tain, as well as the number of operations to produce, the uniform distribution of drug in granular solids is much less and more specific for latex-generated solid dispersions. Therefore, simpler, more specific manufacturing instructions are possible. Direct compression ingredients and lubricants can be added, or lubricants can be added to the entrapment product and tableted directly, with weight variation being the major factor impairing content uniformity. Entrapment may be compared to wet granulation as far as time to produce a finished tablet; availability and effectiveness do not appear to be problems for molecular scale drug entrapment (1–7).

For scale-up operations, a general scheme might include the steps indicated in Scheme I. The molecular scale drug entrapment method described herein appears to have great potential for distributing drugs uniformly, especially low dose, highly potent drugs where the usual blending techniques may be inadequate or unreliable.

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## ACKNOWLEDGMENTS AND ADDRESSES


Received November 28, 1973, from the *Industrial and Physical Pharmacy Department, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907*

Accepted for publication July 31, 1975.

Presented at the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, San Diego meeting, November 1973.

Supported by the Purdue Research Foundation.



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# Contact Angles and Wetting of Pharmaceutical Powders


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**Abstract** □ Contact angles of pharmaceutical powders were determined by the $h$–$\epsilon$ method, which consists essentially of measuring the maximum height of a drop of liquid formed on a presaturated compact of the material. Determinations with aspirin as the test material indicate that the measured value is independent of the particle size of the powder and the porosity of the cake. The method was extended to include determinations on mixed powder systems. The results show that the hydrophobic material dominates with large particle-size powders; with small particle sizes, a linear relationship between the cosine of the contact angle of the mixed system and the proportion of the components is obtained. Results are presented for a wide variety of materials of pharmaceutical interest.



**Keyphrases** □ Powders, pharmaceutical—contact angles and wetting determined by $h$–$\epsilon$ method, effect of particle size and porosity of cake □ Contact angles—pharmaceutical powders, determined by $h$–$\epsilon$ method, effect of particle size and porosity of cake □ Wetting—pharmaceutical powders, effect of particle size and porosity of cake □ Aspirin powder—contact angles and wetting determined by $h$–$\epsilon$ method, effect of particle size and porosity of cake


The wetting of solid materials usually implies the replacement of air on the surface of a solid by a liquid. In addition to the components of the system, the type of wetting is also important. Osterhof and Bartell (1) distinguished between three types of wetting, namely those of adhesion, immersion, and spreading. The distinction between these three types may be made by considering the model, suggested by Parfitt (2), of a solid cube being immersed in a liquid (Fig. 1).

## THEORY

The energy changes that take place when these processes occur may be written in terms of the measurable quantities of the liquid–vapor interfacial tension and the contact angle. If it is assumed that the solid surface before wetting is in equilibrium with the vapor of the liquid (1, 2), then:

$$W_a = -\gamma_{LV^\circ}(\cos\theta + 1) \qquad \text{(Eq. 1)}$$

$$W_i = -\gamma_{LV^\circ}\cos\theta \qquad \text{(Eq. 2)}$$

$$W_s = -\gamma_{LV^\circ}(\cos\theta - 1) \qquad \text{(Eq. 3)}$$

**Table I—Measured Values of Contact Angles of Materials of Pharmaceutical Interest**

| Material | Standard | Surface Tension, dynes/cm | Density Liquid, g/cm³ | Density Solid, g/cm³ | Porosity[a] | Drop Height[a], cm | cos θ | θ° |
|---|---|---|---|---|---|---|---|---|
| Acetaminophen[b] | BP | 67.7 | 1.000 | 1.27 | 0.298 | 0.185 | 0.514 | 59 |
| Aminosalicylic acid[b] | USP | 68.3 | 0.998 | 1.52 | 0.363 | 0.170 | 0.534 | 57 |
| Aspirin[c] | Ph. Ned. | 59.4 | 1.001 | 1.40 | | | See Table II | |
| Caffeine[c] | Ph. Ned. | 60.3 | 1.001 | 1.23 | 0.185 | 0.102 | 0.736 | 43 |
| Chloramphenicol[d] | Ph. Ned. | 63.2 | 1.000 | 1.51 | 0.150 | 0.199 | 0.513 | 59 |
| Chloramphenicol palmitate[e] | — | 71.7 | 0.999 | 1.20 | 0.199 | 0.510 | −0.569 | 125 |
| Dicalcium phosphate dihydrate[f] | — | 72.3 | 0.999 | 2.40 | — | ~0.000 | ~1.000 | 0 |
| Hexobarbital[c] | Ph. Ned. | 67.1 | 0.999 | 1.35 | 0.164 | 0.399 | 0.041 | 88 |
| Lactose[c] | Ph. Ned. | 71.6 | 1.071 | 1.54 | 0.135 | 0.057 | 0.868 | 30 |
| Magnesium stearate[c] | Ph. Ned. | 72.3 | 0.999 | 1.07 | 0.224 | 0.503 | −0.520 | 121 |
| Potassium chloride[g] | Analytical grade | 74.5 | 1.160 | 1.98 | 0.048 | 0.028 | 0.935 | 21 |
| Phenacetin[c] | Ph. Ned. | 61.5 | 0.999 | 1.33 | 0.179 | 0.313 | 0.202 | 78 |
| Phenobarbital[c] | Ph. Ned. | 71.8 | 1.000 | 1.33 | 0.261 | 0.263 | 0.347 | 70 |
| Polyethylene[h], high density | Laboratory reagent | 72.3 | 0.999 | 0.94 | 0.233 | 0.425 | −0.182 | 100 |
| Salicylic acid[c] | Ph. Ned. | 63.3 | 0.999 | 1.42 | 0.185 | 0.404 | −0.224 | 103 |
| Sodium chloride[c] | Ph. Ned. | 76.3 | 1.190 | 2.17 | 0.093 | 0.046 | 0.885 | 28 |
| Sulfadiazine[c] | Ph. Ned. | 72.2 | 0.999 | 1.48 | 0.168 | 0.287 | 0.328 | 71 |
| Polytef[h] | Laboratory reagent | 72.3 | 0.999 | 2.39 | 0.036 | 0.462 | −0.385 | 113 |

[a] See Table III. [b] A. C. F., Amsterdam, The Netherlands. [c] Lamers and Indemans, 's-Hertogenbosch, The Netherlands. [d] Pharmachemie, Haarlem, The Netherlands. [e] Nogepha, Amsterdam, The Netherlands. [f] Emcompress Special, Ed. Mendell Co., New York, N.Y. [g] Merck, Darmstadt, West Germany. [h] British Drug Houses, Poole, England.

where $W_a$, $W_i$, and $W_s$ are the changes in free surface energy for the adhesion, immersion, and spreading processes, respectively; $\gamma_{LV^0}$ is the liquid–vapor interfacial tension; and $\theta$ is the contact angle. For the process of wetting to occur, the appropriate value of $W$ must be negative. Since $\gamma_{LV^0}$ is always positive, the wetting process is determined by $\cos\theta$. Thus, measurements of the contact angle will give useful indications of wettability.

Pharmaceutically, wetting is not an end in itself but is the preliminary step in another process, *e.g.*, dispersion or dissolution, both *in vitro* and *in vivo*. In the preparation of dispersions, surfactants are often employed to aid in the wetting of insoluble powders (3). The role of wetting in the dissolution of drugs is not established.

Solvang and Finholt (4) stated that the change to a hydrophilic character probably was responsible for the increased dissolution rate of hydrophobic drugs after granulation with a binder. Kawashima *et al.* (5) concluded that improvement in wetting caused the increased dissolution rate of salicylic acid powder after spray drying with acacia. Allen and Davies (6) reported increases in the dissolution rate and amount of absorption of a highly lipid-soluble drug after admixture with lactose, seemingly due to increased wettability.

Newton and Razzo (7), however, after a detailed study on the release of drugs from hard gelatin capsules, concluded that wetting was not the controlling feature of drug release from capsules. The contact angle is one parameter controlling the penetration of liquids into capillaries in capsules and tablets; but evidence of the importance of the penetration rate in, for example, the subsequent dissolution of a drug from capsules is conflicting (8, 9).

