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Research paper

A study on the coherence of compacted binary composites of microcrystalline cellulose and paracetamol

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Abstract

This paper describes and interprets the coherence and the tensile strength of bi-component compacted tablets, composing a mixture of a poorly compactable drug, paracetamol and a very cohesive and ductile carrier, microcrystalline cellulose (MCC), Avicel® PH 102, using the concepts of the stored elastic strain in conjunction with the particle size and the relative volume fraction of the powders. Cylindrical compacts of the bi-component tablets, at various compositions formed at a common ultimate stress of 99 MPa, were subsequently fractured using the indirect tensile test method (Brazilian test method) to obtain a measure of their tensile strength. Various inter-relations between the compaction and tensile rupture characteristics are described. A simple model, which may predict the required volume fraction of MCC to produce a cohesively viable tablet is suggested, and applied to the current system. The results show to some extent the consistency of the suggested model with the experimental results.

Keywords: Coherence; Tensile strength; Paracetamol; Microcrystalline cellulose; Avicel®; Brazilian test

1. Introduction

In general, all materials have the ability to store some elastic strain. However, the extent of the stored elastic strain will greatly vary for different materials, and will depend upon the intrinsic nature of the material. There are many instances where a brittle material, or its surface, has significantly reduced the cohesion or adhesion compared to that of a ductile material. For example, Gane et al. [1] observed a remarkable reduction in the adhesion of a highly cleaned ductile alloy in vacuum when it was exposed to oxygen at room temperature. The reason was attributed to the brittleness of the oxide layer, which was capable of storing a significant amount of the elastic strain as compared to that of the ductile metal. Similarly, the spheres of the glass ballotini, which are brittle and store elastic strains, do not cohere to each other, but using a ductile material such as a paste like 'Plasticine', the spheres can be effectively cohered to each other. The same principles are true in case of the MCC, a ductile excipient with a highly cohesive nature, and paracetamol, a brittle drug. The compactibility of the latter, which forms a poor compact with extremely weak junctions, may be improved by mixing it with the former material. This leads to a production of a cohesively viable tablet [2].

The strength or the cohesion of a compact may be sensed through its fracture properties and one convenient way to examine the cohesion of a compact is by using the indirect measurement of tensile stresses through compressive loading. The failure stress in terms of the cross section in a plane containing the load axis is known variously as the 'Brazilian', 'diametral compression', or 'cylinder split'. The Brazilian test is largely free from sensitivity to surface conditions and fabrication problems. In addition, there is uniformity of (theoretical) stress distribution, avoidance of machine co-linearity problems and specimen axes, and lower coefficients of variation [3–9]. This procedure was introduced into pharmaceutical practice by Fell and Newton, [10], and was adopted in the current study.

2. Materials and experimental methods

2.1. Material

Both the excipient, microcrystalline cellulose (MCC), Avicel® PH 102, and the drug, paracetamol, were supplied

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by Merck Sharp and Dohme, and manufactured by FMC, USA, and Sigma-Aldrich Chemie, Germany, respectively. The mean particle sizes of the MCC and the paracetamol powders used in this study were 80 μm and 10 μm with true densities of 1600 and 1300 kg/m^3, respectively.

2.2. Preparation

Mixtures of MCC and paracetamol at various mass ratios ranging from 1:9 to 9:1 were prepared using a 'serial dilution' method. The mass of each tablet was selected to be 0.001 kg (1 g).

The tablets were uniaxially compacted, between a mirror-polished platen and a single acting upper punch, in a cylindrical 16 mm diameter hardened stainless steel die manufactured by Specac, UK.

The compactions were carried out using a commercial universal testing machine (Lloyds EZ 50, UK), at a cross-head speed of 0.1 mm/s for loading and 0.0167 mm/s for unloading. All the tablets were compacted to an ultimate imposed normal stress of 99 MPa. The compacted tablets were ejected from the die after the removal of the lower platen at the end of each run, and a force was applied to the upper punch using the Lloyds testing machine with a constant cross-head speed of 0.083 mm/s.

