Fluidized bed film coating of an interactive powder mixture to produce microencapsulated 2–5 μm particles

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Previous work has shown an interactive (ordered) powder mixture, formed from 2–5 μm salicylic acid and a coarse spray-dried sugar, is stable when fluidized. The micronized material adheres to the carrier during fluid bed air suspension and may be film coated with a polymer. This process offers a novel method of microencapsulating very fine particulates, providing a way of manufacturing enteric-coated and sustained release microdose drug delivery systems. Different processing conditions were used in an attempt to optimize the retention of micronized model drug beneath the film. The effect of altering the following variables was investigated; polymer spray rate, addition of a third component which adhered to the binary adhesion units, and different materials of construction for the mixer used to form the interactive mixture. The microencapsulated adhesion units retained 90–95% of the micronized model drug. A statistical evaluation of the content uniformity showed that a very uniform dispersion was formed (CV <5%, 99% confidence). Multilayer film-coated adhesion units were also produced using a sequence of mixing and coating operations. This process offers a method of film coating microdose quantities of a drug, to produce a free flowing product, possessing excellent content uniformity.

Traditionally, the mixing of a coarse excipient with a cohesive drug (<5% wt) has been termed ordered mixing. However, in recent discussions of mixing terminology, Egermann & Orr (1983) and Thiel (1984) have suggested that a mixture formed between such binary components is best termed an interactive mixture. Each unit in the mixture, formed by particle interaction, is called an adhesion unit, and segregation of these entities is referred to as adhesion unit segregation.

Stephenson & Thiel (1980) showed it was possible to fluidize an interactive mixture with minimal loss of the micronized component. They suggested this may enable a film coating to be sprayed onto the fluidized mixture, thereby microencapsulating the 2–5 μm particles adhering to the surface of the larger carrier particles. The production of film-coated adhesion units, formed from micronized salicylic acid and coarse spray dried dextrose or lactose, was reported by Thiel & Nguyen (1984). Binary mixtures containing 0·1, 1 and 5% of cohesive component were coated and gave a retention beneath the film of 75–95%; the lowest values occurred with the 0·1% mixture. Some experiments were also performed introducing a third component (talcum powder), which under some conditions appeared to stabilize

the binary mixture and yielded a higher percentage microencapsulation. However, other experiments designed to study the mixture stability during fluidization did not support the hypothesis that the addition of the third component increased the mixture stability.

The objectives of this work were to determine the optimum processing conditions, with respect to maximizing the salicylic acid retention, and to investigate further the effect of adding a third component. The 0·1% lactose system was used, as this had been shown to be the least stable in previous work (Thiel & Nguyen 1984). Fig. 1a illustrates the addition of a third component to an interactive binary mixture. The talcum powder adheres to the binary adhesion units and may stabilize the original mixture. The production of multilayer microencapsulated particles was also investigated (Fig. 1b) using mixing and coating operations in sequence.

MATERIALS AND METHODS

Production of mixtures

Interactive mixtures were prepared from micronized salicylic acid and 35 mesh spray dried lactose (De Melkindustrie Veghel, Holland). Mixing was performed in an earthed stainless steel cube mixer fitted with an internal agitator (Thiel & Stephenson 1982) load 3 kg, cube 17 rev min^{-1}, agitator 35 rev min^{-1},
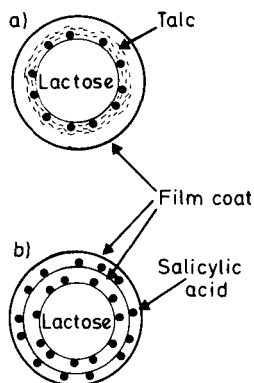
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FIG. 1a. Addition of a third interactive component (talc or magnesium stearate) to a preformed binary adhesion unit. b. Multilayer microencapsulated adhesion unit.

300 min. Some mixtures were also produced in a Perspex Erweka cube mixer (type KB 15/UG, capacity 3·4 litres) load 1 kg, cube 40 rev min^{-1}, 180 min, to assess the effect of changing the material of construction.

Ternary mixtures were manufactured in the stainless steel mixer, by adding the third component (talc or magnesium stearate) to the preformed binary interactive mixtures and blending for a further 120 min. Particle size information for the materials is presented in Table 1.

Table 1. Particle size.

