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Tableting Characteristics of Micro-aggregated Egg Albumin Particles Containing Paracetamol

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Abstract

The tableting characteristics of micro-aggregated egg albumin particles containing paracetamol were evaluated and compared with non-micro-encapsulated paracetamol and coagulated egg albumin particles.

Mean yield pressure values of micro-aggregated egg albumin particles containing paracetamol and coagulated egg albumin particles were 30·5 and 49·3 MPa, respectively, which were lower than the mean yield pressure obtained for paracetamol (97·5 MPa). Paracetamol tablets obtained with micro-aggregated egg albumin particles did not show the capping characteristic of conventional paracetamol tablets. Crushing strength of paracetamol tablets obtained with egg micro-aggregated particles was similar to that obtained using paracetamol granulated with povidone and gelatin as binders at 3 and 6% (w/w) concentrations. Drug release from the paracetamol tablets depends on the choice of excipients. Crospovidone showed good protective characteristics for the tableting of micro-aggregated particles.

Crushing strength of paracetamol tablets formed from egg albumin-coated particles could be increased using crospovidone or microcrystalline cellulose as fillers and was decreased by the use of magnesium stearate. Nevertheless, magnesium stearate was useful to decrease the ejection force.

Egg albumin is widely used for micro-encapsulation processes (Deasy 1984; Tomlinson 1989). In a previous work (Torrado-Durán et al 1991), egg albumin was used to manufacture micro-aggregated egg albumin particles containing paracetamol. These micro-aggregated albumin particles were able to improve the flow characteristics of paracetamol and partially mask its bitter taste. With this new micro-encapsulation method it is not necessary to use either organic solvents or oils to prepare the albumin micro-aggregated particles containing paracetamol. For this reason, this method can be interesting and useful for industrial purposes. These micro-aggregated particles have good flow characteristics and good relative bioavailability (Torrado-Durán et al 1991).

In the present work, we explore the tableting characteristics of these micro-aggregated egg albumin particles containing paracetamol in comparison with non-micro-encapsulated paracetamol and coagulated egg albumin particles without paracetamol.

Crushing strength of paracetamol tablets obtained using micro-aggregated egg albumin particles was compared with the crushing strength obtained with paracetamol granulated with povidone and gelatin. The possible addition of different fillers (lactose, microcrystalline cellulose, mannitol and crospovidone) in order to increase the crushing strength of the paracetamol tablets was explored. The drug release of some of these formulations and the effect on crushing strength after addition of different amounts of magnesium stearate was also studied.

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Materials and Methods

Materials

Paracetamol BP (Fisons Ltd, UK), egg albumin (Ovosec, Spain), lactose NF 80M (Sheffield, USA), microcrystalline cellulose NF (Avicel PH 101, FMC, USA), mannitol NF (ICI Americas Inc, USA), gelatin (Amend, USA), magnesium stearate NF (Durkee Foods SCM, USA), povidone (polyvinylpyrrolidone NF, PVP K29/32, GAF, USA) and crospovidone NF (polyplasdone XL-10, GAF, USA) were obtained from the sources indicated.

Methods

Preparation of micro-aggregated egg albumin particles containing paracetamol. The method previously reported (Torrado-Durán et al 1991) was used. Paracetamol was added to an aqueous egg albumin solution and stirred to produce a suspension. The system was then heated to coagulate the albumin and to promote the formation of micro-aggregated egg albumin particles. These particles were then isolated by decantation, dried at 50°C for 12 h and sieved to obtain a particle size of 0·4–0·25 mm. The final paracetamol content in the micro-aggregated particles was 66% w/w.

Coagulated egg albumin particles. An aqueous egg albumin solution was heated at 60°C for 1 h. The coagulated egg albumin particles were then dried in an oven at 50°C for 12 h and sieved.

Paracetamol granulation. Paracetamol was granulated in a planetary mixer using an aqueous solution of two different binders, povidone and gelatin. Both binders were used at two different concentrations of the final dried granules, 3 and 6% w/w. The granules were sieved and the fraction between 0·4 and 0·25 mm was isolated.