2.3. Brazilian test

As MCC in particular, and also paracetamol, like most of the pharmaceutical drugs, in general, are sensitive to ambient humidity and absorbed moisture. The tablets were dried in a high vacuum oven for a minimum duration of 24 h and at a 60 °C temperature. The Brazilian style compression was carried out with Lloyds EZ 50 using a 1 kN transducer. Each tablet was fractured diametrically between two parallel platens at a cross-head speed of 0.0116 mm/s, utilising two square pieces of cardboard, 0.25 mm in thickness, as 'the padding' to insure an even distribution of stress and consequently to acquire a mode I failure (tension mode). To obtain a compliance equation for these pieces of cardboard, 24 pieces of the cardboard were cut into square geometry and mounted over a block of aluminium. Using Lloyds EZ 50 U.T.M., an ultimate reaction force of 0.9 kN, at a cross-head velocity of 0.01 mm/min, was applied and the resultant loading and unloading curve was plotted. A mathematical software (Origin) was utilised to fit a model to the loading curve. The following equation was acquired from curve fitting:

$$[F = 0.98(h - 0.19)^{2.7}] \pm 5\% \quad (1)$$

where F was the reaction force and h was the imposed displacement. This relationship was used to correct the Brazilian test force/displacement data in order to obtain the 'true' response of the compact.

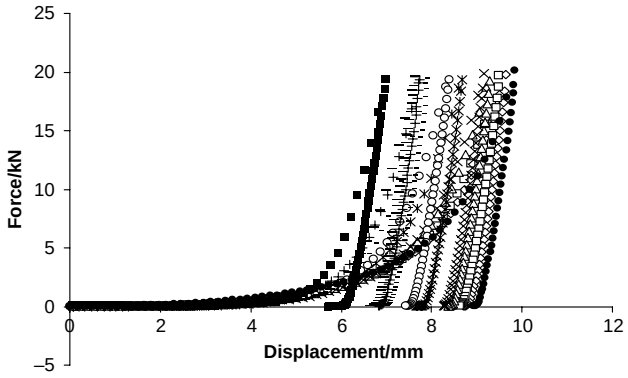

Fig. 1. The compaction profile of mixed tablets at various ratios compacted to ultimate force of 20 kN, ◇, 10% paracetamol/90% MCC; □, 20% paracetamol/80% MCC; △, 30% paracetamol/70% MCC,; ×, 40% paracetamol/60% MCC; *, 50% paracetamol/50% MCC, ○ 40% MCC/60% paracetamol, +, 30% MCC/70% paracetamol, _, 20% MCC/80% paracetamol, ▬, 10% MCC/90% paracetamol •, 100% MCC, ■, 100% paracetamol.

3. Results and discussion

3.1. Compaction

Figure 1 demonstrates the loading and unloading curves of various bi-component tablets compacted to an ultimate compaction force of 20 kN; 99 MPa. Two points are worth noting in this figure. First of all is the induction phase, where the displacement is significantly changing with a near zero load and may be attributed to the friability of the loose compact. In order to have a better insight of the induction phase, this part was magnified substantially for some of the tablets; Fig. 2. This figure shows that the magnitude of the induction phase is strongly dependent upon the mass fraction of the paracetamol. Hence the higher the mass fraction of paracetamol the greater is the magnitude of the induction phase and the greater the ability to store a significant amount of elastic strains. Consequently the powder mass is more friable which leads to a less coherent and poorly compactable tablet.

The second notable point in Fig. 1 is the extent of the displacement of the powder, which has increased in proportion to the MCC mass fraction. In addition, the total work done on

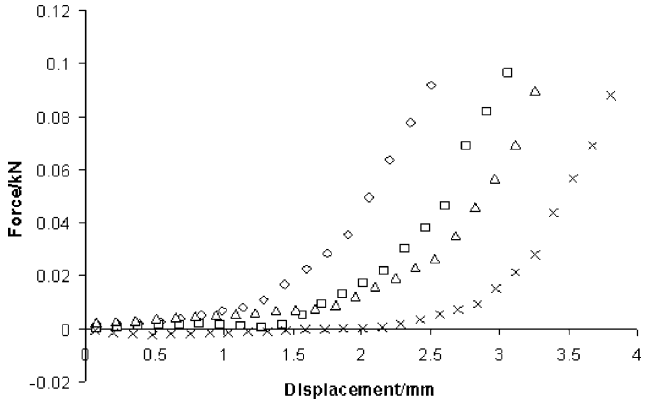

Fig. 2. The induction phase, for compaction, of four binary tablets (◇, 20% paracetamol/80% MCC; □, 40% paracetamol/60% MCC; △, 60% paracetamol/40% MCC; ×, 80% paracetamol/20% MCC).

