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DISSOLUTION PERFORMANCE RELATED TO PARTICLE SIZE DISTRIBUTION FOR COMMERCIALLY AVAILABLE PREDNISOLONE ACETATE SUSPENSIONS

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ABSTRACT

Dissolution performance for three commercially available parenteral prednisolone acetate suspensions was analyzed using a diffusion based model. Physicochemical properties of the drug and particle size characteristics of the formulation were included in the model as important determinants of dissolution performance.

The model describes the dissolution profile for each formulation with a single characteristic value, the dissolution rate constant. For Products I and II with similar particle size characteristics, the model sufficiently describes the dissolution profile for each formulation but does not provide conclusive evidence about reasons for differences in dissolution performance between the two products. For Product III, the model sufficiently describes the dissolution profile and adequately includes the effect of a bimodal distribution of larger drug particles.

This approach to the analysis of dissolution data for suspension formulations is suggested as being useful during the formulation process to provide for predetermined dissolution characteristics, as an evaluative tool in quality assurance, and for correlating in-vivo and in-vitro product performance.

INTRODUCTION

Commercial formulations of otic, ophthalmic, and parenteral suspensions of prednisolone acetate and other insoluble steroids are subject to variations in drug release rate. Particle size and formulation variables such as viscosity have been shown to affect the dissolution rate of otic/ophthalmic formulations of prednisolone acetate[1]. The biological equivalence of two commercial prednisolone acetate formulations has been evaluated in rabbits, with no differences being shown between drug levels in the cornea and aqueous humor and in mean decrease in corneal inflammation after topical therapy[2]. However, this study did not demonstrate whether these formulations were similar in particle size, which would, in part, account for their similar performance. For formulations of dexamethasone having differing particle size distributions, the aqueous humor and corneal concentration profiles were found to be significantly different in rabbits[3].

In general, consideration of both dissolution and particle size data should enhance the interpretation of data concerning biological equivalency. These data should also be useful to interpret in-vitro dissolution data and compare release rates between formulations in the context of a kinetic model. A diffusion based model incorporating particle size, drug solubility, and drug diffusion coefficient yields a rate constant which could then be used to efficiently compare the formulations and to predict performance characteristics.

A previous study demonstrated the applicability of a particular diffusion model to the interpretation of the release characteristics of laboratory formulated prednisolone acetate suspensions[4]. An objective of the present study is to extend this model to the analysis and interpretation of dissolution rate data and particle size data for three commercially available parenteral suspensions of prednisolone acetate.

BACKGROUND ON DATA ANALYSIS

Akers et al.[5] have mentioned three reasons for formulating parenteral suspensions:

1. solubility limitations precluding formulation as a solution
2. considerations concerning physicochemical stability
3. objectives relating to retarding or controlling drug release rate.

Formulation of prednisolone acetate as a parenteral suspension is related to these critical factors, with dissolution rate being particularly important to therapeutic effectiveness. The aqueous solubility of steroids is very limited[6]. In addition, release rates from parenteral suspensions can be controlled by formulating the suspensions with particle size specifications.

Dissolution profiles for suspension formulations reflect intrinsic physicochemical properties of the drug, such as solubility, and formulation characteristics, such as particle size distribution. Thus, a model based analysis of these profiles should also reflect drug properties and formulation characteristics, and also describe the profile with a single characteristic value, i.e., the dissolution rate constant.

A diffusion based model which accounts for intrinsic physicochemical drug properties and particle size has been discussed by Higuchi and Hiestand[7]. According to this model, the weight fraction undissolved, WFU, for a multisized particle population at time t is given by

$$WFU = \sum_{I=1}^{N} [(AOI)^2 - (Kt)]^{3/2}/(AOI)^3 \cdot F(I) \qquad \text{(Eq. 1)}$$

where:

I = channel number corresponding to the particle size range of the electronic particle size counter

N = total number of channels

AOI = initial radius of particle size in the Ith channel (cm)

F(I) = fraction of the total volume (weight) of particles in the Ith channel

$K = 2DC_s/\rho_d$.

The dissolution rate, K (cm^2/sec), includes the drug diffusion coefficient, D (cm^2/sec), drug solubility, C_S (gm/cm^3), and drug

density, ρ_d (gm/cm^3). In cases where sink conditions are not maintained, the model is modified by multiplying K by the fractional concentration gradient, $(C_S-C_T)/C_S$, remaining at time t where C_T (gm/cm^3) is the concentration of drug dissolved at time t.

For particles in the micron size range, a question arises as to whether both convection and diffusion contribute to the dissolution process. Mauger et al.[8] have suggested that steroid particles having radii equal to or less than 10 microns are subject primarily to diffusional effects corresponding to the Higuchi-Hiestand model.