Filler granulation. Lactose, Avicel PH 101, mannitol and crospovidone were granulated with water, dried and sieved to obtain a size fraction of 0·4–0·25 mm.

Compaction analysis. The experimental powders (pure paracetamol and egg albumin materials) were tableted at 275 MPa (±25 MPa) using an instrumented eccentric tablet press (Brzeczko 1989) (Arthur Colton Co., model 321). Tablets of 8·9 mm diameter, weighing approximately 225 mg were prepared at a machine speed of 20 tableting cycles min^{-1}. The following materials were tableted: formulation I, paracetamol; formulation II, coagulated egg albumin particles; formulation III, micro-aggregated egg albumin particles containing paracetamol.

Quantitative analysis of compaction data was carried out in accordance with the Heckel equation (Heckel 1961a,b):

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

The relative density D is given by the ratio between the apparent density of the compact at pressure P and the true density of the powder. K is the slope of the straight line portion, the reciprocal of which is referred to as the mean yield pressure. True density was measured by helium displacement using a multivolume pycnometer (Micromeritics).

Punch force transmission ratio (R), which is the ratio of maximum lower punch force to the maximum upper punch force, was also determined.

Tableting and crushing strength. Micro-aggregated egg albumin particles containing paracetamol alone or in combination with different excipients (lactose, Avicel PH 101, mannitol, crospovidone, magnesium stearate) were obtained. These materials were tableted at different pressures using an instrumented rotary tablet press (Stokes B-2). Flat-faced tablets of 11 mm diameter, weighing 250 mg, were obtained at a machine speed of 30 tablets min^{-1}. For determining tablet crushing strength, a mechanical strength tester (hardness tester HT-300, Key, USA) was used.

Scanning electron microscopy. A scanning electron microscope (JEOL-JSM-T-200, USA) was used to study the surface characteristics of the different materials.

Drug release. The dissolution was performed according to the USP XXII for paracetamol tablets using phosphate buffer, pH 5·8.

Ejection force. Ejection force was measured and expressed as unit ejection force, which is the ejection force normalized for the tablet-die wall contact area (Mitrevej & Augsburger 1980).

Results and Discussion

Fig. 1 shows the Heckel plot of pure paracetamol, coagulated egg albumin particles and micro-aggregated egg albumin particles containing paracetamol. The initial part of the compression cycle shows a nonlinear consolidation at low compressional loads, indicating rearrangement and particle fragmentation (Duncan-Hewitt & Weatherly 1990)

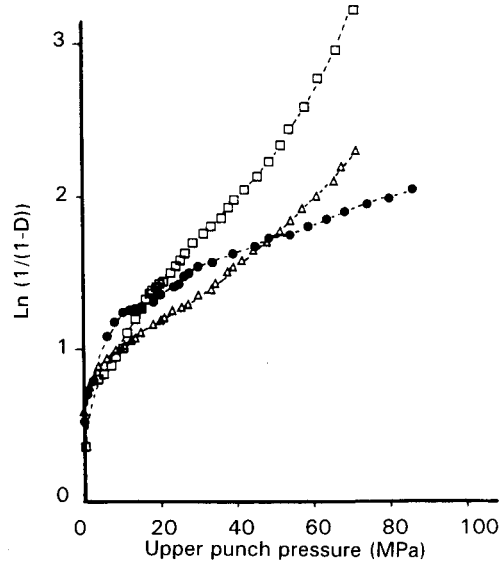

FIG. 1. Heckel plots of paracetamol (●), coagulated egg albumin particles (△), and egg albumin micro-aggregated particles containing paracetamol (□).

in all the three materials tested. This type of behaviour is more evident for paracetamol than for the coagulated egg albumin particles. As the load is increased, a linear plot results indicating elastic and plastic deformation.

