II, the 200-mg capsule (D) and the 400-mg tablet (E) resulted in approximately equal *MDT* estimates (0.80 *versus* 0.79 hr). The 400-mg capsule (C), however, was more slowly absorbed with an average *MDT* of 1.27 hr. The differences for the pairwise comparisons of A *versus* B, C *versus* D, and C *versus* E were statistically significant.

Cumulative Fraction Absorbed Relative to the Oral Solution (CFA_{rel})—Modified Wagner-Nelson plots of mean CFA_{rel} *versus* time for the ibuprofen products are presented as Fig. 2. Inspection of the plots suggests that, on the average, Formulations A and C required 4–6 hr to achieve an extent of absorption within 95% of the oral solution. Formulations B, D, and E, however, reached the same endpoint by the 2-hr sampling time.

Statistical comparisons of the CFA_{rel} estimates at each sampling time up to 6 hr are shown in Table IV. The 300-mg tablet (B) resulted in significantly greater mean CFA_{rel} values at 1, 1.5, and 2 hr than the 300-mg capsule (A). The 400-mg tablet (E) and the 200-mg capsule (D) exhibited similar mean CFA_{rel} estimates with a significant difference occurring only at the 20-min sampling time. The 400-mg capsule (C) results were significantly less than those for Formulation D at 1, 1.5, 2, and 3 hr and those for Formulation E at 1.5, 2, and 3 hr. Since no differences were observed in the extent of absorption among the products studied, the relatively low estimates of CFA_{rel} resulting from Formulations A and C were indicative of their slower rates of absorption.

DISCUSSION

Though all of the commercially available ibuprofen products studied were equivalent with respect to the amount of drug absorbed from the dosage forms, they differed markedly in terms of absorption rate. Specifically, the 300-mg tablet (B) was more rapidly absorbed than the 300-mg capsule (A), and the 400-mg tablet (E) and the 200-mg capsule (D) were more rapidly absorbed than the 400-mg capsule (C).

The results of a previously reported study indicated that a pilot plant lot of the 300-mg capsule was bioequivalent to the innovator's 300-mg tablet (3). The present study suggested that some change associated with scale-up to commercial production resulted in a less rapidly absorbed dosage form.

Since bioequivalence has been defined as equivalence in both extent and rate of drug absorption (10), it has been concluded that Formulations A and C were bioinequivalent to the innovator's products (B and E) due to their slower absorption rates. Whether this conclusion could be translated to indicate clinical inequivalence could not be determined from these studies. It would be hypothesized, however, that differences in clinical efficacy might be observed when ibuprofen is administered as single doses for the relief of mild to moderate pain.

A more general conclusion resulting from these studies was that the potential exists for bioavailability problems among ibuprofen solid oral dosage forms.

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The Role of Surfactants in the Release of Very Slightly Soluble Drugs from Tablets

HANS SCHOTT ˣ, LILIAN CHONG KWAN *, and STUART FELDMAN ‡

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*Present address: William H. Rorer, Inc., Fort Washington, PA 19034. ‡Present address: College of Pharmacy, University of Houston, Houston, TX 77030.

Abstract □ The ability of surfactants to accelerate the *in vitro* dissolution of very slightly soluble drugs has been ascribed to wetting and/or micellar solubilization. Deflocculation as a mechanism to accelerate dissolution has not been investigated. In the present study, the effect of a surfactant on the dissolution kinetics of prednisolone from tablets and the mode of action of the surfactant were investigated. The dissolution of prednisolone at 37° in 0.1 *N* HCl containing different concentrations of the nonionic surfactant, octoxynol 9, followed zero-order kinetics. The rate constant was increased by 15, 150, and 950% when octoxynol was added to the dissolution medium at 0.0039 and 0.032% (~0.5 and 4.0 times the critical micelle concentration) and incorporated into the tablets (for a final concentration of 0.0039%), respectively. The surface tensions of the dissolution media were 71, 35, and 31 dyne/cm for 0, 0.0039, and 0.032% octoxynol, respectively. The largest decrease in surface tension corresponded to the smallest increase in dissolution rate, indicating that wetting was unimportant. The micellar solubilization capacity of octoxynol was much too small to account for the increases in dissolution rate. Microscopic particle size measurements and sedimentation volume determinations showed the pronounced deflocculation of prednisolone by the surfactant. The observed increases in specific surface area at the two octoxynol concentrations were in good quantitative agreement with the increases in dissolution rate according to the Noyes–Whitney equation.

Keyphrases □ Deflocculation—surfactants, release of very slightly soluble drugs, tablets, dissolution kinetics □ Surfactants—release of very slightly soluble drugs, tablets, dissolution kinetics □ Kinetics—dissolution, surfactants, release of very slightly soluble drugs, tablets, deflocculation

The most likely mechanisms by which surfactants could speed up the release of very slightly soluble drugs from tablets are wetting, micellar solubilization, and deflocculation (1). The purpose of the present study was to assess their relative importance in accelerating the dissolution of prednisolone by octoxynol.

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Table I—Tablet Compositions

Ingredients[a]	Weight in Formulation, mg I	II	III
Microcrystalline cellulose	75	75	75
Octoxynol	—	35	35
Lactose	100	100	100
Prednisolone	25	25	—
Magnesium stearate	5	5	5
Lactose	295	260	285
Total	500	500	500

[a] Listed in order of addition.

BACKGROUND

Wetting—The wetting process consists in replacing a solid–air interface with a solid–liquid interface. Wetting agents speed up the penetration of gastric fluid into the tablets and, hence, tablet disintegration. This effect, which is due to the lowering of contact angles and of surface and interfacial tensions of the aqueous medium by the surfactants, has been well documented (2–22).

The improper use of surfactants could conceivably retard the dissolution of solid drugs by dewetting. When hydrophilic solid surfaces of relatively high charge density come into contact with aqueous solutions of ionic surfactants of the opposite charge, the surface-active ions are chemisorbed by an ion-exchange mechanism with their hydrocarbon chains oriented toward the aqueous phase. This process reduces the *zeta* potential of the solid surface to very low values or even zero (23). It also covers that surface with hydrocarbon chains, rendering it more hydrophobic and poorly wetted. The contact angles of water on such hydrophilic surfaces as barium sulfate (24) and glass (25) were thus increased from 0 to 60° or more.

The following observation also illustrates this point. The addition of the anionic surfactant, dioctyl sodium sulfosuccinate, to water increased the rate of penetration into a powder bed of negatively charged aspirin particles but lowered the rate of penetration into a bed of positively charged magnesium oxide particles (8).

