

The Coating and the Encapsulation of an Interactive Powder Mixture and its Application to Sustained Release Preparations

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Abstract—Fine cohesive isoprenaline HCl particles adhered to the surface of coarser potato starch particles to form interactive mixtures. These were coated with magnesium stearate by dry mixing. To check if there was a lowering of homogeneity in the latter stage, the degree of mixing was investigated before and after adding magnesium stearate. The surface appearance of magnesium stearate-coated interactive mixtures became smoother as mixing time increased or the temperature of the powder bed during mixing was raised. Ultimately, the magnesium stearate encapsulated the particles of interactive mixture. The coated interactive mixtures improved sustained release of isoprenaline HCl over the starch mixtures alone, the effect depending on the density of the magnesium stearate. Only in encapsulated mixtures was the release rate of drug decreased as the amount of magnesium stearate increased. The release of isoprenaline HCl from the interactive mixtures followed first-order kinetics. A linear relationship existed between the first-order rate constant and the reciprocal thickness of the magnesium stearate film, indicating a diffusion-controlled system with the film having some pores.

The random mixing theory has been extensively explored (Lacey 1943; Poole et al 1964; Harnby 1967). Randomization requires equally sized and weighted particles, with little or no surface effects, showing no cohesion or interparticle interaction, to achieve the best results; it cannot be applied to all practical mixing situations, especially where cohesive or interacting particles are mixed.

Travers & White (1971) showed that fine cohesive particles adhered to the surface of a coarser excipient. The term "ordered mixing" was given to this phenomenon by Hersey (1975). The concept of ordered mixing is useful in explaining powder mixing of cohesive or interacting fine particles. Ordered mixing does not require equally sized or weighted particles, but involves particle interaction, i.e. van der Waals forces, surface tension, frictional pressure, electrostatic charge or any other forms of adhesion (Hersey 1974; Staniforth & Rees 1981, 1982; Staniforth et al 1981, 1982). Ordered mixtures are frequently more homogeneous than random mixtures; their standard deviations are unaffected by sample size.

The term "ordered mixing" has been used for the mixing of interactive particles in comparison with random non-interactive mixing. By considering that real mixing operations are a process of disordering, Egermann et al re-defined ordered mixtures so as to feature a degree of homogeneity higher than that conforming to random mixtures (Egermann & Orr 1983; Egermann 1985, 1989). Instead of "ordered mixture", he used the term "interactive mixture" for mixtures in which fine particles adhered to the carriers.

Many applications of interactive powder mixing (formerly called "ordered powder mixing") in the pharmaceutical field have been studied (Ishizaka 1989). In particular, interactive mixing has potential advantages for the manufacture of low dosage tablets and capsules. Crooks & Ho (1976) and

Johnson (1979) have investigated the use of interactive mixtures for direct compression tableting. Thiel & Nguyen (1982, 1984) made granules from interactive mixtures. Westerberg et al (1986) studied the relationship between the drug dissolution rate and core materials of interactive mixtures.

The development of sustained drug delivery systems has long been a major research area of pharmaceuticals. Some papers report that the addition of a hydrophobic lubricant, such as magnesium stearate, to a solid decreases the release rate of the drug (Levy & Gumtow 1963; Samyn & Jung 1970; Motycka & Nairn 1978). Others report that the binding strength of tablets dramatically decreases as the mixing time of particulate solids with magnesium stearate is increased. This phenomenon is caused by the formation of a lubricant film on the substrate resulting from the adhesion to the substrate surface of magnesium stearate molecules sheared from magnesium stearate crystals during the mixing process (Ampolsuk et al 1974; Bolhuis et al 1975; Lerk & Bolhuis 1977; Murthy & Samyn 1977; Iranloye & Parrott 1978). Koishi et al (1984), Nakagawa et al (1984) and Honda et al (1989) studied the microencapsulation of interactive mixtures using the dry mixing method and found that the interactive drug/excipient mixture, encapsulated with magnesium stearate or wax, showed sustained drug-delivery.

The purposes of the present study were to develop encapsulation of interactive drug/excipient mixtures by dry mixing with magnesium stearate, to discuss the segregation behaviour during the encapsulation process and to evaluate the release characteristics of the products.