Yield pressure of the three materials tested is shown in Table 1. Yield pressure for paracetamol (formulation I) was 97·5 MPa, which is in good agreement with the values reported previously by other authors, between 96·9 and 110 MPa (Roberts & Rowe 1985; Hussain et al 1991). Unfortunately, direct compression of the paracetamol powder resulted in tablets which capped after compression, and for this reason, the crushing strengths of these tablets were not determined. The high capping propensity of paracetamol has been pointed out by different authors (Krycer & Pope 1982; Malamataris et al 1984). On the other hand, the yield pressure of coagulated egg albumin particles (formulation II) and micro-aggregated egg albumin particles containing paracetamol (formulation III) were 49·3 and 30·5 MPa, respectively. The low yield pressure of the micro-aggregated particles suggests good compression properties. When the crushing strength of these tablets was studied, it was seen that tablets made from coagulated egg albumin alone were weak, and their crushing strength could

Table 1. Mean value and standard deviation (in parenthesis) of true density, yield pressure, lubrication and crushing strength data for the three tested materials.

Material	True density ($g\,cm^{-3}$)	Yield pressure (MPa)	Lubrication	Crushing strength (N)
Formulation I	1·29 (<0·01)	97·5 (8·9)	0·75 (0·06)	—
Formulation II	1·33 (<0·01)	49·3 (10)	0·81 (0·03)	<1
Formulation III	1·31 (<0·01)	30·5 (4·3)	0·76 (0·02)	120 (5)

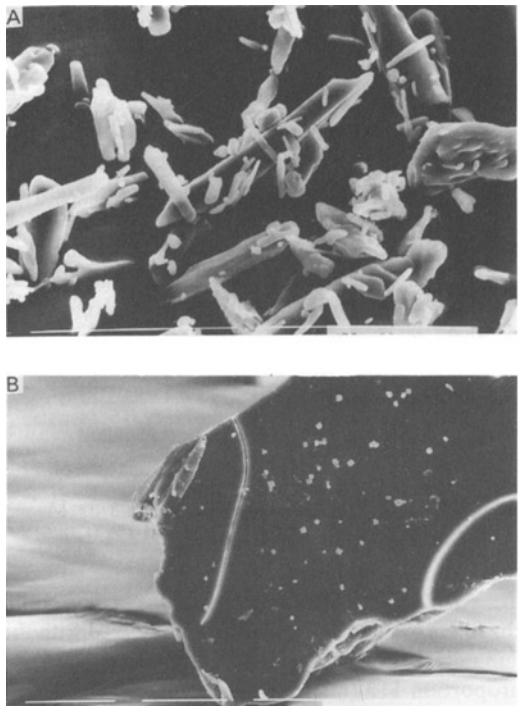

FIG. 2. Scanning electron micrographs of: A. paracetamol crystals (bar = 100 μm), B. coagulated egg albumin particles (bar = 100 μm).

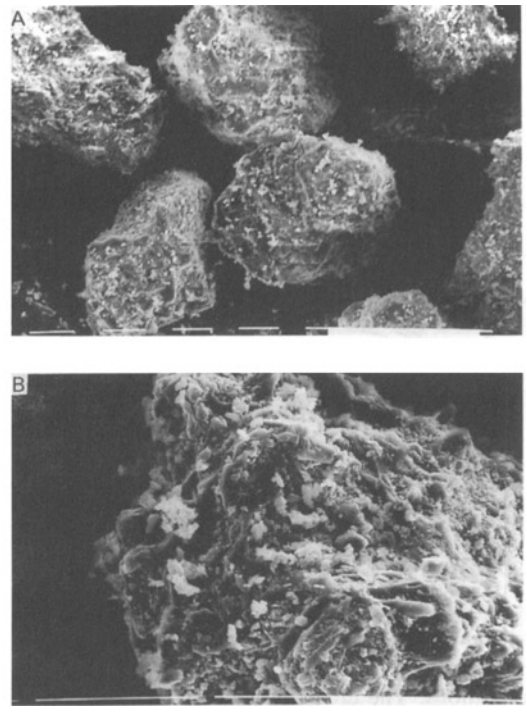

FIG. 3. Scanning electron micrographs of egg albumin micro-aggregated particles containing paracetamol (bar = 100 μm): A. appearance and morphology of the particles, B. details of the surface.

not be measured. Tablets of micro-aggregated egg albumin particles containing paracetamol showed high crushing strength.

