Precorneal Retention of Topically Instilled Micronized Particles

Keyphrases □ Micronized particles—precorneal retention, effect of particle size □ Ophthalmic preparations—micronized particles, precorneal retention, effect of particle size

To the Editor:

Aqueous suspensions of micronized drugs are commonly used for topical delivery of low-solubility therapeutic agents to the eye. Previous work was performed to assess the *in vivo* performance of ocular suspensions (1–4), but these studies were primarily drug oriented; they did not quantitate the effects of the physical aspects of the dosage form itself. Parameters specifically important for an ophthalmic suspension include intrinsic solubility, dissolution rate, and particle size.

The particle size of a suspended drug determines the surface area available for dissolution of the drug into the tears and also largely determines the irritation potential of the dosing system. Irritation can cause excessive tearing and accelerated drainage of the instilled dose. To minimize this irritation potential, ophthalmic suspensions generally are prepared using various cost-increasing micronization techniques. This report presents recent preliminary data on the behavior of micronized particles in the precorneal area of the eye and demonstrates the influence of particle size on ocular retention.

Male albino rabbits were used for the particle dynamics studies since most previous ocular work was performed with this species. The animals were preconditioned to sit motionless in specially designed wooden boxes. A normal upright posture was maintained, and local or general anesthetics were not used due to their known effects on tear dynamics (5).

A topical dose of an aqueous suspension containing radiolabeled microspheres[1] was placed carefully into the ocular sac along the lower lid margin using a micropipet. The normal response of the animal is to blink upon instillation, so no further manual mixing or blinking was attempted since it might abnormally force a portion of the dose down the nasolacrimal duct. Immediately after dosing, a γ-probe[2] was positioned to cover the precorneal area without touching the animal; drainage loss and retention of the labeled particles were monitored as a function of time by external scintigraphy[3]. Animals were watched closely by a technician, and all head movements and blinking were recorded carefully. Head movement terminated an individual run due to alteration of the spacial relationship of the precorneal microsphere pool and the monitoring probe.

The results of the studies using 3- and 25-μm particles are shown in Fig. 1. The marked dependence of particle retention on both dosing volume and particle size is readily apparent from these data. Immediately upon instillation of a 3% (w/v) suspension of 3-μm spheres, a washout process swept away a fraction of the dose. Since the duration of this washout phase was dependent on the volume instilled, the percent retention for each dosing volume was different and decreased as the volume was increased. However, since the total number of spheres instilled also varied with the dosing volume, it was not sufficient simply to consider percent retention as a measure of the volume effect as illustrated by the data presented in Table I.

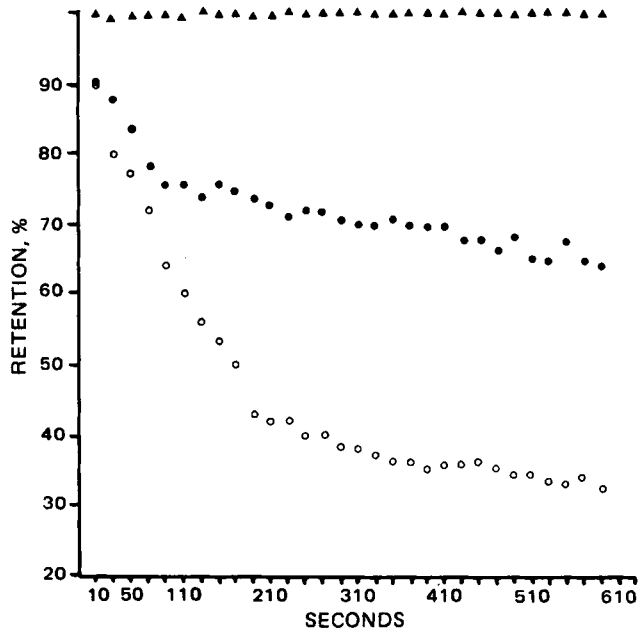

Figure 1—*Precorneal retention of topically instilled micronized particles. Key:* ●, *25-μl dose of 3% (w/v) 3-μm suspension;* ○, *50-μl dose of 3% (w/v) 3-μm suspension; and* ▲, *25- and 50-μl doses of 3% (w/v) 25-μm suspension (both dosing volumes gave virtually identical curves).*

It is clear from this analysis that the twofold increase in percent retention for the 25-μl dose compared with the 50-μl dose exactly offset the twofold sphere number difference between the two dosing volumes. As a result, the total number of spheres retained, as represented by the plateau region in Fig. 1, was the same. It would be tempting to attribute this effect to a maximum surface coverage limit for the conjunctival sac, but this cannot be stated with certainty. Theoretically, if such were the case, a 10-μl dose of the 3-μm suspension should give 100% retention since the total number of spheres instilled would be less than the plateau value for the larger doses. However, the data (Table I) show that the 3-μm spheres still suffered significant washout loss before being deposited within the protective folds of the conjunctiva.

The data for the 25-μm particles (Fig. 1) strikingly contrast with those for the smaller particles. Particle re-

Table I—Ocular Retention of a 3% (w/v) Suspension of 3-μm Particles as a Function of the Dosing Volume

Dose Volume, μl	Milligrams of Spheres	Total Number of Spheres	Percent Retention	Number Retained
50	1.5	8.6×10^7	33	2.8×10^7
25	0.75	4.3×10^7	65	2.8×10^7
10	0.3	1.7×10^7	70	1.2×10^7

[1] Tracer microsphere, Medical Products Division, 3M Co., St. Paul, MN 55101. Radiolabeled microspheres are polystyrene spheres that have been sized under rigid control standards, made radioactive, and annealed to seal radioactivity so that no leaching occurs. The microspheres may be obtained in a range of specific diameters labeled with various isotopes. The microspheres used in the current studies were 3.2 ± 0.6 and 25.7 ± 1.2 μm with a ^{141}Ce label, an isotope with a half-life of 32 days and 145 kev γ-energy. For these initial studies, the spheres were simply suspended in isotonic saline.

