

- (226) E. Bailey, M. Fenoughty, and J. R. Chapman, *ibid.*, **96**, 33(1974).
- (227) J. A. Luyten and G. A. F. M. Rutten, *ibid.*, **91**, 393(1974).
- (228) G. M. Anthony, C. J. W. Brooks, I. MacLean, and I. Sangster, *J. Chromatogr. Sci.*, **7**, 623(1969).
- (229) D. Exley and J. Chamberlain, *Steroids*, **10**, 509(1967).
- (230) A. Zmigrod, S. Ladany, and H. R. Lindner, *ibid.*, **15**, 535(1970).
- (231) D. G. Kaiser, R. G. Carlson, and K. T. Kirton, *J. Pharm. Sci.*, **63**, 420(1974).
- (232) J. A. F. Wickramasinghe, W. Morozowich, W. E. Hamlin, and S. R. Shaw, *ibid.*, **62**, 1428(1973).
- (233) W. Vogt, K. Jacob, and M. Knedel, *J. Chromatogr. Sci.*, **12**, 658(1974).
- (234) S. J. Clark and H. H. Wotiz, in "Modern Methods of Steroid Analysis," E. Heftman, Ed., Academic, New York, N.Y., 1973, p. 72.
- (235) R. T. Nuttall and B. Bush, *Analyst*, **96**, 875(1971).
- (236) A. R. Prosser and A. J. Sheppard, *J. Pharm. Sci.*, **58**, 718(1969).
- (237) V. Viswanathan, F. P. Mahn, V. S. Venturella, and B. Z. Senkowski, *ibid.*, **59**, 400(1970).
- (238) D. K. Feeter, M. F. Jacobs, and H. W. Rawlings, *ibid.*, **60**, 913(1971).
- (239) A. J. Sheppard, W. D. Hubbard, and A. R. Prosser, *J. Ass. Offic. Anal. Chem.*, **52**, 442(1969).
- (240) J. Vessman and S. Stromberg, *J. Pharm. Sci.*, **64**, 311(1975).
- (241) G. G. Gallo, N. Rimorini, L. F. Zerilli, and P. Radaelli, *J. Chromatogr.*, **101**, 163(1974).
- (242) J. H. Hengstman, F. C. Falkner, J. T. Watson, and J. Oates, *Anal. Chem.*, **46**, 34(1974).
- (243) P. Erdtmansky and T. Goehl, *ibid.*, **47**, 750(1975).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the Research and Development Division, Ciba-Geigy Corp., Suffern, NY 10901

RESEARCH ARTICLES

Influence of Hydrophobic Materials on Dissolution of a Nondisintegrating Hydrophilic Solid (Potassium Chloride)

J. VALERIE FEE*, D. J. W. GRANT*, and J. M. NEWTON

Abstract □ A nondisintegrating hydrophilic solid was covered with coatings of hydrophobic materials as a model to study their influence on dissolution rates. Both solution and sublimation techniques were satisfactory for producing coatings of stearic acid. Only a sublimation method was applicable to magnesium stearate, but the resulting coating consisted mainly of a pyrolysis product, stearone. Reductions in dissolution rates in a continuous-flow system could best be interpreted by assuming that they reflected changes in the area of the hydrophilic solid exposed to the solvent. This concept is based on the assumptions that the intrinsic dissolution rate of uncoated potassium chloride did not change and that no dissolution occurred from coated areas. The most important factors controlling the dissolution rate were the strength of attachment of the hydrophobic coat to the surface of the hydrophilic substrate and the thickness of the coat.

Keyphrases □ Dissolution—potassium chloride, a nondisintegrating hydrophilic solid, effect of hydrophobic coating materials □ Potassium chloride disk—effect of hydrophobic coating materials on dissolution

The most common method of ensuring adequate lubrication of the interface between powders and metals during tablet and capsule manufacture is the addition of materials, such as stearic acid and magnesium stearate, in the form of powders. These materi-

als, being hydrophobic in nature, inhibit the penetration of aqueous fluids into the final product (1, 2). This limitation of access results in retarded dissolution rates of tablets (3) and capsules (2-4).

The hydrophobic material, in addition to reducing the rate and extent of penetration of fluid into the preparation, can reduce the dissolution rate of individual particles by covering their surface. In formulated systems, it is difficult to decide which of these two effects is the rate-controlling step in the release of drugs from preparations. For example, liquid penetration of capsule formulations may or may not correlate with drug release (5). Moreover, because the spatial distribution of the lubricant in the final preparation is unknown, the extent and thickness of the hydrophobic covering of the drug particles are also unknown. It is, therefore, difficult to measure the effect of added hydrophobic materials on the dissolution rate of the individual particles within a preparation.

