If you desire the pump to start immediately, are working with a viscous solution or a catheter, incubate the pre-filled pump in sterile saline at 37°C for at least 40 hours. (Refer to Section III for complete instructions.)

When the environment in which the pump is to be used is significantly different from normal mammalian body temperature (37°C) and osmolality (310 milliosmols/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 Vb.

ALZET Mini-Osmotic Pumps, Model 2004, should be removed upon completion of their stated delivery duration of osmotic pump implantation. After this time, due to continued attraction of water into the pump, it may leak and fail a concentrated salt solution, resulting in local irritation or an increased inflammatory exudate calculated based on nominal duration. Refer to the equation in Section Vb, part B, for complete instructions on how to determine the exact delivery duration and maximum osmolality conditions for any given osmotic pump.

II. Checklist for Satisfactory Performance of the ALZET Mini-Osmotic Pump

A. Dosage Calculations

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

\[ \text{Rate of infusion (\mu g/hr)} = \frac{\text{mass of infusion drug}}{\text{Volume of infused drug}} \]

where the volume rate of infusion drug is calculated from the following equation:

\[ \text{Rate of infusion (\mu g/hr)} = \frac{\text{mass of infusion drug}}{\text{Volume of infused drug}} \]

and the concentration of the infused drug is calculated from the following equation:

\[ \text{Concentration of infused drug} = \frac{\text{mass of infused drug}}{\text{Volume of infused drug}} \]

C. Administration of ALZET Mini-Osmotic Pumps

The vehicle-drug combination to be delivered is compatible with the guidelines.

Use the mean pumping rate and fill volume information specific to the pump model being used. ALZET pumps have been exposed to a sterilizing dose of radiation from a 137Cs source. DURECT recommends that good sterile technique be used when filling and handling of ALZET pumps and during the surgical implantation of the vehicle-drug combination to be delivered is compatible with the guidelines.

Good sterile technique is used during the filling, handling, and implantation of ALZET pumps. It is essential that each pump is filled completely with solution and that each filling is verified by monitoring and handling of ALZET pumps and during the surgical implantation of the vehicle-drug combination to be delivered is compatible with the guidelines.

III. Instructions for Filling ALZET Mini-Osmotic Pumps

It is essential that each pump is filled completely with solution and that each filling is verified by monitoring and handling of ALZET pumps and during the surgical implantation of the vehicle-drug combination to be delivered is compatible with the guidelines. (To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section Vb.)

Correct operation of ALZET pumps can be verified by monitoring the zero level of the fluid in the pump reservoir, by checking for a continuous delivery rate as determined by the amount of solution remaining in the pump at the end of its pumping period (Refer to Section VII for a description of these verification techniques.)

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, up to 25% in water. ALZET pumps are not compatible with aliphatic and acromatic 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 vehicles to be compatible with ALZET pumps.

V. 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, up to 25% in water. ALZET pumps are not compatible with aliphatic and acromatic 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 vehicles to be compatible with ALZET pumps.
Note that the solvents listed above are known to be compatible with the reservoir material of the pump. Caution must be taken to assure that no chosen solvents are incompatible with tissues and fluids at the site of administration.

If the solution you wish to use is not listed in Table 1, an ALZET® chemical compatibility test is recommended for you to assess and solvent compatibility with ALZET® pumps. The test provides you with the information that all of your chosen solvents are compatible with your pump systems and vehicles before use with osmotic pumps. DURECT strongly recommends not using any use of the solvents listed under the following circumstances:

1. When the solvent you wish to use does NOT appear in Table 1.
2. When the agent is in its free base form.
3. When the agent is known to be toxic to various polymeric materials.

To order an ALZET test kit, call 877-922-9338 (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 solutes must be prepared in order to preclude the risk of too high a room temperature when the pump is being filled.

ALZET® pumps are used to deliver concentrated homogenous viscous solutions with a viscosity of less than 100,000 centipoise. Suspensions may be used because the pump dilutes the suspension to form a solution. To ensure uniform delivery, suspensions must remain homogeneous throughout the duration of delivery.

V. Implantation of the ALZET Mini-Osmotic Pump In Vivo

The ALZET® Mini-Osmotic Pump can be implanted subcutaneously in an animal that weighs at least 20 grams. For subcutaneous placement, a small incision is made in the skin between the scapulae. Using a hemostat, a small skin incision is made to expose the subcutaneous connective tissues. The pump is inserted into the pocket with the flow moderator pointed away from the incision. The skin incision is then closed with wound clips or sutures. For intraperitoneal placement, make a small midline incision in the skin below the rib cage of an animal weighing at least 150 grams. Another small skin incision is made to expose the peritoneum. The incision is then closed, the inflow modulator is inserted, and then the skin incision is closed with either wound clips or sutures. Be sure to remove any care or back up on the tubing and release the tubing for delivery, or day 42 after implantation. (This expiration date is calculated based on normal diffusion. Refer to the equation in Section 4.C to calculate the exact delivery duration and maximum expiration date for this lot of osmotic pumps.)