Material	Particle size
Lactose 35 mesh	Spherical >95% in range 425–710 µm (sieve analysis)
Salicylic acid— micronized	Spherical, normal distribution $\bar{x} = 4\cdot1$ µm, s = 1·9 µm (projected area, microscope)
Talc	Irregular 5–30 µm (Ferets dia., microscope)
Magnesium stearate	Irregular 1–10 µm (Ferets dia., microscope)

Adhesion of talc and magnesium stearate

Talc and magnesium stearate were used to form the third component with the lactose—salicylic acid mixture in an attempt to stabilize the mixture further during fluidization. To assess the affinity of talc and magnesium stearate for the lactose carrier particles, binary mixtures of each were made (120 min, Erweka mixer) at various concentrations,

0·5–2·0%. Initially the 35 mesh lactose was screened on 300 µm to remove any fines. The material was then mixed with talc or magnesium stearate to form an interactive mixture. The resulting binary mix was placed on a 250 µm sieve and shaken for 5 min; the amount of minor component passing through the mesh was measured to assess the strength of adhesion.

Fluidized bed film coating

One kilogram of the interactive mixture, containing model drug (salicylic acid), was placed in the fluidization chamber of the Aeromatic fluid bed (STREA-1). The mixture was fluidized with warm air at 70 °C and the polymer solution sprayed onto the particles. The coating solutions used were 10% aqueous polyvinylpyrrolidone (PVP, BASF, Kollidon 30) and 5% aqueous cellulose acetate phthalate (CAP) in dilute sodium hydroxide (pH 9). The rate of spraying was carefully selected to give the most rapid polymer addition consistent with minimum granulation of the mixture. The correct conditions were established by trial and error, using sieve analysis before and after coating. Two basic methods of applying the polymer solution were used: constant and high initial rate. The volumetric rates used are shown in Fig. 2. After coating, the batch was dried by
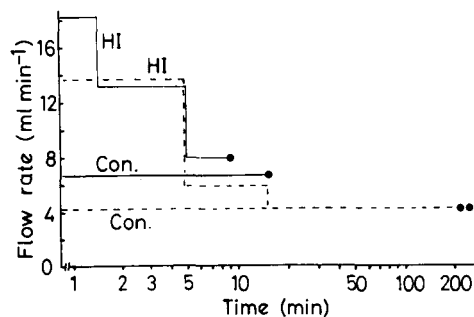

FIG. 2. Volumetric rates of application of PVP (———— 1% wt film) and CAP polymer (– – – – 5% wt) solutions using constant (Con.) and high initial (HI) flow rates.

fluidizing with warm air for 20 min. Samples were then removed to permit determination of the quantity of salicylic acid. Ten 500 mg samples were taken with a thief and a 70 g bulk sample for sieve analysis, to enable the distribution of salicylic acid in the different size fractions to be determined. Details of the sampling and assay methods are given by Thiel & Nguyen (1984). A fluorimetric method was used to determine salicylic acid in the CAP microencapsulated material and UV spectrophotometry for the PVP-coated material.

From the distribution of salicylic acid in the different size fractions, the demixing potential was calculated from

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

where $\bar{p}$ is the mean content of the mixture expressed by proportion, w the weight percent in a given size range, and p the proportion of minor component associated with that fraction. The use of DP% as a measure of the potential for a mixture to demix, as a result of adhesion unit or constituent segregation, is discussed by Thiel & Nguyen (1982, 1984).

Production of multilayer microcapsules

Application of a film coating to an interactive mixture, followed by a second mixing operation and coating was used to produce multilayer microcapsules, as shown in Fig. 1b. Adhesion units with a primary film of PVP were manufactured from 0·1 and 1% mixtures. The second mixing operation used the same concentration of salicylic acid, mixed for 120 min, 40 rev min⁻¹ in the 3·4 litre Erweka mixer. As the results presented later show, the micronized salicylic acid adhered to the PVP film to an extent comparable with lactose.

Content uniformity of the microcapsules

Orr & Sallam (1978) expressed concern about content uniformity tests for low dosage pharmaceuticals. The presence of small numbers of agglomerates of minor component, caused by inadequate mixing, leads to superpotent dosage units. To test the efficiency of the mixing process used in this work, fifty 500 mg samples were removed from some batches of the microencapsulated adhesion units. The samples were assayed individually and the content CV and coefficient of skewness $(\sqrt{b_1})$ calculated

$$\sqrt{b_1} = \sqrt{(m_3^2/m_2^3)}$$ (2)

where m_2 and m_3 are the second and third moments about the arithmetic mean. For further details of the test for skewness refer to Orr & Sallam (1978).

