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Characterization of surface coverage of coarse particles coated with stearic acid

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Summary

Acetylsalicylic acid (ASA, 250–355 μm) and glass beads (180–250 μm) were treated with 0–16% w/w coloured and uncoloured stearic acid (SA) by Continuous Multi-Purpose Melt Technology (Lejus Medical AB, Sweden). The resulting particles were characterized by analysis of content SA, particle size, specific surface area and particle shape. Efforts were made to characterize the surface coverage by microscopy, a dissolution rate technique and colour measurement. It was found that the stearic acid formed thin layers partly covering the ASA particles and glass beads. The surface coverage could be quantitatively estimated by the dissolution rate technique. The data also suggest that colour measurement could be used as a rough estimation of the surface coverage.

Introduction

Continuous Multi-Purpose Melt Technology ‘CMT’ (Lejus Medical AB, Sweden) has been developed for both granulation and coating of particulate materials. By applying a coating of aqueous-insoluble materials (e.g., stearic acid) on coarse particulate drugs it is possible in principle to achieve taste masking, improved drug stability or extended release.

For these applications it is of importance to adjust and control the degree of surface coverage. Percentage surface coverage of magnesium stearate films on sodium chloride has been estimated by using energy-dispersive X-ray analysis (Hussain et al., 1988). This method is, however, relatively complex and expensive, and hence not appropriate for routine use.

The aim of this study was to investigate the possibilities of using some simple techniques for characterization of surface coverage of melt-coated coarse particles, with emphasis on two techniques for quantitative characterization of degree of surface coverage: determination of initial dissolution rate and colour measurement.

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Experimental

Materials

Core materials

Two materials with smooth surface texture were chosen as test materials:

(1) Acetylsalicylic acid (ASA, Monsanto 7013, Monsanto, U.K.) was dry-sieved to obtain the fraction 250–355 μm.

(2) Glass beads (Microperl dry-sieved to 180–250 μm, Ernströms Mineral AB, Sweden) were used as an additional model material, to gain some information about the thickness and nature of the coating layer. This material is of narrow size range and regular shape, which facilitates microscopic measurements. The amorphous properties of glass can also be used to accomplish good contrast between glass cores and crystalline coating materials, by microscopy using polarized light.

Coating materials

Stearic acid (SA, Unichema, The Netherlands) was considered to be a suitable material for preparation of melts, since it has an appropriate melting range and is insoluble in water.

Coloured stearic acid was prepared by addition of < 0.05% w/w lipophilic red dye. This was done to improve the resolution of the technique using colour measurement.

Methods

Coating of core particles

The principle of CMT is presented in Fig. 1 (Ivarson, 1982). The particles are fed by a powder screw to a rotating disc and are thrown outwards by the centrifugal force. The melted coating material is pumped through channels in the rotating disc and is ejected on the upper side of the disc where it is dispersed in air and forms a liquid curtain, through which the particles have to pass.

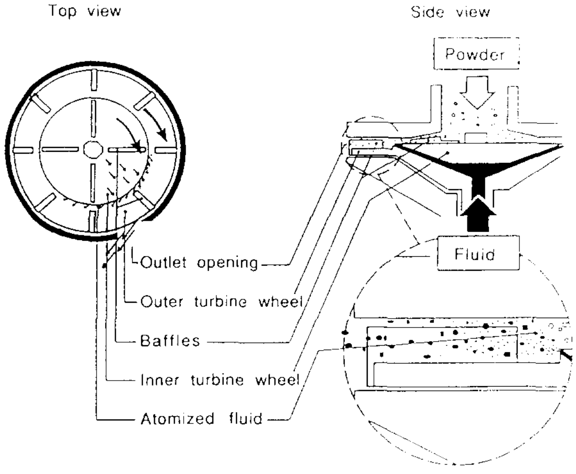

Fig. 1. The principle of the melt-granulating apparatus.

The amount of SA added to the core materials ranged from 0 to 16% w/w. SA was applied as one single treatment or as multiple successive treatments (Tables 1 and 2). ASA and glass beads were also passed through the apparatus without addition of SA as controls.