Solubilization—Micellar solubilization occurs only when the dissolved surfactant is present at concentrations exceeding its critical micelle concentration. In most instances, the amount of surfactant that can be conveniently incorporated into a tablet supplies less than that needed to exceed the critical micelle concentration once the surfactant is dissolved and uniformly distributed throughout the gastric fluid. Owing to their size, shape, and chemical nature, most drug molecules capable of being solubilized by micelles cause little or no reduction in the critical micelle concentration.

Immediately after ingestion, aqueous fluid penetrates into tablets and begins to dissolve the surfactant contained therein. This process could temporarily produce, inside the tablets, a surfactant solution of concentration well in excess of the critical micelle concentration. This transitory micellar solution may temporarily dissolve a very slightly water-soluble drug by micellar solubilization. After the tablets disintegrate and/or the surfactant is leached out, the surfactant solution inside the tablets is diluted by the entire volume of gastric fluid and its concentration drops below the critical micelle concentration. As the micelles dissociate, the solubilized drug precipitates. However, this precipitation produces a colloidal dispersion of the drug characterized by a large specific surface area, and, therefore, by a high subsequent dissolution rate. The fine particle size of the drug during precipitation is maintained by the low drug solubility and a small concentration. This combination results in a low degree of supersaturation and provides little precipitating solid drug for growth of the nuclei. Adsorption of the surfactant and of pepsin and mucin dissolved in the gastric fluid onto the nuclei further limits their growth.

Numerous publications deal with the effect of micellar solubilization on the dissolution rate of very slightly soluble drugs from tablets (26–38).

Table II—Tablet Characteristics

Property	Formulation I	Formulation II
Weight ± *SE*[a], mg (*N*)[b]	499.7 ± 1.0 (30)	500.0 ± 1.0 (10)
Diameter ± *SE*, mm (*N*)	12.77 ± 0.01 (14)	12.84 ± 0.02 (5)
Thickness ± *SE*, mm (*N*)	2.76 ± 0.02 (30)	2.76 ± 0.02 (5)
Prednisolone Content ± *SE*, mg (*N*)	25.1 ± 0.1 (6)	Not assayed
Hardness ± *SE*, kg (*N*)	8.1 ± 0.1 (4)	1.4 ± 0.1 (4)

[a] Standard error. [b] Number of determinations.

Table III—Tablet Disintegration Times

Tablet Composition[a]	Liquid Medium[b]	Disintegration Times, min Mean[c] ± *SD*[d]	Range
I	A	107.0 ± 9.3	23.2
I	B	104.3 ± 14.5	44.6
I	C	67.4 ± 3.7	9.5
II	A	18.5 ± 0.8	2.0

[a] See Table I. [b] Medium A is 0.1 *N* HCl, B is 0.1 *N* HCl + 0.0039% octoxynol, and C is 0.1 *N* HCl + 0.032% octoxynol. See text for properties. [c] Mean of 6 tablets. [d] Standard deviation.

Miscellaneous—A few investigators found that surfactants incorporated into tablets or dissolution media had no effect on the disintegration and/or dissolution times (39, 40). Others observed reduced dissolution times in the presence of surfactants but did not identify the mode of action of the surfactants (41). Still other investigators rejected surface tension lowering and micellar solubilization as causes for the observed increase in dissolution rate, because these factors were not large enough to account for the magnitude of that increase, but offered no alternative explanation (42).

In the case of relatively hydrophilic tablets, surfactants reduced the disintegration times by weakening adhesion, as shown by reduced tablet hardness, rather than by enhancing the penetration of the dissolution medium (43–45). Nonionic surfactants increased the rate of dissolution according to their hydrophile–lipophile balance. Increases in the rate of disintegration depended on the chemical category of the nonionic surfactant (46).

Deflocculation—Deflocculation, deaggregation, or peptization is the breaking up or dispersing of aggregates or secondary particles into smaller aggregates or primary particles. This process increases the specific surface area of the solid drug particles and, thereby, their rate of dissolution. It enhances the bioavailability of very slightly soluble and practically insoluble drugs, whose absorption is limited by their dissolution rate.

The role of surfactants in deflocculating or deaggregating the solid phase in lyophobic aqueous and nonaqueous dispersions and suspensions is well recognized (47). However, the possibility that surfactants employed as tablet excipients increase the dissolution rate of very slightly soluble drugs by peptization or deflocculation has, to the best of our knowledge, neither been explicitly recognized nor documented (48).

However, it was postulated that the presence of sodium lauryl sulfate dissolved in the granulating liquid greatly increased the rate of dissolution by preventing the formation of agglomerates of hydrophobic drug particles in the tablet (49). The increase in the dissolution rate of aspirin from tablets in the presence of surfactants (17) was ascribed to "a wetting and/or deaggregation effect" (21).

The present data on the release of prednisolone from tablets in the presence of a nonionic surfactant show that the major mechanism through which the surfactant increased the dissolution rate of this very slightly soluble drug was a deflocculating or peptizing action.

EXPERIMENTAL

Materials—Prednisolone was anhydrous, USP grade, and micronized[1]. Octoxynol 9, an anhydrous, viscous liquid[2], and microcrystalline cellulose[3] were NF grade. Magnesium stearate[4], supplied as an impalpable powder, and spray-dried lactose[5] were USP grade. All other chemicals were American Chemical Society reagent grade. Water was twice distilled.

Tablet Preparation—Three formulations of 500-mg tablets were prepared by triturating 5.000 g of the ingredients, enough to make 10 tablets, in a mortar and pestle in the order of addition listed in Table I. Microcrystalline cellulose was included to absorb the liquid octoxynol and prevent it from rendering the tablet excessively soft. The 75-mg portion of microcrystalline cellulose was the minimum amount required to absorb 35 mg of octoxynol and maintain their mixture as a nonsoggy, free-flowing powder. The lactose was incorporated in two portions. The

[1] Schering Corp., Bloomfield, N.J.
[2] Triton X-100 of Rohm & Haas Co., Philadelphia, Pa. It is a branched octylphenol adduct with an average of 9–10 ethylene oxide units.
[3] Avicel PH 102, FMC Corp., Marcus Hook, Pa.
[4] Mallinckrodt Inc., St. Louis, Mo.
[5] Foremost Dairies, Inc., supplied by Smith Kline & French Labs., Philadelphia, Pa.