Table 1
Summary of the total, elastic and plastic works done during the compaction of various binary tablets

Material/mass fraction	Total work/J	Elastic work/J	Plastic work/J	Total displacement/mm	Final volume/mm^3
100% MCC	31.04	6.49	24.55	8.92	740.54
[a]90%M.+10%P.	28.41	6.34	22.07	8.71	771.69
80%M.+20%P.	26.43	6.37	20.06	8.62	782.74
70%M.+30%P.	25.37	6.20	19.17	8.38	785.75
60%M.+40%P.	23.98	6.36	17.62	8.26	811.88
50%M.+50%P.	22.57	6.26	16.31	7.67	828.96
40%M.+60%P.	20.85	6.34	14.51	7.45	822.93
30%M.+70%P.	18.08	6.36	11.72	6.83	804.84
20%M.+80%P.	17.21	6.54	10.67	6.95	855.08
10%M.+90%P.	15.78	6.64	9.14	6.66	856.09
100% paracetamol	14.5	6.71	7.79	5.75	923.00

[a] M., MCC; P., paracetamol.

each tablet during the compaction process, Fig. 1, is highly dependent upon the total displacement of the single acting upper punch. The total work (Table 1) was obtained by integrating the area encompassed by the loading curve [11]. An almost constant elastic recovery or parallel unloading curves is noted for all the range of compositions. The elastic recovery may be calculated by integrating the area constituted by the unloading curve. The irrecoverable plastic work can be acquired from the difference of the above two types of works.

In Fig. 3, it may be observed that the total and the plastic works have increased almost linearly in proportion to the MCC mass fraction. The elastic work though, was almost constant for all range of compositions, and did not vary much with the increase of the MCC mass fraction; see also the intercept in Fig. 4. Thus, the coherence of the tablet, and the strength of its junctions are strong functions of the MCC composition. In Fig. 5, it may be observed that there is almost a linear interrelationship between the final volume of binary tablets and the plastic work. Therefore, this relationship may be defined as

$$\mathrm{PW} = \mathrm{kV} \tag{2}$$

where PW, k, V are the plastic work, a constant and the final volume, respectively. However, volume decreases inversely to relative density. Ramirez et al. [12] compared different mathematical models for the tensile strength as a function of relative density of binary tablets. Kuentz et al. [13], and [2] suggested the following model

$$\sigma_\mathrm{t} = \mathrm{k}(\rho - \rho_\mathrm{c})^{T_f} \tag{3}$$

where σ_t is the tensile strength of a binary tablet, k is a constant, ρ and ρ_c are the relative and critical densities, and T_f is the fracture exponent and equals to 2.7.

In this study we examine the replacement of $(\rho - \rho_c)$ term by the plastic work dissipated, as this seems to a more fundamentally appropriate parameter to describe the origin of the tensile strength. As there is an almost linear correlation between the plastic work and the final volume in Fig. 5, the equation can be written:

$$\sigma_\mathrm{t} = \mathrm{k}(\mathrm{PW})^{T_f} \tag{4}$$

The above expression was used to fit the data in Fig. 7 with a power law trend (see later).

