J. Pharm. Pharmacol. 1984, 36: 145–152
Received August 9, 1983

Fluidized bed film coating of an ordered powder mixture to produce microencapsulated ordered units

W. J. THIEL* AND L. T. NGUYEN

School of Pharmaceutics, Victorian College of Pharmacy Ltd., 381 Royal Parade, Parkville, Victoria 3052, Australia

Very finely divided particulate salicylic acid (2–5 μm) was microencapsulated using conventional fluidized bed coating techniques. The process involved spray coating a preformed ordered mixture, in which the micronized particles are adsorbed on the surface of a coarser carrier material. The mixtures contained 0·1, 1·0 and 5·0% weight of microfine model drug (salicylic acid). Between 75 and 95% of the micronized particles were retained on the carrier surface beneath the film. This process offers a novel method of microencapsulating very fine particulate materials, which may find an application in the production of enteric coated and sustained release microdose products. A recent publication on electrostatic charge interactions in ordered mixtures reported that the addition of a third component can affect the stability of a binary ordered mixture. Addition of 2% talc increased the stability of some mixtures during coating and resulted in the microencapsulation of a significantly greater amount of micronized model drug. A 0·1% salicylic acid binary ordered mixture retained 74% of model drug beneath the film, the 0.1% ternary mixture (2% talc) gave a mean retention of 99%.

Travers & White (1971) showed that fine cohesive particles adsorbed on the surface of a coarser excipient and suggested that this type of mixture could have pharmaceutical applications. The term *ordered mixing* was given to this phenomenon by Hersey (1975). Ordered mixing has potential advantages for the manufacture of low dosage tablets and capsules. Crooks & Ho (1976) and Johnson (1979) have investigated the use of ordered mixtures for direct compression tableting. Johnson (1979) concluded that the benefits could only be realized if ordered unit segregation (Yip & Hersey 1977) was avoided.

Stephenson & Thiel (1980a) showed that preformed ordered mixtures were mechanically stable when fluidized for 1 h. The adsorption forces were sufficiently strong to prevent the micronized component elutriating from the fluidization chamber, thus opening the way to processing mixtures using air suspension techniques. The granulation of an ordered mixture, to prevent ordered unit segregation, was cited as a potential application. Recent work by Thiel et al (1983) and Thiel & Nguyen (1982) has shown that using this method it is possible to produce homogeneous granules containing 0·1% model drug.

The other application discussed by Stephenson & Thiel (1980a) was fluidized bed film coating of an ordered mixture to produce microencapsulated ordered units. Fluidization techniques offer a relatively simple way of applying a uniform film of a desired thickness, but the method is usually restricted to particles greater than 200 μm; below this size, particle agglomeration becomes a serious problem. Using specialized fluidization equipment it is possible to encapsulate smaller particles, Fanger (1974) shows the lower limit as approximately 40 μm. However, if the micronized particles (2–5 μm) are adsorbed on a coarser carrier (300–700 μm), the ordered units can be processed in conventional equipment. Film coating of very fine particulate materials is then possible; the microencapsulated ordered unit is shown in Fig. 1a.

Ordered unit segregation decreases the homogeneity of a mixture; the magnitude of the change in homogeneity depends on the distribution of micronized model drug on the different size fractions of carrier. Thiel & Nguyen (1982) defined the demixing potential (DP%) of a mixture as the coefficient of variation of model drug in the different size fractions

$$DP\% = \frac{100}{\bar{p}} \sqrt{\Sigma \frac{w}{100} (p - \bar{p})^2} \qquad (1)$$

where w is the weight % in a particular size range, p is the proportion by weight of micronized material

* Correspondence.

and $\bar{p}$ is the average content of the mixture given by

$$\bar{p} = \frac{\Sigma pw}{\Sigma w} \quad (2)$$

An ideal mixture has a DP value of zero, indicating an equal proportion of micronized particles is associated with each size fraction of carrier. The homogeneity of such an ideal mixture cannot be affected by order unit segregation. Thiel & Nguyen (1982) and Thiel et al (1983) showed that granulation of preformed ordered mixtures reduced the value of DP to 4–10%. Film coated granules (Fig. 1b) may provide an alternative method of microencapsulating fine particles.