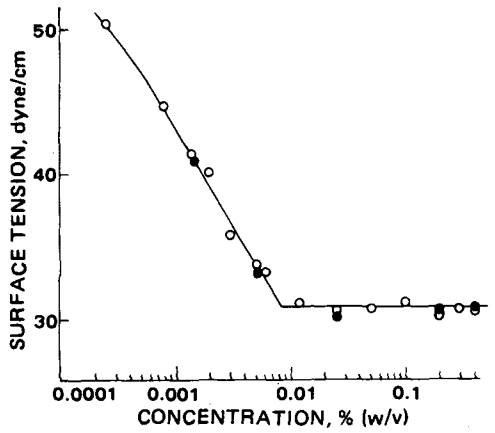

Figure 1—*Surface tension of octoxynol solutions in 0.1* N *HCl at 37° as a function of surfactant concentration. Key: (●) equilibration time 1 hr; (○) equilibration time 24 hr.*

first was added between the surfactant and the prednisolone to minimize direct contact between the latter two ingredients.

A cylindrical stainless steel die with a diameter of 1.27 cm (0.5 in) and a flat-faced punch were used on a hydraulic press[6] equipped with a pressure gauge. The 500-mg aliquots were compressed for 30 sec with a weight of 4536 kg (10,000 lbs), which corresponds to a pressure of 50,900 psi. This weight produced tablets of more uniform disintegration times than did 2268 kg (5000 lbs).

Tablet hardness was measured with a manual, spring-operated tester[7].

Liquid Media—The three media used for disintegration and dissolution studies consisted of 900 ml of 0.1 *N* HCl maintained at 37.0 ± 0.2°. Medium A contained no other additives. Its surface tension was 71.1 dyne/cm. Medium B contained 0.0039% (w/v) octoxynol, *i.e.*, 35 mg in 900 ml, and had a surface tension of 35.4 dyne/cm. Medium C contained 0.032% (w/v) octoxynol and had a surface tension of 30.9 dyne/cm. Since the critical micelle concentration of octoxynol in 0.1 *N* HCl at 37° is 0.0083%, the surfactant concentrations in Media B and C correspond approximately to 0.5 and 4.0 times the critical micelle concentration, respectively.

Tablet Disintegration—Disintegration times were measured with the USP apparatus[8]. The plastic disks (50) were omitted. The 1-liter beaker was jacketed, and water from a constant-temperature bath at 37° was circulated through the jacket. Individual disintegration times, measured for each tablet, were the times required for all fragments to fall through the 10-mesh bottom screen.

Prednisolone Dissolution—A USP single-position dissolution apparatus (50) was used with the basket rotating at 100 ±5 rpm[8]. Aliquots were withdrawn at predetermined intervals and filtered before analyzing for dissolved prednisolone to remove suspended, insoluble tablet ingredients as well as any colloidally dispersed prednisolone that may have been present. Pressure filtration through membrane filters[9] with a pore size of 0.22 μm was employed. The stainless steel barrel of the pressure filter holder was thermostated at 37°.

Prednisolone assay by direct UV absorption spectroscopy was not sensitive enough. Therefore, a colorimetric assay based on the Porter and Silber method (51) was developed. It will be described in a separate publication. Its accuracy and reproducibility in the presence of the tableting ingredients were evaluated as follows: A tablet containing 25.0 mg of prednisolone was triturated with 10 ml of methanol to dissolve the prednisolone and the entire mass was diluted to 1.000 liter with 0.1 *N* HCl. Prednisolone assays were performed in duplicate on filtered aliquots. This procedure was repeated with two additional tablets, for a total of six determinations.

Four to six dissolution experiments were conducted at each of the four experimental conditions. Octoxynol interacted with the acid phenylhydrazine solution to produce a faint yellow tint. To compensate for this effect, comparable concentrations of octoxynol were incorporated into the blank solutions.

Octoxynol Dissolution—The release rate of octoxynol from tablets made according to Formulation III was determined by measuring the

[6] Carver Laboratory Press, model C, Fred C. Carver Inc., Summit, N.J.
[7] Stokes Hardness Tester, Pennwalt Corp., Warminster, Pa.
[8] Scientific Glass Apparatus Co., Bloomfield, N.J.
[9] Millipore Corp., Bedford, Mass.

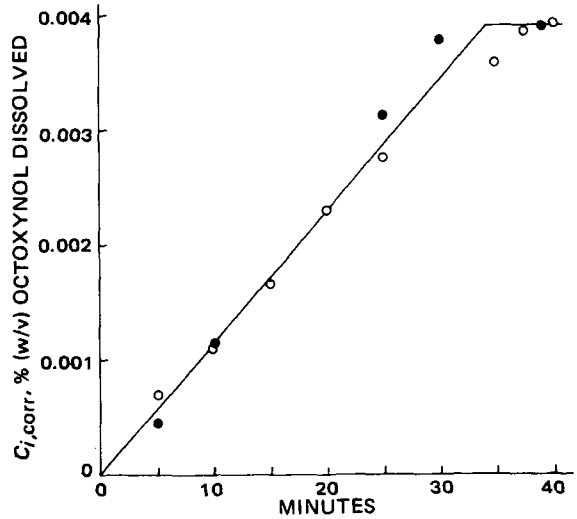

Figure 2—*Dissolution profile of octoxynol;* $C_{i,corr}$ *represents the concentration of dissolved octoxynol in percent (w/v) calculated according to Eq. 2. Key: (●) Tablet 1; (○) Tablet 2.*

surface tension of the dissolution medium as a function of time. A calibration plot of surface tension *versus* octoxynol concentration was prepared at 37° in 0.1 *N* HCl. When the octoxynol concentration in the dissolution medium exceeded the critical micelle concentration, octoxynol determinations were made by surface tension measurements at 37° on aliquots after appropriate dilution with 0.1 *N* HCl to concentrations below the critical micelle concentration.

Surface tensions were measured with a Wilhelmy balance[10] equipped with a sand-blasted platinum blade on 40-ml portions of octoxynol solutions or aliquots of the dissolution medium. These solutions were equilibrated at 37.0 ± 0.1° for 1 hr or 24 hr prior to the measurements.

Micellar Solubilization of Prednisolone—The solubility of prednisolone in 0.1 *N* HCl solutions containing octoxynol at concentrations ranging from 0 to 0.128% was determined by colorimetric and gravimetric assays. In both methods, 50-mg portions of prednisolone triturated to a fine powder were mixed with 50-ml portions of the dissolving media in amber glass bottles. The bottles were flushed with nitrogen, stoppered, and shaken on an oscillating water bath[11] at 37°.

For the colorimetric assay, 5-ml aliquots were withdrawn after 2, 6, and 16 days of shaking, filtered through 0.1-μm membrane filters, and assayed according to the modified Porter and Silber method (51). The blank solutions contained octoxynol at the same concentrations as the test solutions.

In the gravimetric method, the suspensions were shaken at 37° for 3, 6, or 22 days. The entire 50-ml suspension volumes containing 50 mg of prednisolone were then filtered through tared fritted glass filtering crucibles. The filters, containing the undissolved prednisolone, were washed and dried to constant weight at 100°.

