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

ALZET osmotic pumps, Model 2ML1, should be removed upon completion of their delivery duration or by day 10 after implantation. After this time, due to the enclosed flow moderator inside the pump, it may swell and leak a concentrated salt solution, resulting in local irritation around the pump. (Refer to the equation in Section VI part A to calculate the exact delivery duration and maximum explanation date for this lot of osmotic pumps.)

Via a catheter, ALZET pumps can be used to deliver substances into the ventricle for intracerebral, into the brain, or into other body tissue, solid or tissue. (For instructions on how to prepare the pump for these applications, refer to Section VII.)

Correct operation of ALZET pumps can be verified by monitoring blood levels of drug during the course of the experiment, by determining the residual amount of solution remaining in the pump at the end of the experiment, or by testing in vitro. (Refer to Section VIII for a description of these verification techniques.)

III. Instructions for Filling ALZET Osmotic Pumps

It is essential that each pump is filled completely with solution and that correct filling is verified by the method detailed below. Air bubbles trapped in the pump reservoir or attempting to insert the flow moderator into the pump may result in unpredictable pumping rate fluctuations. Solutions should be at room temperature during filling.

DURECT recommends that good sterile technique be used during the filling and handling of ALZET pumps and during the surgical implantation procedure. If sterility of your solution is a concern, fill the pumps through a 0.22 µm syringe-end filter (e.g., Millex® GV, Millipore Corporate Headquarters 290 Concord Road, Billerica, MA 01821; 978-715-4321). During filling and implantation, ALZET pumps should be handled with surgical gloves. Skin oils in large quantity may interfere with the performance of a pump if the pump comes in contact with them. The pump assembly can also be widened slightly by being wiped with an aqueous solution of 70% isopropanol immediately before use. Do not soak the pump in 70% isopropanol.

Perform the following steps when filling ALZET pumps:

Step 1. Weigh the empty pump together with its flow moderator.

Step 2. Filling the pump is accomplished with a small syringe (3 ml) and the provided blunt-tipped, 25 gauge filling tube. Use of a larger syringe leads to rapid filling of the pump, which can produce bubbles inside, into the reservoir, or through the syringe and attach the filling tube. It is essential that the syringe and attached tube be held at a 90° angle.

Step 3. With the flow moderator removed, hold the pump in an upright position and insert the filling tube through the opening at the top of the pump. If it can go no further, this places the tip of the tube near the bottom of the pump reservoir.

Step 4. While the plunger of the syringe is still moving, hold the pump in an upright position. When the solution appears at the outlet, stop filling and carefully remove the tube.

Step 5. Wipe off the excess solution and insert the flow moderator while the white flange is flush with the pump. The insertion of the flow moderator will displace some of the solution from the filled pump. This overflow should be wiped off. To function properly, the flow moderator must be fully inserted into the body of the pump.

Step 6. Weigh the filled pump. The difference in the weights obtained in Steps 1 and 6 should be equal to the net weight of the solution loaded. For most dilute aqueous solutions, the weight in milligrams (mg) is approximately the same as the volume in microliters (µl). The fill volume should be over 90% of the Mean Fill Volume indicated in the lot specifications at the top of this instruction sheet. If so, the filled pump will be ready for use. If not, there may be some problems inside the pump. Evacuate the completely filled pump refill (Refst 1-6).

If back pressure is encountered, the filling tube can be cocked at a slight angle and the filling syringe slowly retracted, or by moving the filling tube back forth and forth, or by inserting and removing the flow moderator several times before inserting the filling tube.

If 80% of the syringe volume is filled, stop filling. The remaining volume of the reservoir should be tested at the lot specifications at the top of this instruction sheet, call ALZET Technical Information Services for assistance at 800-692-2990 (U.S. and Canada).

IV. Solvent and Agent Compatibility With ALZET Osmotic Pumps

The pumps are compatible with aqueous solutions, dilute acids and bases, dilute or low concentrations of DMSO and alcohol, and up to 100% propylene glycol or polyethylene glycol. ALZET pumps are not compatible with strong acids and basic hydrocarbons, such as heptane, toluene, and natural oils. Contact with such substances can result in a pump malfunction. Table 1 provides examples of commonly used solvents known to be compatible with the pump.

<table>
<thead>
<tr>
<th>Solvent/Agent</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids, with pH greater than 1.8</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Water, distilled</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Ethanol, up to 15% in water</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>DMSO, up to 50% in water or polyethylene glycol</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>DMSO, up to 50% in ethanol (± 15%) and water</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>culture media (1% benzyl alcohol as bacteriostatic)</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Cyclobetin</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Dextrose, up to 5%, in water or NaCl</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>N,N-Dimethyl formamide (DMF), up to 25% in water</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Polyethylene glycol, neat or in water</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Ring’s solution (with or without lactate)</td>
<td>Partially soluble or insoluble</td>
</tr>
<tr>
<td>Saline, 0.9% (or other aqueous salt solution)</td>
<td>Partially soluble or insoluble</td>
</tr>
</tbody>
</table>

Note: A solvent or agent may be compatible with the reservoir material of the pump. Caution must be taken to ensure the selected solvent is not biocompatible with tissues and fluids at the site of administration.
If the solvent you wish to use is not listed in Table 1, an ALZAID® chemical compatibility test kit is available to you to assess agent and solvent compatibility with ALZET pumps. The test provides a preliminary assessment of the pump component materials for testing your agents and vehicles before use with osmotic pumps. DURECT recommends the use of this test kit under the following circumstances:

1. When the solvent you wish to use does NOT appear in Table 1.
2. When the solvent is being used base-free.
3. When the agent is known to be tendentious to any of the plastic materials.

To order an ALZET test kit call, 877-822-5938 (toll-free in the U.S. and Canada).

A solution which generates gases within the pump during use makes the pumping rate highly unpredictable. Also, solutions with precipitated solute particles must be filtered properly. Only filter solutions to be used. Solutions which are filtering too slowly to fill the pump is being fill.

This equation is applicable only to the Model 2ML1. Note that as Q above 42°C have been found to cause fluctuating delivery rates and are not recommended. The equation is predictive within ±10%. Environmental temperatures can be used to determine the quantity of drug delivered because the pump imbibes saline. Opening a open pump is not a reliable means for verifying pumping performance.

A. Determination of Average Pumping Rate

The reservoir volume of ALZET® osmotic pumps is slightly larger than that required for their calculated pumping volume. Therefore, the pumping duration some of the drug solution will remain in the pump. This solution can be aspirated from the pump using the supplied blunt-tipped filling tube and a vacuum source. The volume of this solution can be used to estimate the pumping rate. This method is recommended for the accurate determination of the pumping rate.

B. Determination of the In Vitro Pumping Rate

ALZET pumps are supplied with a specified volume pumping rate determined in isotonic saline at 37°C (± 0.5°C). In the event that the user finds it necessary to test the pumping rate for the complete 7 days. As U.S. and Canada.

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