To investigate this problem, it is helpful to consider model systems. The present work describes a model in which the type, thickness, and area of cover

of the hydrophobic layer and the method of applying it were each varied. The influence of these variables on the dissolution process of a hydrophilic substrate was studied, without interference from penetration problems, by means of the apparatus for determining dissolution rates described previously (6).

EXPERIMENTAL

Materials—The hydrophilic disk used as a model substrate was spectroscopic grade potassium chloride¹. The hydrophobic coating materials were stearic acid, grade I², and magnesium stearate, superfine grade³. The solvents used in coating techniques were all analytical grade⁴. The dissolution medium was glass-distilled water.

Preparation of Potassium Chloride Disks—This procedure was carried out as described previously (6) to provide a transparent disk in a creep-resistant metal ring.

Coating Disks by Evaporation from Solvents—The hydrophobic material was dissolved in a solvent that had previously been shown not to interact with the disk surface. Solutions were applied in 0.1-ml volumes and allowed to evaporate under normal atmospheric conditions. By varying solute concentration and the number of applications of solution, the final quantity of coat on the surface could be controlled.

Coating Disks by Sublimation—The basic process was to allow vaporized hydrophobic material to condense onto one surface of a disk cooled at the end of a finger containing ice and water. The pressure of the vapor phase was maintained at 0.05 mm Hg. The rate of application of heat and the final temperature used to vaporize the hydrophobic material were varied to meet the requirements of the system and to provide different quantities of coat. When vaporization and condensation were complete, the heating source was removed and the system was slowly allowed to reach atmospheric conditions.

Determination of Quantity of Coating—The quantity of hydrophobic material covering the potassium chloride disk was determined by placing the disk and holder in the detection path of an IR spectrophotometer⁵ and observing the extinction values of the carbonyl absorption peaks. Calibration curves were obtained by incorporating known quantities of coating material within the disk. Comparison of the extinction at different disk orientations provided a check on the uniformity of the coating.

Observation of Disk Surface—The surface of the coated disk was observed with an optical microscope and, after suitable pretreatment, with a scanning electron microscope⁶.

Determination of Dissolution Rates—The rate at which potassium chloride dissolved in water was determined using the apparatus described previously (6). Measurements were carried out at flow rates that provided laminar flow but corresponded to the region in which forced convection of the solvent existed. The Reynolds number for solvent flow was close to 1300.

RESULTS

Coating with Stearic Acid—Solution Coating—A number of different organic liquids were examined for their suitability as coating solvents. Coated disks were examined by optical microscopy and by determining the IR spectra at different disk orientations. Light petroleum (bp 60–80°) gave the most complete coatings, which reduced the dissolution rate of the potassium chloride substrate. In no case, however, were the coatings even. They consisted of flakes of stearic acid about 100 μm long (Fig. 1). The coefficient of variation of the extinction values of coated disks at different disk orientations was about 8%.

Sublimation Coating—Vaporization at 126° for 6 min produced an even covering of the disk with no detectable change in IR ex-

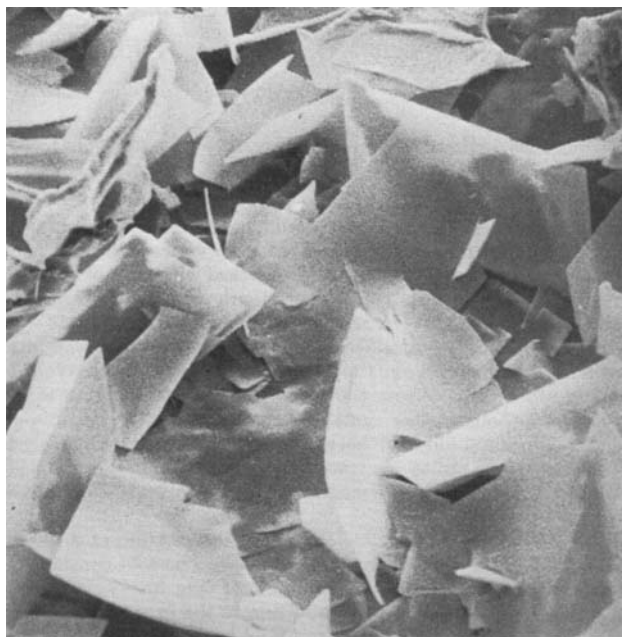


Figure 1—Scanning electron micrograph of the coating of stearic acid formed on a potassium chloride disk by evaporation from a solution of stearic acid in light petroleum (bp 60–80°) ($\times 208$).

tinction with different disk orientations. The covering was entirely different in nature from that produced by solution coating (e.g., Figs. 1 and 2). Stearic acid deposited as globules approximately 2.5 μm in diameter.