TABLE 1

Processing characteristics of SA coatings on ASA particles and specific surface area of ASA particles

Type of SA	SA content [a] (% w/w)	Number of treatments [b]	Specific surface area [c] (1/cm)
Uncoloured	0	0	408 ± 56
	0	1	548 ± 8
	2.0	1	516 ± 29
	4.1	2	640 ± 31
	6.4	3	699 ± 61
	9.0	4	715 ± 2
	4.1	1	527 ± 10
	8.2	1	478 ± 3
	16.4	1	370 ± 17
Coloured	2.1	1	541 ± 12
	4.2	2	544 ± 37
	6.3	3	547 ± 5
	8.3	4	523 ± 11
	5.6	1	496 ± 19
	8.2	1	408 ± 6
	3.5	1	529 ± 21

[a] Nominal content, i.e., content calculated from feeding rates of ASA and SA to the melt granulation apparatus.

[b] The content of SA was either applied as 1 single treatment or as up to 4 successive treatments.

[c] Volume-specific surface area with 95% confidence interval.

TABLE 2

Characteristics of uncoated and coated glass beads

Type of stearic acid	Nominal SA content (w/w %)	Experimental SA content (w/w %)	Number of treatments [a]	Particle diameter [b] (μm)	Specific surface area [c] (1/cm)	Shape coefficients [d]
Uncoloured	0	0	0	220 ± 3	309 ± 3	6.7
	1.8	1.9	1	223 ± 4	319 ± 5	7.1
	3.6	4.0	2	226 ± 3	304 ± 1	6.9
	5.4	6.0	3	227 ± 4	302 ± 2	6.8
	7.0	8.0	4	240 ± 5	301 ± 4	7.2
	3.5	3.2	1	230 ± 4	293 ± 16	6.7
	4.8	5.0	1	232 ± 4	289 ± 3	6.7
	6.3	5.9	1	234 ± 4	287 ± 4	6.7
	7.9	7.0	1	238 ± 5	280 ± 3	6.9
Coloured	1.9	1.8	1	227 ± 4	292 ± 13	6.6
	3.8	3.9	2	231 ± 4	297 ± 10	6.8
	5.6	6.1	3	234 ± 4	295 ± 9	6.9
	7.9	8.0	4	240 ± 4	294 ± 19	7.0
	1.9	2.2	1	223 ± 4	288 ± 4	6.4
	4.7	5.0	1	228 ± 4	291 ± 17	6.6
	8.0	7.0	1	232 ± 5	283 ± 10	6.6
	3.3	3.5	1	229 ± 4	289 ± 10	6.6
	6.2	5.8	1	234 ± 4	290 ± 10	6.8

[a] The content of SA was applied either as 1 single treatment or as up to 4 successive treatments.

[b] Arithmetic mean diameter by number as measured by microscopy with 95% confidence limits.

[c] Volume-specific surface area as measured by permeametry with 95% confidence limits.

[d] Surface-volume shape coefficient according to Heywood (1954) and Allen (1975), calculated from [b] and [c].

Primary characterization of coated particles

Content of coating material. The content of SA on the glass particles was determined using a gravimetric method. 2.5 g particles were washed with 50 ml acetone (analytical grade) and placed in an ultrasonic bath for 15 min. The acetone was discarded and the particles were washed three more times with fresh acetone and were then allowed to dry overnight. The loss on washing was then calculated. The assay of stearic acid content was not used for ASA particles. Results are mean values of two measurements.

Particle size. The glass bead particles were photographed in a scanning electron microscope at 35 times magnification. Martin's diameter, in a predetermined direction, of at least 100 particles was measured under a magnifying lens and the arithmetic mean diameter by number was calculated (Ragnarsson and Johansson, 1988). No characterization of particle size was performed for ASA because of the unsymmetric shape of the ASA particles.

Specific surface area. The specific surface area was determined by dynamic gas permeametry (Eriksson et al., 1990). Powders were packed for measurement in a specially constructed sample tube to a height of approximately 500 mm. The diameter of the tube was 10 mm for glass particles and 21 mm for ASA particles. Calculations were made according to the slip flow-equation. Results are mean values of three measurements.

Particle shape. Approximate values of Heywood's surface-volume shape coefficients for the glass bead particles were estimated from arithmetic mean diameter by number and specific surface area (Heywood, 1954; Allen, 1975).

Methods for estimating surface coverage

Microscopy. All materials were qualitatively investigated by scanning electron microscopy and by optical light microscopy using polarized light.