A particle size analysis of the formulation yields a value for F(I) for each initial particle size, AOI. Upon dissolution testing, a profile of WFU versus time is generated for each formulation. The particle size data and a value for K can be incorporated into equation 1 to generate calculated values for WFU at various times t. When K is varied as a fitting term, the resulting calculated dissolution profile can be compared with the experimental dissolution profile. Alternatively, K can be calculated using independently determined values for D, C_S, and ρ_d. In either case, this analysis provides for an evaluation of two important characteristics: curve level or distance and curve shape[9]. Curve level reflects the distance between the experimental and calculated dissolution profiles, while similar curve shape means that the curves do not intersect and diverge throughout the time frame of interest. Similar curve shape implies that the proposed model is a physically reasonable representation of the underlying dissolution process.

A key feature of this approach to the analysis of suspension dissolution data is the incorporation of particle size distribution data unique to a given formulation. This is critical when comparing various formulations of the same drug where physicochemical properties are invariant and particle size distribution governs the difference between dissolution performance.

EXPERIMENTAL

Particle-Size Analysis

All particle-size data were obtained with a resistance particle counter (Coulter Counter TA II, Coulter Electronics, Hialeah, FL) that employs the basic automated principle of sizing particles for a 16-channel (size) distribution analysis and converts the volumetric size of the particle to the equivalent spherical diameter. The calibration materials for the 200-μm aperture tube were 9.6 micron polystyrene beads (Coulter Electronics, Hialeah, FL).

Particle-size determinations of the suspensions were made using a balanced electrolyte (Isoton, Coulter Electronics, Hialeah, FL) saturated with prednisolone acetate and filtered twice through a 0.22-μm filter to avoid particulate contamination. Suspension samples for particle-size analysis were maintained at a dilution consistent with avoiding coincidence errors when added to the saturated electrolyte. Total particle counts were allowed to accumulate for approximately 60 seconds. The particle-size distribution data obtained from the particle counter were provided by a numeric display of the cumulative and differential distributions and by oscilloscope and histogram displays. The mean initial particle radius of the size range in each channel was incorporated into equation 1 for the calculation of WFU at various times t.

Dissolution Testing and Drug Assay

All reported dissolution data were obtained using a device described by Shah *et al*[10], with sample basket removed. (Apparatus made available courtesy of The Upjohn Co., Kalamazoo, MI). The basic features of the apparatus are a jacketed large volume flask, a rotating filter assembly, and an external variable-speed magnetic stirrer. The rotating filter assembly provides variable intensity of mild laminar liquid agitation and also functions as an *in situ* nonclogging filter to permit efficient continuous filtration of dissolution fluid samples during the dissolution process. The assembly is suspended on the flared end of a glass capillary pilot tube and freely rotates in the center of the flask

by means of the external magnetic stirrer coupled with a magnetic bar embedded in the assembly bottom. A 0.5- μm porosity sintered stainless steel filter was employed on the assembly.

One liter of distilled water was transferred into the flask, and the fluid was allowed to equilibrate at 37°C. The stirring speed of the rotating filter assembly was set at 300 rpm, with a strobe lamp used to standarize the speed. Using a peristaltic pump (Masterflex Pump, Cole-Parmer, Chicago, IL), fluid samples were continuously withdrawn through the filter and the capillary pilot tube at the rate of 100 ml/min, circulated through a flow-cell in the spectrophotometer, and returned to the flask. The system was allowed to run for at least 15 minutes to ensure the consistency of the flow and stirring rate. The spectrophotometer (Perkin-Elmer Double-Beam, Coleman 124 Hitachi, Ltd., Tokyo, Japan) was then calibrated for zero absorbance at 247 nm with the dissolution medium flowing through the reference cell. This methodology provided a continuous spectrophotometric assay of prednisolone acetate dissolution from suspension. A standard curve had been generated at 247 nm which showed good linearity throughout the drug concentration range of interest.

The dissolution experiment was started by injecting a measured total weight (10 mg) of prednisolone acetate as the commercial suspension at a fixed position in the flask using a syringe fitted with a long needle. Provided that 100% drug dissolution occurred during the study, this total amount injected gave a final concentration of 10 μg/ml, a concentration which approaches 59% of prednisolone acetate's solubility (C_S =17 μg/ml). Thus, for these experiments, dissolution occurred under non-sink conditions.