Coating with Magnesium Stearate—Solution Coating—A solvent system that would provide an even cover without dissolving away the disk surface could not be found. Hence, no dissolution rate tests could be undertaken.

Sublimation Coating—To ensure vaporization of the magnesium stearate, it was necessary to heat the substance at 260° for 2 hr. The IR spectrum of the resulting coated disk did not correspond to that of magnesium stearate. It appeared that decomposition had occurred, probably the pyrolytic decarboxylation reaction



Figure 2—Scanning electron micrograph of the coating of stearic acid formed on a potassium chloride disk by sublimation of stearic acid ($\times 1900$).

¹ B.D.H. Chemicals Ltd., Poole, Dorset, BH12 4NN, England.

² Sigma London Chemical Co.

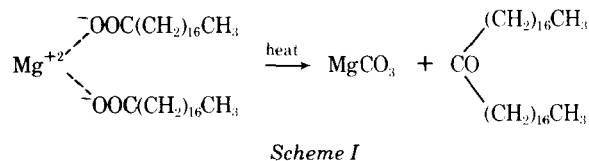
³ Bush, Boake and Allen Ltd., London, N1, England.

⁴ Koch-Light Laboratories Ltd., Colnbrook, Buckinghamshire, SL3 0BZ, England.

⁵ Unicam SP200, Pye Unicam Ltd., Cambridge, CB1 2PX, England.

⁶ Cambridge Stereoscan Mark 2A, Cambridge Instrument Co., Cambridge, England.

typical of Group II A salts of fatty acids (Scheme I).



The product of this reaction would be stearone (diheptadecyl ketone or pentatriacontan-18-one). In accordance with this reaction, the IR spectrum was virtually identical with that of stearone prepared by the decarboxylation of stearic acid through heating with finely divided iron (7), removal of unchanged stearic acid with sodium hydroxide, decolorization with charcoal, and recrystallization from light petroleum (bp 100–120°). The mass spectrum of the material removed from the disk provided confirmation of the structure, although other materials also appeared to be present. These materials could have been stearic acid formed by hydrolysis of magnesium stearate by traces of moisture, other fatty acids present as impurities in the magnesium stearate, and ketones from their pyrolysis.

The coating itself was even, since the IR spectrum at different orientations showed no detectable variation. The coat consisted of closely packed globules, 1–4 μm in diameter (Fig. 3).

Coating with Stearone—In addition to the *in situ* production of stearone, the influence of this material by solution and sublimation coating was also studied.

Solution Coating—Due to the low solubility of stearone (about 1.5 g/liter) at 20° in light petroleum (bp 60–80°), several applications of 0.1 ml of such solutions were required to cover the disk adequately. The coatings were similar to solution coatings of stearic acid; they were uneven (with a coefficient of variation in IR extinction at different orientations of about 8%) and consisted of flakes about 10 μm long (Fig. 4).

Sublimation Coating—The quantity applied was varied by altering the conditions of application of heat and final temperature. As with other sublimed coatings, there was no detectable variation in the IR extinction at different disk orientations. The scanning electron micrographs (e.g., Fig. 5) confirm the evenness of the coat but show that it consisted of loosely packed aggregates of globules and not of individual globules of the type produced by the sublimation of stearic acid or magnesium stearate. The diameter of the aggregates was about 10 μm; the diameter of the globules, of which they were composed, was about 1 μm.