Materials and Methods

Materials

Dry potato starch, as a carrier, was sieved in the range of 200–250 mesh (mean particle size; 65 μm). Isoprenaline HCl as a model drug and magnesium stearate as a coating

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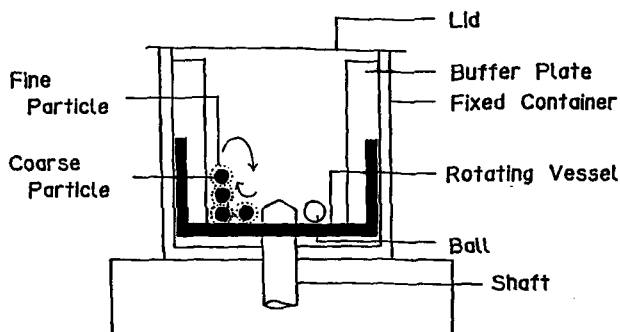


FIG. 1. Schematic diagram of centrifugal rotating type mixer.

material were crushed to $5\ \mu\text{m}$ by jet-milling (mean particle size: $2.5\ \mu\text{m}$ for isoprenaline HCl, $1.0\ \mu\text{m}$ for magnesium stearate). Particle sizes were determined by scanning electron microscopy.

Preparation of interactive mixtures

Interactive mixing was carried out in a centrifugal rotating type mixer equipped with four buffer plates (Fig. 1). In the vessel the powders are mixed by convection depending on both centrifugal force and the effect of buffer plates.

The vessel containing $0.1\ \text{g}$ isoprenaline HCl, $9.9\ \text{g}$ potato starch and ten stainless steel balls ($50\ \text{mm}$ diameter), to break up powder agglomerates formed during the mixing, was allowed to rotate at $300\ \text{rev}\ \text{min}^{-1}$ for 10 min. The operation was carried out at 23°C .

Coating of interactive drug/excipient mixture with magnesium stearate

To $10\ \text{g}$ of interactive mixture, $0.3\ \text{g}$ of magnesium stearate was added and mixed for 60 min at 35 , 50 and 70°C using an infrared lamp. Mixing was carried out under various coating conditions (Table 1).

The measurement of degree of mixing

After mixing, twenty $200\ \text{mg}$ samples were taken randomly from interactive mixtures and magnesium stearate-coated interactive mixtures. Each sample was added to $100\ \text{mL}$ of

$0.01\ \text{M}$ HCl and heated to 75°C . After the fatty acid salt became transparent, the mixture was cooled to room temperature, followed by the addition of $0.01\ \text{M}$ HCl to adjust the total volume to $100\ \text{mL}$. It was then filtered and the light absorption of the filtrate was measured at $278\ \text{nm}$. The isoprenaline HCl concentration in the filtrate was determined from the standard Beer's law plot.

The degree of mixing was determined by the coefficient of variation (CV) among 20 samples.

Release test

Release tests of the samples were carried out at $37 \pm 0.1^\circ\text{C}$ using a standard paddle method (Japanese Pharmacopoeia X). As a release medium, $600\ \text{mL}$ of the first fluid ($\text{pH}\ 1.2$) in a disintegration test (JPX) was used. It was prepared by mixing $2.0\ \text{g}$ of NaCl, $24.0\ \text{mL}$ of 10% (w/v) HCl and water to give $1000\ \text{mL}$ of solution. The paddle was set at a position $2.5\ \text{cm}$ from the bottom of the release apparatus filled with the release medium and was rotated at $200\ \text{rev}\ \text{min}^{-1}$. A weighed amount of the sample ($700\ \text{mg}$) was filled into a gelatin capsule which, with the sinker, was placed in the release apparatus.

Portions of $5\ \text{mL}$ of the release medium were sampled at selected times through a membrane filter ($1\ \mu\text{m}$) and volume of release medium kept constant by addition of portions of the first fluid (same volume and temperature) immediately after sample withdrawal. The concentration of released isoprenaline HCl was determined spectrophotometrically at $278\ \text{nm}$.

Results and Discussion

Evaluation of degree of mixing

Kozatani et al (1969) showed that good miscibility was obtained when the CV was less than 6.18% , assuming that the drug content gives a normal distribution. In the present study the same criterion was used to evaluate the degree of mixing.

For interactive mixtures of isoprenaline HCl and potato starch (Sample A), the CV was 3.5% .

Fig. 2 shows the effect of the amount of magnesium

Table 1. Coating conditions for interactive mixtures with magnesium stearate.