An analytical methodology was also 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

A basic objective of this study was to test the applicability of the Higuchi-Hiestand model for describing dissolution kinetics of sized, commercially formulated prednisolone acetate suspensions. While this model is appropriate for characterizing dissolution profiles of artificially-generated, well-controlled distributions of particle sizes, testing of a more complex system of industrially-milled drug powders suspended with a number of additives provides some measure of the general applicability for this model.

Three commercial preparations of sterile prednisolone acetate suspension, U.S.P., were chosen and dissolution tested. Particle size profiles, based on volume, are given as histograms in Figure 1. For each suspension, the majority of the particles ($\geq$ 80%) are of a size ($\leq$10 μ radius) such that dissolution should be primarily diffusion based. The mean particle radius for Product I and II is 4.48 and 4.95 microns (10^{-4} cm), respectively, (a 9.5% difference) and 9.60 microns for Product III (nearly twice as large as the means of Products I and II). The particle size distributions of Products I and II show close resemblance. Thus, it is expected that these products would have similar dissolution profiles. Product III has a broader size distribution with larger drug particles, predictive of a slower rate of release.

The dissolution profile for Product I is shown in Figure 2 where each data point represents the average of three dissolution runs. The data were reproducible and the variance was not found to be a function of time. Upon observation, the shapes of the theoretically generated curve with a consideration of non-sink conditions (solid line) and the experimentally determined dissolution profile (individual data points) of Product I are similar. This suggests that the Higuchi-Hiestand model is appropriate for describing the dissolution kinetics of this particle population.

The dissolution of Product I is relatively fast, with half of the drug dissolved in two minutes. The solid line for Figure 2 is based on the Higuchi-Hiestand model for a multisized particle