Measurement of dissolution rate. The dissolution rate of ASA particles was measured by the USP XXI paddle method at 100 rpm. It was observed in pre-trials that the paddle method gave slightly more reproducible results than the basket method. The dissolution medium was 0.1% w/w polysorbate 80 in water. The high polysorbate concentration was used, since it was considered important to avoid wetting problems with the relatively hydrophobic particles. The liquid medium was transferred to a flow cell in a spectrophotometer (LKB Ultrospec 4052). The amount of drug dissolved was assayed at 274 nm every minute until 20 min. Absorbance values were recorded on a computer (LKB dissolution software, LKB Biochrom Ltd, Cambridge, U.K.). The dissolved fractions of ASA were then plotted against time and the initial dissolution rate was determined by extrapolating to time zero. Results presented are mean values of three measurements. For obvious reasons, no dissolution tests were made for the glass bead materials.

Calculation of degree of surface coverage from dissolution rate. The degree of surface coverage can be defined as:

$$d_{sc}(\%) = \left[1 - \left(\frac{S_{\text{uncovered}}}{S_{\text{total}}}\right)\right] \times 100 \qquad (1)$$

where d_{sc} is the degree of surface coverage; $S_{\text{uncovered}}$ is the uncovered surface area of coated particles; and S_{total} is the total surface area.

According to Noyes-Whitney's equation the rate of dissolution under sink conditions is governed by the diffusion constant, the thickness of the diffusion layer, the surface area of the dissolving substance, and the solubility of the substance. Provided that all other parameters are held constant, the initial rate of dissolution will be dependent only on the surface area exposed to the dissolution medium. Hence the values for surface area in Eqn 1 could be replaced by values for initial dissolution rates:

$$d_{sc}(\%) = \left[1 - \left(\frac{K_{\text{coated}}}{K_{\text{uncoated}}}\right)\right] \times 100 \qquad (2)$$

where K_{coated} is the initial dissolution rate of coated particles and K_{uncoated} is the initial dissolution rate of uncoated particles.

It is assumed that the diffusion of drug molecules through the hydrophobic film is negligibly small compared to the dissolution from uncovered drug surfaces. This is a reasonable assumption when a relatively large fraction of drug is uncovered. It is also assumed that all uncovered surfaces are wetted and that the coating layer remains intact long enough to allow a determination of initial dissolution rate. Eqn 2 has been used by Johansson and Nicklasson (1986) to investigate film formation of magnesium stearate.

If the particle surface area is changed during processing, e.g., due to fragmentation of core material, the increase in surface area has to be compensated for by introducing weight-specific surface areas in the formula:

$$d_{sc}(\%) = \left[1 - \left(\frac{K_{\text{coated}} \times Sw_{\text{uncoated}}}{K_{\text{uncoated}} \times Sw_{\text{coated}}}\right)\right] \times 100 \qquad (3)$$

where Sw is the weight-specific surface area for coated and uncoated particles, respectively.

The degree of surface coverage was calculated from the initial dissolution rates and the specific surface areas according to Eqn 3.

Colour measurement. Tristimulus colorimetry is a method where colour of different objects can be quantitatively characterized. Light of a known spectral energy falls on the sample specimen and the reflected light is diverted into different beams which are allowed to pass through different colour filters, before the intensity of light is measured by photodetectors. The result is expressed by three coordinates in any of a number of arbitrary scales. In this study Hunter's L,a,b scale was used, where L describes lightness; a measures redness when positive and greenness when negative; and b measures yellowness when positive and blueness when negative (Nyqvist, 1982). Alcorn et al. (1988) used tristimulus colorimetry to evaluate efficiency of coating of tablets. It should be noted that this method has been developed to quantitate the sensation of colour in the human eye and brain rather than to objectively measure a physical parameter. However, it seems reasonable to assume that values of colour coordinates in heteroge-

TABLE 3

Binary mixture systems used for evaluation of reflected colour measurements

Component 1	Component 2
Nonpareil, white, spherical	Nonpareil, red, spherical
Stearic acid, white, spherical, 250 μm	Glass beads, spherical, 180–250 μm
Stearic acid, red, spherical, 250 μm	Glass beads, spherical, 180–250 μm
Stearic acid, white, rod-shaped, 250–355 μm	ASA, white, rod-shaped, 250–355 μm

neous subjects will depend on the colour of different surfaces and on the relative fraction of areas having a certain colour. If it could be assumed that the projected surface area is representative of the total surface area, then colour coordinates could be a measure of surface coverage, when the colours of the core material and the coating layer are different.

All coated materials were packed in a glass sample cup and the reflected colour was measured in a Gardner XL-805 Tristimulus Colorimeter (Pacific Scientific, Gardner Laboratory Division, Bethesda, MD, U.S.A.). Results presented are mean values of ten determinations.