Sample	Temperature ($^\circ\text{C}$)	Magnesium stearate (g)	Mixing time (min)
A	Uncoated mixture	—	—
B	35	0.1	30
C	35	0.3	5
D	35	0.3	30
E	35	0.3	60
F	35	0.5	30
G	50	0.1	30
H	50	0.3	5
I	50	0.3	30
J	50	0.3	60
K	50	0.5	30
L	70	0.1	30
M	70	0.1	60
N	70	0.3	5
O	70	0.3	30
P	70	0.3	60
Q	70	0.5	30
R	70	0.5	60

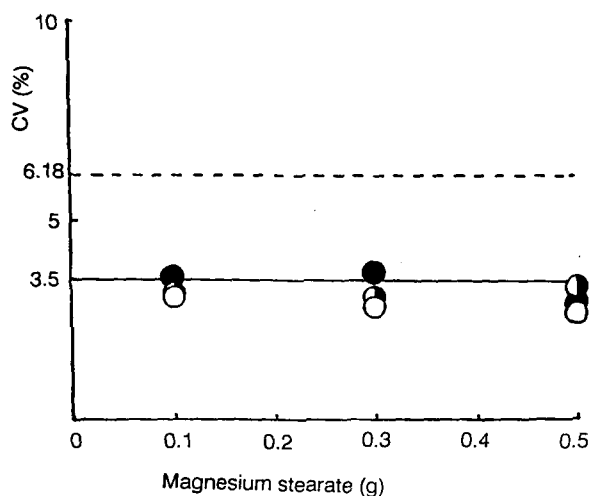


FIG. 2. CV for magnesium stearate-coated interactive mixtures as a function of amount of magnesium stearate. Key: \circ , prepared at 35°C ; \bullet , 50°C ; \bullet , 70°C . Mixing time was 30 min.

stearate on the degree of mixing at three different temperatures. For any temperature or any amount of magnesium stearate, the CV was also essentially equal to 3.5%. The miscibility was also unaffected by the mixing time.

These results therefore confirm that mixing of drug and excipient attain good miscibility whether magnesium stearate was present or not.

Observations of surface appearance

Fig. 3 shows the magnesium stearate-coated interactive

mixtures and their surface appearances after adding 0.3 g magnesium stearate to the interactive mixtures and mixing for 60 min at 35, 50 and 70°C, respectively (Honda et al 1989). Many fine magnesium stearate particles are seen on the surface of mixtures prepared at 35°C. The surface appearance of the coated interactive mixtures becomes smoother as the preparation temperature increases. At 70°C no magnesium stearate particles are seen on the surface. Therefore, the interactive mixtures can be regarded as having been encapsulated by magnesium stearate.