3.2. Transverse compression; Brazilian test

In Fig. 6, it may be seen that the strain, which can be defined as $(D_0 - D/D_0)$ where D_0 is the initial diameter of the compact and D is the current diameter is nearly a linear function of the imposed force. There is, however, a notable induction period; typical of a strain of 0.005 units. The failure strain increases in proportion to the MCC mass fraction. This may be an indication that the ductility, and hence the durability, of the tablets vary as with the MCC mass fraction, in a way that the higher the MCC mass fraction the more ductile is the tablet. On the other hand, the slopes (Table 2) obtained from fitting a linear trend to the curves in Fig. 6 indicate that the stiffness of a tablet is also dependent upon the mass fraction of MCC. The larger the MCC fraction the greater is the stiffness and the strain to rupture of the tablet. The stiffness values span a factor of twenty and the strain a factor of eight.

All tablets showed a normal tension mode of fracture using the Brazilian test method and the tensile strength for each tablet was calculated using the following equation (2, 14,15):

$$\sigma_x = 2P/\pi Dt \tag{5}$$

where σ_x is the tensile strength of the testing sample, P is the fracture force, D is the die diameter and t is the thickness of the sample.

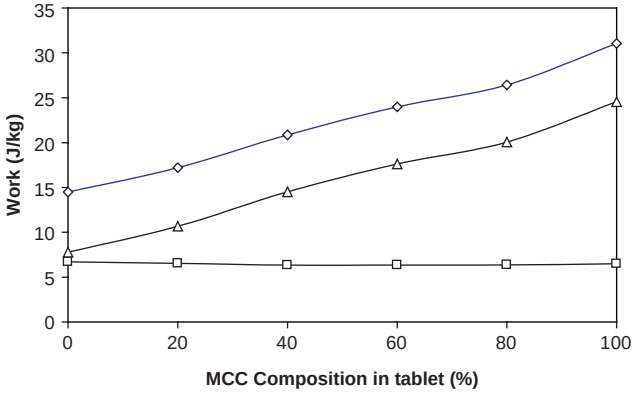

Fig. 3. The total work done on various bi-component and pure tablets, compacted to ultimate pressure of 99 MPa, as a function of MCC composition (◇, total work; △, plastic work; □, elastic work).

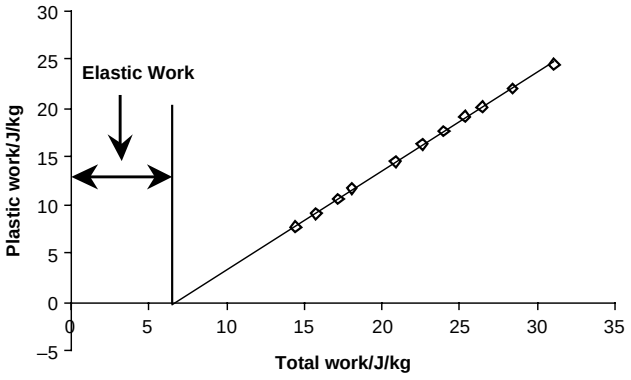

Fig. 4. The linear correlation between the plastic and total work for various binary and pure tablets compacted to ultimate stress of 99 Mpa.

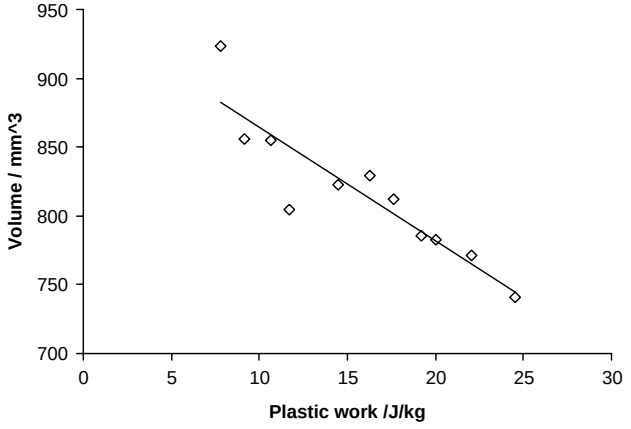

Fig. 5. The final volume of various binary and pure tablets, compacted to ultimate stress of 99 MPa, as a function of their plastic work.