The following systems and parameters were studied in order to initially evaluate the effects of some experimental parameters on the results from colorimetry: (a) white paper with red spots of known total surface area; (b) binary mixtures of different coloured particles of approximately the same size and shape (Table 3); (c) SA particles of different size and shape; and (d) ASA particles of different size. The colour coordinates were recorded according to Hunter's L,a,b scale. Results presented from these pre-trials are mean values of ten determinations.

Results and Discussion

Primary characterization of coated particles

Analysis of content SA on glass beads showed that the actual content of stearic acid agreed reasonably well with the nominal content, which was calculated from the feeding rates of the raw materials to the CMT apparatus (Table 2). It was therefore assumed that this was also the case with ASA particles.

Table 2 shows the mean particle diameter for glass beads treated with different amounts of SA. It can be seen that the layer of the SA was rather thin, 10 μm or less. Mean particle diameters for uncoloured particles also suggest that the layer may be thinner on particles prepared by successive melt treatment, than on particles prepared by one treatment, when the content of SA is the same. This interpretation was supported by the surface area measurements, where data for coated ASA particles are also reported (Table 1), although the differences in surface area between ASA prepared by successive treatments and ASA prepared by a single treatment could also be explained by more extensive crushing in the mixer in the case of multiple treatments. However, the difference in coating layer thickness between particles prepared by multiple treatments and by single treatments could not be seen in the case of coloured SA as in the case of uncoloured SA.

With glass beads no crushing was observed as with ASA particles. That crushing occurred in the case of ASA but not in the case of glass may be due to either the elongated particle shape of ASA particles compared to the spherical glass beads or differences in intraparticulate bonding structure.

Differences between particles coated with uncoloured and coloured SA can be seen also in surface area (Tables 1 and 2), especially in the case of ASA particles. Particles prepared by multiple treatments had a higher specific surface area than particles prepared by single treatment, in the case of uncoloured SA. With coloured SA, particles prepared by multiple treatments also had a higher specific surface area but in that case the difference was smaller.

The differences observed between uncoloured and coloured SA indicate, that addition of the lipophilic dye changes the properties of the melt in some way.

Surface-volume shape coefficients for glass particles are shown in Table 2. Values ranged from 6.4 to 7.2, which shows that the particles kept their spherical form to a great extent.

Characterization of surface coverage

Microscopy

Microphotographs showed that the SA formed a rather smooth and thin layer, partly covering the particle surfaces. The fraction of surface area coated with stearic acid seemed, as expected, to increase with an increasing amount of SA. The coverage of glass particles was easily observed by optical light microscopy using polarized light or scanning electron microscopy (Fig. 2). The coverage of ASA particles was more clearly observed by scanning electron microscopy than by optical light microscopy, although none of the techniques gave as good results as with glass particles. That the use of polarized light was more effective in the case of glass particles than in the case of ASA could be due to the great difference in crystallinity between glass and SA. Since ASA is not amorphous like glass, the difference in crystallinity between ASA and SA is not pronounced and low contrast results. The smoother surface texture of glass beads compared to ASA contributes to a better result for glass particles in both microscopic techniques.

Measurement of dissolution rate

The dissolution profiles of uncoloured coated ASA particles (Fig. 3) showed that the dissolution rate did not always decrease with increasing SA content. The release rates of multiply coated particles were generally higher than those for corresponding particles prepared by one single coating. The higher release rate of multiply coated particles may depend on the increased surface area of the ASA particles, probably due to fragmentation during the coating process. That fragmentation occurred in the case of ASA particles, especially when passing through multiple treatments, was confirmed by surface area measurements (Table 1). The release of coloured coated ASA particles did not substantially differ from the release of uncoloured particles.

Most particles showed a sigmoidal release profile. It might be assumed that this was due to a short lag time before the particles were totally wetted. When estimating the initial dissolution rate, by extrapolating to time zero, time zero was set to the end of this lag time.