For additional information and/or procedures, contact DURECT Technical Support at 800-692-2990 (U.S. and Canada). A video demonstrating several surgical implantation procedures is available at no charge.

6. Place the pump in sterile 0.9% saline at 37°C for 40 hours. This will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in 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 via ALZET® Mini-Osmotic pumps, DURECT recommends that the ALZET® pump users verify the blood levels of drug at several points during the course of infusion. In the event that determination of circulating blood levels at post-infusion points is critical to your research, we recommend using an in vitro assay to measure residual volume in the pump reservoir after use. Experimental use of the osmotic pumps in conjunction with the in vitro assay for estimating the pumping rate of osmotic pumps.

Note that the weight of a completely or partially discharged pump cannot be used to determine the quantity of drug delivered because it may be less than 10% of the delivered amount. Cutting open a spent pump is not a reliable means for verifying pumping rates.

A. Determination of Average Pumping Rate

The reservoir volume of mini-osmotic pumps is slightly larger than that required for any in vivo delivery (28 days). As a result, at the end of the pumping duration some of the drug solution will remain in the pump. To minimize error due to the pump from the supplied blunted-filling tubing and a 1 ml syringe. Recovery of the drug solution is performed by rinsing the reservoir with an additional solvent. The active agent in the solution which was recovered from the reservoir is analyzed by spectrophotometric analysis.

To calculate the average pumping rate, the difference between the amount of drug loaded and the residual amount in the pump is divided by the elapsed time.

B. Determination of the In Vitro Pumping Rate

All ALZET® pumps are provided with a specified pumping volume rate determined in isotonic saline at 37°C (±0.5°C). In the event that the user needs to verify the pumping rate, DURECT recommends that the following steps be taken:

Step 1. Prepare a solution of known concentration of an indicator dye in isotonic saline at a volume such that the pumping rate of the pump will be the basis for the pumping rate calculation. Therefore, the indicator dye solution is prepared by diluting an indicator dye in saline in a solution of the indicator in saline. (One such indicator is FD&C Blue #1 dye, available from Sigma Chemical Co., St. Louis, MO 63106; 1:400-325x10-4 x7470; catalog #5601.)

Step 2. Fill the ALZET pump with the indicator solution according to Section 4.B.

Step 3. Place the ALZET pump into a 10 ml test tube filled with 7 ml of isotonic saline and pre-incubated at 37°C (± 0.5°C). Cap the tube to prevent evaporation.

Step 4. Record the starting time of the incubation.

Step 5. Transfer the ALZET pump to a new test tube filled with 7 ml of isotonic saline and pre-incubated at 37°C (± 0.5°C). Cap the tube to prevent evaporation.

Step 6. Repeat Step 5 for 28 days.

Steps 7. Stop each time except for the time-in-between transfers. When the pump is to be used with a catheter, or when solutions are being delivered.

D. Determination of Pumping Duration

The duration of pumping can be computed from the following equation:

\[ D = \frac{V}{V_0} \]  

In this equation, \(D\) is duration in hours, \(V\) is the pump's reservoir volume in ml, and \(V_0\) is pumping rate in ml/hr as listed in the Actual List Specifications section.

E. Predicting Pump Performance Outside Mammalian Reservoirs

The pumping rate can be calculated to predict the pumping rate in heterogeneous animals or in those whose body fluids are not isotonic with mammals:

\[ Q = \frac{Q_0 \times (1 - 0.030 \times 0.050 + 0.03)}{1} \]  

Here \(Q\) is the specified pumping rate of the pumps at 37°C in ml/hr, \(Q_0\) is the rate of the pump at 37°C in ml/hr, \(D\) is the duration of pumping, \(V\) is the volume in ml, \(V_0\) is the volume in ml, \(T\) is the temperature of the pump in °C, and \(T_0\) is the temperature of the pump in °C.

F. Recovery of Drug Solution

1. Remove the translucent end-cap from the flow moderator, revealing the flange is flush with the surface of the pump. The syringe attached to the syringe tip is used to aspirate the pump as necessary.

2. Attach to the stainless steel tube a piece of polyethylene or vinyl catheter tubing with an inside diameter (I.D.) of 0.058 mm (0.02 - 0.03 inches). Polyethylene tubing, commonly called PE-60 (I.D. = 0.03 inches) is a good choice for most applications. After attachment, the catheter should fit snugly onto the length of the stainless steel tube above the white flange (about 3 mm).

3. Fit the catheter and attached stainless steel tube using a syringe. Leave the catheter in place until the distal end of the catheter can be removed.

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

5. Insert the flow modulator all the way into the pump until the white flange is flush with the end cap of the pump. The syringe attached to the distal end of the catheter can now be removed.

6. Place the pump in sterile 0.9% saline at 37°C for 40 hours. This will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the catheter. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

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