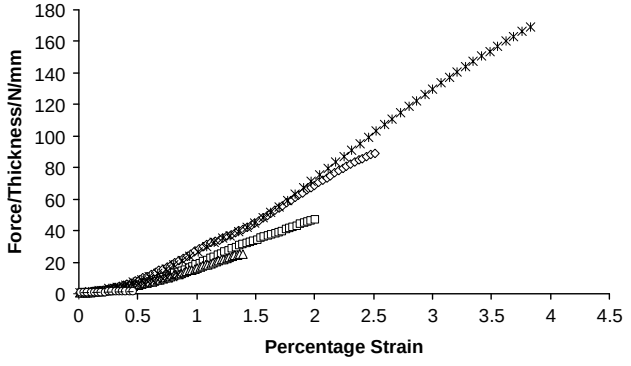

Fig. 6. The fracture profile of a few bi-component, pure MCC and pure paracetamol tablets (◇, 20% paracetamol/80% MCC; □, 40% paracetamol/60% MCC; △, 60% paracetamol/40% MCC; ×, 80% paracetamol/20% MCC; *, pure MCC; ○, pure paracetamol).

The interrelationship between the volume fraction of paracetamol and the tensile strength of the tablets is shown in Fig. 7. In Fig. 7, it may be observed that there are apparently two distinctive and approximately linear parts for the tensile strength response of these bi-component tablets, compacted to optimum stress of 99 MPa. The first linear part (0.46–1 paracetamol volume fraction) is where the behaviour and the tensile strength of the tablets is apparently almost entirely

Table 2
The slope of the curves in Fig. 6, obtained by fitting a linear trend to the curves, and the strain to rupture in the same figure

Material	Slope/N	Strain to failure %
Pure MCC	178.33	3.83
80% MCC +20% paracetamol	148.39	2.51
60% MCC +40% paracetamol	104.58	2.00
40% MCC +60% paracetamol	78.46	1.39
20% MCC +80% paracetamol	60.17	0.84
Pure paracetamol	8.63	0.46

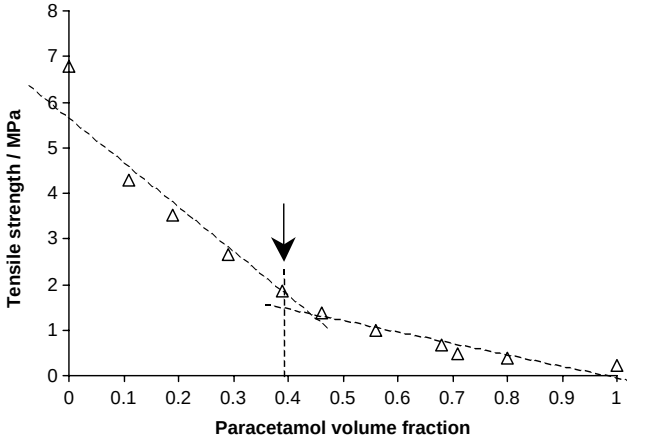

Fig. 7. Graphical representation of the tensile strength of the bi-component tablets as a function of paracetamol volume fraction.

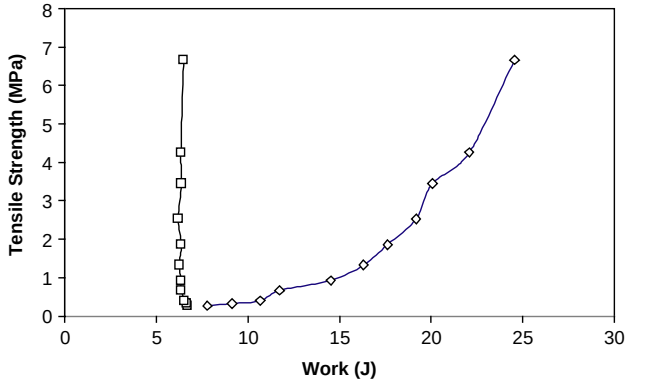

Fig. 8. The tensile strength of various bi-component and pure MCC and paracetamol tablets as a function of their plastic (◇) and elastic (□) work.

controlled by the paracetamol component. The second linear portion (0–0.39 paracetamol volume fraction or 0.61–1 MCC volume fraction) is where the MCC contribution seems to control and dominate the tablets tensile strength response.