Scanning electron microscopy was used to clarify the surface characteristics of the particles.

Fig. 2 shows the appearance of paracetamol and coagulated egg albumin particles. Both materials have a crystalline appearance and smooth surface.

Fig. 3 shows the appearance of the micro-aggregated egg albumin particles containing paracetamol.

Micro-aggregated egg albumin particles containing paracetamol (Fig. 3) have a rough surface in contrast with the smooth surface of the egg albumin particles. Thus, although the size of the particle is similar, the specific surface area is different and this factor can affect the compression characteristics, especially if materials consolidate mainly by plastic deformation (Karehill et al 1990).

A characteristic of micro-aggregated egg albumin particles containing paracetamol is a high moisture content (Torrado-Durán et al 1991) and an increasing moisture content in paracetamol powder has been reported to decrease the mean yield pressure of paracetamol (Garr & Rubinstein 1992).

This remarkable improvement in the compression properties of paracetamol achieved by using micro-aggregated egg albumin particles can be due to the binding properties of albumin. The elastic compression behaviour of paracetamol (Obiorah 1978) can be changed to a more plastic behaviour when paracetamol is granulated with binding agents (Obiorah & Shotton 1976; Doelker & Shotton 1977). Moreover, the addition of polymeric binders increases the crushing strength of paracetamol tablets (Rowe 1990).

As is shown in Fig. 1, paracetamol behaved as a fragmenting material when tableting, while the coagulated egg albumin particles had a compression behaviour similar to that of a plastically flowing material. Egg albumin micro-aggregated particles containing paracetamol showed a plastic behaviour. This is in good agreement with the results described by Ilkka & Paronen (1993) using binary mixtures, where a plastically flowing component had a greater effect on the compression behaviour of the mixture than the fragmenting component.

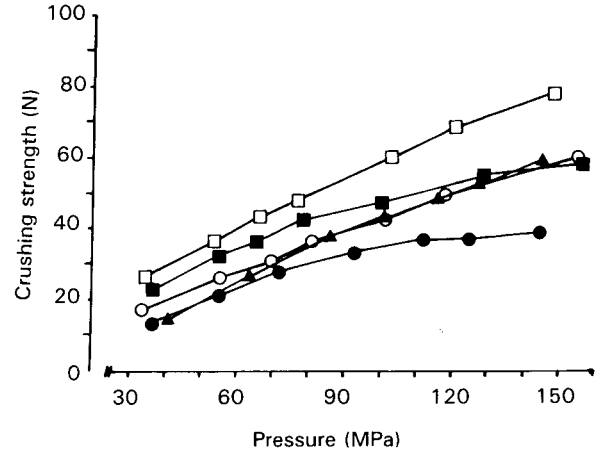

FIG. 4. Crushing strength vs compressional pressure of different paracetamol tablets. ● Conventional granulation using gelatin at 3% w/w; ○ conventional granulation using gelatin at 6% w/w; ■ conventional granulation using povidone at 3% w/w; □ conventional granulation using povidone at 6% w/w, and ▲ micro-aggregated particles containing paracetamol.