Measurements of the contact angle of tablet surfaces have been undertaken to optimize film-coating techniques (10–12) and to

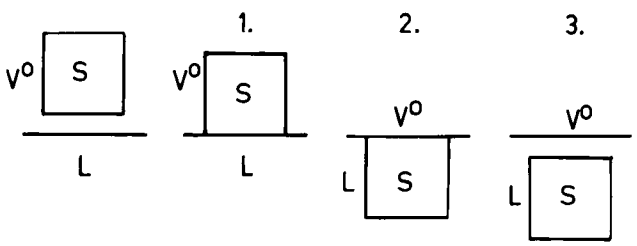


**Figure 1**—*Stages involved in the complete wetting of a solid cube (S) by a liquid (L). Key: 1, adhesional wetting; 2, immersional wetting; and 3, spreading wetting.*

study drug release from matrixes (13). In view of the importance of wetting and the scarcity of data available, it was decided to measure the contact angles of pharmaceutical powders.

Direct measurement of the contact angle of powders is not feasible; an indirect method must be used. Heertjes and Kossen (14) examined the methods available, and their results indicate the superiority of the $h$–$\epsilon$ method. This technique was adopted for this study.

The theory and technique of the $h$–$\epsilon$ method were described previously (15, 16) and extended (17). Essentially, a drop of liquid is formed on a cake of the test material, which has been previously saturated with the liquid. By using the equation of Padday (18), relating the height of a large liquid drop to the contact angle, and by correcting for "surface porosity," the contact angle may be determined. The relationships derived previously (16, 17) are:

$$\text{for } \theta > 90^\circ \qquad \cos\theta = -1 + \sqrt{(2 - Bh^2)\frac{2}{3(1-\epsilon_V)}} \qquad \text{(Eq. 4)}$$

$$\text{for } \theta < 90^\circ \qquad \cos\theta = 1 - \sqrt{\frac{2}{3(1-\epsilon_V)}Bh^2} \qquad \text{(Eq. 5)}$$

where $h$ is the height of the liquid drop, $\epsilon_V$ is the volume porosity of the cake, and $B = \rho_L g/2\gamma_{LV^0}$, where $\rho_L$ is the liquid density, and $g$ is the acceleration due to gravity. In the derivation of these equations, assumptions are made that allow the determination of surface porosity in terms of the measurable volume porosity.

These equations apply to single materials. Pharmaceutical systems are, however, frequently mixtures and may be treated as follows. The mixture considered is a two-component system compressed into a porous cake and saturated with an appropriate liquid. Let $f$ be the area fraction of Component 1 particles and $1 - f$ be the area fraction of Component 2 particles. If $\epsilon_S$ is the surface porosity, *i.e.*, the fraction of the solid surface wet by the drop, then:

$$(\gamma_{S_{1,2}V^0})_{por} = \epsilon_S\gamma_{LV^0} + (1-\epsilon_S)\gamma_{S_{1,2}V^0} \qquad \text{(Eq. 6)}$$

and:

$$\gamma_{S_{1,2}V^0} = f\gamma_{S_1V^0} + (1-f)\gamma_{S_2V^0} \qquad \text{(Eq. 7)}$$

where $\gamma$ is the interfacial tension; and the subscripts $S_1$, $S_2$, $S_{1,2}$, por, $V^0$, and $L$ refer to Solid 1, Solid 2, the solid mixture, the porous system, the vapor, and the liquid, respectively. Hence, com-

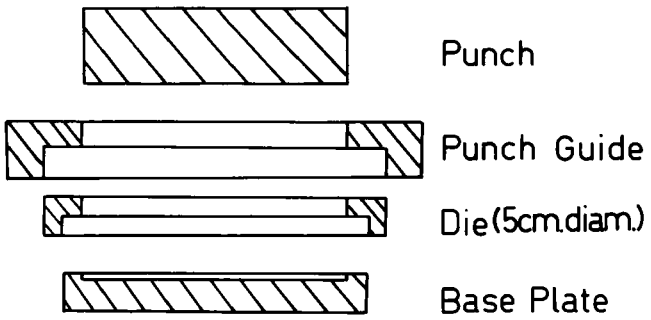


**Figure 2**—*Assembly for producing compacts for contact angle determination.*

bining Eqs. 6 and 7 gives:

$$(\gamma_{S_{1,2}V^\circ})_{por} = \epsilon_S\gamma_{LV^\circ} + (1-\epsilon_S)[f\gamma_{S_1V^\circ} + (1-f)\gamma_{S_2V^\circ}] \quad \text{(Eq. 8)}$$

