SOLUTIONS}

When the environment in which the pump is to be used differs significantly from that of mammalian body temperature (37°C) and osmolality (310 milliosmols/l), the pumping rate of ALZET pumps will be altered. To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI.

ALZET Mini-Osmotic Pumps, Model 2004, should be removed upon completion of the drug delivery duration or by day 44 after implantation. After this time, due to continual attraction of water into the pump, if the pump is not reconstituted to its concentrated salt solution, resulting in local irritation around the pump. (*This expiration date is calculated based on the nominal duration of delivery. Refer to the equation in Section VI, part C to calculate the exact delivery duration and maximum expiration date for this lot of mini-osmotic pumps."

* Via a catheter, ALZET pumps can be used to deliver substances to the venous or arterial circulation, into the brain, or into any organ, tumor, or solid tissue. (For instructions on how to prepare the pump in vitro for these applications, refer to Section VII.)

** III. Instructions for Filling ALZET Mini-Osmotic Pumps

I. Technical Description of the ALZET Mini-Osmotic Pump Model 2004

A. Complete Mini-Osmotic Pump System with Flow Moderator in Place

1. Nominal Performance (at 37°C)

<table>
<thead>
<tr>
<th>Component</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pumping Rate</td>
<td>0.25 μl/hr</td>
</tr>
<tr>
<td>Duration</td>
<td>28 days</td>
</tr>
<tr>
<td>Reservoir Volume</td>
<td>200 μl</td>
</tr>
</tbody>
</table>

The nominal performance is a target for all pumps manufactured. Individual lots of pumps may vary from this target within limits. The actual pumping rate and fill volume of this particular lot (derived by statistical testing) are listed with the lot specifications on the top of this instruction sheet.

II. Dimensions, Overall

<table>
<thead>
<tr>
<th>Component</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>3.0 cm</td>
</tr>
<tr>
<td>Diameter</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>Weight (empty)</td>
<td>1.1 g</td>
</tr>
<tr>
<td>Total Displaced Volume</td>
<td>1.0 ml</td>
</tr>
</tbody>
</table>

III. Instructions for Filling ALZET Mini-Osmotic Pumps

1. If you desire the pump to start immediately, are working with a viscous solution, or if you wish to attach a catheter, initiate the pump in warm saline at 37°C for at least 40 hours. (Refer to Section V for complete instructions.)

2. The drug to be delivered is stable in the vehicle solution at 37°C for 21 days. The vehicle-drug combination to be delivered is compatible with the pump material. Caution must be taken to ensure the chosen solvent is also biocompatible with tissues and fluids at the site of administration.

3. Good sterile technique is used during the filling, handling and storage of ALZET pumps. The pumps are compatible with aqueous solutions, dilute acids and bases, dilute or low concentrations of DSMO and alcohol, and up to 50% glycerol. ALZET pumps are not compatible with aliphatic and aromatic hydrocarbons, such as heptane, toluene, xylene or any other solvents known to be incompatible with the pump.

4. The pumps are compatible with solvents known to be compatible with the pump.

5. Filters, EMD Millipore Headquarters, 290 Concord Road, Billerica, MA 01821, 978-452-4232, are recommended for these applications, refer to Section VII for instructions on how to prepare the pump in vitro for these applications.

6. The pumps are compatible with saline, isopropanol and alcohols. The pumps are not compatible with acetone, hexane, heptane, toluene, xylene or any other solvents known to be incompatible with the pump.

7. When the environment in which the pump is to be used differs significantly from that of mammalian body temperature (37°C) and osmolality (310 milliosmols/l), the pumping rate of ALZET pumps will be altered. To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI.

8. The mass rate of drug infusion is calculated using the following equation:

\[
\text{q} = \frac{\text{P}}{\text{T}}
\]

Where \( q \) is the mass rate of drug infusion (μg/min), \( P \) is the pumping rate (μl/hr), and \( T \) is the time (hr).

** TABLE 1**

List of Solvents Compatible With the Reservoir Material of ALZET Mini-Osmotic Pumps

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Acetone</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Acetone-isooctane</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Toluene</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Xylene</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Methanol</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>Partially compatible</td>
</tr>
<tr>
<td>Water</td>
<td>Partially compatible</td>
</tr>
</tbody>
</table>

Note that the solvents listed above are known to be compatible with the reservoir material of the pump. Caution must be taken to ensure the chosen solvent is also biocompatible with tissues and fluids at the site of administration.
If the solvent you wish to use is not listed in Table 1, on an ALZET® catheter, or when viscous solutions are being pumped, place the prefilled pumps in 0.9% saline for at least 40 hours at 37°C to qualify the pumps. The variation in pumping rate is less than 10%, with a standard error of the mean of 5% in most cases. The variation in pumping rate is highly unpredictable. Also, solutions with precipitated active agent will not yield reliable results.

B. Determination of the Volume Pumped

1.  When the solvent you wish to use is not listed in Table 1.

2.  If the solvent you wish to use is not listed in Table 1, you may use the following steps to test your agent and the catheter tubing with an inside diameter (I.D.) of 0.03 inches. Polyethylene tubing, commonly called PE-60 (I.D. = 0.03 inches) or PE-50 (I.D. = 0.02 inches) is a good choice for most applications. After attachment, the catheter should cover the entire length of the stainless steel tube above the white flange.