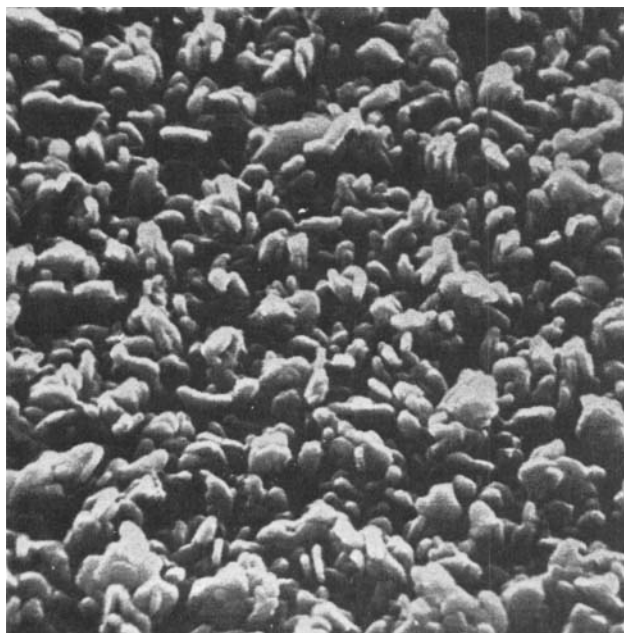


Figure 3—Scanning electron micrograph of the coating formed by the sublimation product of magnesium stearate on a potassium chloride disk (×1850).

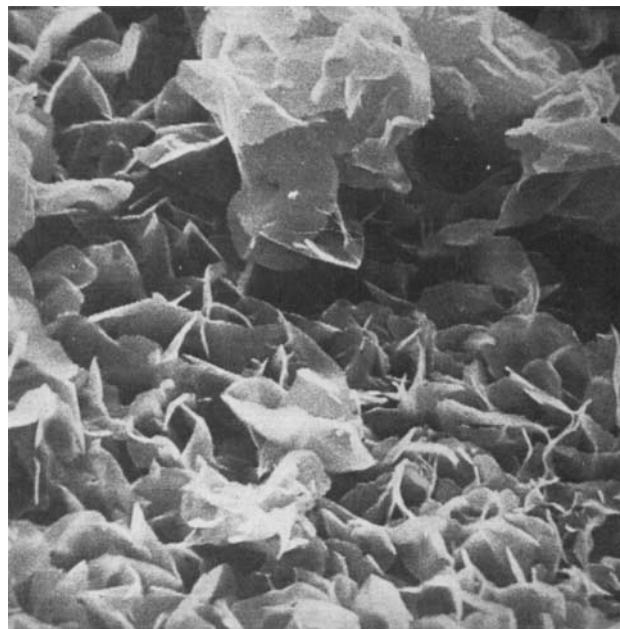


Figure 4—Scanning electron micrograph of the coating of stearone formed on a potassium chloride disk by evaporation from a solution of stearone in light petroleum (bp 60–80°) (×2050).

Influence of Hydrophobic Coatings on Dissolution of Potassium Chloride—Determinations of the dissolution rates of disks of potassium chloride that had been subjected to the solution or sublimation process, without hydrophobic material, established that these coating processes themselves in no way influenced the dissolution. Therefore, the effects produced were due to the presence of the hydrophobic coat and varied with the material and method of application.

In a flowthrough dissolution system such as that used here, a constant concentration, *c*, of dissolved material indicates a constant rate of dissolution, *dm/dt*, of the dissolving solid. Figure 4 in Ref. 6 illustrates this state for an uncoated disk of potassium chloride. Any change in concentration of dissolved material indicates a

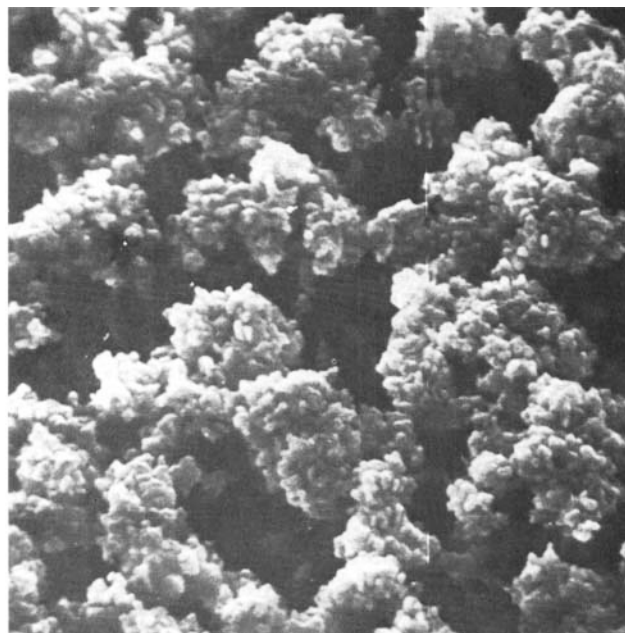


Figure 5—Scanning electron micrograph of the coating of stearone formed on a potassium chloride disk by sublimation of stearone (×2080).