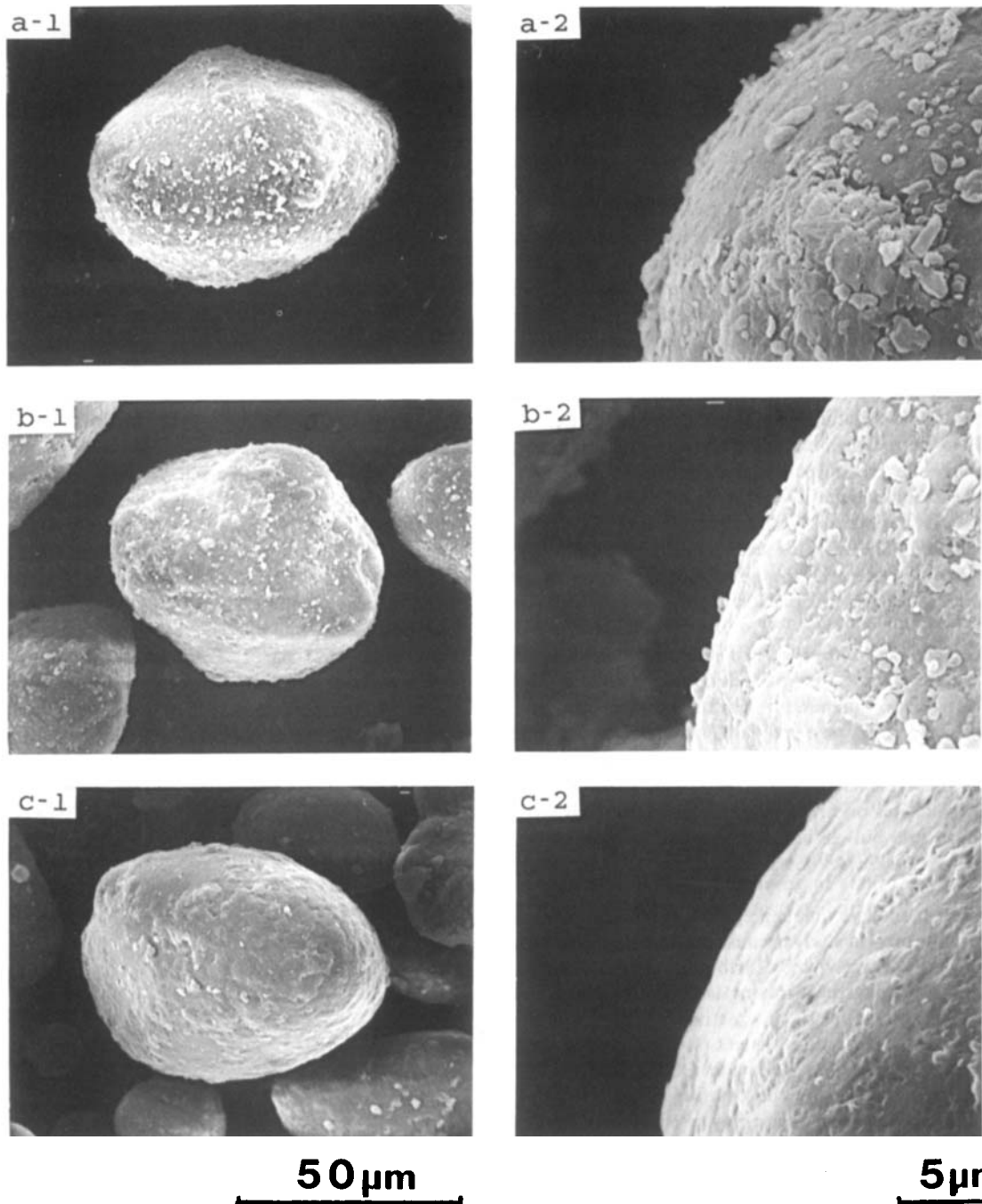


FIG. 3. Scanning electron micrographs showing changes with temperature of surface appearance of magnesium stearate-coated interactive mixtures. Key: a, prepared at 35°C; b, 50°C; c, 70°C. The amount of magnesium stearate was 0.3 g and mixing time was 60 min.

This encapsulation was affected by the length of mixing time and the amount of magnesium stearate (Honda et al 1989). The longer the mixing time, the smoother the surface. The interactive mixtures could be regarded as being encapsulated, after mixing for 60 min.

For constant mixing time and temperature, samples with the least amounts of magnesium stearate had the smoothest surfaces. For example, with samples G, I and K, the rank order of smoothness of the surface was $G > I > K$. However, in conditions which combined a long mixing time and high temperature (samples M, P, R), all interactive mixtures had smooth surfaces, indicating encapsulation. Thermal energy generated through friction and the impact between powders or powder and apparatus, melts the edge of magnesium stearate particles or shears them off, causing them to stick to the interactive mixtures. Thus, the magnesium stearate particles on the surface merge with each other to form a film. While the surface becomes smoother as the supply of energy grows, the demand for energy also grows as the number of magnesium stearate particles increases. Therefore, if the supplied energy is large enough to cause magnesium stearate to form a film, the interactive mixtures are encapsulated, independent of the amount of magnesium stearate; if an insufficient amount of energy is supplied, the surface roughness increases as the amount of magnesium stearate grows.

Discussion on segregation of interactive mixtures

Yip & Hersey (1977) defined two distinct types of segregation occurring in interactive mixtures: "interactive (ordered) unit segregation" and "constituent segregation".

Interactive unit segregation occurs in mixtures containing multisized carrier particles (Jones 1970; Thiel et al 1983). In pharmaceutical mixtures, this leads to drug-rich and drug-lean areas of powder, even though no change occurs in the distribution of adherent particles on individual coarse particles.

Constituent segregation, when the fine particles are dissociated from the coarse particles, occurs when a third component such as magnesium stearate is added to interactive drug/carrier mixtures. Lai & Hersey (1979) suggested that the third component either adheres preferentially to the carrier particles, displacing the original drug particles from their adhesion sites or strips drug particles effectively from carrier particles, but is not itself bound to the carrier particles. In either case, the homogeneity of the mixture decreases.

