Continuous Drug Infusion Model with an Implantable Osmotic Pump

Introduction

Implantable continuous infusion osmotic pumps have several applications in preclinical drug development. The pumps enable continuous, controlled dosing and thereby allow the achievement of steady state conditions and accurate compound delivery. The following are some of the applications of continuous infusion osmotic pumps.

- Preclinical studies of some therapeutic agents such as hormones and growth factors are challenging due to poor bioavailability. Implanted osmotic pumps can circumvent these difficulties and enable continued development of such therapeutic agents. Drugs with fast clearance rates require frequent dosing to maintain appropriate drug levels. With continuous drug infusion, steady state concentrations can be maintained obviating the need for frequent dosing.
- For therapeutic agents that have a narrow therapeutic index, continuous infusion can help to ensure that drug levels are maintained at therapeutic levels while avoiding potentially toxic concentrations.
- In cases where the pharmacokinetics of a drug is unknown, the use of implanted continuous infusion pumps can be useful in establishing required parameters.
- Implantable osmotic pumps can be used to compare the efficacy of drugs delivered by injection versus those given by continuous infusion. This may be especially important in the development of chemotherapeutic agents.
- Osmotic pumps such as those supplied by ALZET® can be connected to a catheter and thereby enable delivery of chemotherapeutic agents directly to a tumor.
- Continuous infusion can also be a useful to monitor cell proliferation in tissues over time using labeling agents such as bromodeoxyuridine. This method is frequently used to determine the carcinogenic potential of compounds. It has also been used to measure the chemotherapeutic drug efficacy in tumors. By combining the technique with a washout period, stem cell populations in different organs can be identified as long-term label retaining cells.
- The use of continuous infusion pumps can also enhance bio-luminescence imaging studies. The pumps enable continuous delivery of bio-luminescent substrates.

Continuous Drug Infusion Model

Noble Life Sciences has developed a model using implantable osmotic pumps for continuous drug infusion into mice or rats as part of preclinical development studies. Continuous infusion studies have been conducted with conventional mice, nude mice, NOD/SCID mice and rats. Many types of compounds, e.g., small molecules, peptides or proteins, can be loaded into ALZET® osmotic pumps. The pumps can then be implanted to provide continuous infusion and the rate of drug release can be controlled. The protocol outlined below was used to study plasma drug concentrations using two different formulations of the same compound.

Sample Protocol

The following is an example of a protocol for a pharmacokinetic study with seven-day continuous infusion using an osmotic pump connected to a jugular catheter in Sprague-Dawley rats to test two different formulations.

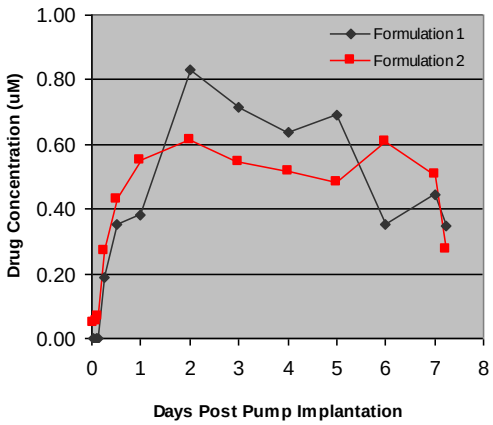
Twelve Sprague-Dawley rats were used in the study. Animals were double cannulated in both the jugular vein and aorta. ALZET® 2ML1 osmotic pumps were filled with the test compound in either of two different formulations and the concentration was adjusted to deliver 10mg/kg/day. Osmotic pumps were filled with test compound according to manufacturer's instructions and equilibrated in sterile normal saline at 37°C for 4 hours. Pumps were implanted under the skin mid-scapula on Day 1, attached to the jugular catheter, and the incision sealed with several stitches. Blood was sampled through the aortic catheter at 2,3,4,6,12,24,28 hours and then daily for seven days. On day 7, the pumps were removed and a final blood sample was collected 4 hours after the pumps were removed. The concentration of the drug in blood was determined using LC-MS.

Results

The concentration of the drug using either of the two formulations increased during the first 2-3 days after the osmotic pumps were implanted. See figure at right.

Subsequently drug levels reached a steady state from day 3 to day 6. Concentrations of the drug in formulation 1 reached higher levels than that with formulation 2.

Drug levels declined around day 6 with sharp declines noticed after pump removal.



Summary

Noble Life Sciences has both the surgical skill and the experience in pharmacokinetic studies to deliver your agent utilizing our continuous infusion protocols for preclinical drug development. Noble's continuous infusion capability is useful for a variety of studies:

- Oncology: For the study of chemotherapeutic agents, continuous drug infusion can be used to ensure that even slowly dividing cells in a tumor are exposed to the drug.
- Stem Cell Research: Continuous infusion of bromodeoxyuridine can be used to identify slowly dividing cells.
- Gene Transfection or Gene Silencing: Continuous infusion can ensure that all target cells receive the intended gene vector, siRNA or shRNA.
- Neuroscience Research: Studies can be facilitated by continuous infusion that allows direct delivery of substances to the brain, bypassing the blood-brain barrier.