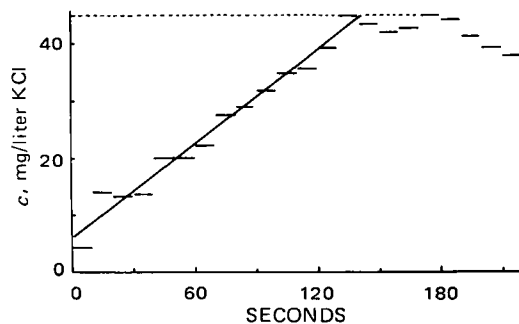


Figure 6—Time dependence of the concentration of potassium chloride in the effluent of the dissolution apparatus from a potassium chloride disk covered with a solution coating of stearic acid (0.298 mg/cm^2).

corresponding change in the dissolution rate, c being directly proportional to dm/dt (Eq. 3 in Ref. 6).

Influence of Stearic Acid—Solution Coating—For all quantities of stearic acid applied, c and dm/dt were considerably lower than those of the uncoated disk and increased with time until all coating was removed or until disk erosion brought about a decrease in area (Fig. 6). In general, the rate of increase in c (and dm/dt) decreased with an increasing quantity of stearic acid applied. Thus, the dissolution behavior of these coated disks differed in two fundamental ways from that of uncoated disks.

Sublimation Coating—In spite of the even coating, a covering corresponding to 0.269 mg/cm^2 produced no significant change in the release of potassium chloride. Therefore, either the coating did not retard the interfacial motion of the solvent and solute molecules or it was readily removed from the disk surface by the dissolution test procedure.

Influence of Magnesium Stearate—The covering resulting from the sublimation process produced a considerable reduction in c (and dm/dt). Again, there was an increase in c with time, but two linear sections were present in this case (Fig. 7), which is a further departure from the uncoated system.

Influence of Stearone—Solution Coating—A covering corresponding to 0.140 mg/cm^2 had little effect on potassium chloride dissolution (Table I); a steady level of c (and dm/dt) only slightly less than that for the uncoated disk was observed. Thicker coatings provided the linear increase in c (and dm/dt) observed with solution coatings of stearic acid.

Sublimation Coating—When the covering corresponded to 0.281 or 0.565 mg/cm^2 , c (and dm/dt) increased with time until a constant level, slightly lower than that for the uncoated disk, was obtained (Fig. 8). A thicker coating, 1.2 mg/cm^2 , gave, throughout a run, approximately constant values of c and dm/dt about 60% of those for the uncoated disk.

DISCUSSION

In the dissolution system (6) used here, relative motion between the fluid and solid phase is both controlled and defined. The method provides a system where penetration between particles is not involved; in addition to studying the dissolution process, an indication of the strength of attachment to the solid surface can be obtained.

If attachment to the surface is weak, the coating can be removed by the moving fluid. The dissolution process then corresponds to that for the uncoated disk. Alternatively, if attachment is strong and there is complete covering of the surface, total or partial inhibition of dissolution results, depending on whether the coating blocks or retards the movement of solvent and solute molecules to and from the surface. Between these two extremes, a range of possibilities exist.

For example, covering of the surface may be incomplete at a microscopic or macroscopic level, thus allowing varying areas of contact between the solvent and surface. If these areas remain constant because of firm attachment of the coating, the dissolution rate is constant but smaller and there is a reduced constant level of potassium chloride in the solution. If, however, attachment of the covering is not firm or dissolution of the coat takes place, an increase in dissolution rate and concentration occurs. Once a break

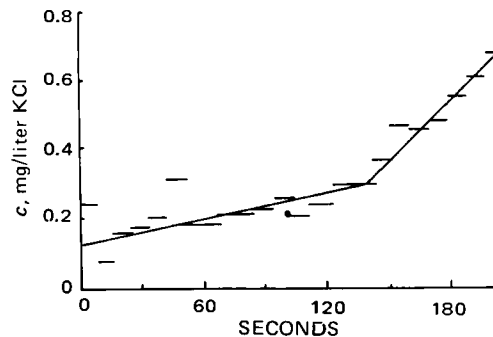


Figure 7—Time dependence of the concentration of potassium chloride in the effluent of the dissolution apparatus from a potassium chloride disk covered with the sublimation product of magnesium stearate (0.594 mg/cm^2).

in the coating is made, dissolution of the substrate can take place underneath it.