In Fig. 4 the degree of surface coverage, corrected for total surface area, has been calculated from Eqn 3 and plotted versus content of stearic acid. The coverage increased with increasing content of SA. Especially Fig. 4a suggests that there is a curved relationship between degree of sur-

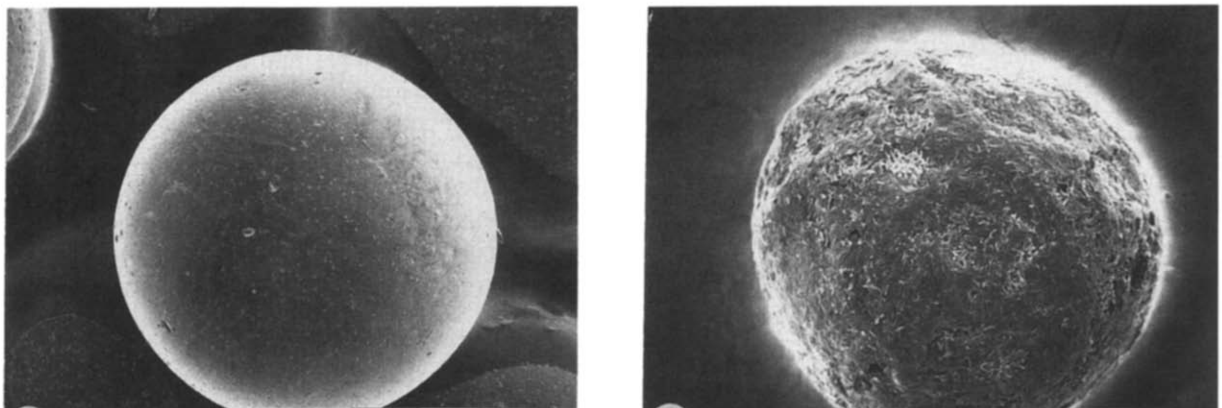

Fig. 2. Scanning electron micrographs. a. Uncoated glass bead. b. Glass bead coated with SA; scale bars are 100 μm.

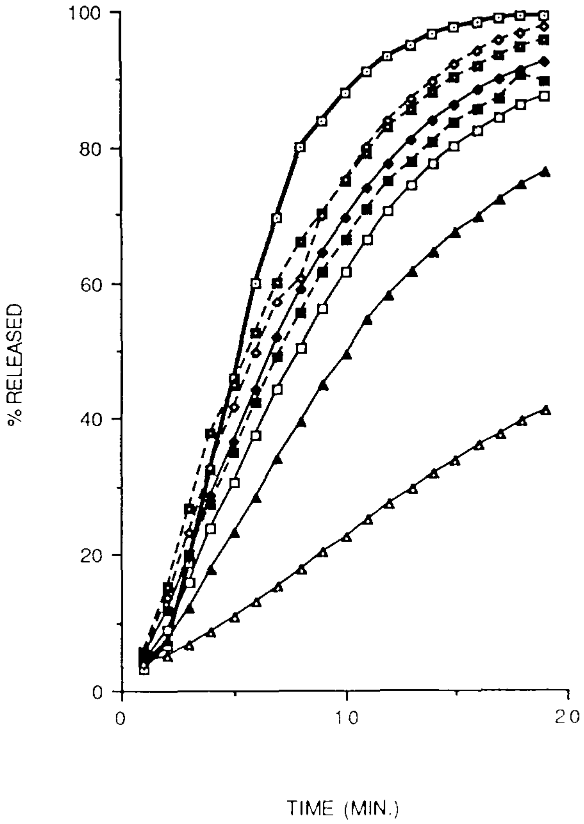

Fig. 3. Dissolution profiles for ASA particles with different content uncoloured SA (number of processings in parentheses): ⊡, 0% SA (0); ◆, 2.0% SA (1); ■, 4.1% SA (2); ◇, 6.4% SA (3); ■, 9.0% SA (4); □, 4.1% SA (1); ▲, 8.2% SA (1); △, 16.4% SA (1). Dashed lines designate multiply coated particles.

face coverage and SA content. This is not unexpected, since it seems reasonable that the probability of melted SA hitting an uncoated surface will decrease as the degree of surface coverage increases.

No significant difference in degree of surface coverage between particles prepared by a single treatment and successive treatments was obtained.

Colour measurement

The colour measurements showed that the a-coordinates gave the greatest response in changes in amount of SA, except in the case of uncoloured SA on ASA where the b-coordinates gave the greatest response. Hence a-coordinates were used to describe the colour, except in the case of uncoloured SA on ASA where b-coordinates were used.

