Introduction

Most ophthalmic preparations containing corticosteroids are suspension formulations in which the active drug substance (e.g., prednisolone acetate) is suspended in a preserved, buffered, aqueous vehicle. The ability to deliver uniform dosages of suspension formulations has been studied both from a clinical (Raizman, et al.) and industry (Roberts and Nelson) perspectives. Factors such as agglomeration, and caking have been shown to affect the ability to resuspend prednisolone acetate suspensions; and lack of adequate resuspension can compromise dose uniformity. Suspension formulations all have a “shake well before use” instruction, but shaking compliance by patients has been estimated to be only 37% (Apt, et al.). Recently, a novel, stereo, defluorinated ophthalmic emulsion (0.05%), has been introduced in an emulsion formulation (Durezol™, Sirion Therapeutics, Tampa, FL). The dose uniformity of an emulsion formulation has not been reported. Presumably, since the drug is dissolved in the oil phase of the emulsion and the emulsified oil droplets are submicron in size and do not coalesce, mixing prior to instillation is not necessary to achieve adequate dose uniformity.

The aim of the current study is to compare the dose uniformity of prednisolone acetate suspension preparations to an emulsion formulation under different simulated patient usage conditions.

Study Design

Generic prednisolone acetate ophthalmic suspension (USP) 1% (Falcon Pharmaceuticals, Ltd., Fort Worth, TX), Pred Forte prednisolone acetate ophthalmic suspension (USP) 1% (Allergan, Inc., Irvine, CA), and Durezol were evaluated in this study. The effects of orientation during storage, shaking intensity, and shaking duration on the uniformity of dispensed drops were determined. In each case, a bottle was stored in a defined orientation for 12 hours. Following storage, the bottle was shaken (using a wrist-action mechanical shaker) or not according to the study design (see below).

Storage orientation

<table>
<thead>
<tr>
<th>Shaken or not</th>
<th>Shaking speed</th>
<th>Shaking duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upright</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Inverted</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Upright</td>
<td>Slow</td>
<td>5 sec</td>
</tr>
<tr>
<td>Upright</td>
<td>Fast</td>
<td>3 cm amplitude</td>
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</tbody>
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After shaking, 2 drops were dispensed into a tared glass vial, this was repeated at 4-hour intervals each day, simulating O/E patient dosing. The storage/dispensing regimen was repeated each day until the bottle was emptied or no additional material could be dispensed. On days 1, 2, 3, 5, and 15 the drug content from each of the 4 dispensing procedures was analyzed. On the other days, only the first and fourth of the four dispensed samples were analyzed. The drug content was analyzed by a validated HPLC assay and the results reported as percent label claim.

Dose uniformity of prednisolone acetate ophthalmic suspensions compared to Durezol™ (difluprednate ophthalmic emulsion), 0.05%

Results

The dose uniformity of each product after inverted bottle storage without shaking prior to dispensing is shown in Figure 1. As expected, when the bottle is stored in an inverted position, the suspended particles settle in the tip and are dispensed in high concentration early, resulting in a high potency (max = 212% of label claim) in generic prednisolone acetate (PA) suspension. Pred Forte (PF) and PA also exhibited significant variation (range = 19% to 721%, respectively). In each case, the suspension formulations trended from high potency to low potency as the bottle was consumed. Essentially no drug remained in the bottles containing suspensions in the final 25% of study period. The emulsion product (Durezol) provided excellent dose uniformity (max = 95.5%, min = 96.2%, range = 7.3%), indicating the emulsion remained stable and no separation of the oil and aqueous phases occurred.

A different trend in dose uniformity was observed in suspension formulations when the bottles were stored upright without shaking prior to dispensing (other than inverting to dispense the drops). In Figure 2, the suspension formulations are compared to the Durezol emulsion. Again, the uniformity of the Durezol emulsion was excellent at all time points, while the suspension formulations, especially the generic PA product, showed a trend from low potency to high potency. In the generic PA, values as high as 230% of label claim were observed with excessive variation (range = 225%). Even when the bottles were shaken at slow speed for 5 seconds prior to dispensing (Figure 3), the low potency to high potency trend was observed in the generic PA product but was not apparent in the PF product. PF displayed a range of 26% (max = 312%, min = 51%) compared to PA, where the range was 39% (max = 155%, min = 12%). In all cases, the Durezol emulsion displayed very consistent dose uniformity.

The effect of shaking speed was most pronounced in the generic PA product, where slow shaking for 5 min resulted in the same low to high trend previously observed (Figure 4), but an interesting trend was seen with fast shaking for 5 min in both PA and PF (Figures 4 and 5). After shaking for 5 minutes at high speed, better uniformity was observed, the overall potency, however, was significantly higher. The average potency for PA with fast shaking was 113% of label claim (max = 121%, min = 109%, range = 12%), compared to an average of 104% of label claim (max = 155%, min = 18%, range = 137%) seen with slow shaking for 5 minutes. It is unclear why the values observed with fast shaking were uniformly high and above label claim with no values found below label claim. It is possible the drop tip became clogged during dosing and some low potency material actually remained in the bottle but was not analyzed. Shaking speed and duration had no effect on the Durezol emulsion, where all data points fell within the range of 225%.

Conclusions

Durezol exhibited excellent dosage uniformity under all conditions studied, confirming there is no need to shake this product before use. A general trend of high potency at the beginning of use was observed in both suspension formulations when the bottle was stored inverted and not shaken before dispensing. Extreme variation in uniformity was observed with suspension material in the beginning of use of a bottle and near-zero potency at the end of bottle use.

A general trend of low potency to high potency was observed in prednisolone acetate suspensions when the bottles were stored and dispensed in a manner similar to actual patient usage. This was particularly evident with the generic PA. Clinically, better post-surgical outcomes have been described in patients using PF compared to generic PA. The results presented here provide evidence of both extreme variation in drug concentration between doses and a trend from low to high dosing over the time period similar to actual patient usage.

Shaking speed had a pronounced effect on dosage uniformity of the suspension products, particularly generic PA. Potency was observed to be higher with fast shaking in both prednisolone acetate suspensions. We hypothesize this is a result of foam formation generated by the rapid shaking motion and benzalkonium chloride preservative. The actual mass of each dispensed drop was lower and the drug particles may have partitioned in the foam, resulting in higher potency. The bottles presumed to be empty may have had subpotent product left, but this was never analyzed.

References