However, interactive unit segregation is unlikely to have occurred in the present study because the potato starch, used as carrier, has a narrow size distribution (200–250 mesh). Furthermore, the degree of mixing is almost constant and equal to the value for the interactive mixtures whether magnesium stearate is present or not (see Fig. 2), and there are no free particles after adequate mixing (see Fig. 3). Therefore, two models for the coating of an interactive mixture with magnesium stearate may be proposed (Fig. 4b). In model b-1, magnesium stearate strips off fine isoprenaline HCl particles from the carrier potato starch particles during the mixing. The agglomerates of magnesium stearate and drug again adhere to the carrier potato starch particles. In this case, some drug particles exist in the outer surface layer of the particles. In model b-2, magnesium stearate covers the

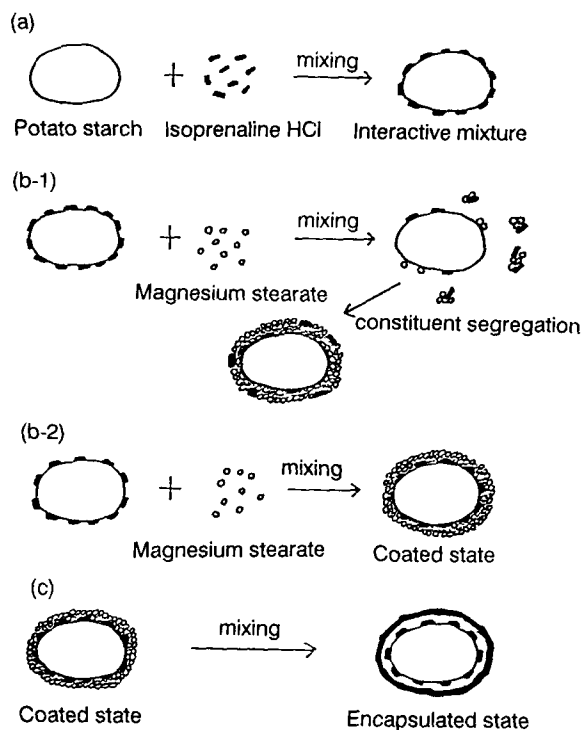


FIG. 4. Encapsulation of an interactive mixture by magnesium stearate.

interactive mixtures, so all isoprenaline HCl particles are assumed to be evenly dispersed over the surface of potato starch particles, just below the magnesium stearate layer.

In model b-1, it is doubtful that the CV would remain constant after adding magnesium stearate because this model is based on Hersey's segregation hypothesis mentioned above. Moreover, scanning electron microscopic observations of the interactive mixtures show that fine isoprenaline HCl particles adhere to the potato starch surface without retaining their original shapes as a result of mixing. When the drug is adhered in this way, it may be difficult to strip the drug particles according to model b-1.

In model b-1, the isoprenaline HCl particles on the outer

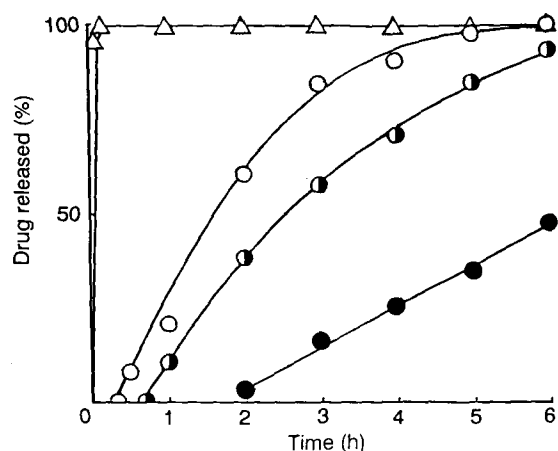


FIG. 5. Effect of magnesium stearate coating temperature on drug release. Key: ○, prepared at 35°C; ◐, 50°C; ●, 70°C; △, uncoated interactive mixtures. The amount of magnesium stearate was 0.3 g and mixing time was 60 min.