Fig. 5 shows the results of the pre-trials, performed in order to evaluate the effect of various fractions of coloured surface area on colour coordinates. In all investigated systems tristimulus coordinates varied with the fraction of total surface area having a certain colour. This justifies the assumption above, that measurements of reflected colour can be used as a method to quantitate surface coverage. In the case of a flat surface (a sheet of paper) with red spots covering different fractions of surface area there seemed to be a

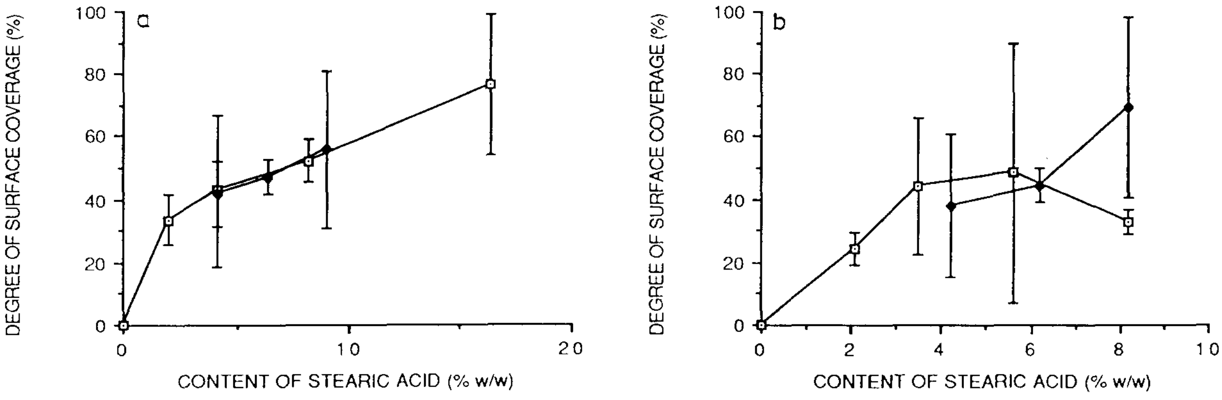

Fig. 4. Degree of surface coverage vs content of stearic acid: ⊡, single treatment; ■, successive treatments. a. Uncoloured SA. b. Coloured SA. Error bars represent the 95% confidence interval for the mean.

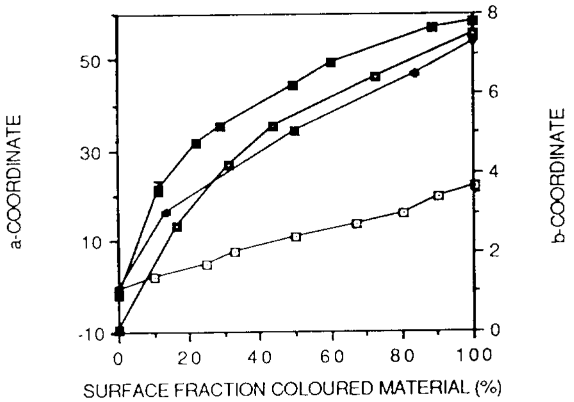

Fig. 5. Influence of component proportions, in binary systems, on colour coordinates. ⊡, partly red-coloured paper; ◆, red and white nonpareil particles; ◘, uncoloured irregular SA and ASA; ■, coloured spherical SA and glass beads. Colour coordinates are expressed as a-coordinates for all mixtures except for the last where b-coordinates are given. Error bars represent the 95% confidence interval for the mean (if excluded they are falling within the symbol).

linear correlation between the tristimulus coordinates and the fraction of coloured surface area. A linear correlation was also seen with mixtures of uncoloured spherical ASA and glass beads (not shown). There was, however, no linear correlation between tristimulus coordinates and fraction of surface area with the other binary powder mixtures, which demonstrated a curved relationship. This could be due to reflection phenomena in the powder bed. That a linear relationship was seen in the case of uncoloured SA and glass might be explained by the small difference in colour between these materials.

Table 4 shows that the colour coordinates were also dependent on the particle size and shape of SA. This could be a confounding factor when trying to quantitate surface coverage.

The colour coordinates of melt-coated particles increased with increasing amounts of SA, as shown in Fig. 6. The curved relationship between colour coordinates and content SA is not surprising since a linear relationship between cooordinates and fraction of coloured surface area could not be seen for most of the powder materials in the pre-trials (Fig. 5).

In the case of uncoloured materials there is a difference between particles prepared by a single treatment and those prepared by successive treatments. This difference is not seen in the case of coloured stearic acid.

