If you desire the pump to start immediately, are working with a viscous solution or pre-filled pump, perform the following:

- Let the pre-filled pump in sterile saline at 37°C for at least 4 to 6 hours preferably overnight. (Refer to Section VI part B for complete instructions.)

- When the environment in which the pump is to be used differs significantly from the associated in vitro verification temperature and osmolality conditions, refer to the equation in Section VI part D.

ALZET Micro-Osmotic Pumps, Model 1002, should be removed upon completion of their delivery duration or by day 21* after implantation. After the pump has been explanted, the actual pumping rate and fill volume can be determined by monitoring blood levels of the drug during the experiment, by determining the residual amount of drug remaining in the pump at the end of the experiment, or by testing the drug levels in the pump and refill at the end of their delivery duration or by day 21* after implantation. (Refer to Section VII for a description of these verification techniques.)

- In vitro.
- In local irritation around the pump. (*this explantation date is dependent upon completion of their delivery duration or by day 21* after implantation.)

- Place the syringe and attached tube be free of air bubbles.
- Place the fill tube near the solution reservoir.
- Draw the solution into the syringe and attach the fill tube. It is essential that the syringe and attached tube be free of air bubbles. If you wish to attach a catheter, incubate the pump and refill (Steps 1-6).
- Place the fill tube near the solution reservoir.
- Draw the solution into the syringe and attach the fill tube.
V. Implantation of the ALZET Micro-Osmotic Pump in Vivo

The ALZET micro-osmotic pump can be implanted subcutaneously in an animal or, following percutaneous placement, a small incision is made in the skin between the scapulae. Using sterile technique, locate the subcutaneous connective tissues and insert the catheter. Place the necessary pump component materials for testing your agents and administer the agent for which you are testing. Strongly recommend the use of this test kit under the following circumstances:

1. If the agent you wish to use is not listed in Table 1, an ALZET® chemical compatibility test kit is available to allow you to assess agent and solution compatibility. (See Table 2 and refer to the ALZET® test kit provided with the necessary pump component materials for testing your agents and solutions before proceeding.)

   a. If the test procedure strongly recommends the use of this test kit under the following circumstances:

   b. If the agent is not a free-base form.

   c. If the agent is known to bind tenaciously 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 gas within the pump during use makes the pump rate highly unpredictable. Also, solutions with precipitated solids may significantly reduce the total pump volume. To avoid these difficulties, it is recommended that you fill the pump with a solution that is sterile and isotonic to the albumin concentration of the host animal. Osmotic pumps containing non-isotonic solutions may cause serious health problems. Note that only the Model 1002 is applicable only to the Model 1002. Note that as Q decreases in proportion to the osmotic pressure (atm), the coefficient of variation of each pump’s time-dependent pumping rate highly unpredictable. Also, solutions with precipitated solids may significantly reduce the total pump volume. To avoid these difficulties, it is recommended that you fill the pump with a solution that is sterile and isotonic to the albumin concentration of the host animal. Osmotic pumps containing non-isotonic solutions may cause serious health problems. (Note that the solvents listed above are known to be compatible with the ALZET® pump.

3. Fill the catheter and attached stainless steel tube using a syringe. Leave the catheter adapter in the syringe, and then attach the catheter to the catheter adapter. Fill the catheter to operating pressure.

4. Following the instructions above (Section II), fill the ALZET pump. The flow moderator is already installed in the catheter.

   a. If the flow moderator all the way into the pump until the catheter is flush with the surface of the pump. The syringe attached to the distal end of the catheter can be now removed.

   b. Place the pump in sterile 0.9% saline at 37°C for at least 4–6 hours (overnight) to allow the pump to begin operating before implantation, and eliminate the chances of an occlusion or stenosing in the catheter. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