RESULTS AND DISCUSSION

Table 2 shows the results from the experiments designed to assess the adhesion of talcum powder and magnesium stearate to 35 mesh lactose (>300 μm). The 1% magnesium stearate and 0·8% talc interactive binary mixtures were stable, no detectable loss occurring on sieving on 250 μm mesh for 5

min. In contrast, the 2% talc mixture was unstable with a little more than half (52·8%) of the talc being dislodged. Two percent was the concentration Thiel & Nguyen (1984) used. These results were then used to determine the concentration of third component added to form ternary mixtures, in an attempt to increase the stability of the salicylic acid—lactose binary interactive mixture.

The effects of film coating of binary and ternary mixtures with 5% CAP is presented in Table 2. The 0·1% binary interactive mixture of salicylic acid was coated at constant rate and using a high initial rate. The same conditions were used to microencapsulate the 0·1% salicylic acid mixture with which 2% talc had been blended. Several replicate experiments were performed at each condition; Table 2 shows the mean % of salicylic acid retained (±95% CI) based

Table 2. Film coating (5% CAP) of a 0·1% salicylic acid interactive mixture, effect of spray rate and addition of talc.

Talc concn	Microencapsulation % (±95% CI)	
	Constant flow rate	High initial flow rate
0%	63·3 (±0·6)	
	77·3 (±1·5)	95·1 (±1·8)
	65·0 (±0·5)	96·1 (±0·6)
	55·7 (±0·7)	
2%	79·9 (±2·1)	
	84·4 (±2·0)	96·2 (±1·4)
	64·9 (±0·6)	100·2 (±2·0)

on the assay of ten 500 mg samples. The most noticeable feature is the poor reproducibility of results when a constant flow rate of polymer solution was used. Despite this variability, the addition of 2% talc appears to have little effect on the percentage of salicylic acid microencapsulated, the significant factor yielding an increased retention being the use of the high initial flow rate of coating solution. This leads to a rapid build-up of polymer over the adhesion units, which quickly protects the surface from erosion of salicylic acid. In previous work, Thiel & Nguyen (1984) used a variety of different coating solution rates. In the light of the results in Table 2, their conclusion that 2% talc increased the stability of the 0·1% lactose mixture is incorrect. This was almost certainly due to differences in rate of application of the polymer spray. This explains the anomaly reported by Thiel & Nguyen (1984) between the coating results and tests of interactive mixture stability during prolonged fluidization, during which 2% talc was shown to have no effect.

Application of a 1% PVP film coating was found to

yield more reproducible results. Table 3 presents results for the two different spray rates, for binary and ternary mixtures containing 0·8 and 2% talc. From the results of talc adhesion to the carrier the 0·8% ternary system was more stable than the 2%. However, the results show the addition of talc has little or no effect on the percent microencapsulation. The spray rate in the fluidized bed has a significant effect, an increase of 10–14% is achieved by using the high initial flow rate.

Table 3. Film coating (1% PVP) of a 0·1% salicylic acid interactive mixture, effect of spray rate and addition of talc.

Talc concn	Microencapsulation % (±95% CI)	
	Constant flow rate	High initial flow rate
0%	81·6 (±0·6)	93·0 (±1·0)
	80·2 (±1·5)	92·8 (±0·7)
	85·5 (±0·6)	94·7 (±0·7)
0·8%	84·3 (±0·7)	93·6 (±0·9)
		95·3 (±0·4)
2%	84·7 (±1·8)	
	89·8 (±1·3)	

Similar results were obtained for magnesium stearate (Table 4), addition of 0·5 and 1% magnesium stearate did not increase the mixture stability during application of the film. Again, the flow rate of polymer solution to the spray nozzle in the fluidized bed gave significant differences, the percentage microencapsulation achieved being similar to the results in Table 3. Magnesium stearate, mixed for the time used to form the ternary mixtures (120 min) has been shown to form a continuous hydrophobic barrier on granules (Bossert & Stamm 1980), and also stable ternary interactive mixtures (Stewart 1981). However, the adhering layer of magnesium stearate does not increase the adhesion unit stability during fluidization and film coating. The result in Table 4 for 1% magnesium stearate, high initial flow rate, shows a decrease in percent retention compared with the 0 and 0·5% results.

The 100% adhesion results for talc and magnesium stearate indicate they will form stable interactive mixtures (with the exception of 2% talc), yet there is no evidence in Tables 2–4 that addition of the third component stabilizes the system during coating in the fluidized bed. This is contrary to the results of Staniforth et al (1982), measured using an ultracentrifuge method; both talc and magnesium stearate were shown to increase the mixture stability. The rate at which the polymer solution is sprayed onto the fluidized mixture is the critical factor. Optimizing

Table 4. Film coating (1% PVP) of a 0·1% salicylic acid interactive mixture, effect of spray rate and addition of magnesium stearate.