Sedimentation Volumes of Prednisolone Suspensions—Suspensions containing 50 mg of prednisolone in 50 ml of 0.1 *N* HCl with different octoxynol concentrations were prepared as described under Micellar Solubilization. Each suspension was vigorously shaken on the shaker bath for 3 days at 140 oscillations/min and poured immediately into a glass funnel with a top diameter of 12 cm connected to a 12-ml graduated glass centrifuge tube with a conical bottom. The volume of the bottom milliliter could be read with an accuracy of ±0.01 ml.

Particle Size Distribution of Prednisolone Suspensions—The number and sizes of the coarse particles contained in 0.1 ml of suspensions prepared as in the preceding section were determined by withdrawing a 0.1-ml aliquot immediately after vigorous shaking, using a graduated pipet with a tip of 2-mm i.d. The size of every coarse particle in that volume was measured with a magnifying glass and a ruler. Since the coarse particles were irregular, their equivalent spherical diameters were recorded.

The number and sizes of the fine particles were measured with a hemacytometer. A drop of a suspension was put into the counting chamber. When the cover glass was placed over it, the liquid layer was reduced to a thickness of 0.1 mm. The dimensions of every particle in four adjacent

[10] Surface Tensiometer, VWR Scientific, Baltimore, Md.
[11] Shaker bath, model 50, Precision Scientific Co., Chicago, Ill.

Table IV—Dissolution Rate of Prednisolone from Tablets in Three Dissolution Media and Zero-Order Dissolution Rate Constants

Tablet Composition[a]	Dissolution Medium[b]	Dissolution Time, min	Prednisolone Dissolved, %[c] Mean ± SD[d]	(N')[e]	Rate Constant ± SD[f], %/min	(N)[g]
I	A	10	3.5 ± 0.8	(4)		
		30	6.7 ± 2.7	(6)		
		50	12.3 ± 1.4	(5)	0.218 ± 0.011	(32)
		75	18.8 ± 2.7	(5)		
		105	23.4 ± 3.2	(5)		
I	B	10	1.9 ± 0.5	(4)		
		30	7.7 ± 1.3	(4)		
		50	13.3 ± 3.0	(4)	0.251 ± 0.007	(20)
		80	20.5 ± 2.5	(4)		
		120	29.5 + 3.1	(4)		
I	C	10	6.4 ± 2.1	(4)		
		25	13.7 ± 2.3	(3)		
		40	22.0 ± 3.4	(3)	0.547 ± 0.010	(20)
		60	32.0 ± 1.8	(3)		
		90	48.3 ± 2.9	(3)		
II	A	5	15.8 ± 0.5	(2)		
		10	24.9 ± 4.6	(5)		
		15	30.8 ± 0.2	(2)		
		20	46.7 ± 5.8	(4)	2.284 ± 0.067	(16)
		25	56.3 ± 2.0	(3)		
		30	96.7 ± 3.8	(4)		
		35	104.2 ± 0.2	(2)		
		40	98.7 ± 2.0	(3)		
		60	100.2 ± 5.1	(3)		

[a] See Table I. [b] See Footnote *b* of Table III for composition and text for properties. [c] The amount in each tablet, namely, 25 mg, represents 100%. [d] Standard deviation. [e] Number of tablets. [f] Standard deviation calculated by Eqs. 5 and 6. [g] Total number of measurements; $N - 1$ is the degree of freedom.

0.2-mm squares, corresponding to a volume of $4 \times (0.2\text{ mm})^2 \times 0.1\text{ mm} = 0.016\text{ mm}^3$, was measured by means of a microscope equipped with an eyepiece micrometer. Since the fine particles were rod-shaped, their lengths and diameters were recorded.

RESULTS

The tablet characteristics are listed in Table II. The small standard errors of the averages indicate that the properties were reproducible.

Tablet Disintegration—Disintegration times are listed in Table III. All tablets, regardless of the presence or absence of octoxynol, retained their integrity during most of the duration of the disintegration test. Only toward the end did they break up into separate fragments.

In liquid Medium A (0.1 *N* HCl), the tablets disintegrated into coarse grains which settled quickly. When octoxynol was added to the disintegrating liquid (Media B and C) or incorporated into the tablets, they disintegrated into fine granules that remained suspended in the liquid, turning it turbid.

Comparing the mean disintegration time of 107.0 min in the absence of octoxynol with the mean value of 104.3 min in the presence of 0.0039% octoxynol by means of the *t* test shows that their 2.5% difference is not statistically significant even at the 20% probability level.

Increasing the octoxynol content of the liquid medium to 0.032% reduced the disintegration time by 37% compared to no octoxynol and by 35% compared to 0.0039% octoxynol. These differences are statistically significant because the two calculated *t* values are larger than the 0.1% critical value for *t*. Incorporation of octoxynol into the tablets reduced the disintegration time by 82%.

The observation that the shortest disintegration times were obtained when octoxynol was incorporated into the tablets may in part be due to their reduced hardness (Table II). However, the major cause is probably the temporary high concentration of dissolved octoxynol inside the tablets as the disintegration liquid penetrates them and leaches the surfactant out of the microcrystalline cellulose granules.

The spread of the individual disintegration times about their mean, as represented by the standard deviation and range, was largest when the medium contained 0.0039% octoxynol and smallest when the octoxynol was incorporated into the tablet, paralleling the rank order of the disintegration times themselves. The rank order of the breadth of the statistical dispersion of the individual values about their means remained the same regardless of whether the standard deviation and range were expressed as percent of the means or as absolute values.

Octoxynol Dissolution Rate—Micelles of nonionic surfactants are slow to dissociate and the nonassociated surfactant molecules are slow to reach equilibrium adsorption at the air–water interface. While most measurements to establish the concentration–surface tension relationship were made after equilibrating the octoxynol solutions at 37° for 1 hr, some surface tensions were measured after 24 hr of equilibration. As is seen in Fig. 1, longer equilibration times did not result in noticeably lower surface tensions.

The calibration plot of surface tension *versus* the log of concentration is linear between the critical micelle concentration of 0.0083% (w/v) (surface tension = 30.9 dyne/cm) and 0.0008% (surface tension = 44.7 dyne/cm). This concentration range corresponds to the region of saturation adsorption of the surfactant at the air–water interface. The least-squares correlation between surface tension, γ, in dyne/cm and octoxynol concentration, C %, (w/v), valid for this concentration range, is:

$$\gamma = 2.59 - 13.62 \log C \qquad \text{(Eq. 1)}$$

with a correlation coefficient of 0.993 ($N = 8$).