This study investigated the production of microencapsulated particles of model drug by the direct application of a film coating to an ordered mixture, as shown in Fig. 1a. The spray rate was chosen to give minimum agglomeration of the ordered units. Recent work on electrostatic charge interactions by Staniforth & Rees (1982) and Staniforth et al (1982) has shown that the addition of a third component alters the stability of a binary ordered mixture. The effect of addition of 2% talc on the mixture stability during coating was investigated.

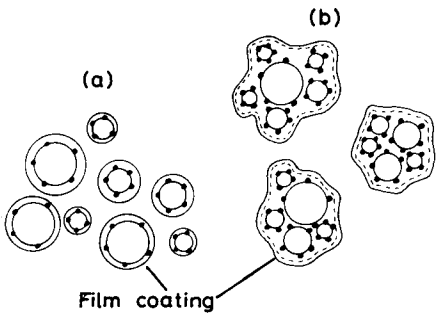

FIG. 1. (a) Microencapsulated ordered units (b) Film coated granules (agglomerated ordered units) - - - - - granule extent.

MATERIALS AND METHODS

Production of mixtures

Ordered mixtures, containing 0·1, 1·0 and 5·0% of micronized salicylic acid and direct compression vehicles, were produced in a Revolvo cube mixer fitted with an internal agitator (load 3 kg, cube 17 rev min^{-1}, agitator 35 rev min^{-1}, 300 min mixing). The cube of the mixer was fabricated from stainless steel and was electrically earthed. Two excipients were used, spray dried lactose (35 mesh) De Melkindustrie Veghel, Holland, and Emdex (dextrose) Edward Mendell, U.S.A. The Emdex was sieved and the fraction used contained 95% weight in the range 350–710 μm. The lactose comprised 95% in the range 425–710 μm. The micronized salicylic acid had a particle size of 2–5 μm, determined by optical microscopy.

Ternary mixtures were produced by adding 2% weight of talc to preformed 0·1, 1 and 5% ordered mixtures of salicylic acid and lactose. After addition of the talc, the three components were mixed for a further two hours in the cube mixer. Staniforth et al (1982) showed the addition of 2% talc improved the stability of a 1% ordered mixture of salicylic acid and sucrose.

Coating

One and a half kilograms of ordered mixture was transferred into the fluidization chamber of the Aeromatic fluidized bed (size 1, laboratory unit, capacity 1–2 kg). The mixture was spray coated with a 5% solution of cellulose acetate phthalate (CAP) in aqueous sodium hydroxide (pH 7–8). The coating conditions are given in Table 1; the rate at which the coating solution was applied gave minimal agglomeration of the ordered units. The duration of spraying varied between 3 and 7 h, giving a coating of 1·7–7·3% weight. Some coating experiments were also performed using 3% aqueous hydroxyethylcellulose and 8% CAP in a mixed organic solvent (50% wt methylene chloride and methanol). After coating, the material was dried for 20 min with warm air. Ten 500 mg samples were removed using a concentric cylindrical sampling thief and were assayed for salicylic acid.

Table 1. Coating conditions.

Bed weight	1·5 kg
Coating solution	5% aqueous CAP, pH 7–8
Solution rate	200–300 ml h^{-1}
Atomizing air pressure to spray	150–200 kN m^{-2}
Inlet air temperature	70 °C
Bed temperature during coating	35–45 °C
Fluidizing air flow rate	50–60 m^3 h^{-1}
Duration of coating	3–7 h

Mixture stability during fluidization

The mechanical stability of the ordered mixtures, when subjected to prolonged fluidization, was studied by fluidizing at ambient temperature, air flow rate 40 m^3 h^{-1}, for 7 h. Four 500 mg samples were removed with a sampling thief at 5, 15, 30, 60, 120, 180, 300 and 420 min. The samples taken were assayed for salicylic acid and the mean content and standard deviation calculated. The stability of differ-

ent concentration binary and ternary mixtures was investigated.

Fluidization chamber overhead filters

During all coating and stability experiments, the fluidization chamber was equipped with the standard overhead filters normally used for granulation. Fine material was periodically blown off the filters and returned to the bed during continuous fluidization. The filters prevented the elutriation of bed material with a particle size greater than 20–30 μm.

Analytical methods

The samples of ordered mixtures and hydroxyethylcellulose microcapsules were assayed by uv spectrophotometry in 50% aqueous ethanol at the wavelength of 300 nm.