Similarly:

$$(\gamma_{S_{1,2}L})_{por} = (1-\epsilon_S)\gamma_{S_{1,2}L} \quad \text{(Eq. 9)}$$

and:

$$\gamma_{S_{1,2}L} = f\gamma_{S_1L} + (1-f)\gamma_{S_2L} \quad \text{(Eq. 10)}$$

Thus, combining Eqs. 9 and 10 gives:

$$(\gamma_{S_{1,2}L})_{por} = (1-\epsilon_S)[f\gamma_{S_1L} + (1-f)\gamma_{S_2L}] \quad \text{(Eq. 11)}$$

Young's equation (18) for a porous mass consisting of two components may be written:

$$\cos\theta' = \frac{(\gamma_{S_{1,2}V^\circ})_{por} - (\gamma_{S_{1,2}L})_{por}}{\gamma_{LV^\circ}} \quad \text{(Eq. 12)}$$

where $\theta'$ is the apparent contact angle of the liquid on the porous mixed system. Substituting Eqs. 8 and 11 into Eq. 12 and rearranging give:

$$\cos\theta' = \epsilon_S + (1-\epsilon_S)(f)\frac{\gamma_{S_1V^\circ} - \gamma_{S_1L}}{\gamma_{LV^\circ}} + (1-\epsilon_S)(1-f)\frac{\gamma_{S_2V^\circ} - \gamma_{S_2L}}{\gamma_{LV^\circ}} \quad \text{(Eq. 13)}$$

which gives:

$$\cos\theta' = \epsilon_S + (1-\epsilon_S)[f\cos\theta_1 + (1-f)\cos\theta_2] \quad \text{(Eq. 14)}$$

where $\theta_1$ and $\theta_2$ are the contact angles of the liquid against Solids 1 and 2, respectively. From the work of Cassie (19):

$$f\cos\theta_1 + (1-f)\cos\theta_2 = \cos\theta_{1,2} \quad \text{(Eq. 15)}$$

where $\theta_{1,2}$ is the contact angle of the liquid against the mixed system. Hence, substituting Eq. 15 into Eq. 14 gives:

$$\cos\theta' = \epsilon_S + (1-\epsilon_S)\cos\theta_{1,2} \quad \text{(Eq. 16)}$$

The equation of Padday (18) written for a saturated porous mixed mass is:

$$\cos\theta = 1 - \frac{\rho_L g}{2\gamma_{LV^\circ}}h^2 = 1 - Bh^2 \quad \text{(Eq. 17)}$$

Combining Eqs. 16 and 17 gives:

$$\cos\theta_{1,2} = 1 - \frac{B}{1-\epsilon_S}h^2 \quad \text{(Eq. 18)}$$

This equation is analogous to those derived previously (16, 17) and can be treated in a similar manner to determine $\cos\theta_{1,2}$ by means of Eqs. 4 and 5.

## EXPERIMENTAL

**Materials**—The materials used, together with the suppliers and relevant standards, are listed in Table I. They usually were used as supplied to give values that may be better guides to behavior under practical conditions. Where size fractions were required, initial sieving was carried out on a vibration sieve machine[1], followed by sieving of the required size fraction using an air jet sieve[2]. Milled samples were produced by an air jet mill[3]. Saturated solutions of the materials were prepared by allowing excess solid to equilibrate with distilled water in a constant-temperature room (23°).

**Table II—Contact Angles of Aspirin of Varying Particle Sizes and Porosities**

| Size Fraction, μm | Porosity | Drop Height, cm | cos θ | θ° |
|---|---|---|---|---|
| 125–180 | 0.093 | 0.286 | 0.297 | 73 |
| 150–210 | 0.105 | 0.297 | 0.262 | 75 |
| 150–210 | 0.141 | 0.287 | 0.272 | 74 |
| 150–210 | 0.246 | 0.262 | 0.291 | 73 |
| 600–850 | 0.075 | 0.299 | 0.269 | 73 |
| Unfractionated[a] | 0.145 | 0.292 | 0.265 | 75 |

[a] Mean particle size by air permeability = 13 μm.