When determining the dissolution rate of octoxynol from tablets, 40-ml aliquots were withdrawn from the 900-ml medium for surface tension measurements. These withdrawals represented substantial reductions in the volume of the medium and in the amount of dissolved surfactant. Correction was made by the following equation, derived for that purpose:

$$C_{i,\text{corr}} = \left[\frac{900 - (i-1)40}{900}\right] C_{i,\text{obs}} + \frac{40}{900} \sum_{i-1=1}^{i-1} C_{i-1,\text{obs}} \qquad \text{(Eq. 2)}$$

where $C_{i,\text{corr}}$ is the surfactant concentration in the dissolution medium at the time when the ith aliquot was withdrawn, corrected for the withdrawal of all previous aliquots, *i.e.*, $C_{i,\text{corr}}$ is the concentration that would have been measured if no aliquots had been withdrawn previously. The surfactant concentration in the ith 40-ml aliquot is $C_{i,\text{obs}}$. Both $C_{i,\text{corr}}$ and $C_{i,\text{obs}}$ are expressed as percent (w/v). The summation term starts with the second aliquot, *i.e.*, with $i - 1 = 1$ or $i = 2$; in this term, $i \neq 1$. The summation term is always one aliquot behind the other two terms of Eq. 2.

The values for $C_{i,\text{obs}}$ were obtained from the surface tensions either by means of the calibration plot of Fig. 1 or at octoxynol concentrations between 0.008% and the critical micelle concentration, by Eq. 1.

The presence of debris of insoluble tablet ingredients suspended in the dissolution medium did not affect the surface tension measurements, nor was there substantial adsorption of octoxynol by the debris. The surface tensions of the following media were identical within the precision of the measurements, namely, ±0.1 dyne/cm, at comparable nominal octoxynol concentrations: (*a*) octoxynol solutions in 0.1 *N* HCl, before and after filtration through membrane filters with pore sizes of 0.22 and 0.1 μm; (*b*) octoxynol solutions in dissolution media containing disintegrated tablets, before and after filtration through 0.22- and 0.1-μm filters.

Tablets made from Formulation III and a dissolution medium of 0.1 *N* HCl were used to study the rate of release of octoxynol. A plot of the octoxynol concentration in the dissolution medium *versus* time, obtained with two tablets, was linear and went through the origin (Fig. 2). A plot of the logarithm of the concentration of dissolved octoxynol *versus* time

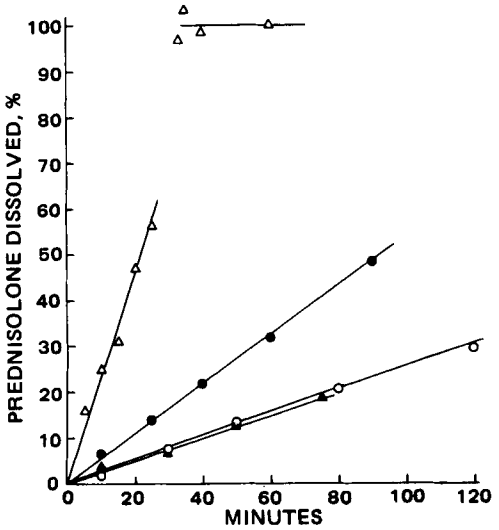

Figure 3—*Effect of octoxynol on the dissolution rate of prednisolone in 0.1 N HCl at 37°. Key: (▲) no octoxynol; (○) 0.0039%, (●) 0.032%; and (△) 0.0039% equivalent octoxynol in tablet but none added to medium.*

was concave toward the time axis. After a dissolution period of 35 min, at which time all of the octoxynol had been dissolved, the tablets disintegrated completely and all fragments fell through the screen of the dissolution basket.

The dissolution of octoxynol from tablets follows zero-order kinetics. The slope of Fig. 2, calculated by the method of least squares, is 0.000112% (w/v)/min, the correlation coefficient is 0.990. The total amount of octoxynol present in the tablet, 35 mg, dissolved in the 900-ml volume of dissolution liquid, would have produced a concentration of 0.00389% (w/v). Therefore, the dissolution rate constant of octoxynol is:

$$k = \frac{dC}{dt} = \left(\frac{0.000112\%\ (w/v)}{\text{min}}\right)\left(\frac{100\%}{0.00389\%\ (w/v)}\right) = 2.88\%/\text{min} \qquad \text{(Eq. 3)}$$

where percent refers to the amount of octoxynol released, expressed as percent of the total amount present or C_∞.

Prednisolone Dissolution Rate—Octoxynol is an effective deflocculating agent and may have dispersed some of the solid prednisolone into colloidal particles. If these particles passed the 0.22-μm membrane filter, they would be assayed together with the dissolved prednisolone, resulting in an excessively high dissolution rate.

When three 5-ml portions of a dissolution medium were filtered in succession through a membrane filter with a pore size of 0.22 μm and an additional three 5-ml portions of the same medium were filtered in succession through a membrane filter with a pore size of 0.1 μm, all six filtrates had identical prednisolone contents. Moreover, the filtrates were clear and did not exhibit Tyndall beams. These facts indicate that only molecularly dissolved prednisolone, and possibly prednisolone solubilized in micelles, were present in the filtrates, and that the membrane filters did not absorb measurable quantities of the steroid. No colloidally dispersed and undissolved prednisolone was present in the filtrates.

The accuracy and reproducibility of the prednisolone assay in the presence of the tableting ingredients was evaluated by assaying three tablets containing 25.0 mg each of prednisolone as described above. After trituration with methanol to dissolve the steroid, the entire mass was diluted to 1.000 liter with 0.1 *N* HCl. Duplicate assays on filtered aliquots for each tablet gave the following results: The mean of six values of prednisolone concentration was 25.05 mg/liter, the standard error 0.07 mg/liter, and the range 0.4 mg/liter. The standard error represents only 0.3% of the mean.