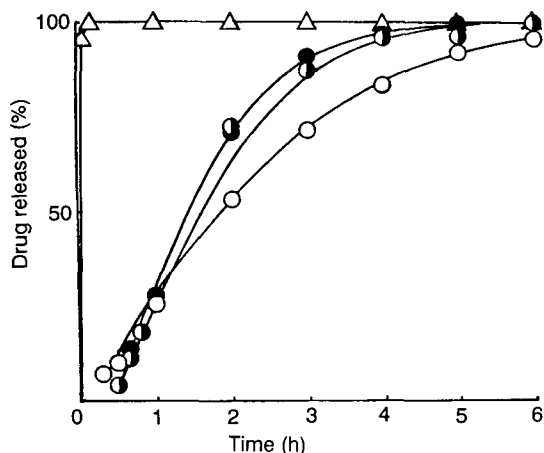


FIG. 6. Effect of the amount of added magnesium stearate on drug release. Key: ○, prepared with 0.1 g magnesium stearate; ●, 0.3 g; ●, 0.5 g; △, interactive mixtures. Temperature was 50°C and mixing time was 30 min.

surface of the particles would be released first, and then those of the inner layer. As isoprenaline HCl is a soluble drug, this release pattern would indicate "the burst effect" (Chien 1979). On the other hand, in model b-2 where the interactive mixtures are coated with magnesium stearate, all the drug particles exist below the layer of magnesium stearate and the release pattern would indicate the existence of a "lag time" for the drug to diffuse through the layer of magnesium stearate. In the release tests (some of which are shown in Figs 5, 6), all the samples exhibited a "lag time" but not "the burst effect", favouring model b-2.

Release rate of isoprenaline HCl

Fig. 5 shows the effect of the temperature of the powder bed during mixing on the release of the drug. The release rate decreases and the lag-time increases with rising preparation temperature (Table 2). These results indicate that the encapsulated sample, which was prepared at 70°C and has the smoothest surface, exhibits the most effective sustained release. Sustained release also depends on the length of the mixing time.

Samyn & Jung (1970), Murthy & Samyn (1977) and Iranloye & Parrott (1978) report that with the increase of the amount of magnesium stearate, the release rate decreases. However, our experiments show the result of changes in the amount of magnesium stearate is also affected by temperature and mixing time.

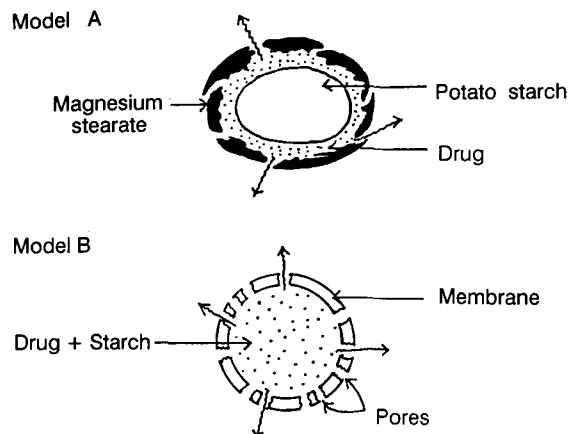


FIG. 7. Diffusion control of drug release. A, model of encapsulated interactive mixture; B, model having a partially water-soluble polymer membrane.

Figure 6 shows the effect of the amount of magnesium stearate on the release of drug (samples G, I, K). The encapsulated sample with the least amount of magnesium stearate (G) has the slowest initial release rate. On the other hand, for encapsulated samples (M, P, R), the sample with the highest amount of magnesium stearate has the longest lag-time and slowest initial release rate. By electron microscopic observations of the samples after the release test (10 h), it was found that for sample G, the magnesium stearate film covers almost all the surface of the potato starch, while for the samples I and K, some "flake-like" masses of magnesium stearate were seen on the surface. Samples M, P and R were not destroyed by release testing and almost kept their shell shape. Consequently, the release of drug from magnesium stearate-coated interactive mixtures is likely to be controlled by the magnesium stearate film. Moreover, this layer, as a film, has fine cracks or small capillary-like pores. The possible mechanism of drug release from coated interactive mixtures, (Fig. 7A) would resemble that of the system where a partially soluble membrane encloses a drug core (Fig. 7B) and dissolution of part of the membrane allows for diffusion of the constrained drug through the pores in the polymer coat (Lee & Robinson 1979). Diffusion controlled release of this type follows first-order kinetics.

By plotting $-\ln(C/C_0)$ versus t for all the release tests, where C = amount of drug remaining at time t , and C_0 = initial amount of drug, straight lines are obtained from the origin to

Table 2. Drug release from interactive mixtures.

