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Dissolution Profiles for Multisized Prednisolone Acetate Suspensions

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Abstract □ Particle-size measurements and *in vitro* dissolution characteristics of commercial and formulated suspensions of prednisolone acetate were determined using a resistance particle counter and a spinning filter apparatus, respectively. Significant differences in dissolution rates were noted for the commercial suspensions. Particle size affected dissolution but did not account for all observed variations in the dissolution rate. Formulation differences, specifically the presence of hydroxypropyl methylcellulose, in suspensions seemed to be important in dissolution.

Keyphrases □ Prednisolone acetate—multisized suspensions, dissolution profiles and particle-size measurements □ Suspensions, multisized—prednisolone acetate, dissolution profiles and particle-size measurements □ Dissolution—multisized suspensions of prednisolone acetate, effect of particle size □ Particle size—effect on dissolution of prednisolone acetate suspensions □ Glucocorticoids—prednisolone acetate, multisized suspensions, dissolution profiles and particle-size measurements

The dissolution rate and *in vivo* physiological availability of drugs are important research areas (1–5). The dissolution rate of a solid dosage form such as a tablet or a capsule can be the rate-limiting step in availability for the *in vivo* absorption of the active ingredient (6–8), particularly for poorly soluble or poorly wetted drugs (9).

At present, almost all dissolution rate research efforts are directed toward tablets and capsules. Although suspensions share many physical–chemical characteristics of tablets and capsules with respect to the dissolution process, they are almost completely ignored. Since tablets and capsules disintegrate into powder suspensions, pharmaceutical suspensions share the dissolution process as a rate-limiting step for absorption and bioavailability.

Bates *et al.* (10) studied the dissolution rates of nitrofurantoin tablets and suspensions and commented that it was inconsistent to provide a USP dissolution test for nitrofurantoin tablets without including a dissolution rate test for the suspension. They concluded that: "the rationale underlying the official dissolution rate specification for nitrofurantoin tablets appears quite arbitrary and inconsistent with the dissolution profile and potential toxicity of the official suspension dosage form."

These comments substantiate a need to pursue dissolution rate testing of suspension dosage forms. In the current study, the dissolution and particle-size profiles of several commercially available suspensions were determined to obtain information about brand-to-brand variation and formulation characteristics directly related to dissolution.

Commercially available steroid ophthalmic/otic suspensions were studied. They represent a dosage form that requires dissolution as a prerequisite to therapeutic availability. These products contain a poorly soluble micronized steroid in a suitable vehicle. The solubility and particle-size characteristics of these products make them desirable prototype suspensions to study.

EXPERIMENTAL

Dissolution Testing—All reported dissolution data were obtained using a device[1] described by Shah *et al.* (11). The basic features of the apparatus are a large volume fluid container, a rotating filter assembly, and an external variable-speed magnetic stirrer. The sample basket was removed.

The rotating filter assembly provides variable intensity of mild laminar liquid agitation and also functions as an *in situ* nonclogging filter to permit efficient intermittent or continuous filtration of dissolution fluid samples during the dissolution process. The assembly is suspended and freely rotates in the center of the flask on the flared end of a glass capillary pilot tube. The assembly rotates by means of a controlled, variable-speed, external magnetic stirrer coupled with a magnetic bar embedded in the bottom part of the assembly. A 0.5-μm porosity sintered stainless steel filter also was employed.

One liter of distilled water was transferred into the flask, and the fluid was allowed to equilibrate at 25°. The stirring speed of the filter assembly was 960 rpm. A strobe lamp[2] was used to standardize the stirring speed.

Filtered fluid samples were continuously withdrawn through the capillary pilot tube at the rate of 100 ml/min and were circulated through the spectrophotometer and back to the flask. Air bubbles were periodically released from an air trap. The system was allowed to run for at least 15 min to ensure the consistency of the flow and stirring rate. The spectrophotometer[3] was then calibrated for zero absorbance at 246 nm with the dissolution medium in the reference cell. The baseline on the stripchart[4] paper also was adjusted corresponding to zero absorbance.

[1] The dissolution apparatus was made available through the courtesy of The Upjohn Co., Kalamazoo, Mich.
[2] Glass Instrument Co., Quincy, Mass.
[3] Perkin-Elmer double-beam spectrophotometer, Coleman 124, Hitachi, Ltd., Tokyo, Japan.
[4] Chart recorder model SRG, Sargent-Welch Scientific Co., Cleveland, Ohio.