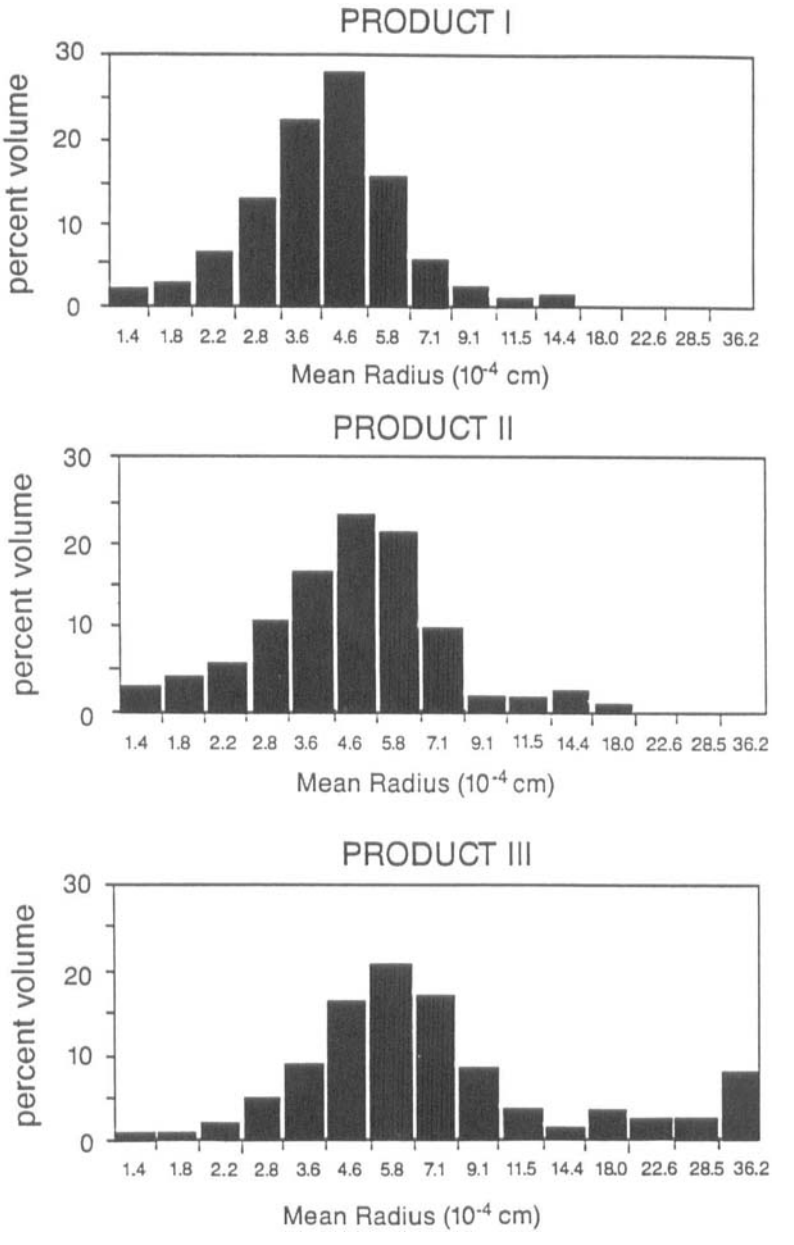

FIGURE 1
PARTICLE SIZE DISTRIBUTIONS FOR THREE COMMERCIAL PREDNISOLONE ACETATE SUSPENSIONS: I, II, AND III

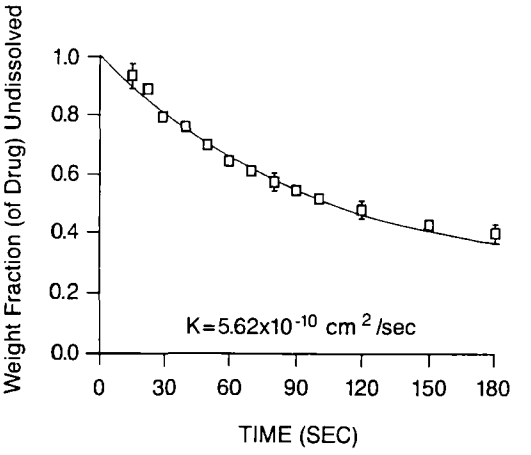

FIGURE 2
DISSOLUTION PROFILE FOR PRODUCT I PREDNISOLONE ACETATE SUSPENSION
(Solid line from Higuchi-Hiestand Model)

population, with K, the dissolution rate constant, varied in order to simulate a representative profile which approximates the experimental data. The theoretical dissolution rate constant for prednisolone acetate is 1.31×10^{-10} cm^2/sec, which was determined from the following data for the drug: $D = 5 \times 10^{-6}$ cm^2/sec, $C_S = 1.7 \times 10^{-5}$ gm/cm^3, and $\rho_d = 1.3$ gm/cm^3.

The Higuchi-Hiestand model, in describing the dissolution of Product I, shows good correlation throughout the dissolution profile. This curve was generated using a K value of 5.62×10^{-10} cm^2/sec, a factor 4.3 times faster than theory predicts. The variation between the experimental data and the fitted curve was evidenced by a total sum of squares of 5.10×10^{-3}, n=13.

The dissolution profile for Product II is shown in Figure 3. The dissolution rate constant, with a consideration of non-sink conditions, was varied to give the best approximation to the experimental data, with the calculated profile for Product II giving reasonable correspondence to the experimental data (total sum of squares of 9.86×10^{-3}, n=13).

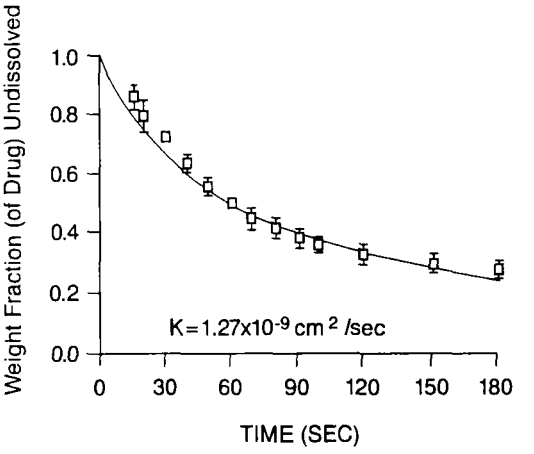

FIGURE 3
DISSOLUTION PROFILE FOR PRODUCT II PREDNISOLONE ACETATE SUSPENSION
(Solid line from Higuchi-Hiestand Model)

The calculated K value for the dissolution of Product II using the Higuchi-Hiestand model is 9.7 times faster than theory predicts (1.27×10^{-9} cm^2/sec). While micronized drug particles have consistently exhibited higher rates of dissolution than would be anticipated, these rate differences have varied from 3.5 to 4 times larger for prednisolone acetate[4]. Similarly, Product I has a dissolution rate about 4 times faster than theory predicts.

In principle, the rate constants for Products I and II should be equivalent. According to equation 1, the rate constant is dependent on D, C_S, and ρ_d and not on formulation variables. Reference to the Appendix shows that the formulation factors potentially affecting D and C_S, such as viscosity-inducing agents and surfactants, are similar for each product. Thus, the reason for a differing K value for each product is not evident. When comparing the dissolution performance for Products I and II, it is noted that the time for 50% dissolution (T_{50}) for Product I is 110 seconds while that for Product II is 60 seconds. The similar