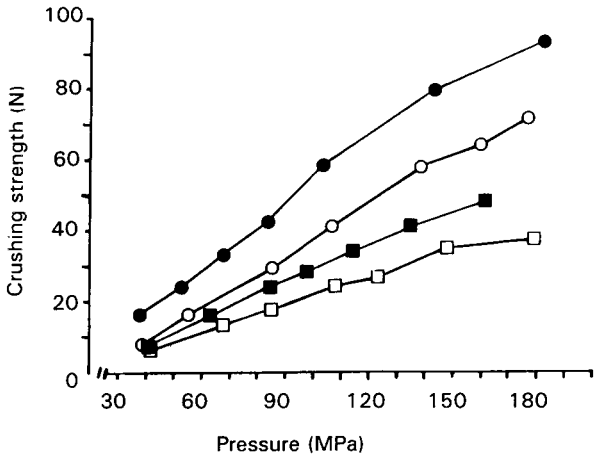

FIG. 5. Crushing strength vs compressional pressure of tablets produced by binary mixtures of egg albumin micro-aggregated particles containing paracetamol with different fillers at a ratio 1:3 (filler: micro-aggregated particles). ● Avicel PH 101; ○ crospovidone; ■ lactose; and □ mannitol.

Conventional granules of paracetamol were obtained using povidone and gelatin as binders at two different concentrations. The crushing strength of tablets obtained with these granules at different compressional pressures were compared with micro-aggregated egg albumin particles containing paracetamol. Fig. 4 shows that tablets obtained with micro-aggregated egg albumin particles have a crushing strength lower than that obtained with granules obtained using povidone as a binder at a 6% concentration. Nevertheless, micro-aggregated egg albumin particles have a crushing strength similar to that obtained after granulation with povidone at a 3% concentration or gelatin at 6% concentration, and slightly higher than that obtained using gelatin at 3%.

The addition of different fillers (lactose, Avicel PH 101, mannitol and crospovidone) in order to increase the crushing strength of the paracetamol tablets was explored. To this end, the fillers were granulated, dried and mixed with the egg albumin micro-aggregated particles containing paracetamol at a proportion 1:3 (filler: micro-aggregated particles).

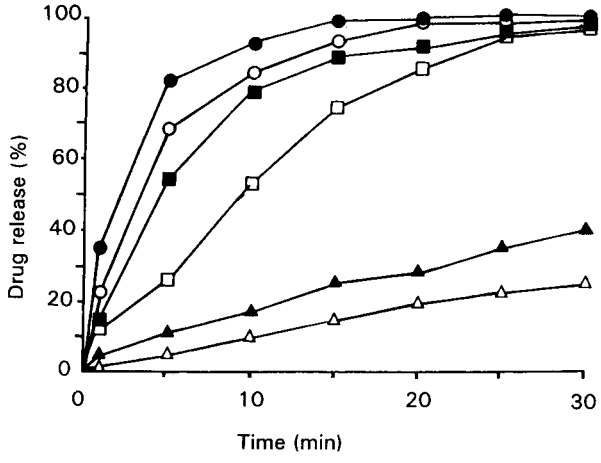

FIG. 6. Drug release at different times of the following formulations: ● micro-aggregated particles containing paracetamol; tablets of micro-aggregated particles containing paracetamol with crospovidone (ratio 3:1), tableted at ○ 115 MPa and at ■ 197 MPa; tablets of micro-aggregated particles containing paracetamol with Avicel (ratio 3:1), tableted at □ 129 MPa and at ▲ 185 MPa; and △ tablets of micro-aggregated particles containing paracetamol tableted at 108 MPa.

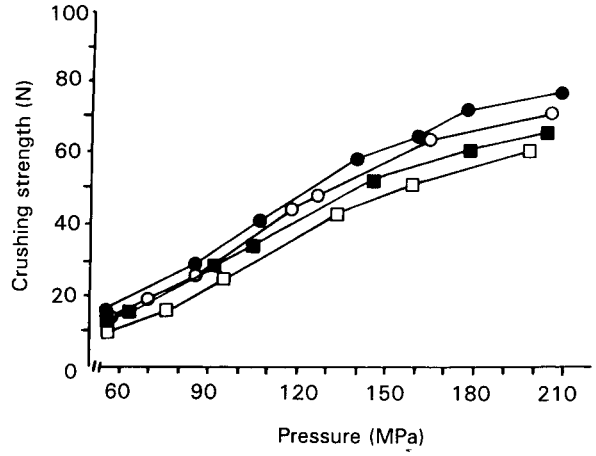

FIG. 7. The effect of magnesium stearate admixture on crushing strength of tablets of a mixture of micro-aggregated particles containing paracetamol with crospovidone (ratio 3:1). Magnesium stearate at 0% (●); 0·1% (○); 0·5% (■); and 1% (□).