VII. Verifying the Accuracy of ALZET Micro-Osmotic Pumps

To verify that experimental results are derived from continuous administration of the drug solution, DURECT recommends that ALZET® pumps be filled with the agent and amount of solution indicated on the label on each pump (or on the pump package insert). This step is mandatory in all catheter applications. To determine the pump rate of an ALZET® micro-osmotic pump, calculate the volume pumped during each 48-hour period. To do this, place the prefilled pumps in 0.9% saline for at least 4–6 hours (overnight) to allow the pump to begin operating before implantation, and eliminate the chances of an occlusion or stenosing in the catheter. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

A. Determination of Average Pumping Rate

   1. Step 1. Prepare a solution of known concentration of an indicator dissolved in isotonic saline at 37°C. In the event that the user needs to know the pumping rate, DURECT recommends that the following steps be taken:

   2. Fill the ALZET pump with the indicator solution according to Section III. The method given a good measure of reproducibility – up to 10% in the subcutaneous placement.

   3. Place the ALZET pump into a 10 ml test tube prefilled with 71°C (or 37°C) 0.9% saline, at 37°C. Cap the tube to prevent evaporation.

   4. Record the starting time of the incubation.

   5. Step 1. Transfer the pump to a new test tube filled with 15 ml of isotonic saline at 37°C, or 0.9% saline, at 37°C. Record the precise time of the transfer and/or the time interval between transfers.

   6. Step 2. Repeat Step 1 for 14 days. Collect the infusate from the pump reservoir periodically during the course of infusion. In the event that determination of circulating blood drug concentration is required, the pump can be removed from the animal and the residual drug solution can be extracted from the reservoir with additional isotonic saline. To calculate the average pumping rate, the difference between the amount of drug infusate and the residual amount in the pump is divided by the elapsed time.

B. Determination of the In Vitro Pumping Rate

   1. Place the pump into a 10 ml test tube prefilled with 7°C (or 37°C) 0.9% saline. Cap the tube to prevent evaporation.

   2. Record the starting time of the incubation.

   3. Transfer the pump to a new test tube filled with 15 ml of isotonic saline at 3°C, or 0.9% saline, at 3°C. Record the precise time of the transfer and/or the time interval between transfers.

   4. Step 1. Prepare a solution of known concentration of an indicator dissolved in isotonic saline at 37°C. In the event that the user needs to know the pumping rate, DURECT recommends that the following steps be taken:

   5. Fill the ALZET pump with the indicator solution according to Section III. The method given a good measure of reproducibility – up to 10% in the subcutaneous placement.

   6. Step 2. Repeat Step 1 for 14 days. Collect the infusate from the pump reservoir periodically during the course of infusion. In the event that determination of circulating blood drug concentration is required, the pump can be removed from the animal and the residual drug solution can be extracted from the reservoir with additional isotonic saline. To calculate the average pumping rate, the difference between the amount of drug infusate and the residual amount in the pump is divided by the elapsed time.

VIII. Additional Technical Information About ALZET Osmotic Pumps

A wealth of information on ALZET® pumps and their uses is available through ALZET Technical Support. Through this complimentary service you can request:

• A wealth of information on ALZET® pumps and their uses is available through ALZET Technical Support. Through this complimentary service you can request:

   1. A video of commonly used surgical implantation procedures

   2. Presentation materials for authors presenting their work

   3. Information about ALZET Brain Infusion Kits, ALZET catheters and other products

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

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10200 El Camino Real
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408-865-1406 (Facsimile)
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408-865-1406 (Facsimile)

Information about ALZET Osmotic Pumps

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www.alzet.com
alzet@durect.com (e-mail)
408-865-1406 (Facsimile)

X. Warranty

For a period of 12 months from date of sale, DURECT warrants that the pumps shall be free from defects in materials and workmanship, and, in the event, deliver its stated releases at the rate and within the period indicated when used in accordance with the rate and within the period indicated when used in accordance with the manufacturer’s recommendations. DURECT warrants that the products which you have received are free from defects in materials and workmanship for a period of 12 months from date of sale. In the event that determination of circulating blood drug concentration is required, the pump can be removed from the animal and the residual drug solution can be extracted from the reservoir with additional isotonic saline. To calculate the average pumping rate, the difference between the amount of drug infusate and the residual amount in the pump is divided by the elapsed time.

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