The samples of CAP microencapsulated ordered units were analysed using a Perkin-Elmer 3000 fluorescence spectrometer. The samples were dissolved in a buffer solution of disodium hydrogen orthophosphate and sodium hydroxide (pH 11), the volume being adjusted with buffer to give an appropriate concentration. The excitation wavelength used was 310 nm and the emission measured at 405 nm. Calibration of the instrument over the concentration range 0·1 to 1 μg ml^{-1} showed good linearity. Preliminary work, using excitation and emission spectra and a uv absorbance versus wavelength scan, indicated the CAP did not interfere with the salicylic acid assay at the selected wavelengths. The accuracy and precision of the assay (including dilution) were determined for a standard solution containing 0·5 mg ml^{-1}. After a 1000 fold dilution, the mean concentration (±95%) of ten samples of standard was 0·496 (±0·004) μg ml^{-1} with a coefficient of variation (c.v.) = 1·1%.

Determination of DP% for the microencapsulated material

An 80 g bulk sample of CAP microencapsulated ordered mixture was taken by allowing the 1·5 kg batch to discharge from a hopper. A sample container was passed through the discharging stream at set time intervals. The 80 g bulk sample was sieved for 20 min (Endecotts test sieves, B.S. 410). Four 500 mg samples were removed from each size fraction and the individual salicylic acid content determined fluorometrically (All sets of four samples had a c.v. ≤5·2%). The distribution of micronized salicylic acid in the different size fractions was quantified by calculating the DP% value using equation 1. Previously, Thiel & Nguyen (1982) established that the hopper flow method removed representative samples from a batch of material.

Statistical analysis of the results

A computer program (MLTCOMP) was used to perform multiple comparisons between the means of independent groups of data. The program performed a one-way ANOVA to test for equality of means in the various treatment groups. An ordered list was printed which identified individual means or subgroups of means which were statistically significantly different at the α level. The program calculated simultaneous confidence intervals on the significant differences between group means. The statistical theory (the S and T-method of multiple comparison) on which the program computations are based is described by Scheffé (1959).

RESULTS AND DISCUSSION

The stability of the different strength binary ordered mixtures during prolonged fluidization are shown in Figs 2 and 3. The error bars indicate the 95% for the mean percentage of micronized salicylic acid retained. The mixtures made with Emdex (Fig. 3) were more stable than spray dried lactose (Fig. 2).

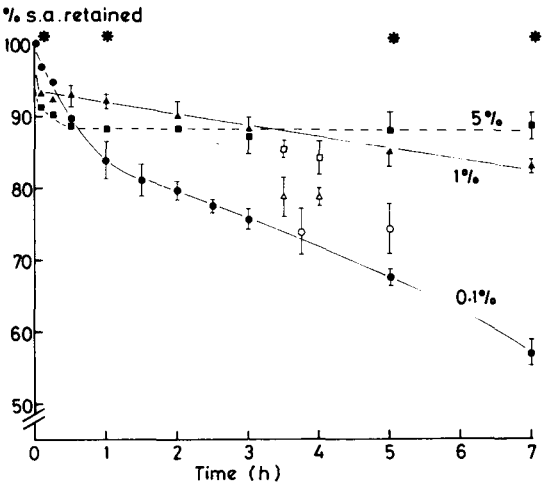

FIG. 2. Fluidization stability of lactose ordered mixtures, ■ 5% s.a., ▲ 1% s.a., ● 0·1% s.a. Coating with aqueous CAP, □ 5%, △ 1%, ○ 0·1%. * Means % s.a. retained are significantly different (MLTCOMP α = 0·05). Error bars indicate 95% CI.

This is in agreement with the findings of Staniforth et al (1981), who used an ultracentrifuge method to investigate interparticulate forces in ordered mixtures. The program MLTCOMP was used to perform a multiple comparison of the mean % of

salicylic acid retained at each sample time. The times at which the three means in the different concentration mixtures were statistically significantly different ($\alpha = 0{\cdot}05$) are indicated in Figs 2 and 3.

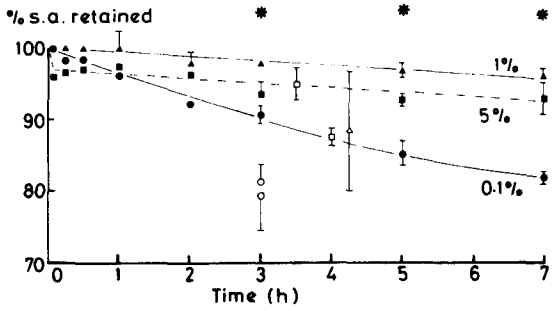

FIG. 3. Fluidization stability of Emdex ordered mixtures, ■ 5% s.a., ▲ 1% s.a., ● 0·1% s.a. Coating with aqueous CAP, □ 5%, △ 1%, ○ 0·1%. * Means % s.a. retained are significantly different (MLTCOMP $\alpha = 0{\cdot}05$). Error bars indicate 95% CI.