All test conditions (*i.e.*, fluid temperature, stirring rate, cycling through the flowcell, and calibration of the spectrophotometer) were adjusted properly. The dissolution experiment was started by injecting a measured amount of suspension (0.5 ml except for Product A which was 1 ml) at a fixed position in the beaker using a syringe fitted with an extra long needle. The strip-chart paper was marked at the exact same time that the suspension was introduced into the flask. The recorder was switched to "stand by" until the drug readings, which were taken periodically, reached a plateau. The plateau of the curve was recorded and represented the equilibrium value. Generally, 2 hr was needed to reach equilibrium in this study.

The absorbance of dissolution profiles was then edited from the chart recording. For this report, the absorbance was edited at 5-sec intervals until 200 sec and then at every 100-sec interval until 1500 sec. The edited value was then used to calculate the weight fraction undissolved at any time t by simply dividing each absorption value by the equilibrium value and subtracting the resulting fraction from one.

Particle-Size Analysis—All particle-size data were obtained with a resistance particle counter[5] that employs the basic automated principle of sizing particles for a 16-channel (size) distribution analysis.

One convenient aspect provided by this instrument is that the volumetric size of the particle is automatically converted to the equivalent spherical diameter without any calculations by the operator. The calibration materials for the 50- and 200-μm aperture tubes were 2.02-μm diameter latex[6] beads and 27–28-μm diameter Lycopodium[7], respectively.

To avoid coincidence errors, size distribution must be measured within the limits given in the instrument manual. A meter on the instrument facilitates this process. A reading of approximately 0.05 on the concentration meter essentially eliminates coincidence problems.

The particle-size distribution data obtained from the resistance particle counter were provided by a numeric display of the cumulative and differential distributions. An oscilloscope display and the histograms were also available. Readout of total particle counts accumulated in the active channels was available during accumulation and held until the counter was reset. Also available were elapsed time data. Accumulations were continued for approximately 60 sec.

Electrolyte Preparation—Particle-size determinations of the suspensions were made using a balanced electrolyte[8] saturated with prednisolone acetate. Particulate contamination of the electrolyte was avoided by filtering the saturated solutions twice through a 0.22-μm filter[9].

Sample Preparation and Assay—The handmade suspensions were prepared in a glass mortar. Air-micronized prednisolone acetate[10] was triturated with presaturated water with or without hydroxypropyl methylcellulose[11], depending on the experiment.

The dissolution of prednisolone acetate from a suspension was measured by a spectrophotometric assay. A Beer's law plot was obtained at 246 nm. The linearity throughout the full range of concentrations was evidenced by a correlation coefficient of 0.9998.

An analytical methodology was developed to determine if components in the formulations, other than prednisolone acetate, interfered with the assay. A sample of the commercial suspension was filtered through a 0.22-μm filter, and the filtrate was diluted to the same concentration as that used for the actual dissolution study. These solutions showed little or no absorbance.

RESULTS AND DISCUSSION

Prednisolone acetate suspensions were chosen as the first product to be tested. This drug product was chosen for the following reasons: (*a*) multiple brands were marketed, (*b*) formulations were available from the labels, (*c*) dissolution of the active ingredient could be followed spectrophotometrically, (*d*) only the active ingredient was suspended, and (*e*) the dissolution rate was presumed to be the rate-limiting step for therapeutic availability.

Commercially available products were purchased from a pharmaceutical source other than directly from the manufacturer. Product A (ophthalmic suspension) contained prednisolone acetate, 0.12%; phenylephrine hydrochloride, 0.12%; antipyrine, 0.1%; benzalkonium chloride; polysorbate 80; boric acid; sodium citrate–sodium bisulfite; edetate disodium–sodium chloride; hydroxypropyl methylcellulose; and purified water.

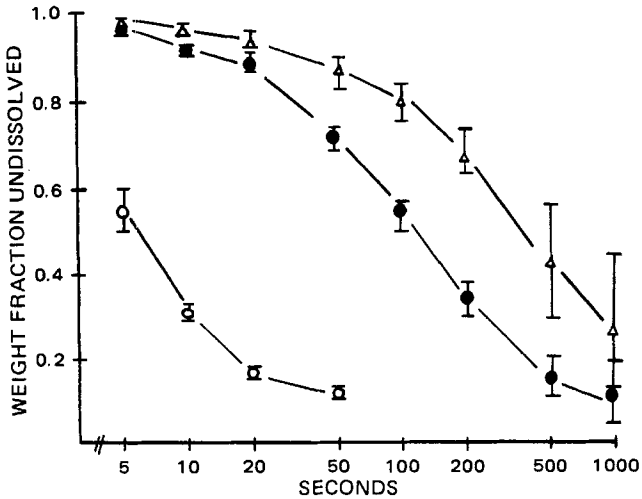

Figure 1—*Dissolution profiles for three commercial prednisolone acetate suspension products. Key: ○, Product A; ●, Product B; and △, Product C. Each point is the average of three experiments, and the bars show the extremes of the experiments.*