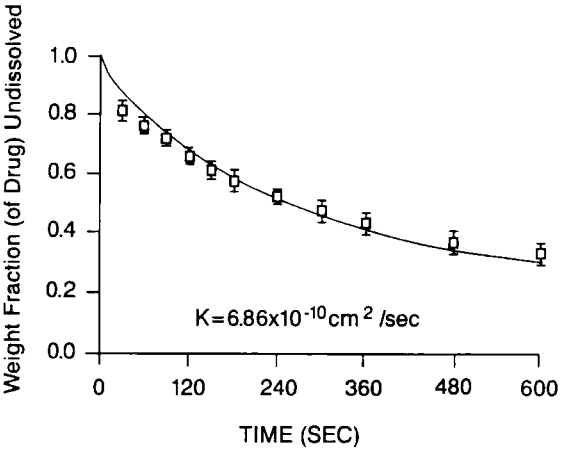

FIGURE 4
DISSOLUTION PROFILE FOR PRODUCT III PREDNISOLONE ACETATE SUSPENSION
(Solid line from Higuchi-Hiestand Model)

particle size distribution for both products does not predict this difference.

An apparent limitation associated with model application to commercial products is the aspect of manufacturing procedures for a product (i.e., process variables) and how these procedures differ for another product. For example, the difference in dissolution performance between Products I and II may be related to the process used for the milling of the prednisolone acetate for Product II, which may have generated micronized particles energetically[11,12] and geometrically[13] different from the micronization process used for Product I. Therefore, without a knowledge of the manner in which a drug is processed, there is a limit to the conclusions that can be drawn when model testing commercially formulated drug products. Despite this, it is of interest to note that the Higuchi-Hiestand model still provides a reasonable description of drug dissolution kinetics of Products I and II based on particle size distributions.

The dissolution profile for Product III is given in Figure 4. The dissolution of Product III is slower than that of Product I or II, and the time axis in Figure 4 has been expanded accordingly. For example, the T_{50} for Product III is 245 seconds compared to a T_{50} of 110 seconds for Product I. This slower dissolution appears to be related to the particle size distribution. A comparison of the particle size histograms of the three products (Figure 1) shows that the range of particle sizes and the mean particle size (9.60 microns) for Product III are greater than for Products I and II (4.48 and 4.95 microns, respectively). In particular, the volume of particles larger than 10 microns in radius for Product III is significantly increased (20% vs. 2.5% - 5%). The presence of these large drug particles seem to be reflected in a more extended release of Product III with respect to time.

For Product III, the best approximated dissolution profile to the experimental data, using the Higuchi-Hiestand model, gives a K value of 6.86×10^{-10} cm^2/sec, which is 5.2 times faster than theory predicts. The calculated curve for Product III differs in its closeness of approximation to each experimental point throughout the dissolution profile, as evidenced by a sum of squares value of 10.3×10^{-3} ($n = 12$). A consideration of the particle size distribution for Product III (Figure 1) verifies that the shape of the distribution is bimodal rather than symmetrical. The kinetics of release for this type of particle distribution may be less predictable than for a symmetrical distribution in which the mean particle radius characterizes that for the particle population. The possibility also exists that those particles 10 microns or larger in radius (20% of Product III particle population, by volume) may initially dissolve as a function of both diffusional and convective effects. These observations support the significance of an appreciation of the underlying particle size distribution for a drug sample when the goal is characterization of drug release rate kinetics.

The results of this study demonstrate that diffusion based dissolution models can be applied to describing dissolution

kinetics of commercially formulated drug suspensions. This model based approach integrates physicochemical properties of the drug with particle size distribution characteristics of the formulation as important determinants of dissolution performance. The resulting analysis describes the dissolution profile with a single value via the dissolution rate constant. This analysis can be useful during the formulation development phase to provide for predetermined dissolution performance, as an evaluative tool for quality assurance purposes, and for correlating in-vitro and in-vivo product performance.

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APPENDIX

PREDNISOLONE ACETATE SUSPENSIONS
COMMERCIAL INJECTABLE FORMULATIONS

Products I[a] and II[b] - Each ml contains:

Active: Prednisolone Acetate	25 mg
Inactives: Polysorbate 80	2 mg
Sodium Carboxymethylcellulose	1 mg
Sodium Chloride	9 mg
Preservative: Benzyl Alcohol	9 mg
Solvent: Water for Injection	q.s.

[a] (Buffered with Sodium Acetate and Acetic Acid)
[b] (pH adjustment with Sodium Phosphate and Citric Acid)

Product III - Each ml contains:

Active: Prednisolone Acetate	25 mg
Inactives: Methylcellulose	**0.25 mg**
Sodium Citrate	30 mg
Preservatives: Benzyl Alcohol	9 mg
Methylparaben	**1.8 mg**
Propylparaben	**0.2 mg**
Solvent: Water for Injection	q.s.

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