3.3. Data analysis

It is of interest to examine the correspondence of the tensile strength (Brazilian) and the works (plastic and elastic) expended or recovered in the compaction process. Fig. 8 shows the tensile strength as a function of the plastic work of formation as the composition is varied. Assuming that where there is no plastic work expended then no tensile coherence

will be detected; then zero–zero may be taken as a point. It is then noted that the relationship is highly non-linear but is continuous. The tensile strength increases sharply at ca. 2 MPa which corresponds to a paracetamol volume fraction of ca. 0.4; see Fig. 7. However, note that a power law fitting to the plastic work data in Fig. 8 yielded an index of ca. 2.86, which is close to the universal exponent $T_f = 2.7$ (see Fig. 5 and Eqns. 3 and 4). However, this index is around three fold greater than the index value suggested by Archard [16], for stress dependence of the contact area of an interface plastic contact. Although, at this stage there is no comprehensive explanation for this discrepancy, the reason may be attributed to geometry factors, the stored elastic strain and the plastic volume work of crack which will all contribute in the right direction and can affect greatly the total plastic work. In contrast, the tensile strength is independent of the elastic work contribution; Fig. 8. The variation of the tensile strength of the bi-component tablets with various volume fraction of paracetamol may be schematically shown as follows [17]; basically these are pictorial representation of first order percolation models (Fig. 9):

Phase 1: MCC–MCC contacts, where the tablet has a distinctive high tensile strength. This scenario is anticipated for pure MCC tablet, Phase 2: MCC–paracetamol–MCC contacts, tablet does not relax much; therefore, still high tensile strength is expected, Phase 3: paracetamol–paracetamol contacts where the tablet starts to relax and the tensile strength decreases, Phase 4: complete coating of MCC particles by paracetamol