The results show the findings of Stephenson & Thiel (1980a), concerning the mechanical stability of ordered mixtures, need to be qualified when prolonged periods of fluidization are used. The lowest concentration mixtures (0·1%) were the least stable at times $t \geq 1$ h. With lactose, the 5% mix was the most stable at 7 h and virtually all the salicylic acid loss occurred during the first 30 min fluidization. In contrast, the Emdex 1% mixture retained the greatest percentage at $t \geq 3$ h.

Fig. 4 shows the fluidization stability results for the 0·1% binary and ternary mixtures (2% talc added) with lactose carrier; addition of talc had no stabilizing effect during fluidization. The % of salicylic acid retained in the ternary mixture was significantly lower for $t \geq 3$ h (Students t-test, $P < 0{\cdot}05$). This observation differs from that reported by Staniforth et al (1982), in which a 1% ordered mixture of sucrose and salicylic acid showed an increased stability after addition of talc.

Table 2 shows the mean % of micronized salicylic acid retained in the samples taken from the CAP film coated ordered mixtures; between 74 and 95% microencapsulation was achieved. The content coefficient of variation (c.v.), sample size and % weight of coating are tabulated and the subgroups of means which are not statistically significantly different are indicated (MLTCOMP 0·05). Each coating experiment was replicated twice (except Emdex 1%) and gave reasonably reproduceable results, although a c.v. > 5% occurred for samples taken from two of the batches. Significantly greater retention occurred with the 0·1 and 1% Emdex mixtures than for lactose. At 5% concentration, Emdex was significantly above lactose in only one of the two coating experiments. These results are in general agreement with the fluidization stability of the mixtures; Emdex mixtures were more stable and the % retention was lowest in the most dilute mixtures. The multiple comparison in Table 2 shows the % retention for lactose 1% was not significantly greater than for the 0·1% mixture. A similar situation occurred with Emdex, where one of the 5, 1 and 0·1% coated mixtures are bracketed together as not significantly different.

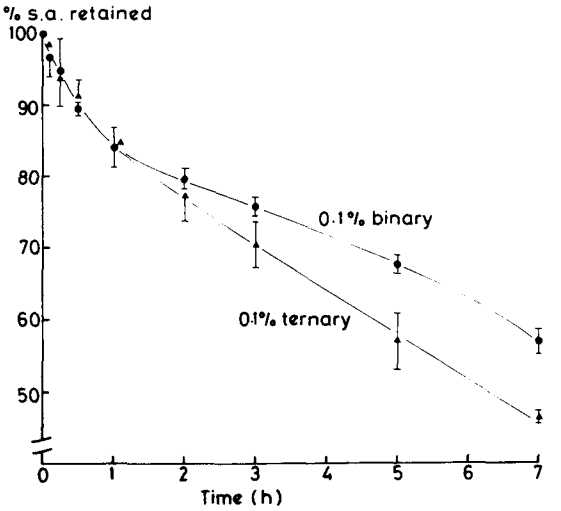

FIG. 4. Fluidization stability, ● 0·1% s.a., lactose binary mixture, ▲ 0·1% s.a., 2% talc, lactose ternary mixture.

The coating results have been plotted in Figs 2 and 3, at the coating time used. Because the layer of micronized salicylic acid adhering to the carrier is being progressively protected as coating proceeds, higher retention values were expected than for the mixture stability during fluidization. However, in almost all cases the % retained in the microcapsules was significantly lower. The surface forces responsible for the formation of ordered mixtures are not well understood. The effect of increased humidity during aqueous coating appears to reduce the stability of the mixture. In earlier studies, Stephenson & Thiel (1980b) and Thiel & Stephenson (1982), high humidity (85% RH) did not affect the formation of ordered mixtures.

The micronized salicylic acid on the carrier surface

Table 2. CAP microencapsulation of 0·1 to 5% ordered mixtures.

