Letters to the Editor

Off-Label Antibiotic Preparation

Dear Editor:
Sterile ophthalmic injections with 2 antibiotics (ceftazidime and vancomycin) and 1 glucocorticoid (dexamethasone) are used at University Hospital of Geneva in some patients with infectious complications after intraocular surgeries. This is an off-label indication. They are administered as intravitreal injections and need to be prepared just before utilization, because the substances are unstable in aqueous solution.1 For patient safety, the preparation must be done in a sterile environment (clean rooms) in the pharmacy, which receives these prescriptions as emergency requests. To improve the preparation’s safety and medicines’ availability, it was decided to prepare in advance a series of ophthalmic syringes, freeze them, and stock them in a deep freezer (<−18°C). Previous stability studies offer information about freezing–thawing procedures and storage of these drugs,2–6 but no data were available concerning the stability of ophthalmic injections in aqueous humour–like solutions such as balanced salt solution (BSS).

One hundred thirty syringes of 1 ml of each substance were prepared under a good manufacturing practices class A laminar-airflow hood (class B clean room background): ceftazidime (Fortam, GlaxoSmithKline, Munchenbuchsee, Switzerland; 500 mg) and vancomycin (Vancocin, Eli Lilly & Co., Indianapolis, IN; 500 mg) were reconstituted and diluted with artificial aqueous humor solution (BSS) (intravitreal injection) to obtain final concentrations of 22.5 mg/ml and 10 mg/ml, respectively; an aqueous solution of dexamethasone (Méphamésone, Mepha Pharma AG, Aesch, Switzerland)4 was tested at a concentration of 4 mg/ml. The 3 solutions were then filtered for sterilization on a 0.22-μm Minisart filter (Sartorious AG, Goettingen, Germany). Analyses were performed on 7 syringes of each drug immediately after preparation: high-performance liquid chromatography assays, determination of pH and osmolarity, European Pharmacopoeia sterility test, and limulus test for the control of endotoxins. Obtained results were considered as reference values (100%) of day 0. A stability-indicating high-performance liquid chromatography method of dosage was previously developed and validated for each substance in our laboratory, using the STP Pharma Practiques_13 (2003) protocol (p1–138). The linearity and precision (intraday and interday assay variability) of the 3 methods were satisfactory (Table 1 [available at http://aaojournal.org]).

The rest of the prepared syringes were frozen at <−18°C for 6 months. During this period, each 15th day in the 3 first months and every 30 days during the 3 last months, 7 syringes of each substance were thawed by keeping them for 20 minutes at room temperature. The same analyses described above (high-performance liquid chromatography assay, pH, osmolarity, sterility, and endotoxin control) were performed. The mean concentration of the active ingredient was calculated from 3 determinations for each substance at different sampling times. The solutions were considered stable when the concentrations obtained were between 90% and 110% of their initial values.

During the stability study, the 3 substance concentrations did not vary more than 5% from the initial values on day 0, with one exception: vancomycin (9%) on day 15 (Fig 1 [available at http://aaojournal.org]). This difference could be caused by a time delay between thawing the syringes and preparing the vials. A study at room temperature was developed to test the stability after thawing, and it indicated that the 3 products were chemically stable for at least 6 hours.

No breakdown product was detected in any assay. The pH and osmolarity remained stable throughout the study period. For each tested drug—ceftazidime, vancomycin, and dexamethasone, respectively—the pH values were comprised in the intervals 6.5 to 7.1, 6.0 to 6.1, and 8.5 to 8.9, and the osmolarity values were comprised in the intervals 316 to 346, 200 to 215.5, and 360 to 393 milliosmole per kilogram. These values were compatible with intravitreal administration.7 All the syringes were sterile for the considered period, and no presence of endotoxins was identified.

The results of the present study demonstrate that the ready-to-use injectable syringes of ceftazidime, vancomycin, and dexamethasone are stable after being frozen for 6 months and thawed before analyses. They maintain a stable concentration, pH, osmolarity, and sterility.

Our approach has some important advantages. First, the possibility to create a stock of ophthalmic injections makes them readily available for administration to patients. As such, it improves drug availability. Also, it allows greater efficiency for the pharmacy because emergent requests for preparation are no longer needed. There are important disadvantages because our approach may not satisfy local regulatory requirements and our testing is not as detailed or complete as stability tests required by many regulatory agencies.

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References
Table 1. Validation Results of the Ceftazidime, Vancomycin, and Dexamethasone Assays

<table>
<thead>
<tr>
<th>Validation Parameters</th>
<th>Ceftazidime</th>
<th>Vancomycin</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient $R^2$</td>
<td>0.9994</td>
<td>0.9988</td>
<td>0.9981</td>
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<tr>
<td>Recovery and interval of confidence</td>
<td>100.7±2.9%</td>
<td>102.3±4.5%</td>
<td>100.8±3.9%</td>
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<tr>
<td>Intraday precision</td>
<td>0.73%</td>
<td>1.53%</td>
<td>1.76%</td>
</tr>
<tr>
<td>Interday precision</td>
<td>1.3%</td>
<td>2.03%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Figure 1. Stability study results.