TABLE 4

Colour coordinates for some particles of different size and shape

Type of particle	Shape	Particle size (μm)	Colour coordinate [a]
Uncoloured SA	Irregular	< 250	4.48 ± 0.08
		250–500	7.48 ± 0.03
		500–1 000	9.34 ± 0.2
Uncoloured SA	Spherical	250	1.68 ± 0.01
		500	1.72 ± 0.02
Coloured SA	Irregular	< 180	47.6 ± 0.4
		180–250	48.1 ± 0.3
		250–500	44.8 ± 0.3
		500–1 000	51.1 ± 0.2
Coloured SA	Spherical	< 200	55.9 ± 0.1
		250	58.3 ± 0.1
		500	58.7 ± 0.1
ASA	Irregular	< 180	0.30 ± 0.09
		250–355	0.05 ± 0.07

[a] For ASA and uncoloured SA, b-coordinate; for coloured SA, a-coordinate; with 95% confidence interval.

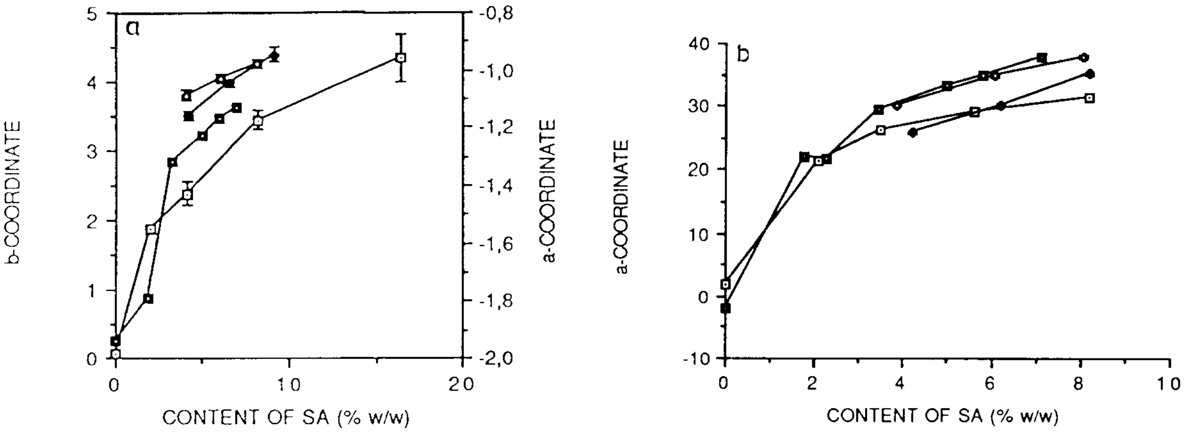

Fig. 6. Colour coordinates vs content SA: ⊡, ASA particles single treatment; ◆, ASA particles successive treatments; ■, glass beads single treatment; ◇, glass beads successive treatments. a. Uncoloured SA. b. Coloured SA. Colour coordinates are expressed as a-coordinates except in the case of uncoloured SA on ASA particles where b-coordinates are given. Error bars represent the 95% confidence interval for the mean (if excluded they fall within the symbol).

Comparison of methods for characterization of surface coverage

The values for degree of surface coverage obtained by the dissolution rate technique agreed with qualitative estimations based on microscopic investigations.

Fig. 7 shows that there may be some correlation between the degree of surface coverage obtained by dissolution rate techniques and colour coordinates in the case of ASA particles. It is not unexpected that the graph seems to be curved, since it was shown above that a curved relationship exists between colour coordinates and fraction of different surface area for powders (Fig. 5). There is also a difference between materials prepared by a single treatment and multiple treatments, at least in the case of uncoloured materials (Fig. 7a). These deviations from a perfect correlation could be attributed to effects on colour coordinates caused by thickness of coverage, surface roughness, particle size and particle shape. It