Product B (otic–ophthalmic suspension) contained prednisolone acetate, 2.5 mg/ml; neomycin sulfate, 5.0 mg/ml; sodium citrate; polyethylene glycol 4000; povidone; myristyl γ-picolinium chloride; sodium hydroxide and/or hydrochloric acid when necessary to adjust the pH; and water for injection.

Product C (ophthalmic suspension) contained prednisolone acetate, 0.25%; phenylephrine hydrochloride, 0.125%; benzalkonium chloride, 0.01%; hydroxypropyl methylcellulose, 0.2%; sodium bisulfite, 0.2%; edetate disodium; monobasic and dibasic sodium phosphates; sodium chloride; and water.

The results of the dissolution studies for the three commercial prednisolone suspensions are shown in Fig. 1. The dissolution of Product A was the most rapid; 80% dissolved in about 20 sec.

The initial release rate of Product B was much more rapid than that of Product C; the half-life of B occurred at approximately 110 sec, and the half-life of C occurred at approximately 550 sec. Moreover, 65% of Product B dissolved in about 200 sec, while only about 30% of Product C dissolved in the same period.

Since dissolution characteristics are closely related to particle size, a

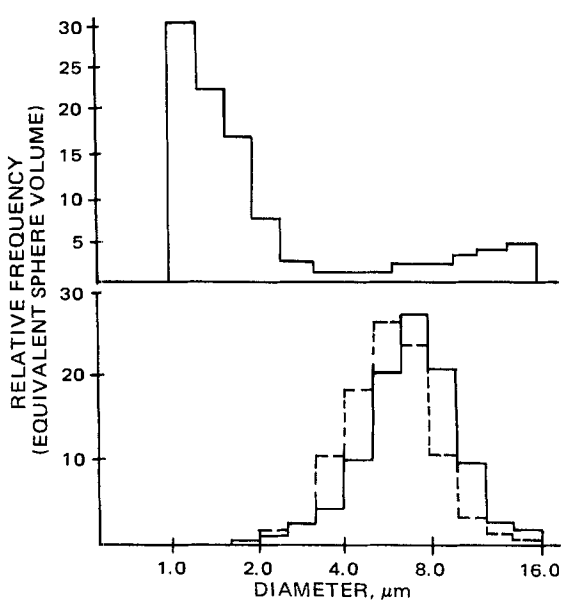

Figure 2—*Particle-size distributions of Products A (—, top), B (- - -, bottom) and C (—, bottom) measured by an automated counter using a 50-μm aperture tube.*

[5] Coulter counter model TA, Coulter Electronics, Hialeah, Fla.
[6] Lot 11001, Coulter Electronics, Hialeah, Fla.
[7] Coulter Diagnostics, Miami Springs, Fla.
[8] Isoton, distributed by Coulter Electronics, Hialeah, Fla.
[9] Millipore Corp., Bedford, Mass.
[10] Prednisolone acetate USP, code 6610, MI19636, Schering Corp., Kenilworth, N.J.
[11] Methocel 60 HG, 4000 cps, lot QP-291021-A, Dow, Midland, Mich.

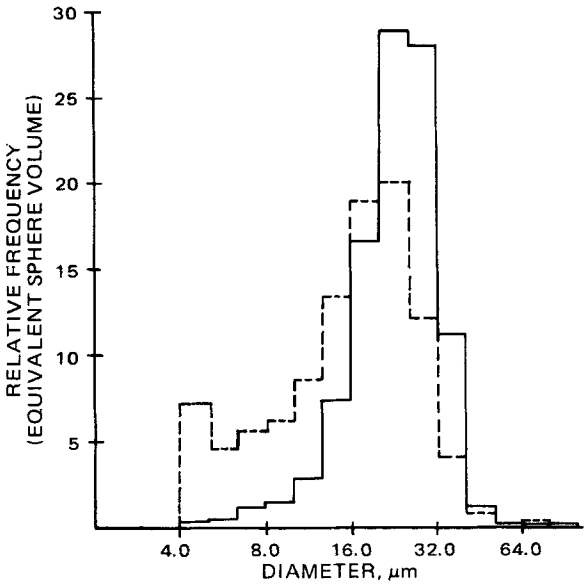

Figure 3—*Particle-size distributions of suspensions of prednisolone acetate (- - -) and prednisolone acetate with hydroxypropyl methylcellulose (——) measured by an automated counter using a 200-μm aperture tube.*