**Methods**—*Contact Angle Measurements*—These measurements were carried out as detailed by Kossen and Heertjes (16). Compacts of the test powder were prepared using the arrangement shown in Fig. 2. After application of the required pressure, the punch, the punch guide, and the die were removed, leaving the cake of material in the base plate. The pressures used were as low as possible, consistent with the production of a stable cake, and were applied by means of a hydraulic press[4] and measured by a load cell[5]. In general, the pressure applied was between 100 and 200 kg/cm$^2$.

Porosities were calculated from a knowledge of the sample weight and dimensions. Presaturation of the compacted powder bed was accomplished either by spraying or, where possible, by simply dropping liquid onto the compact. Saturated solutions of the test materials were used to prevent dissolution.

After saturation, the cake plus base plate was placed on a horizontal table and surrounded by a cover equipped with viewing windows and a small hole to allow entry of a fine needle. The appropriate saturated solution was slowly dropped onto the cake surface from the needle, and readings of the drop height were taken with a cathetometer[6] until additional drops caused no increase in height. The contact angle was calculated from the appropriate equation, 4 or 5. All measurements were carried out at 23° and at least in duplicate.

*Liquid and Solid Properties*—The densities and surface tensions of the liquids and the densities of the solids were determined by a balance[7], a tensiometer[8], and an air comparison pycnometer[9], respectively. The liquid measurements were carried out at 23°.

## RESULTS AND DISCUSSION

Initial experiments were conducted to assess the influence of particle size and porosity on the calculated contact angle. Aspirin was chosen as the test material because it is readily available in a range of particle sizes and forms stable compacts at low pressures. The results from the determinations are given in Table II. As can be seen, despite the assumptions implicit in the method, the results from a wide variety of particle sizes and porosities were remarkably consistent. This consistency was also observed (16) for organic liquids on ground sodium chloride compacts of different porosity. The extension of these determinations to changes both in porosity and particle size confirms the usefulness of the method.

The results from the samples produced by air jet milling are

[1] E. M. L. type 200-67, Haver and Boecker, Oelde, West Germany.
[2] Alpine Machinery Ltd., Augsburg, West Germany.
[3] Gem. T. Helme Chemicals Inc., Helmetta, N.J.
[4] M-30, Research and Industrial Instruments, London, England.
[5] WASA, Sonco, N. V. Rotterdam, The Netherlands.
[6] Precision Tool and Instrument Co., Surrey, England.
[7] Mohr, G. Kern, Ebingen, West Germany.
[8] Du Nuoy K 8600, Krüss, Hamburg, West Germany.
[9] Model 930, Beckman Instruments Ned. N. V., Amsterdam, The Netherlands.

**Table III—Variation of Contact Angle of Aspirin with Time after Jet Milling**

| Time after Milling, hr | Porosity[a] | Drop Height[a], cm | cos θ | θ° |
|---|---|---|---|---|
| 0 | 0.267 | 0.415 | −0.275 | 106 |
| 24 | 0.339 | 0.359 | −0.028 | 91 |
| 30 | 0.337 | 0.334 | −0.036 | 87 |
| 48 | 0.312 | 0.292 | +0.173 | 80 |
| 72 | 0.331 | 0.268 | +0.230 | 77 |
| 120 | 0.343 | 0.268 | +0.223 | 77 |

[a]These values are the means of more than one determination as a guide to the porosities used and the drop heights attained. To calculate cos θ, each set of values was treated as an individual, and the cos θ value in the table is the mean of the individual values.

shown in Table III. The initial high values of the contact angle immediately after milling fell with time to a value slightly higher than the mean of the values observed for the unmilled size fractions. This result indicates a change in the surface characteristics of the material, induced by the milling process, which is slowly reversible (UV assay confirmed no degradation had occurred on milling). Such effects may be brought about during milling, for example, by the creation of clean surfaces, formation of electrostatic charges, or changes in polymorphic form. The underlying cause of the observed changes in contact angle after milling was not investigated, but the results show that the technique provides a sensitive measure of the surface characteristics of a material.