The results obtained provide examples of these effects. The total inhibition of the dissolution process was never obtained; it was impossible to provide complete cover with attachment sufficiently strong to exclude movement of solvent and solute molecules across the hydrophobic barrier. The alternative extreme of a coating that did not affect dissolution was obtained with sublimation coatings of stearic acid at 0.269 mg/cm^2 and solution coatings of stearone at 0.140 mg/cm^2 (Table I). The disappearance of the coat during the test supports the hypothesis that the moving fluid removes the coating and refutes the supposition that the coat retards solvent and solute movement across it. The former hypothesis is further supported by the fact that increasing the quantity of stearone sublimed onto the disk did reduce the final dissolution rate (Table I).

With all other coatings, there was a change in dissolution rate during the dissolution test. The observed dissolution rate, dm/dt , is given by:

$$\frac{dm}{dt} = GA \quad (\text{Eq. 1})$$

where m is the mass of dissolved material at time t , G is the intrinsic dissolution rate, and A is the area from which dissolution takes place. Any change in the dissolution rate implies a change in G and/or A . Visual observation of the disk suggests that a change in area is the most likely.

As a first approximation, it is postulated that: (a) the hydrophobic coating reduces to zero the rate of dissolution of the substrate directly beneath it, and (b) the intrinsic dissolution rate from the uncoated regions is equal to that from an uncoated disk. The observed dissolution rate, dm/dt , is then equal to the total rate of dissolution from the uncoated regions of the disk and, according to Eq. 1, is proportional to the exposed area, A , the constant of proportionality being the intrinsic dissolution rate, G . Thus, dm/dt provides a measure of the area that has lost its hydrophobic coating.

The rate of increase of the dissolution rate with respect to time, i.e., d^2m/dt^2 , reflects the rate of change in area with time, dA/dt .

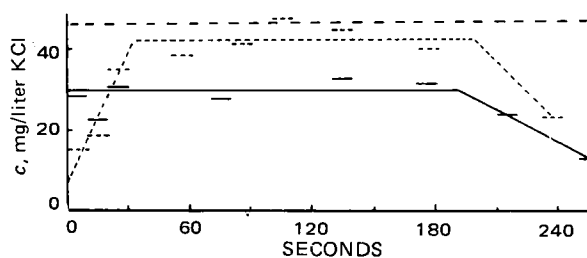


Figure 8—Time dependence of the concentration of potassium chloride in the effluent of the dissolution apparatus from a potassium chloride disk covered with sublimation coatings of stearone. Key: ---, uncoated disk; —, 0.281 mg/cm^2 stearone; and - · -, 0.565 mg/cm^2 stearone.

Table I—Influence of Hydrophobic Materials, when Applied as Coatings, on the Dissolution Properties of Potassium Chloride in Water at Reynolds Number 1300 for Solvent Flow

Coating System	Values at Zero Time				Rates of Change with				Time Taken to Remove Coat, sec		After 120 sec	
	Amount of Coat, mg/cm ²	Concentration of Potassium Chloride, c ₀ , μg/dm ³	Dissolution Rate (dm/dt) ₀ , μg/sec	Area Exposed, A ₀ , mm ²	Area Exposed, %	Change in Concentration, dc/dt, mg/dm ³ sec	Change in Dissolution Rate, d ² m/dt ² , μg/sec ²	Change in Area, dA/dt, mm ² /sec	Calculated	Observed	Dissolution Rate, μg/sec	Surface Uncoated, %
None	0.298	28.6	871	819	61.7	0.276	8.76	0.812	0	0	1410	100
	0.530	5.79	184	17.01	12.8	0.121	3.15	0.298	142	140	1242	86.7
	0.632	0.143	39.2	3.09	0.30	0.121	3.10	0.298	446	—	382	27.1
	0.726	1.25	161	3.46	2.33	0.0794	0.275	0.0251	435	—	404	29.3
	0.821	0.929	24.4	2.34	1.70	0.0332	0.871	0.0836	5,230	—	48.9	3.4
Stearic acid by sublimation	0.863	0.166	25.38	0.507	1.76	0.0334	1.55	0.148	1,560	—	129	8.3
	1.244	0.587	20.7	1.88	0.38	0.0342	0.121	0.0109	907	—	190	13.5
	0.269	29.6	902	848	63.9	Initial change rapid, then zero	0.121	0.0109	12,000	0	35.2	12.4
	0.178	0.400	10.80	1.045	0.79	0.073 ^a	2.10	0.198	—	—	1410	100
	0.584	0.122	3.29	0.319	0.74	0.003 ^b	0.0291	0.008	—	—	—	—
Magnesium stearate pyrolysis product by sublimation	0.667	0.098	2.65	0.256	0.19	0.033 ^c	4.50	0.036	—	—	—	—
	0.178	—	—	—	—	0.152 ^b	4.58	0.435	—	—	—	—
	0.584	—	—	—	—	0.052 ^c	0.138	0.032	354	—	—	—
	0.667	—	—	—	—	0.0170	0.433	0.042	10,160	—	—	—
	0.140	—	—	—	—	Initial change rapid, then zero	1.22	0.116	3,420	—	—	—
Stearone from solution	0.473	0.752	21.3	2.015	1.52	0.0431	1.22	0.116	1,129	0	1280	91.0
	0.281	8.6	302	27.4	20.6	0.237	18.32	0.756	1,129	140	1280	11.9
	0.565	10.4	292	27.7	20.9	0.656	18.4	1.75	159	50	1202	85.9
	1.20	28.6	815	76.9	57.9	Very small values	—	—	52	—	875	62.2