Carrier	Mix % s.a.	Mean % s.a.*	Subgroups of means†	Sample size	Content c.v. %	% wt coating
Emdex	5	94·6		10	3·2	2·4
Emdex	1	88·4		5	8·3	1·7
Emdex	5	87·5		10	1·9	2·7
Lactose	5	85·4		10	1·8	3·2
Lactose	5	84·1		10	3·7	3·6
Emdex	0·1	81·3		5	2·5	2·4
Emdex	0·1	79·4		5	6·0	2·3
Lactose	1	78·7		10	2·4	3·5
Lactose	1	78·7		10	4·7	3·1
Lactose	0·1	74·3		4	3·1	3·0
Lactose	0·1	74·0		4	2·8	7·3

* Retained under the film coating.
† Subgroups of means bracketed together are *not* singnificantly different (MLTCOMP $\alpha = 0{\cdot}05$).

may react with the basic CAP coating solution (pH 7–8). To test whether this was a significant factor, in terms of the retention under the film, coating experiments were also performed using 3% aqueous hydroxyethylcellulose (HEC). The results show (Table 3) there was a 7–8% decrease in retention when HEC coatings were applied to 0·1 and 1% lactose mixtures. The 5% mixture did not show a difference between the coatings.

An attempt was made to stabilize the binary ordered mixtures by addition of 2% talc. The percentage of micronized material retained in the CAP film coated ternary mixtures is given in Table 4, with a multiple comparison of the means for the different treatments. Addition of 2% talc to the 1 and 5% mixtures had no significant effect. In contrast, a very significant increase occurred with the 0·1% mixture, which resulted in virtually 100% microencapsulation. Each coating experiment was replicated twice and gave reasonable reproducibility. Talc stabilization of a 0·1% mixture also occurred when 3% HEC coatings were used. The % retention in the HEC coated binary mixture was 67·0 which increased to 83·9% when a 2% talc ternary mixture was coated. This result very dramatically illustrates the stabilizing effect of talc reported by Staniforth et al (1982), yet it is not reflected in the fluidization stability data in Fig. 4.

Table 3. Comparison of 3% HEC with 5% CAP aqueous coating solution (lactose carrier).

Mix % s.a.	Coating Sol.	Mean % s.a.*	Subgroups of means†	Sample size	Sample s.d.
5	CAP	85·4		10	1·5
5	CAP	84·1		10	3·1
5	HEC	82·3		10	1·4
1	CAP	78·7		10	3·7
1	CAP	78·7		10	1·9
0·1	CAP	74·3		4	2·3
0·1	CAP	74·0		4	2·1
1	HEC	71·4		10	0·9
1	HEC	68·0		10	0·6
0·1	HEC	67·0		10	3·0

* Retained under film coating.
† Subgroups of means bracketed together are *not* significantly different (MLTCOMP $\alpha = 0{\cdot}05$).

Table 4. The effect of adding 2% talc before coating (lactose carrier).

Mix % s.a.	Mean % s.a.*	Subgroups of means†	Sample size	Sample s.d.
0·1‡	99·4		10	1·1
0·1‡	98·6		10	1·6
5‡	87·4		10	3·0
5	85·4		10	1·5
5	84·1		10	3·1
1‡	83·6		10	1·6
1‡	83·3		10	3·8
5‡	80·8		10	1·8
1	78·7		10	3·7
1	78·7		10	1·9
0·1	74·3		4	2·3
0·1	74·0		4	2·1

* Retained under film coating.
† Subgroups of means bracketed together are *not* significantly different (MLTCOMP $\alpha = 0{\cdot}05$).
‡ Stabilized with 2% talc.

The fluidization stability test is of limited use for prediction of % retention when film coatings are applied. A possible explanation of these observations is that there are insufficient sites on the surface of the carrier to which the talc can adhere in the 1 and 5% lactose mixtures, but at lower concentrations (0·1%) the talc can bind firmly to the carrier, stabilizing the previously adsorbed salicylic acid particles. However, this does not explain the difference between the 0·1% fluidization stability and coating results. The application of the polymer or the higher humidity during coating also appears to play a role in the stabilization of the mixture by talc.

Further investigation of this aspect of the work is required.