Sample	$k \times 10^3$ (min^{-1})	CC	t50 (min)	Initial release rate (% min^{-1})	Lag time (min)	Thickness of film (μm)
E	11.5	0.996	92	0.42	31	
G	7.86	0.998	107	0.33	19	
I	14.6	0.998	81	0.69	34	
J	7.11	0.996	148	0.39	51	
K	15.5	0.998	79	0.73	34	
M	7.56	0.994	133	0.77	41	0.27
N	31.2	0.996	62	0.93	40	
O	6.80	0.980	219	0.49	117	
P	2.77	0.995	371	0.17	121	0.81
R	1.97	0.990	501	0.13	145	1.36

CC = correlation coefficients.

more than 90% drug release for all the release tests. In Table 2, first-order rate constants, k , correlation coefficients (CC) and t_{50} values (time needed for 50% drug release) of the samples are listed. From these results, all the rates were found to follow first-order kinetics. Therefore, it can be said that the release of the drug from magnesium stearate-coated interactive mixtures, is diffusion-controlled (Fig. 7).

In model B (Fig. 7), the fraction of soluble polymer in the membrane is the dominant factor in controlling drug release rate. Similarly, in model A, the appearance of the particle is the dominant factor. The situation where many magnesium stearate particles with their original shapes exist on the surface is equivalent to the situation where a large area of the membrane is soluble polymer; there are many pores in the membrane.

Furthermore, if the area of the particle and the diffusion coefficient are assumed constant, then k is inversely proportional to the membrane thickness. For samples M, P and R which are encapsulated sufficiently, the thickness of the magnesium stearate film is calculated by the following equation, on the assumption that interactive mixtures and potato starch have the same radius and the membrane is dense:

$$\varepsilon = \frac{4/3 \times \pi r_1^3 \times d_1}{4\pi r_1^2} \times \frac{f}{d_2}$$

where r_1 is the radius of potato starch, d_1 and d_2 are the densities of potato starch and magnesium stearate, respectively, and f is the fraction of magnesium stearate in coated mixtures. The calculated film thicknesses (ε) are also listed in Table 2. A plot of k against $1/\varepsilon$ gave a straight line of slope $1.9 \times 10^3 \mu\text{m min}^{-1}$ which is consistent with diffusion-controlled release from the encapsulated interactive mixtures.

Finally, no organic solvent was used in the preparation method which might therefore be expected to find new pharmaceutical applications.