^a Change of slope at t = 90 sec, c = 7 mg/dm³. ^b Change of slope at t = 164 sec, c = 0.3 mg/dm³. ^c Change of slope at t = 345 sec, c = 1.45 mg/dm³.

This can be seen by differentiating Eq. 1 with respect to time:

$$\frac{d^2m}{dt^2} = G \frac{dA}{dt} \quad (\text{Eq. 2})$$

Also, as in Eq. 3 of Ref. 6, the rate of dissolution can be expressed in terms of the concentration, *c*, of dissolved potassium chloride and the volumetric flow rate, *dV/dt*:

$$\frac{dm}{dt} = c \frac{dV}{dt} \quad (\text{Eq. 3})$$

which, on differentiating with respect to time, *t*, at constant volumetric flow rate, *dV/dt*, gives:

$$\frac{d^2m}{dt^2} = \frac{dc}{dt} \frac{dV}{dt} \quad (\text{Eq. 4})$$

where *dc/dt* is the rate of change of potassium chloride concentration, *c*, with time. This equation enabled *d²m/dt²* to be calculated in Table I. Comparison of Eqs. 2 and 4 gives:

$$G \frac{dA}{dt} = \frac{dc}{dt} \frac{dV}{dt} \quad (\text{Eq. 5a})$$

or:

$$\frac{dA}{dt} = \frac{1}{G} \frac{dc}{dt} \frac{dV}{dt} \quad (\text{Eq. 5b})$$

Values of *dA/dt* in Table I were calculated from this equation. The time, *T*, taken for the total surface area of the substrate to be exposed to the solvent by complete removal of the coating is obtained by integrating *dt/dA* over the total increase in exposed area:

$$T = \int_{A_0}^{A_T} \frac{dt}{dA} dA \quad (\text{Eq. 6})$$

where *A₀* is the initial exposed area of the disk (when *t* = 0) and is usually very small⁷, and *A_T* is the final exposed area of the disk. The *A_T* value was almost always the total area of the disk surface (132.73 mm²); but with a sublimed coating of stearone at 0.565 mg/cm², *A_T* was 85.9% of this value. If *G*, *dc/dt*, and *dV/dt* are constant, Eq. 5 indicates that *dt/dA* will be constant. The reciprocal, *dA/dt*, will also be constant, and Eq. 6 becomes:

$$T = \frac{dt}{dA} \int_{A_0}^{A_T} dA = \frac{dt}{dA} [A]_{A_0}^{A_T} \quad (\text{Eq. 7})$$

$$\therefore T = (A_T - A_0) / \frac{dA}{dt} \quad (\text{Eq. 8})$$

Thus, the time taken to remove the coating partially or completely can be calculated, as shown in Table I. This approach can be applied to the present results, since *dA/dt* calculated from Eq. 5 was constant. This is true because the flow rate, *dV/dt*, was constant, the intrinsic dissolution rate, *G*, was assumed to be constant, and *dc/dt* was found to be constant, since experiments indicated that *c* was a linear function of time.

Support for the hypothesis, expressed previously in postulates (a) and (b), is provided by the results for sublimed coatings of stearone (0.281 mg/cm² and 0.565 mg/cm²) and solution coatings of stearic acid (0.298 mg/cm²). In these cases, there was excellent agreement between the time taken to remove the coating, calculated by the described method, and the experimentally observed time to reach a constant level of potassium chloride release (Table I). The latter time for other coatings was too long to be experimentally accessible.