Table V—Sedimentation Volumes of Prednisolone Suspensions at Different Octoxynol Concentrations

Octoxynol Concentration, % (w/v)	Sedimentation Volume, ml		
	Coarse Particles	Fine Particles	Total
0	0.20	0.65	0.85
0.0039	0.19	0.23	0.42
0.012	0.16	0.39	0.55
0.016	0.14	1.02	1.16
0.032	0.13	1.32	1.45
0.128	0.05	2.00	2.05

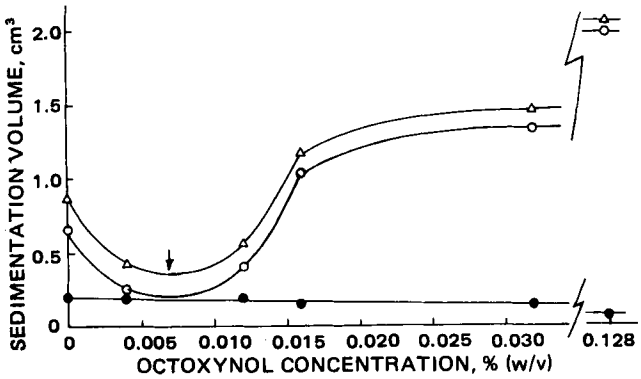

Figure 4—*Sedimentation volume of prednisolone suspensions in 0.1 N HCl at 25° as a function of octoxynol concentration. Key: (●) coarse aggregates; (○) fine; and (△) total volume. Arrow indicates critical micelle concentration.*

The dissolution data are summarized in Table IV. Plots of the logarithms of percent prednisolone dissolved *versus* dissolution time were concave toward the time axis. Plots of percent prednisolone dissolved *versus* dissolution time were straight lines going through the origin, indicating that the dissolution was zero order (Fig. 3).

Dissolution studies were conducted for up to 2 hr. In that period, tablets of Formulation I (no surfactant) in Media A and B released 25–30% of the prednisolone. Under these conditions, tablet disintegration times were somewhat under 2 hr. Nearly half of the prednisolone was dissolved within 1.5 hr in Medium C, where the disintegration time was somewhat >1 hr. When octoxynol was incorporated into the tablet, complete dissolution of the prednisolone occurred in ~30 min, compared with disintegration times of <20 min. Thus, tablet disintegration always preceded complete prednisolone dissolution.

The zero-order rate constants for the dissolution of prednisolone were calculated by (52):

$$k = \frac{\sum tp}{\sum t^2} \qquad \text{(Eq. 4)}$$

where p represents the percent prednisolone dissolved, based on the total amount of prednisolone present in the tablets, namely, 25 mg, and t represents dissolution time.

The standard deviation of k, S_k, was calculated by (52):

$$S_k = \sqrt{\frac{S^2_{t,p}}{\sum t^2}} \qquad \text{(Eq. 5)}$$

The variance of regression is:

$$S^2_{t,p} = \frac{1}{N-1}\left[\sum p^2 - \frac{(\sum tp)^2}{\sum t^2}\right] \qquad \text{(Eq. 6)}$$

where N is the number of measurements and $N-1$ the number of degrees of freedom.

Zero-order dissolution rate constants for the four systems and their standard deviations are listed in Table IV. The mean rate constant in Medium B, containing octoxynol at a concentration of 0.0039% (w/v) or 47% of the critical micelle concentration, is somewhat larger than the one in Medium A without octoxynol. However, the difference between the two values is not statistically significant because the observed t value of 1.816 is smaller than the critical t value at the 5% level for $N_1 + N_2 - 2 = 50$, namely, 2.008 (52).

A higher level of octoxynol in the dissolution medium, 3.9 times the critical micelle concentration, doubled the rate of dissolution. However, the rate of dissolution was increased tenfold when the surfactant was incorporated into the tablet rather than dissolved in the dissolution medium.

Micellar Solubilization of Prednisolone—To ascertain whether micellar solubilization of prednisolone by octoxynol could play a role in speeding up its dissolution from tablets, the solubility of prednisolone in 0.1 *N* HCl solutions containing different concentrations of octoxynol up to 0.128% (w/v) was measured at 37°.

To ensure that equilibration was attained, prednisolone suspensions in 0.1 *N* HCl containing different octoxynol concentrations were shaken at 37° for 2, 6, and 16 days prior to the colorimetric assay, and for 3, 6, and

Table VI—Particle Size Distribution of Prednisolone Suspensions at Different Octoxynol Concentrations

Octoxynol Concentration, % (w/v)	Size Range, μm	Mid-point, D^a, μm	N^b	Number Distribution, Frequency, %	Weight Distribution, Frequency, %
0		Rod-Shaped Particles			
	0–5	2.5	187,500	17.6	0.005
	5–10	7.5	375,000	35.3	0.28
	10–15	12.5	187,500	17.6	0.65
	15–20	17.5	125,000	11.8	1.18
	20–25	22.5	62,500	5.9	1.26
	25–30	27.5	62,500	5.9	2.29
	30–35	32.5	62,500	5.9	3.78
		Coarse Particles			
	0–200	100	380	0.036	0.67
	200–400	300	220	0.021	10.5
	400–600	500	110	0.010	24.2
	600–800	700	70	0.007	42.3
	800–1,000	900	10	0.001	12.9
	Total		1,063,290	100.075	100.015
0.0039		Rod-Shaped Particles			
	0–5	2.5	625,000	37.0	0.02
	5–10	7.5	375,000	22.2	0.36
	10–15	12.5	437,500	25.9	1.96
	15–20	17.5	250,000	14.8	3.07
		Coarse Particles			
	0–200	100	890	0.053	2.04
	200–400	300	360	0.021	22.3
	400–600	500	190	0.011	54.5
	600–800	700	20	0.001	15.7
	Total		1,688,960	99.986	99.95
0.032		Rod-Shaped Particles			
	0–5	2.5	5,562,500	55.3	0.26
	5–10	7.5	3,812,500	37.9	4.77
	10–15	12.5	687,500	6.8	3.98
		Coarse Particles			
	0–200	100	370	0.0037	1.10
	200–400	300	220	0.0022	17.6
	400–600	500	140	0.0014	51.9
	600–800	700	20	0.0002	20.4
	Total		10,063,250	100.0075	100.01

[a] Defined by Eq. 8. [b] Number of particles per milliliter.

22 days prior to analysis by the gravimetric method. In both methods, the longer shaking times did not significantly increase the amount of prednisolone solubilized, indicating that equilibrium had been reached within the shortest shaking times.

The linear relation between the solubility of prednisolone in 0.1 *N* HCl containing octoxynol at concentrations above the critical micelle concentration and the concentration of octoxynol was calculated by the least-squares method. If the solubility limit of prednisolone was expressed in milligrams per liter and the octoxynol concentration in percent (w/v), the colorimetric method yielded an intercept of 309 and a slope of 453. The gravimetric method yielded an intercept of 367 and a slope of 510. According to the *t* test (52), the difference between the two intercepts is not statistically significant at the 5% probability level. Moreover, the intercepts do not differ significantly from the solubility of prednisolone in 0.1 *N* HCl solutions with octoxynol levels between zero and the critical micelle concentration.

Because the difference between the slopes of the two regression lines was not statistically significant either, the two sets of data were pooled. The critical micelle concentration of 0.0083% was subtracted from the total octoxynol concentration C to give the concentration of octoxynol associated into micelles, expressed as percent (w/v). With the solubility of prednisolone S in milligrams per liter as the dependent variable, the equation of the regression line (N = 17) was:

$$S = 342 + 326\,(C - 0.0083) \qquad \text{(Eq. 7)}$$

with a correlation coefficient of 0.804.