References

- Ampolsuk, C., Mauro, J. V., Nyhuis, A. A., Shah, N., Jarowski, C. I. (1974) Influence of dispersion method on dissolution rate of digoxin-lactose and hydrocortisone-lactose triturations. *J. Pharm. Sci.* 63: 117-118
- Bolhuis, G. K., Lerk, C. K., Zijlstra, H. T., Boer, A. H. (1975) Film formation by magnesium stearate during mixing and its effect on tableting. *Pharmaceutisch. Weekblad* 110: 317-325
- Chien, Y. W. (1979) Methods to achieve sustained drug delivery. The physical approach. *Implants*. In: Robinson, J. R. (ed.) *Sustained and Controlled Release Drug Delivery Systems*. Marcel Dekker, New York, pp 259-260
- Crooks, M. J., Ho, R. (1976) Ordering mixing in direct compression of tablets. *Powder Technol.* 14: 161-167
- Egermann, H. (1985) Effects of adhesion on mixing homogeneity II: highest attainable degree of mixing of a polydisperse ingredient and a monodisperse diluent. *J. Pharm. Sci.* 74: 999-1000
- Egermann, H. (1989) Ordered powder mixtures: reality or fiction? *J. Pharm. Pharmacol.* 41: 141-142
- Egermann, H., Orr, N. A. (1983) Ordered mixture-interactive mixtures. *Powder Technol.* 36: 117-118
- Harnby, N. (1967) The estimation of the variance of samples withdrawn from a random mixture of multi-sized particles. *Chem. Eng.* 214: CE270-CE271
- Hersey, J. A. (1974) Powder mixing frictional pressure: specific example of use of ordered mixing. *J. Pharm. Sci.* 63: 1960-1961
- Hersey, J. A. (1975) Ordered mixing: a new concept in powder mixing practice. *Powder Technol.* 11: 41-44
- Honda, H., Yoshizawa, H., Koishi, M. (1989) Dry impact blending preparation and properties of encapsulated polymer and starch. *Zairyo Gijutsu* 7: 55-66
- Iranloye, T. A., Parrott, E. I. (1978) Effects of compression force, particle size and lubricants on dissolution rate. *J. Pharm. Sci.* 67: 535-539
- Ishizaka, T., Honda, H., Kikuchi, Y., Ono, K., Katano, T., Koishi, M. (1989) Preparation of drug-diluent hybrid powders by dry processing. *J. Pharm. Pharmacol.* 41: 361-368
- Johnson, M. C. R. (1979) Powder mixing in direct compression formulation by ordered and random processes. *Ibid.* 31: 273-276
- Jones, T. M. (1970) The effect of glidant addition on the flowability of bulk particulate solids. *J. Soc. Cosm. Chem.* 21: 483-500
- Koishi, M., Ishizaka, T., Nakajima, T. (1984) Preparation and surface properties of encapsulated powder pharmaceuticals. *Applied Biochemistry Biotechnology* 10: 259-262
- Kozatani, J., Kitaura, T., Ashida, K. (1969) The influence of dispensing fine granules on degree of mixing. *Yakuzaigaku* 29: 53-56
- Lai, F. K., Hersey, J. A. (1979) A cautionary note on the use of ordered powder mixtures in pharmaceutical dosage forms. *J. Pharm. Pharmacol.* 31: 800
- Lacey, P. M. C. (1943) The mixing of solid particles. *Trans. Instn. Chem. Eng.* 21: 53-59
- Lee, V. H.-L., Robinson, J. R. (1979) Methods to achieve sustained drug delivery. In: Robinson, J. R. (ed.) *Sustained and Controlled Release Drug Delivery Systems. The Physical Approach. Oral and Parenteral Dosage Forms*. Marcel Dekker, New York, pp 138-149.
- Lerk, C. K., Bolhuis, G. K. (1977) Interaction of lubricants and colloidal silica during mixing with excipients. II. Its effect on wettability and dissolution velocity. *Pharm. Acta. Helv.* 52: 39-44
- Levy, G., Gumtow, R. H. (1963) Effect of certain tablet formulation factors on dissolution rate of the active ingredient. III. Tablet lubricants. *J. Pharm. Sci.* 52: 1139-1144
- Motycka, S., Nairn, J. G. (1978) Influence of wax coating on release rate of anions from ion-exchange resin beads. *Ibid.* 67: 500-503
- Murthy, K. S., Samyn, J. C. (1977) Effect of shear mixing on in vitro drug release of capsule formulations containing lubricants. *Ibid.* 66: 1215-1219
- Nakagawa, A., Ishizaka, T., Yano, K., Koishi, M. (1984) Granule surface modification by dry mixing and applications to sustained release preparations. *Zairyo Gijutsu* 2: 43-54
- Poole, K. R., Taylor, R. F., Wall, G. P. (1964) Mixing powders to fine scale homogeneity-studies of batch mixing. *Trans. Instn. Chem. Engrs.* 42: T305-T315
- Samyn, J. C., Jung, W. Y. (1970) In vitro dissolution from several experimental capsule formulations. *J. Pharm. Sci.* 59: 169-175
- Staniforth, J. N., Rees, J. E. (1981) Powder mixing by Triboelectrification. *Powder Technol.* 30: 255-256
- Staniforth, J. N., Rees, J. E. (1982) Electrostatic charge interactions in ordered powder mixes. *J. Pharm. Pharmacol.* 34: 69-76
- Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1981) Determination of interparticulate forces in ordered powder mixes. *Ibid.* 33: 485-490
- Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1982) Interparticle forces in binary and ternary ordered powder mixes. *Ibid.* 34: 141-145
- Thiel, W. J., Nguyen, L. T. (1982) Fluidized bed granulation of an ordered powder mixture. *Ibid.* 34: 692-699
- Thiel, W. J., Nguyen, L. T. (1984) Fluidized bed film coating of an ordered powder mixture to produce microencapsulated ordered units. *Ibid.* 36: 145-152
- Thiel, W. J., Nguyen, L. T., Stephenson, P. L. (1983) Fluidized bed granulation of an ordered powder mixture reduces the potential for ordered unit segregation. *Powder Technol.* 34: 75-80
- Travers, D. N., White, R. C. (1971) The mixing of micronized sodium bicarbonate with sucrose crystals. *J. Pharm. Pharmacol.* 23: 260S-261S
- Westerberg, M., Johnson, B., Nystrom, C. (1986) Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures. *Int. J. Pharm.* 28: 23-31
- Yip, C. W., Hersey, J. A. (1977) Segregation in ordered powder mixtures. *Powder Technol.* 16: 149-150