The thickest coating of sublimed stearone (Table I) resulted in a practically constant dissolution rate, which was lower than that for

⁷ Values of *A₀* can be obtained by applying Eqs. 1 and 3 at zero time:

$$A_0 = \frac{1}{G} \left(\frac{dm}{dt} \right)_0$$

where:

$$\left(\frac{dm}{dt} \right)_0 = c_0 \frac{dV}{dt}$$

c₀ being the initial concentration of dissolved potassium chloride and (*dm/dt*)₀ being the initial dissolution rate (Table I).

the uncoated disk, suggesting the presence of a residual coating which was difficult to remove. Because of limitations of the duration of the experiment and differing loss of material, it may not always be possible to arrive at this simple result. The other types of results obtained were a continuous linear change, shown in Fig. 6 for solution coatings of stearic acid, and two distinct linear regions, shown in Fig. 7 for sublimation coatings of the pyrolysis product of magnesium stearate. The former result implies that the area available for dissolution increases in a linear manner with time.

The present experiments were unable to show whether the coating is removed by dissolution or erosion ("undermining" of the coating by the dissolution of the potassium chloride beneath it). The two distinct rates of dissolution (Fig. 7) suggest the removal of materials with differing affinities for the substrate. The rate of change of area, dA/dt , and the time, T , taken to remove the coating (Table I) were calculated for these different systems because they provide a means of comparing the relative effects of the coatings and methods of applying them.

Comparison of the results in Table I clearly shows that the sublimed coating of the pyrolysis product of magnesium stearate produced the greatest reduction in dissolution rate. Since this system is associated with the lowest rates of exposure of surface, it apparently exhibits the greatest attraction between surface and coating material. This finding could be attributed to the process of sublimation or to the formation of a mixed coating. Because other sublimed coatings are not always strongly attached, the latter suggestion seems to be more satisfactory.

In general, irrespective of the type of material or coating process (Table I), the thicker the coat the smaller was the initial exposed area, A_0 , and the smaller was the rate of increase in exposed area with time (dA/dt), as expected. The major exception to this rule was provided by the differing thicknesses of sublimed coatings of stearone, where the thickest coat had the largest initial exposed area, A_0 , and the intermediate coating had the greatest rate of exposure, dA/dt . The coatings were composed of aggregates of globules (Fig. 5). Increasing the amount deposited by sublimation increased the size of these aggregates and the number of individual globules attached to the surface. Thus, a thicker coating can provide a greater resistance to the flow; although thicker coatings of sublimed stearone had smaller initial effects on the dissolution processes than did thinner coatings, they had greater sustained effects.

Table I shows that, after 120 sec, during the later stages of the test, the thicker the coat the lower were the dissolution rate and the exposed area. Hence, a fraction of these sublimed coatings ap-

pears to be tenaciously held to the surface, this quantity increasing with the amount of coating applied. Consequently, the attachment of the hydrophobic layers to the ionic substrate is of fundamental importance in determining how the dissolution process is affected.

CONCLUSIONS

The reduction in the dissolution rate of nondisintegrating potassium chloride in a flowthrough system, brought about by hydrophobic coating, is controlled primarily by the force of attachment of the coating to the surface. The results can be explained by assuming that: (a) the intrinsic dissolution rate of potassium chloride, which is not coated, does not change; and (b) the hydrophobic material reduces to zero the dissolution rate of the hydrophilic material it covers. The changes in dissolution rate are, therefore, a measure of the changes in the surface area not coated.

REFERENCES

- (1) D. Ganderton, *J. Pharm. Pharmacol.*, **21**, 219S(1969).
- (2) J. C. Samyn and W. Y. Jung, *J. Pharm. Sci.*, **59**, 169(1970).
- (3) G. Levy and R. Gumtow, *ibid.*, **52**, 1039(1963).
- (4) H. C. Caldwell, *ibid.*, **63**, 770(1974).
- (5) G. Rowley and J. M. Newton, *J. Pharm. Pharmacol.*, **22**, 966(1971).
- (6) J. V. Fee, D. J. W. Grant, and J. M. Newton, *J. Pharm. Sci.*, **65**, 48(1976).
- (7) T. H. Easterfield and C. M. Taylor, *J. Chem. Soc.*, **99**, 2298(1911).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 30, 1974, from the *Department of Pharmacy, University of Nottingham, University Park, Nottingham, NG7 2RD, England.*

Accepted for publication May 2, 1975.

The authors are grateful to Mr. L. Green and to the Wolfson Institute of Interfacial Technology, Nottingham University, for the preparation of the electron scanning photomicrographs and to the Sheffield Regional Hospital Board for providing financial support to Miss J. Valerie Fee.

* Present address: Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh, EH3 9YW, Scotland.

* To whom inquiries should be directed.