The intercept, 342 mg/liter, represents the solubility of prednisolone in the aqueous environment. It is identical with the mean solubility value of prednisolone in 0.1 *N* HCl containing between 0 and 0.008% octoxynol, 343 ± 42 (N = 14).

The slope, 326 mg/liter of prednisolone/% (w/v) micellar octoxynol, represents the solubilizing capacity of octoxynol micelles for prednisolone. For Medium C, containing 0.0320 − 0.0083 = 0.0237% micellar octoxynol, the total solubility of prednisolone S is 350 mg/liter according to Eq. 7. Of this amount, only 8 mg/liter (350 − 342 = 0.0237 × 326 = 8) is solubilized in micelles.

Sedimentation Volumes of Prednisolone Suspensions—The sedimentation volumes of 50-ml suspensions containing 50 mg of prednisolone in 0.1 *N* HCl and different octoxynol concentrations are listed in Table V. Constant sedimentation volumes were reached within 24–48 hr. In the absence or at low concentrations of octoxynol, the suspensions consisted mostly of coarse particles, which were granular aggregates. At intermediate concentrations, in the vicinity of the critical micelle concentration, octoxynol broke these up progressively into fine particles which were rod-shaped. The latter tended to agglomerate into loose flocs at high octoxynol concentrations.

The sediments were stratified into two distinct layers consisting of the coarse and fine particles, respectively, separated by a sharp boundary. The sedimentation volumes of both types of particles were recorded separately and added together in Table V. Octoxynol decreased the sedimentation volumes of the coarse particles in two ways. With increasing concentration, the surfactant peptized progressive amounts of the coarse particles into fine, rod-shaped particles. It also caused the remaining coarse particles to pack more tightly into sediments that were more compact and, hence, occupied progressively smaller volumes.

The sedimentation volume of the fine, rod-shaped particles was not a monotonic function of the octoxynol concentration but went through a minimum in the vicinity of the critical micelle concentration (Fig. 4). The initial decrease was caused by deflocculation of the fine particles into primary rods. Flocs were rarely seen under the microscope below the critical micelle concentration.

As the surfactant concentration increased above the critical micelle concentration, the sedimentation volume of the fine particles increased in two ways. Their number increased because of the progressive breaking up of coarse particles. Moreover, the rod-shaped particles became more extensively aggregated into loose flocs of progressively larger size. Many flocs containing 40–60 rod-shaped particles were observed in 0.128% octoxynol.

Flocculation of the rod-shaped primary particles may be due to bridging by octoxynol micelles. As the surfactant concentration increased, the number and size of the micelles increased, thereby increasing their ability to bridge and bind together rod-shaped prednisolone particles. At concentrations exceeding the critical micelle concentration tenfold or more, cylindrical micelles probably begin to form which, at still higher

concentrations, produce the middle phase (53). Increasing micellar asymmetry increases the number of prednisolone particles on which a single micelle may be adsorbed, cementing them together into flocs.

Particle Size Distribution of Prednisolone Suspensions—Microscopic measurements were conducted on three suspensions in 0.1 *N* HCl containing 0, 0.0039, and 0.032% octoxynol, corresponding to dissolution Media A, B, and C, respectively. The fine particles were rods of length L and width or diameter W. To obtain a particle size distribution which included the fine rod-shaped particles and the coarse irregular particles, a single dimension was needed for the former. The dimension chosen was the surface diameter D (54, 55), *i.e.*, the diameter of a sphere having the same surface area as the rod, because the dissolution rate of very slightly soluble drugs depends largely on their surface area:

$$D = \sqrt{W(L + W/2)} \qquad \text{(Eq. 8)}$$

The particle size distribution data for the three media are listed in Table VI. Number- and weight-distribution frequencies were calculated by standard procedures (54–56). Cumulative plots yielding median diameters were not made because the size distributions are bimodal. However, mean volume–surface diameters D_{vs} (54–56) were calculated:

$$D_{vs} = \sum N_i D_i^3 / \sum N_i D_i^2 \qquad \text{(Eq. 9)}$$

where D_i is the diameter of the midpoint of the ith size range. For the rod-shaped particles, the D values were calculated by Eq. 8.

The D_{vs} values at different octoxynol concentrations and the corresponding specific surface areas, estimated as $6/D_{vs}$, are listed in Table VII. The surfactant increased the specific surface area A of the suspended prednisolone particles by only 10% below the critical micelle concentration but more than doubled it above that concentration.

Within the range of data of Table VII, there is a linear relation between the specific surface area A in cm^2/cm^3 and the octoxynol concentration C in % (w/v):

$$A = 347 + 12{,}900\,C \qquad \text{(Eq. 10)}$$

with a correlation coefficient of 0.99956. This proportionality cannot extend to higher octoxynol concentrations at which the coarse particles are completely broken down because, at these concentrations, the surfactant flocculates the primary, rod-shaped particles extensively.

DISCUSSION

The experimental data afford an assessment of the relative contributions of wetting, micellar solubilization, and deflocculation towards the enhancement of the dissolution rate of prednisolone by octoxynol.

Wetting—The first step in the disintegration of tablets and dissolution of the active ingredient is the displacement of air from the internal surface of the tablet by the dissolution medium, replacing the solid–air with a solid–liquid interface. This wetting process is expedited if the dissolution medium makes a small or zero contact angle on the solid surface. Small contact angles are generally produced by liquids of low surface tension.

The following facts demonstrate that wetting affected neither the disintegration time of the tablets nor the dissolution rate of the active ingredient. Medium A, consisting of 0.1 *N* HCl with a surface tension of 71.1 dyne/cm at 37°, produced only marginally greater disintegration times than Medium B, which consisted of 0.100 *N* HCl + 0.0039% octoxynol with only half the surface tension. Medium C, consisting of 0.1 *N* HCl + 0.032% octoxynol with a surface tension of 30.9 dyne/cm, which is only 4.5 dyne/cm below that of Medium B, reduced the disintegration time by one-third (Table III).

No additional air bubbles were released from the disintegrating tablets after the initial immersion time of 1 min. Therefore, wetting, *i.e.*, the penetration of the dissolution medium into the pores of the tablets and the displacement of the air therein, was completed within that period.

The dissolution rate of prednisolone in Medium B was only marginally higher than that in Medium A, despite the fact that the latter had twice the surface tension of the former. The dissolution rate in Medium C was twice that in Medium B (Table IV), despite the small difference in their surface tensions.