The distribution of salicylic acid in the 5 and 0·1% (talc stabilized) CAP microencapsulated ordered mixtures is shown in Tables 5 and 6. From the sieve analysis of the 80 g bulk sample, the mean proportion was calculated from $\Sigma pw/\Sigma w$ (eqn 2) and the demixing potential (DP%) from equation 1. The DP values indicate that the homogeneity of both film coated ordered mixtures can only be affected to a small extent by segregation. If the coated ordered units segregated to such an extent that the mixture was fractionated as if it had been sieved, the DP values show the coefficients of variation (c.v.) of the segregated material would be 5·6 and 6·5%. The relationship between DP% and the specification c.v. was discussed by Thiel & Nguyen (1982). The coarse lactose carrier used in this investigation gave a relatively uniform distribution of micronized salicylic acid as a function of carrier particle size, and yielded DP values in the range 5–7%. These values are comparable to those obtained with finer carrier materials using fluidized bed granulation (Thiel & Nguyen 1982; Thiel et al 1983). They indicate that there is no advantage to be gained, in terms of the mixture homogeneity, by microencapsulating granules formed from a finer carrier (Fig. 1b) rather than the method used of direct film coating the ordered units (Fig. 1a).

Table 5. The distribution of micronized salicylic acid in the microencapsulated 5% mixture (lactose carrier).

Particle size μm	Wt % (w)	Content by proportion (p) × 10^{-2}
>600	49·5	4·12
500–600	41·6	4·15
425–500	8·1	4·44
106–425	0·7	6·08
<106	0·1	8·16

$\bar{p} = \frac{\Sigma pw}{\Sigma w}$ $4{\cdot}18 \times 10^{-2}$

$\bar{p}$ theoretical $4{\cdot}83 \times 10^{-2}$
Retention 86·5%
DP% (eqn 1) 5·6%

The value of $\bar{p}$ theoretical in Tables 5 and 6 is the content proportion calculated from the weights of materials initially loaded into the cube mixer, and adjusted for the weight of coating sprayed. The % retention of salicylic acid was calculated; for the 0·1% (talc stabilized) mixture the value was 101% and for the 5% material 86·5%. These values are in agreement with those shown in Tables 3 and 4 for the ten 500 mg samples. Tables 5 and 6 show a considerable difference in the particle size distribution of the coated binary and ternary mixtures. The microencapsulated ternary mixture (Table 6) contains more fines and considerably fewer particles >600 μm. The increased fines with the ternary mixture may reflect the talc particles acting as independent nuclei for deposition of the film coating. The decrease in weight per cent >600 μm is probably due to further attrition of the lactose carrier during the additional 2 h mixing with talc.

Table 6. The distribution of micronized salicylic acid in the microencapsulated 0·1% mixture (stablized with 2% talc, lactose carrier).

Particle size μm	wt % (w)	Content by proportion (p) × 10^{-3}
>600	20·1	0·90
500–600	50·2	0·95
425–500	27·3	1·01
106–400	2·4	1·12
<106	0·04	3·02

$\bar{p} = \frac{\Sigma pw}{\Sigma w}$ $0{\cdot}96 \times 10^{-3}$

$\bar{p}$ theoretical $0{\cdot}95 \times 10^{-3}$
Retention 101%
DP% (eqn 1) 6·5%

Attempts were made to film coat mixtures using 8% CAP in a mixed organic solvent (50% wt methylene chloride and methanol). However, the carrier particles disintegrated during coating; after 1 h the fluidized bed contained a large amount of fine lactose dust and sampling showed that more than 90% of the salicylic acid had elutriated from the fluidization chamber. Spraying organic solvent alone had the same effect on the carrier (rapid size reduction) and resulted in 70% loss of micronized salicylic acid after an hour.

Integrity of the film coatings

The microencapsulated ordered units produced with a 2–3% wt film coating (aqueous CAP, pH 7–8) showed no tendency to disintegrate in a 0·1 M solution of HCl, viewed with a microscope at 40× magnification. This indicated the integrity of the film around the ordered units. The dissolution of the film could be viewed if the solution was subsequently made alkaline by addition of NaOH. In the case of the talc stabilized mixtures, dissolution of the film was accompanied by the dispersion of the talcum powder at the film-carrier interface.

Table 7. Application of a second film (aqueous or organic CAP) to ordered mixtures microencapsulated with a primary aqueous CAP film coating (lactose carrier).

Mixture	% wt primary film (aq. CAP pH 7–8)	% s.a. retained*	2° film	% wt film after 2° coating	% s.a. retained†
1% s.a.	3·5	78·7	aq. CAP	9·3	77·7
0·1% s.a. + 2% talc	3·1	99·4	aq. CAP	8·9	99·4
1% s.a.	3·1	79·0	org. CAP	5·4	79·0
0·1% s.a + 2% talc	3·2	98·6	org. CAP	5·4	100·0

* Beneath 1° film.
† Under 2 films.