comparison of the particle-size distributions for Products A, B, and C is shown in Fig. 2. Product A was characterized by a population of small particles; about 70% of the particles, by volume, were less than 2 μm in diameter. The cutoff on the left side of Fig. 2 is the limitation of the 50-μm aperture tubes. The very rapid dissolution profile for Product A correlates with the particle-size analysis, because a particle-size reduction is generally regarded as a means of increasing the dissolution rate. According to label information, Product A utilizes a patented micronization process; at one time the package insert specifically mentioned the relationship between particle size and dissolution rate.

The bottom section of Fig. 2 shows the size distribution of Products B and C using the same scale as for Product A. These two products yielded essentially log-normal distributions with an approximate mean diameter of 6–7 μm. The similar particle-size distributions did not predict the significantly different dissolution profiles that were experimentally determined for these products. Since particle size did not provide an explanation, formulation differences between the two suspensions might have been responsible.

A comparison of the formulas for Products B and C shows that C contains hydroxypropyl methylcellulose whereas B does not. To test the effect of this ingredient, aqueous suspensions containing 0.25% prednisolone acetate and 0.2% hydroxypropyl methylcellulose were prepared. Aqueous suspensions containing just 0.25% prednisolone acetate and prepared in exactly the same manner served as a control. A mortar and pestle were used; this method yielded the finest and most reproducible suspensions compared to any other small-scale method of preparation attempted. No dispersing agent was used because it might have altered the dissolution of the suspensions.

Figure 3 shows the size distribution for these two handmade suspensions. The particle-size analysis for each suspension yielded similar distributions. The suspension containing hydroxypropyl methylcellulose yielded a slightly higher percentage of large particles. The mean particle diameter for the hydroxypropyl methylcellulose-containing formula was approximately 26 μm, whereas the mean particle diameter for the control formula was approximately 22 μm.

The dissolution data (Fig. 4) showed a striking difference between the two handmade prednisolone acetate suspensions that would not be predicted on the basis of particle-size analysis. Hydroxypropyl methylcellulose increased the dissolution time of prednisolone acetate compared to the control suspension. Twenty percent of the hydroxypropyl methylcellulose-containing suspension dissolved in about 750 sec, whereas only 100 sec was required for the control suspension. These data were similar

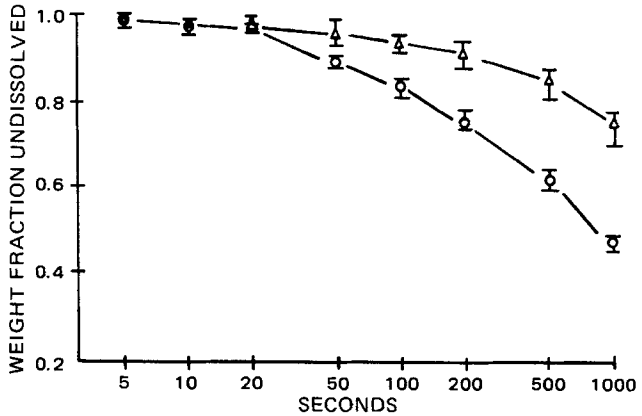

Figure 4—*Dissolution profiles for suspensions of prednisolone acetate (○) and prednisolone acetate containing hydroxypropyl methylcellulose (△) prepared by using a mortar and pestle.*

to those for Products C and B, where C is the hydroxypropyl methylcellulose-containing product. Although Product A also contains hydroxypropyl methylcellulose, the extremely small particle size seemed to dominate to yield a more rapid dissolution rate.

These data suggested that the hydroxypropyl methylcellulose in Product C may be related to its slower dissolution characteristics when compared to Product B, a suspension with similar particle size but without the polymer. It was also evident from a dissolution profile and particle-size analysis for Product A that the particle size can be the dominating factor.

In view of the results, it is believed that dissolution equivalency testing of pharmaceutical suspensions and the factors that cause the dissolution inequivalency, other than particle size, should be the subject of further study.

Although the therapeutic importance of these findings is only speculative, one would argue that the dissolution rate is usually interpreted as being the rate-limiting step for bioavailability. However, the dissolution profiles (Fig. 1) showed that there was inequivalency between the products. Establishment of routine dissolution tests can, therefore, considerably affect the control of lot-to-lot uniformity of the suspension dissolution rate.

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