Since wetting depends markedly on surface tension, while the disintegration times and dissolution rates were not correlated with surface tension, wetting was not a rate-determining step for these processes.

Micellar Solubilization of Prednisolone—According to Eq. 7, 326 mg/liter prednisolone is solubilized by 1% (w/v) or 10,000 mg/liter micellar octoxynol at saturation. The solubilizing capacity of octoxynol is thus 0.0326 g of prednisolone/g of micellar octoxynol; *i.e.*, 0.057 mole of prednisolone/mole of micellar octoxynol, or 18 moles of micellar octoxynol/mole of solubilized prednisolone. This value is typical for micellar solubilization of steroids by nonionic surfactants (57, 58).

The following two facts demonstrate that micellar solubilization cannot play a significant role in the enhancement of the dissolution rate of prednisolone by octoxynol. Medium C, with 0.0320 − 0.0083 = 0.0237% micellar octoxynol, dissolves 350 mg/liter prednisolone at saturation, or a maximum of 315 mg for the actual 900-ml volume of the dissolution medium. Of the latter amount, only 7 mg is solubilized in micelles, while most of the prednisolone is dissolved in the aqueous environment.

Of the 25 mg of prednisolone contained in a tablet, only a small fraction will be solubilized by micelles, <3% if the partition coefficient of prednisolone dissolved in the aqueous phase and in the micelles of a 0.032% octoxynol solution equals the ratio of its solubility limits, namely, (350 − 8)/8 or 43:1.

The greatest enhancement of the dissolution rate of prednisolone was observed with Formulation III (Tables I and IV), where octoxynol was incorporated into the tablets. This 35 mg of octoxynol, if it existed entirely in the micellar form, could solubilize a maximum of 1.1 mg of prednisolone according to Eq. 7, *i.e.*, no more than 5% of the prednisolone present in the tablets. Thus, micellar solubilization cannot play a major role in speeding up the dissolution of prednisolone even in the hypothetical situation where the dissolution medium flowing into a tablet dissolves all of the octoxynol contained therein, and where the micellar solution thus produced becomes saturated with prednisolone inside the tablet before octoxynol begins to diffuse out.

Deflocculation—The tablet disintegration experiments provided a visual demonstration of deflocculation. Even at octoxynol concentrations below the critical micelle concentration, the tablets broke up into fine granules that remained in suspension, compared with coarse, quickly sedimenting grains in the absence of surfactant.

The data of Table VII and Eq. 10 indicate that octoxynol deflocculated the suspended prednisolone and that the extent of deflocculation was proportional to the surfactant concentration. It is interesting to compare quantitatively the increase in dissolution rate with the increase in specific surface area measured at comparable octoxynol concentrations to ascertain whether the deflocculation was extensive enough to produce the observed increases in dissolution rate.

The Noyes–Whitney (59) and Nernst–Brunner (60) equation relates the rate of change of drug concentration C in the dissolution medium with time t to the specific surface area A of the drug particles, the thickness h of the stagnant saturated solvent layer surrounding the drug particle, the solubility limit of the drug, C_s, which is its concentration in the stagnant layer, and the drug concentration C_t in the bulk solvent at time t:

$$\frac{dC}{dt} = \frac{DA}{h}(C_s - C_t) \qquad \text{(Eq. 11)}$$

where D represents the diffusion coefficient of the drug molecules in solution.

The maximum values of C_t in the present experiments, attained when the 25 mg of prednisolone present in the tablets is completely dissolved in the 0.9-liter volume of dissolution medium, is 25 mg/0.9 liter or 28 mg/liter. This value is <10% of the lower prednisolone solubility limit of 342 mg/liter obtained in the absence of octoxynol. Therefore, $C_s \gg C_t$ and $C_s - C_t \cong C_s$. The left term in Eq. 11 represents the zero-order dissolution rate constant k obtained from Fig. 3 and listed in Table IV. Thus, Eq. 11 simplifies to:

$$k = DAC_s/h \qquad \text{(Eq. 12)}$$

indicating that k should be directly proportional to A if h is independent of A.

The last column of Table VII lists the ratios k/A. They increased by a mere 16% while A and k more than doubled. The slight increase in the k/A ratio with increasing k and A values may not be statistically significant despite the consistent trend. If the increase is significant, it can be ascribed to a slight decrease in h caused by an increase in A. A slight decrease in the thickness of the stagnant layer caused by a large reduction in particle size is to be expected.

Of the three possible mechanisms by which octoxynol could have increased the rate of dissolution of prednisolone, only deflocculation was extensive enough to account for the magnitude of the observed rate enhancement. Neither wetting nor micellar solubilization made significant contributions to the observed effect.

Higher octoxynol concentrations, *e.g.*, 16 times its critical micelle concentration, produced extensive flocculation of the primary rod-shaped particles. However, these surfactant concentrations were much larger than those attainable in a practical situation.

Table VII—Mean Volume–Surface Diameters and Specific Surface Areas of Prednisolone Suspensions and Their Relation with Dissolution Rate Constants

Octoxynol Concentration, % (w/v)	D_{vs}, μm	A, cm^2/cm^3	k[a], %/min	k/A, 10^4(%/min)/(cm^2/cm^3)
0	170	353	0.218	6.2
0.0039	154	390	0.251	6.4
0.032	79	760	0.547	7.2

[a] Values of zero-order dissolution rate constant from Table IV.

The highest dissolution rates were obtained when the octoxynol was incorporated into the tablets. The transient, relatively concentrated octoxynol solutions produced inside tablets when the octoxynol was extracted from the microcrystalline cellulose by the inflowing dissolution medium produced the most extensive deflocculation of prednisolone. Even these solutions, however, broke up the coarse particles without flocculating the resulting rod-shaped particles. Moreover, flocs of the rod-shaped particles dispersed readily when the suspending medium of concentrated octoxynol was diluted with water or 0.1 *N* HCl.

Relation between Tablet Disintegration Time and Prednisolone Dissolution Rate—Octoxynol reduced the tablet disintegration time and increased the prednisolone dissolution rate considerably. Therefore, the mean tablet disintegration times t in minutes (Table III) and the zero-order rate constants for the dissolution of prednisolone k, in percent per minute (Table IV), were compared for tablets of Composition I in Media A, B, and C and for tablets of Composition II in Medium A.

The relation between log k and t was linear:

$$\log k = 0.546 - 0.0113\,t \qquad \text{(Eq. 13)}$$

with a correlation coefficient of 0.997. While it is to be expected that a given factor, such as the presence of a surfactant, which reduces disintegration times also increases dissolution rates (61, 62), no physical meaning is ascribed to the fact that the two parameters were related by a linear relationship on a semilogarithmic scale.

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