Table I shows the results from a wide range of pharmaceutical materials together with other relevant information. The wide spectrum of values of these common materials should be noted. In all cases, it was possible to prepare and saturate the cake of material without disrupting its structure. For materials exhibiting contact angles above 90°, *e.g.*, magnesium stearate, saturation of the cake is impossible by spraying or dropping liquid onto the surface; the drop is merely formed on the dry compact. The theoretical derivation of the equation for angles above 90° takes this fact into account. The value for polyethylene (100°) and polytef (113°) are included to show the good agreement between these values and those

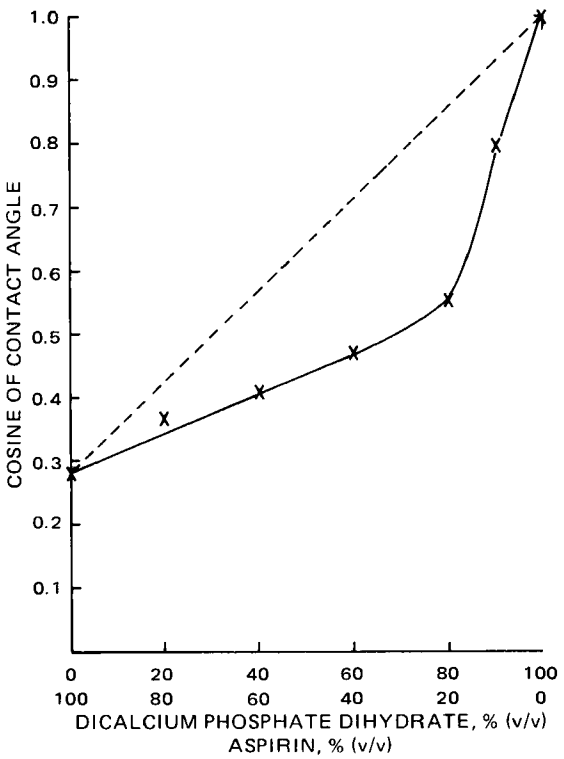


**Figure 3**—*Cosines of the contact angles of mixtures of dicalcium phosphate dihydrate and aspirin, 150–210-μm size fraction. Key: - - -, theoretical line; and ×, experimental points.*

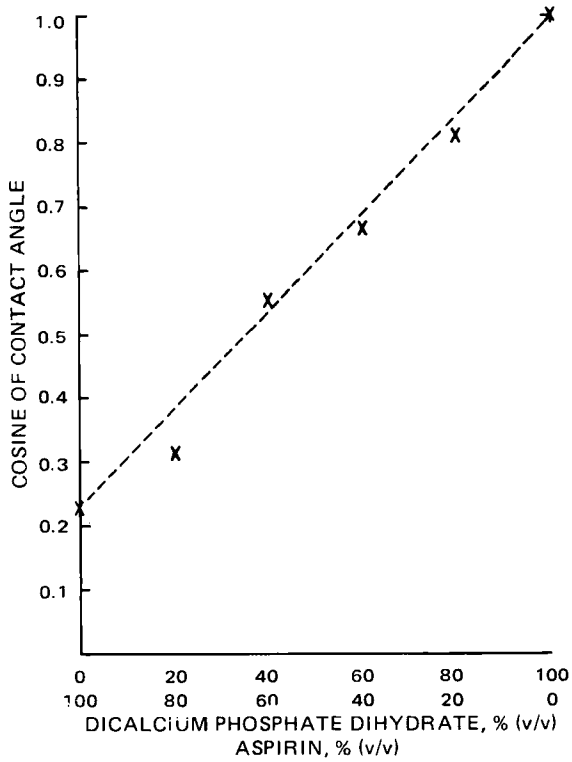


**Figure 4**—*Cosines of the contact angles of mixtures of dicalcium phosphate dihydrate and aspirin, jet-milled fraction. Key: - - -, theoretical line; and ×, experimental points.*

of 94° for polyethylene (20) and of 108° for polytef (21) determined by more conventional means.

To study the contact angle of mixtures, the system of aspirin–dicalcium phosphate dihydrate[10] was chosen. Spreading on a saturated dicalcium phosphate compact was rapid, and no drop height could be measured. Hence, its contact angle may be taken to be 0° or nearly so. The work of Cassie (19) indicates that there should be a linear relationship between the cosine of the contact angle of a heterogeneous surface and the area fraction of the components (Eq. 15).