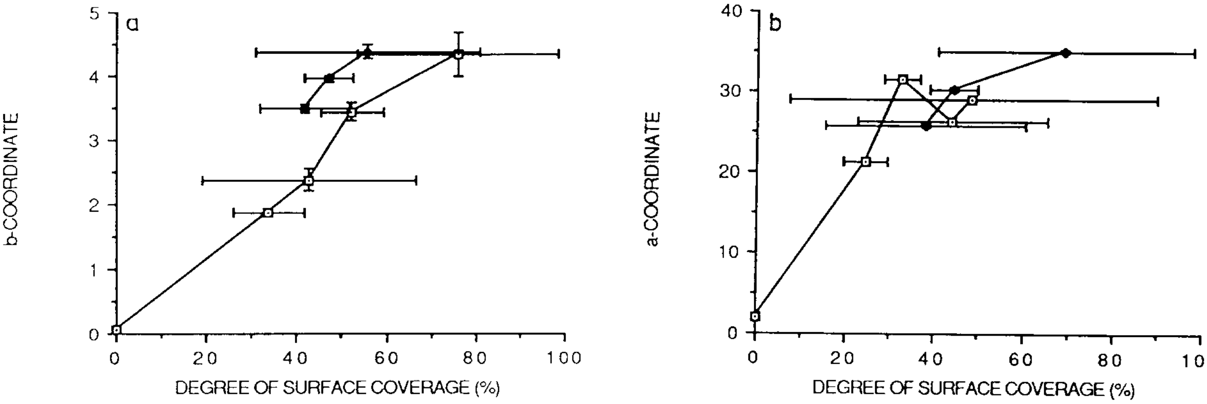

Fig. 7. Colour coordinates vs degree of surface coverage: ⊡, single treatment; ◆, successive treatments. a. Uncoloured SA. b. Coloured SA. Error bars represent the 95% confidence interval for the mean (if excluded they fall within the symbol).

is also possible that the degree of surface coverage determined by rate of dissolution could be influenced by, for instance, porosity of the coating layer or incomplete wetting. That the difference between materials prepared by single treatment and multiple treatments seems to be less in the case of coloured materials than in the case of uncoloured materials, may be interpreted in two ways: the colour increases the accuracy of colorimetry as a measure of the degree of surface coverage, or inclusion of colour in the melt changes the nature of the coating in some way that changes either the reflection of colour or the rate of dissolution. The differences between coloured and uncoloured materials mentioned above (Tables 1 and 2) support the latter alternative.

It could be suggested from error bars in Fig. 7 that variation is lower with colour measurement than with dissolution rate measurement, although it should be pointed out that the values are calculated from ten determinations in the case of colour measurements but only from three in the case of dissolution rate measurements.

Conclusions

It is possible to at least partly cover the surface of particles with melt using CMT. The surface coverage can be measured by a dissolution technique. It should be noted that the degree of surface coverage determined by the rate of dissolution is not an objectively true value, since it could be influenced by a number of parameters other than surface coverage. Nevertheless, most applications of melt-coated drug particles are more or less dependent on the dissolution rate, and the degree of surface coverage obtained by a dissolution technique could perhaps be a useful parameter in the development of the coating process.

The measurement of reflected colour to some extent reflects the surface coverage, and the speed and precision of this method could make it useful, especially when there is a pronounced difference in colour between core and coating material. Coloured melts may increase the applicability of the colorimetric method, although it seems likely that the incorporation of even low amounts of colour can change the properties of the melt. Of course the toxicological aspects of incorporating a colour must also be noted, if the particles produced are intended for in vivo use and not only for technical trials.

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References

Alcorn, G.J., Closs, G.H., Timko, R.J., Rosenberg, H.A., Hall, J. and Shatwell, J., Comparison of coating efficiency between a Vector Hicoater and a Manesty Accela Cota. *Drug. Dev. Ind. Pharm.*, 14 (12) (1988) 1699–1711.

Allen, T., *Particle Size Measurement*, 2nd edn. Chapman and Hall, London, 1975, pp. 77–81.

Eriksson, M., Nyström, C. and Alderborn, G., Evaluation of a permeametry technique for surface area measurements of coarse particulate materials. *Int. J. Pharm.*, 63 (1990) 189–199.

Heywood, H., Particle shape coefficients. *J. Imp. Coll. Chem. Eng. Soc.*, 8 (1954) 25–33.

Hussain, M.S.H., York, P. and Timmins, P., A study of the formation of magnesium stearate film on sodium chloride using energy-dispersive X-ray analysis. *Int. J. Pharm.*, 42 (1988) 89–95.

Ivarson, N., Method and apparatus for continuously mixing a liquid and powder. United States Patent 4, 329, 066 (May 11, 1982).

Johansson, M.E. and Nicklasson, N., Investigation of the film formation of magnesium stearate by applying flow-through dissolution technique. *J. Pharm. Pharmacol.*, 38 (1986) 51–54.

Nyqvist, H., Studies on the physical properties of tablets and tablet granulations. *Acta Universitas Upsaliensis – Abstracts of Uppsala Dissertations from the Faculty of Pharmacy, Uppsala*, 69 (1982) 10–11.

Ragnarsson, G. and Johansson, M.O., Coated drug cores in multiple unit preparations. Influence of particle size. *Drug Dev. Ind. Pharm.*, 14 (1988) 2285–2297.