It was possible to apply further coatings of either aqueous or *organic* CAP solutions to the mixtures with a 2–3% wt aqueous CAP primary film. As shown in Table 7, no further loss of salicylic acid occurred during application of the additional film, which confirmed that the ordered mixture had been totally encapsulated by the primary coating.

CONCLUSIONS

Fluidized bed film coating of an ordered powder mixture is a novel method of microencapsulating very finely divided particulate materials. The final product is a coarse free flowing powder, containing small quantities (0·1–5%) of uniformly dispersed micronized particles beneath the film coating. The value of the demixing potential (DP) ranged from 5 to 7% and indicated the homogeneity of the microencapsulated ordered mixture can be affected to only a very limited extent by segregation.

With the two direct compression vehicles used as carrier particles (lactose and Emdex), only aqueous coating solutions could be applied directly to the ordered mixtures. When organic solutions were sprayed, the carrier particles disintegrated and almost total loss of the micronized model drug occurred. In the aqueous coated binary mixtures, between 74 and 95% of the micronized model drug was retained beneath the film. The least concentrated mixtures (0·1%) gave the lowest percentage retention. Addition of 2% wt talc to the 0·1% mixtures increased the stability during coating and resulted in 99% encapsulation with the aqueous CAP. This contrasted with the results obtained for the 1% and 5% salicylic acid mixtures, during coating no stabilization occurred with ternary mixtures containing 2% talc. The aqueous coating formed a 2–3% wt integral film around the ordered units, further coating using either aqueous or *organic* solutions was then possible. No further loss of micronized salicylic acid occurred during the application of the secondary film.

The stability tests of different concentration ordered mixtures during prolonged fluidization (7 h) showed that between 5 and 45% of the micronized salicylic acid was lost from the fluidization chamber. The findings of Stephenson & Thiel (1980a), that no loss occurs during 1 h of fluidization, needs to be qualified when longer fluidization times are used. The fluidization stability results are not very useful for predicting what will happen during coating of the mixture. Generally, the % retention of micronized model drug was lower in the microencapsulated product than the fluidization stability test would predict. This is probably due to the effect of higher bed humidity during coating. The fluidization stability results for the 0·1% salicylic acid 2% talc ternary mixture showed that talc had no stabilizing effect. This contrasts markedly with the coating results (aqueous CAP) where 99% microencapsulation was achieved with the ternary mixture and only 74% with the binary mix. No firm conclusion can be drawn concerning this result except that other factors (bed humidity or application of the polymer film) besides the addition of talc must also play a role.

Acknowledgements

The authors gratefully acknowledge the financial support of the Australian Research Grants Scheme (F7715193 and F8015114).

We wish to thank Dr Peter Stewart, Department of Pharmacy, University of Queensland for arranging to micronize the salicylic acid.

REFERENCES

Crooks, M. J., Ho, R. (1976) Powder Technol. 14: 161–167

Fanger, G. O. (1974) in: Vandergaer, J. E. (ed.) Microencapsulation, Processes and Applications. Proceedings of the American Chemical Society Symposium, Chicago (1973) Plenum Press, New York, London.

Hersey, J. A. (1975) Powder Technol. 11: 41–44

Johnson, M. C. R. (1979) J. Pharm. Pharmacol. 31: 273–276

Scheffé, H. (1959) The Analysis of Variance. 1st edn. John Wiley & Sons, New York.

Staniforth, J. N., Rees, J. E. (1982) J. Pharm. Pharmacol. 34: 69–76

Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1981) Ibid. 33: 485–490

Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1982) Ibid. 34: 141–145

Stephenson, P. L., Thiel, W. J. (1980a) Powder Technol. 26: 225–227

Stephenson, P. L., Thiel, W. J. (1980b) Ibid. 25: 115–119

Thiel, W. J., Nguyen, L. T. (1982) J. Pharm. Pharmacol. 34: 692–699

Thiel, W. J., Nguyen, L. T., Stephenson, P. L. (1983) Powder Technol. 34: 75–80

Thiel, W. J., Stephenson, P. L. (1982) Ibid. 31: 45–50

Travers, D. N., White, R. C. (1971) J. Pharm. Pharmacol. (Suppl). 23: 260S–261S

Yip, C. W., Hersey, J. A. (1977) Powder Technol. 16: 149–150