Fig. 5 shows the crushing strength of tablets obtained at different compressional pressures. Tablets obtained using Avicel and crospovidone have a higher crushing strength than those obtained with micro-aggregated egg albumin particles containing paracetamol alone.

Since paracetamol doses are usually large, it is impractical to include large amounts of excipients in tablet formulations. For this reason, other proportions were not studied.

Drug release from tablets obtained using micro-aggregated particles containing paracetamol, and after being mixed with crospovidone or Avicel and tableted at different compressional forces, were compared with micro-aggregated particles containing paracetamol. Fig. 6 shows that tablets of egg albumin micro-aggregated particles containing paracetamol have a significantly ($P < 0.01$) slower release than the non-compressed micro-aggregated particles. This

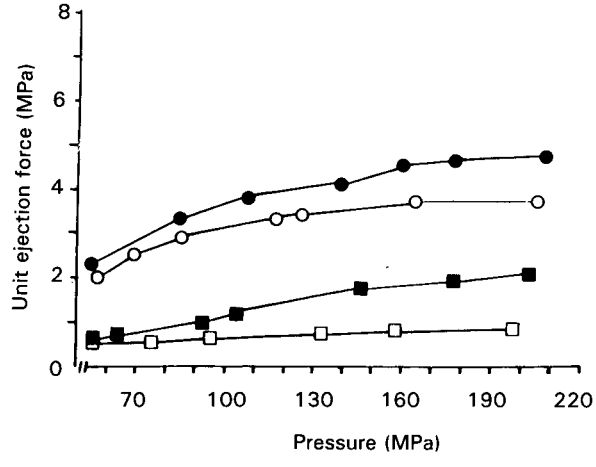

FIG. 8. Effect of magnesium stearate on the unit ejection force of tablets of a mixture of micro-aggregated particles containing paracetamol with crospovidone (ratio 3:1). Magnesium stearate at 0% (●); 0·1% (○); 0·5% (■) and 1% (□).

effect is probably due to the binding of the micro-aggregated particles during compression. A similar effect has been reported for ethyl cellulose microcapsules (Jalšenjak et al 1980; Chemtob et al 1986). This effect can be modified by addition of fillers. Fig. 6 shows that mixtures of crospovidone and Avicel with egg albumin-micro-aggregated particles containing paracetamol makes drug release faster than for tablets without fillers, and more similar to the drug release obtained by the micro-aggregated egg albumin particles before compression. Avicel and crospovidone seem to partially avoid the binding of micro-aggregated particles and the subsequent changes on drug release produced by compression of the micro-aggregated egg albumin particles. This effect is more evident for crospovidone than for Avicel. For this reason, crospovidone seems to have a protective effect for the micro-aggregated particles during compression.

The effect of magnesium stearate on the crushing strength of micro-aggregated particles with crospovidone is shown in Fig. 7. The addition of magnesium stearate decreases the crushing strength of the tablets in a similar proportion to that described for paracetamol DC granules (Hussain et al 1991). Fig. 8 shows how the ejection force is decreased by the use of magnesium stearate.

It can be concluded from the present work that egg albumin can be useful in increasing the compressional characteristics of paracetamol. Egg albumin micro-aggregated particles containing paracetamol have a low yield pressure and show good tableting characteristics. The crushing strength of the tablets can be further improved by using Avicel or crospovidone as fillers. Drug release characteristics of the tablets show that crospovidone has good protective characteristics for the tableting of micro-aggregated particles. The ejection force was decreased when magnesium stearate was used, although a slight decrease in crushing strength was also observed.

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