[2] Sodium iodide crystal (1.9 × 5.1 cm), TASK 5, Packard Instrument Co., Downers Grove, IL 60515.

[3] Model 9012A multichannel analyzer, Packard Instrument Co., Downers Grove, IL 60515.

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tention was rapid, complete, and independent of the dosing volume up to 50 μl, which is about the limit for a rabbit eye without spillage over the lids. Presumably, the larger diameter and greater particle mass resulted in faster deposition so that the suspending vehicle was drained away independently of the particles. The possibility that the observed retention for the larger particles was due to physical obstruction of the drainage apparatus was checked by subsequent instillation of a radioactive solution of [^{67}Ga]gallium citrate. The mean drainage rate constant obtained for a 25-μl dose of this solution in the presence of the 25-μm spheres was 0.52 min^{-1}, and this value corresponds well with the normal value of 0.545 min^{-1} reported previously for the rabbit (5). Particle size clearly plays a significant role in the rate and extent of particle retention for ophthalmic suspensions.

Studies also were carried out beyond the times indicated by Fig. 1. Only the early postinstillation time intervals are shown to define the washout process clearly. Individual runs lasting several hours were performed, and the presence of particles in the conjunctival sac was demonstrated for at least 12 hr. However, studies are continuing to determine the precise kinetics of the gradual loss of particles that follows the initial washout process, particularly for the 3-μm particles. Preliminary evidence shows that blinking and the associated movement of the tear film play a major role in redistributing small particles within the ocular sac. A blink normally pulls a fresh layer of the precorneal film up from the conjunctival sac and over the corneal surface. Lighter particles are pulled up with the film, and this process leads to gradual loss *via* the drainage apparatus during normal tear turnover.

The data from these studies indicate that a lower limit probably exists for particle-size retention in the eye, in addition to the previously recognized upper limit for irritation. This evidence suggests that caution should be used regarding the extent to which the particle size is reduced for such systems and also may explain the recently documented successes of so-called "economy suspensions," systems characterized by somewhat larger particle sizes than more traditional ophthalmic microsuspensions. Presumably, the smallest particles of the distribution range of a micronized suspension are lost rapidly with the washout of the suspending vehicle and contribute minimally to the ocular drug levels. Thus, the observed *in vivo* performance of an ophthalmic suspension probably is due mainly to the larger particles in the size distribution. Further studies are being conducted to establish more definitively the role of particle size for ocular retention and the influences of suspension concentration and vehicle pH.

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Half-Life of *N*-Acetylprocainamide in Rats

Keyphrases □ Procainamide—metabolism to *N*-acetylprocainamide, half-life of *N*-acetylprocainamide in rats □ *N*-Acetylprocainamide—half-life in rats □ Antiarrhythmic agents—*N*-acetylprocainamide, half-life in rats

To the Editor:

Procainamide is eliminated from the body by renal excretion as unchanged drug and through metabolism to *N*-acetylprocainamide. This metabolite has been shown to have antiarrhythmic activity in animals (1, 2) and humans (3, 4) and is eliminated from the body by urinary excretion. Many patients receiving procainamide chronically have shown plasma levels of *N*-acetylprocainamide in excess of the unmetabolized drug (5).

A most significant therapeutic advantage of *N*-acetylprocainamide is that it does not cause development of lupus erythematosus in patients (6). Additionally, the biological half-life of *N*-acetylprocainamide in humans is more than twice that of procainamide (7, 8), which allows less frequent dosing. We showed previously that *N*-acetylprocainamide decreased the heart rate in rats when the plasma concentration was 16.8 μg/ml, which is quite similar to the therapeutic concentrations in humans (9).

Schneck *et al.* (10) investigated the disposition of procainamide and *N*-acetylprocainamide in rats and found biological half-lives of 55 and 51 min, respectively. These results are in contrast to the data obtained in our laboratory. Therefore, the purpose of this communication is to report our preliminary results showing that the half-life of *N*-acetylprocainamide is two to three times longer than that of procainamide in the same rat and that the disposition of both drugs is qualitatively similar to that in humans.

Eight male Charles River[1] rats, 250–450 g, were selected. A cannula was inserted surgically into the jugular vein of each rat 1 day before the experiment (11). Procainamide hydrochloride (75 mg/kg) and *N*-acetylprocainamide hydrochloride (86 mg/kg) were administered intravenously through the cannula in a randomized crossover design. A 3-day washout period was allowed between administration of the two drugs.

Serial blood samples (0.4 ml) were withdrawn at 0 (just before drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hr following dosing, and the plasma was separated immediately. Urine and feces were collected for 48 hr. The concentrations of procainamide and *N*-acetylprocainamide in plasma and urine were determined by a specific high-pressure liquid chromatographic method (12). Plasma concentrations of the unchanged procainamide and *N*-acetylprocainamide were fitted to one-and two-compartment open models, respectively, using a nonlinear re-

[1] Charles River Breeding Laboratories, Wilmington, Mass.

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