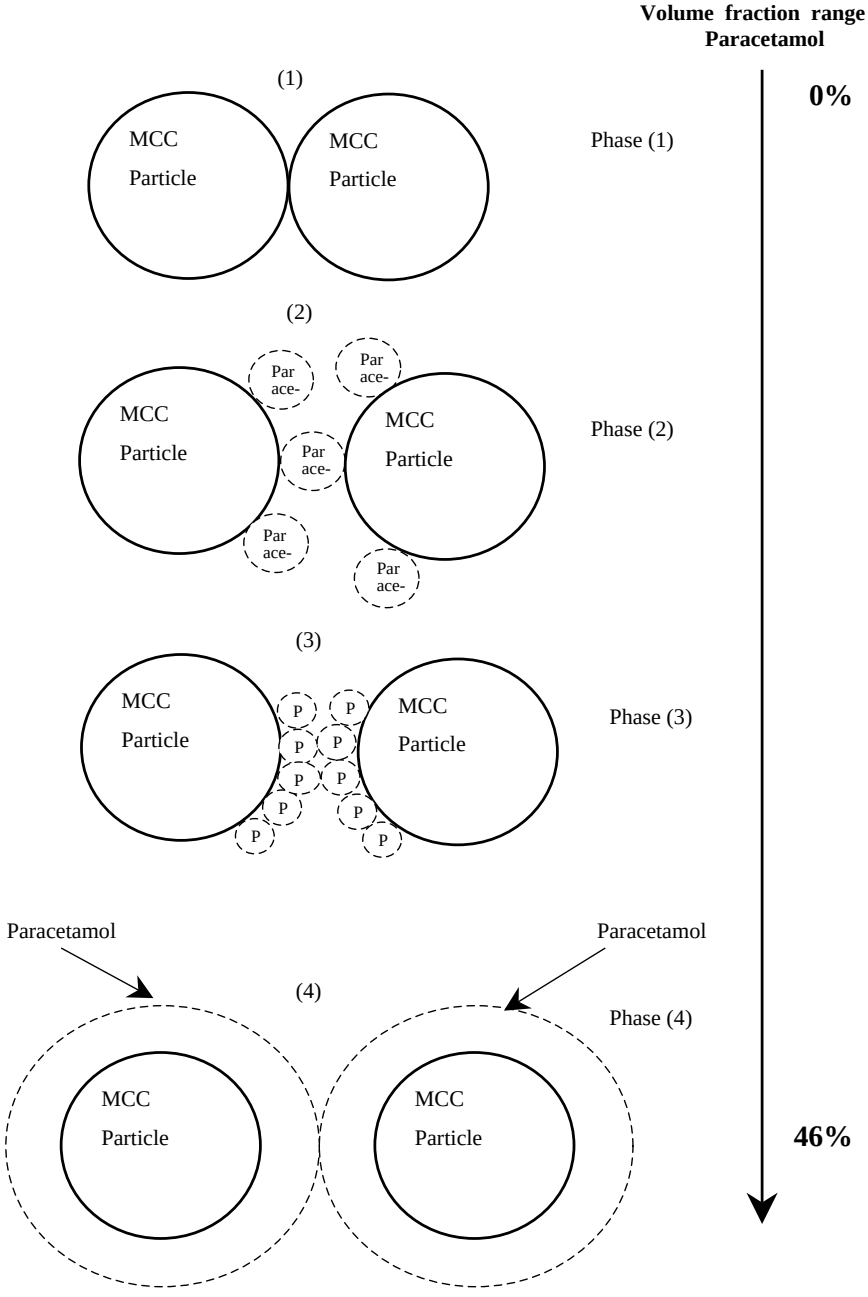

Fig. 9. The behaviour of the bi-component tablets at different mixing ratio of paracetamol and MCC (the images are not to scale).

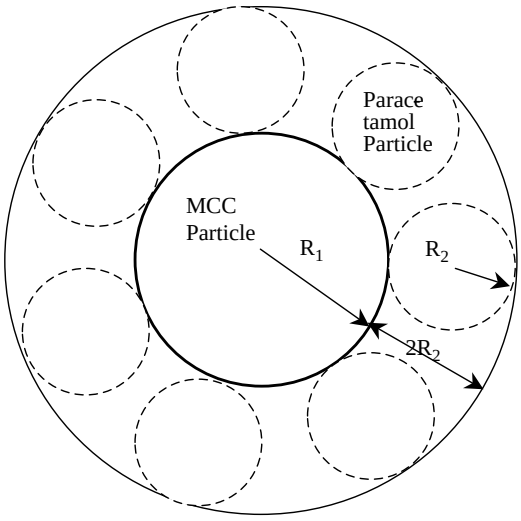

Fig. 10. Schematic of the drug particles adhering to a carrier particle, — is the boundary, ——-, represents the paracetamol (drug) particles, ▬▬ represents the MCC (carrier) particle (the image is not on scale).

particles, tablet relaxation and the tensile strength are dependent upon the fraction of the paracetamol. This is analogous with the brittle oxide on ductile metal [1] discussed earlier.

In the light of this explanation and in order to describe the tensile strength of the bi-component tablets, compacted to ultimate stress of 99 MPa, the following first order model, which may demonstrate the required volume fraction of MCC to form a viable tablet, is proposed. There are two influential factors, which can significantly affect the tensile strength, which must be considered. These two factors are the size of particle and the particle geometry. The intrinsic adhesive properties of the particles are also clearly important. To facilitate the development of this first order model it was assumed that both the drug, i.e. paracetamol, and the excipient, i.e. MCC, particles were perfectly spherical in shape; in reality, they have needle and oblong geometries, respectively. The mean particle sizes of the paracetamol and the MCC powders, used in the current study, were 10 μm and 80 μm, respectively. Additionally, we must assume that intimate mixing is achieved (Fig. 10).

$$\text{Volume fraction of MCC} \approx \frac{d_1}{d_1 + 6d_2} \tag{6}$$

where d_1 and $d_2$are the diameters of the excipient and the drug, respectively.

The above first order model demonstrates the direct proportionality of volume fraction of MCC to the particle size. The volume fraction of MCC decreases in proportion to the reduction of the particle size. It should also be noted that the MCC particles cannot be efficiently ground or reduced in size, as this material is ductile and has a high plastic deformability. However, paracetamol particles can fragment and reduce in size up to a certain critical size at which the particles start to deform plastically [18]. Further details of the compression behaviour of MCC and paracetamol behaviour alone is given in Mohammed et al. [19].