Magnesium stearate concn	Microencapsulation % (±95% CI)	
	Constant flow rate	High initial flow rate
0%	85·5 (±0·6)	94·7 (±0·7)
	81·6 (±0·6)	93·0 (±1·0)
	80·2 (±1·5)	92·8 (±0·7)
0·5%	86·0 (±0·8)	93·8 (±0·5)
		96·4 (±0·9)
1%	84·7 (±0·4)	84·5 (±1·4)

the spray rate resulted in 92–95% microencapsulation of salicylic acid, with minimal granulation of the adhesion units. The time taken to apply the 1% polymer film at high initial rate was 9 min (Fig. 2) and this produced a retention figure (92–95%) that compared with the losses observed by Thiel & Nguyen (1984 see Figs 2 and 4) for interactive mixtures after 10 min fluidization. Spraying the polymer solution at higher rates than in Fig. 2 resulted in significant granulation of the adhesion units. So 92–95% microencapsulation represents the highest values attainable, keeping the adhesion units as discrete coated entities.

Staniforth & Rees (1982) suggested the material of construction of a mixer may be a significant factor determining the quality of the final interactive mixture. Mixtures of 0·1% salicylic acid were produced in earthed stainless steel and Perspex Erweka cube mixers. Microencapsulation with 1% PVP was then performed using constant and high initial flow rates; the results are in Table 5. Once again the rate of spraying was a critical factor, but retention for the mixtures produced in the Erweka (acrylic) mixer was higher than that in the steel mixer. The different materials of construction may have caused this effect, supporting the conjecture of Staniforth & Rees (1982), but it must be stressed that the mixer

Table 5. Film coating (1% PVP) of a 0·1% salicylic acid interactive mixture, effect of spray rate and mixer construction material.

Cube mixer material	Microencapsulation % (±95% CI)	
	Constant flow rate	High initial flow rate
Stainless steel	81·6 (±0·6)	93·0 (±1·0)
	80·2 (±1·5)	92·8 (±0·7)
	85·5 (±0·6)	94·7 (±0·7)
Perspex (acrylic)	92·3 (±1·1)	97·2 (±0·7)
	87·2 (±0·9)	95·9 (±1·6)

designs were also different (stainless, capacity 12·2 litres, 3 kg load, 17 rev min^{-1}, internal agitator; Perspex, capacity 3.4 litres, 1 kg load, 40 rev min^{-1}, three fixed internal rods). The shearing force in the stainless mixer, fitted with the agitator rotating at twice the cube revs, is higher than the Perspex mixer fitted with static bars. However, the Perspex cube produced mixtures which gave a higher percent microencapsulation, indicating the mixtures formed were more stable; the material of construction does seem to be a significant factor.

Production of multilayer microcapsules (Fig. 1b) was achieved by mixing film-coated adhesion units with more micronized salicylic acid and application of another film. The coating solution was applied using a high initial rate. Assaying for salicylic acid at each stage of production permitted the percent retention beneath each film to be calculated (Table 6). The amounts retained for each layer of salicylic

Table 6. Percentage retention of salicylic acid in multilayer microencapsulated interactive mixtures (Fig. 1b), high initial flow rate.

| Batch | Mix concn | Retention of salicylic acid (%) | | | |
		Film 1	Film 2	Film 3	Overall*
I	2 × 0·1%	96·0	93·8		92.3
II	3 × 0·1%	94·7	97·6	96·2	94·3
III	2 × 1%	85·5	83·4		77·00

* Final amount microencapsulated as percent of the theoretical assuming no losses.

acid are similar and indicates that the acid's force of adhesion to the PVP film is similar to that of the lactose carrier. One batch of material was mixed and coated three times to build up a trilayer system of micronized model drug and interposing films. The 0·1% mixtures gave higher retentions than the 1% system, indicating the high flow rate was less successful with respect to optimizing salicylic acid retention in the more concentrated mix.

To assess the adequacy of the mixing operations, the content uniformity of fifty 500 mg samples was analysed statistically. The content was expressed by proportion to eliminate sample mass variations. The sample coefficient of variation (CV) was calculated from the mean proportion and standard deviation, and the value of the coefficient of skewness $(\sqrt{b_1})$ from equation 2; the results are presented in Table 7 and Fig. 3. The CV for all samples was 2·2%, and with 99% confidence the value for all batches was estimated to be less than 5% (Thiel & Nguyen 1982). Statistical testing of $\sqrt{b_1}$, to detect significant positive skewness, gave one significant result and may indicate the presence of small agglomerates of

Table 7. Content uniformity of microencapsulated interactive mixtures (fifty 500 mg samples).

