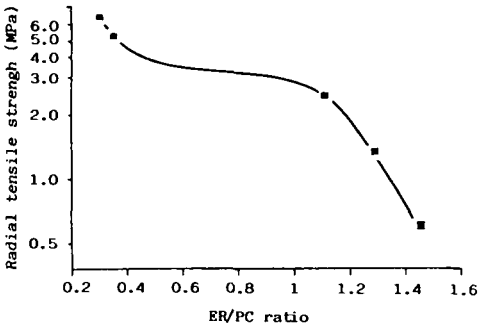

FIG. 4. The relationship between the ER/PC ratio and Log radial tensile strength of the Avicel/paracetamol compacts.

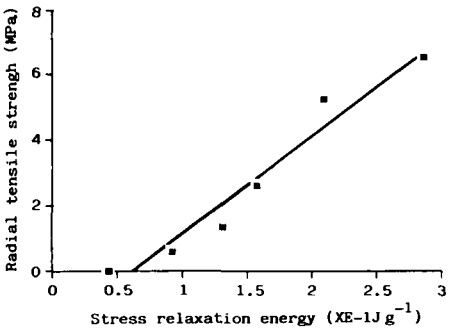

FIG. 6. The relationship between the radial tensile strength and the stress relaxation energy for the Avicel/paracetamol compacts.

undergo particulate rearrangement and deformation but fractures readily and as can be seen on the force-displacement profile, its up-curve is much steeper than that of Avicel. Paracetamol only deforms when the force reaches a certain threshold value but once this point is reached it more or less breaks down spontaneously. Avicel has a lower threshold and when this critical point is reached it tends to absorb energy slowly and hence its up-curve is much shallower and it takes longer to achieve the same end point. For Avicel the deformation process continued even after reaching the maximum applied force and the extent to which it deformed was greater than that of paracetamol.

Elastic energy is not used for bonding, but is stored as deformational energy under stress. The sudden release of this stored energy at the end of the compression cycle, allows the distorted particles to return to their original shape and rupture weak particle-particle bonds. The amount of elastic energy that a material is capable of storing is a constant intrinsic factor and so material compactability is really dependent on its plastic and brittle characteristics. The Eelastic value of Avicel is, however, significantly higher than that of paracetamol (Fig. 5). Sole measurement of Eelastic is somewhat meaningless unless the value is compared with the Ebonding value. The ratio of Eelastic/Ebonding allows the evaluation of both bond formation and bond rupturing, and thus enables the determination of the dominant parameter.

Fig. 6 indicates a good linear relationship between tensile strength and the amount of stress relaxation energy in the compact. This can be reasoned as the ability of the material to undergo internal conversion of elastic to bonding energy. The process not only enhances the particle-particle bonding strength, but also it can reduce the bond weakening effect during decompression. Holding time is therefore considered to be a useful method for improving tablet strength.

Both ER/PC and the energy ratio are measurements of the distribution of elastic and plastic properties. However, it is considered that measurement of the energy ratio is more revealing than the ER/PC ratio. The latter is a measurement of post compression plastic flow and requires holding the compact under stress for a time interval. In addition it assumes that plastic compression is complete by the end of the holding period and that any subsequent deformation results by virtue of elastic recovery. However, it is known that some materials undergo very slow plastic flow. Thus during the decompression stage it is possible for the observed effect to be due to a product of both elastic recovery and plastic flow. This however, does not apply to the energy ratio. Multiple compression can be performed until a constant recompression energy is recorded, which is a measurement of pure elasticity. The true fragmentation or plastic energy can then be accurately computed.

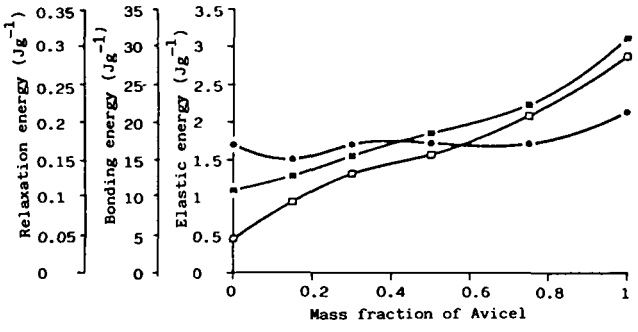

FIG. 5. The bonding energy, stress relaxation energy and elastic energy versus the mass fraction of Avicel in the mixture. ■ Bonding energy. □ Relaxation energy. ● Elastic energy.

Conclusion

Radial tensile strength, friability, ER/PC (elastic recovery/plastic compression) ratio and energy ratio analyses were evaluated for various mixtures of paracetamol and Avicel. A good correlation occurred between the energy ratio and the other variables. Linear relationships were found between log tensile strength and percentage energy ratio and also between tensile strength and stress relaxation energy. Capping occurred when the percentage energy ratio was greater than 15% and the ER/PC was greater than 1·5. To produce Avicel/paracetamol tablets which have acceptable tensile strength and friability, the percentage energy ratio should be greater than 10%. It was also found that a 50% w/w mixture of Avicel/paracetamol had the optimal combination needed as far as the tensile strength, friability and capping tendency were concerned.

Acknowledgements

Acknowledgement is made to Manesty Machines Ltd. for sponsoring the research studentship to one of us (H.C.M.Y); H.M.E. thanks the British Council for the financial support during the visit to the UK.

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