4. Conclusions

The results obtained from the compaction process and the fracture profile of some of the bi-component tablets all exhibited some ductility and hence the coherence of the bi-component tablets is a function of the MCC volume fraction. However, an examination of the tensile strength of bi-component tablets, prepared at various ratios, against the volume fraction of paracetamol showed that, within the scope of this study, paracetamol dominates and controls the behaviour of the bi-component tablets up to a ratio of 46: 54% v/v of paracetamol to MCC, as there is not much change in the tensile strength of the tablets up to the stipulated ratio. However, the behaviour of the bi-component tablets is significantly dependent upon the MCC volume fraction once the latter fraction was or exceeded 61%. The compaction data showed a very marked increase in the plastic work as the MCC mass fraction was increased; a factor of three. Strangely, the elastic work remained unaltered. The low strain induction phase was more marked for the higher paracetamol compositions. The final compaction volume scales linearly with the extent of the plastic work. The corresponding tensile data showed that the orthogonal stiffness of the compact (modulus) increased by a factor of twenty as the MCC compositions ranged from zero to unit volume fraction. In the same range, the strain to rupture changed by a factor of eight. The tensile strength followed a power law of 2.8 with respect to the plastic work and final compact volume, although the plastic work data appear to be more accurate. It is apparent that the tensile strength of the tablet is a strong function of the plastic work required for its formation but not a function of the elastic work recovered. Consequently it is likely that strong and ductile interparticle functions, whose formation dissipated a significant plastic work, are producing strong and tough compacts.

Acknowledgements

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Appendix

The particles of both materials are assumed to be spheres and the volume of the MCC and the paracetamol particles can be evaluated using the following equations.

$$\text{Volume of Avicel particle} = \tfrac{4}{3}\pi R_1^3 \quad \text{(A1)}$$

Volume of adhered paracetamol particles

$$= \tfrac{4}{3}\pi(R_1 + 2R_2)^3 - \tfrac{4}{3}\pi R_1^3 \quad \text{(A2)}$$

where R_1 and R_2 are the effective radii of the MCC and the paracetamol particles, respectively.

Simplifying eqn. (A2) for $R_1 > R_2$ we get

$$\tfrac{4}{3}\pi[R_1^3 + 8R_2^3 + 6R_1^2R_2 + 12R_1R_2^2 - R_1^3] \approx 8\pi R_1^2 R_2 \quad \text{(A3)}$$

Adding Eqns. (A1) and (A3) to evaluate the total volume we have

$$\text{Total volume} \approx \pi R_1^2\left[\tfrac{4}{3}R_1 + 8R_2\right] \quad \text{(A4)}$$

The volume fraction of MCC can be approximated to a first order using eqn. (A4); thus

$$\frac{\text{Volume fraction of Avicel} \approx \frac{4}{3}R_1}{\frac{4}{3}R_1 + 8R_2 \approx \frac{R_1}{R_1 + 6R_2}} \quad \text{(A5)}$$

Therefore, the volume fraction of MCC to form a cohesively viable tablet will be approximately

$$\approx \frac{40}{40+30} \approx \frac{4}{7} \approx 57\%$$

As was pointed out earlier the MCC particle has a significantly larger size in comparison to the paracetamol particle size. In order to examine the effect of the particle size on the volume fraction of MCC two cases will be considered. In the first case the particle size of the latter material is reduced, and in the second case an equal particle size for both, the MCC and the paracetamol is assumed. Hence

$R_1 = 20\ \mu\text{m}$

$R_2 = 5\ \mu\text{m}$

$$\text{Volume fraction of MCC} \approx \frac{20}{20+30} \approx \frac{2}{5} \approx 40\%$$

$R_1 = R_2 = 5\ \mu\text{m}$

$$\text{Volume fraction of MCC} \approx \frac{5}{5+30} \approx \frac{1}{7} \approx 14\%$$

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