3.  Fill the catheter and attached stainless steel tube using a syringe. Leave the syringe attached to the distal part of the catheter.

4.  Following the instructions above (Section VII), fill the ALZET pump.

5.  Insert the syringe for the entire time the pump is running. Insert a needle into the white flange and flush the surface with the pump. The syringe attached to the distal end of the catheter can now be removed.

6.  Place the pump on a level surface and allow it to pump for 40 hours for 30°C. This will allow the pump to begin operating before inflation, and it will minimize the chance of damage due to improper handling of the catheter. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

VIII. Verifying the Accuracy of ALZET Mini-Osmotic Pumps

To verify that experimental results are derived from continuous administration of drug solution, DURECT recommends that ALZET Mini-Osmotic Pump users verify the blood levels of drug at several points during the course of delivery. The specifications on the other side of this instruction sheet provide the basis for calculating the rate of delivery. If the blood level is not possible or is technically unusable, users should measure residual volume in the pump reservoir after expiration. Use a blunt tipped tubing and approximate solution from the pump reservoir.

Note: Placement of a partially empty or damaged pump cannot be used to determine the quantity of drug delivered because the pumping rate is dependent upon the void volume. Cutting open a spent pump is not a reliable means for verifying pumping performance.

A. Determination of Average Pumping Rate

The reservoir volume of ALZET mini-osmotic pumps is slightly larger than the volume pumped. The duration of drug delivery (in days) is calculated as

\[ \text{duration} = \text{volume pumped} / \text{average rate} \]

This calculation must be made before determining the average rate of delivery. The value obtained from this calculation is used to determine the average rate of delivery.

B. Determination of the In Vitro Pumping Rate

1. Place the pump in a 10 ml test tube filled with 7% of isotonic saline and pre-implanted at 37°C (± 0.5°C). Cap the tube to prevent evaporation.

2. Record the starting time of the incubation.

3. Transfer the ALZET pump to a new test tube filled with 7% of isotonic saline. (In this case, 12 hours). Record the precise time of the first and second test tubes before exchanging.

4. Repeat Step 5 for 28 days.

5. Analyze for the concentration of indicator in each test tube. Use a spectrophotometric analyzer (e.g., spectrophotometer) for analysis. This step was determined. After a 40 hour start-up transient, the rate falls rapidly to zero. This method of testing pumping rate of osmotic pumps is to measure their pumping rate in vivo in 37°C saline at 3°C (± 0.5°C). This in vitro method gives a good measure of reproducibility – the coefficient of variation of each pump's time-dependent pumping rate in this range is less than 10%.


IX. Additional Technical Information About ALZET Osmotic Pumps

A. Information on ALZET osmotic pumps and their uses is available through ALZET Technical Support. Through this complimentary service you can request:

• A Technical Information Manual
• A video of commonly used surgical implantation procedures
• Custom searches of the ALZET osmotic pump bibliography of publications
• Presentation materials for authors presenting their work
• Literature about ALZET mini-osmotic pumps, and other products.

To obtain any of these materials, or if you desire additional information, contact ALZET Technical Support.

ALZET Technical Support
DURECT Corporation
10240 Broad Road
Cupertino, CA 95014

800-692-5930 (U.S. and Canada) 808-387-4087 (Outside the U.S.) 408-149-5000 408-367-4036 (Outside the U.S.) 800-692-5930 (U.S. and Canada) 808-387-4087 (Outside the U.S.)
alzet@durect.com (e-mail)
www.alzet.com

W. Warranty

For a period of 12 months from date of shipment, DURECT warrants that ALZET pumps are precision drug administration tools. This section describes the detailed pumping parameters. You should perform testing on your own equipment using the testing procedure described below. The sole and exclusive remedy for any breach of warranty shall be

• Replacement of the ALZET pump for the first 30 days after receipt of the pump.

• A written instruction delivered with such Product.

DURECT CORPORATION

E. Catheter Inlet and Outlet Connections

1. Remove the transparent end-cap from the flow moderator, revealing a short, stainless steel tube protruding from the white plastic flange. The catheter, tubing, and other materials and workmanship, and will, on average, deliver its contents at the rate of self-discharge of the pump. When used in accordance with the written instructions delivered with such Product.

This WARRANTY IS VOID IN ALL OTHER COUNTRIES, EXCEPTED OR DEEMED TO BE IMPOSSIBLE OF PERFORMANCE. DURECT CORPORATION MAKES NO OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE, WHICH ARE HEREBY EXCLUDED. IN NO EVENT SHALL DURECT CORPORATION BE LIABLE FOR ANY DAMAGES, INCLUDING CONSEQUENTIAL DAMAGES. HOWEVER CAUSED, ON ANY THEORY OF LIABILITY, INCLUDING BUT NOT LIMITED TO, CONTRACT, TORT OR OTHER LIABILITY, WHETHER IN AN ACTION OF CONTRACT, TORT OR OTHERWISE, ARISING FROM THE USE OF THE PRODUCT.