The results for mixtures of 150–210-μm particles and jet-milled particles are presented in Figs. 3 and 4. For particles with a narrow size distribution that are not too irregular in shape, the volume fraction of each component may be considered to be equivalent to the area fraction on the surface of the compact. This is the case for the materials chosen. For the large particle-size powders, the results do not obey the relationship of Cassie (19), the hydrophobic fraction being more dominant. The jet-milled mixtures, however, show a close correlation.

The case of contact angles on heterogeneous surfaces was analyzed theoretically (22). One conclusion was that the hydrophobic fraction of the surface would be dominant for advancing angles. As the size of the heterogeneities in the surface became smaller, then the angles would more closely correspond to Cassie's curve (19). In the present experiments, advancing angles were determined, and the results fit in with these concepts. As the particle size was reduced, *i.e.*, the size of the heterogeneities in the surface became smaller, the hydrophobic portion of the surface became less dominant. The results agree more closely with the expected linear relation.

The work described demonstrates the usefulness of the $h$–$\epsilon$ method for the determination of contact angles of pharmaceutical powders and powder mixtures. The importance of these measurements in formulation is currently being studied.

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**ACKNOWLEDGMENTS AND ADDRESSES**

Received May 27, 1975, from the *Laboratory for Pharmaceutical Technology, The University, Ant. Deusinglaan 2, Groningen 8004, The Netherlands.*

Accepted for publication August 8, 1975.

The authors thank K. Zuurman for technical assistance and the Z.W.O. for the award of a grant to J. T. Fell.

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# *In Vivo* and *In Vitro* Evaluation of a Microencapsulated Narcotic Antagonist

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**Abstract** □ Injectable microcapsules containing 75% (w/w) cyclazocine, a narcotic antagonist, were prepared with *dl*-poly(lactic acid) as the coating material. Capsule fractions falling between 105 and 295 μm released about 90% of their cyclazocine in 8 days of rotating-bottle extraction at 37° in pH 7.4 phosphate buffer. Although larger capsules released the drug somewhat more slowly, all capsules released cyclazocine far more rapidly than an ideal capsule should. This rapid release is attributed to macroscopic defects located in the capsule walls. The ability of the capsules to block the action of morphine *in vivo* was assessed by injection of a sesame seed oil suspension into Holtzman rats. A hot-plate test procedure was used to evaluate animal behavior. Capsule doses of 100–250 mg/kg to rats caused significant antagonism of morphine's analgesic effect for 14 days after injection. By Day 17, no antagonism occurred, indicating that the capsules completely released the drug *in vivo* between 14 and 17 days after injection.

**Keyphrases** □ Cyclazocine—injectable microcapsules, *in vivo* and *in vitro* release evaluated □ Microcapsules, injectable—*in vivo* and *in vitro* release of cyclazocine evaluated □ Dosage forms—injectable microcapsules, *in vivo* and *in vitro* release of cyclazocine evaluated □ Narcotic antagonists—cyclazocine, *in vivo* and *in vitro* release from injectable microcapsules evaluated

A significant problem in the long-term treatment and rehabilitation of heroin addicts is their pronounced tendency to undergo drug relapse. One possible means of circumventing this problem would be the injection or implantation of sustained-release preparations of narcotic antagonists, which would, in effect, inoculate the patient against heroin for a prescribed period, preferably 1 month or more. Theoretically, the repeated administration of such a preparation could provide a therapeutically effective level of antagonist for an indefinite treatment period.

An injectable sustained-release formulation must satisfy these requirements:

1. It must be biocompatible and provide uniform sustained release of the antagonist for a specified time.
2. Once the drug has been released, the delivery system must be biodegradable within a relatively brief time.
3. The microcapsules must be easily injected through hypodermic needles of sufficiently small size to be tolerated by patients.
4. The total amount of drug administered to the patient must not approach toxic levels to minimize any risk associated with accidental failure of the delivery system.

Narcotic antagonist formulations that meet several, but not necessarily all, of these requirements were reported recently. Insoluble salts and salt complexes of cyclazocine and naloxone were formulated (1), and several preparations significantly increased the duration of narcotic antagonist activity in mice. Prepared particulate cyclazocine–poly(lactic acid) composites provided sustained release *in vivo* and *in vitro* (2). However, the particles contained only 21% (w/w) of drug and required a 12-gauge needle for injection.

The technique of microencapsulation may provide