Mixture layers × concn	DP% eqn 1	Mean content mg	CV %	$\sqrt{b_1}$ eqn 2	Range about mean (%)
1 × 0·1%	7·9	0·52	2·0	+0·18*	−5 to +5
2 × 0·1%	6·0	1·01	1·5	+0·65†	−2 to +3
1 × 1%	5·2	4·57	2·2	+0·19*	−5 to +3
2 × 1%	5·7	8·26	1·7	−0·57‡	−4 to +3

* Non-significant skew ($P > 0·05$).
† Significant positive skew ($0·01 < P < 0·05$), see Fig. 3.
‡ Significant negative skew ($0·01 < P < 0·05$).

micronized salicylic acid in the adhesion units. The extent of the skewness of the distribution is shown in Fig. 3 and Table 7 (range about the mean). Given that all sample values fell within ±5% of the mean, indicating a very uniform distribution of salicylic acid, the statistically significant value of $\sqrt{b_1}$ has little practical consequence and results from the single value in the right hand tail of Fig. 3. One significantly negative value of $\sqrt{b_1}$ was also obtained,
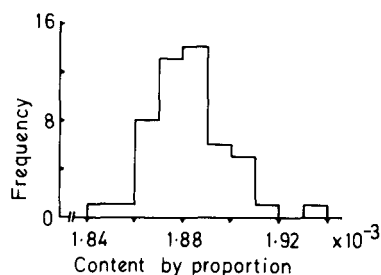

FIG. 3. Distribution of content by proportion in 2 × 0·1% multilayer adhesion units (films 1% wt PVP), the corresponding statistical data is given in Table 7.

for which there is no adequate explanation other than random errors associated with the sampling and analytical procedures. The demixing potential (DP%) for each batch was computed by equation 1. The values of DP% were ≤7·9% and showed that segregation of the microcapsules, for example during filling into hard gelatin capsules, would lead in the worst case to a CV less than 8% for the final dosage units (excluding effects due to fill weight variation).

Once a 1% wt PVP film had been sprayed onto the interactive mixture, the adhesion units were stable with respect to salicylic acid loss during subsequent fluidization. Further polymer could be applied with little change occurring in the percent salicylic acid retained beneath the film. Material which had been microencapsulated with 1% PVP was processed further: the results (Table 8) show the material coated with the initial film was stable during application of the second polymer layer.

Table 8. Application of a second film onto 0·1% salicylic acid mixtures microencapsulated with 1% wt PVP.

Coating (% wt)	Salicylic acid, %, retained after application of the 2nd film
3% HEC	95·4
5% CAP*	93·9
5% CAP*	95·0
3% HPMCP**	94·9
3% HPMCP**	90·9

* Aqueous pH 9.
** 80% ethanol, Shinetsu Chemical HP55.

CONCLUSIONS

Using the interactive mixing process, conventional fluidized bed film coating can be used to microencapsulate finely divided particulates (<5 μm), present at low concentrations. Optimization of the processing method, using a high initial spray rate, permitted 92–95% microencapsulation of a 0·1% mixture. A lower retention (85%) was obtained for a 1% mixture. The material of construction of the mixer used to form the interactive mixtures appeared to have a small but significant effect on the mixture quality; the Perspex cube yielded more stable mixes than the stainless steel mixer. Addition of a third component, talc or magnesium stearate, was shown to have no stabilizing effect during fluidization and coating. The conclusion drawn by Thiel & Nguyen (1984), that a 0·1% mixture was stabilized by adding 2% talc, is incorrect.

The model drug in the microcapsules was uniformly dispersed (sets of fifty 500 mg samples had a CV <5% (99% confidence), all samples falling within ±5% of the mean, and the coefficient of skewness (eqn 2) confirmed the mixing process was effective; no significant agglomerates were detected. The value of the demixing potential (eqn 1) was ≤7·9% for all batches, indicating segregation of the final product would produce only small changes in homogeneity. Once a 1% PVP film had been sprayed, the adhesion units were stable during fluidization and further film solutions could be applied (e.g. an HPMCP enteric coat). A sequence of mixing and coating operations can be used to produce multilayer microcapsules (see Fig. 1b), which gives a method of manufacturing a microdose delivery system with immediate and sustained release characteristics.

The process described in this paper offers a novel method of microencapsulating very fine particulate materials, which may find applications in production of enteric-coated and sustained release microdose delivery systems. The final product is a coarse free-flowing material, which may readily be filled into hard capsules. Because the process is based on the use of interactive mixing, the minor component is very uniformly dispersed in the final product.

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