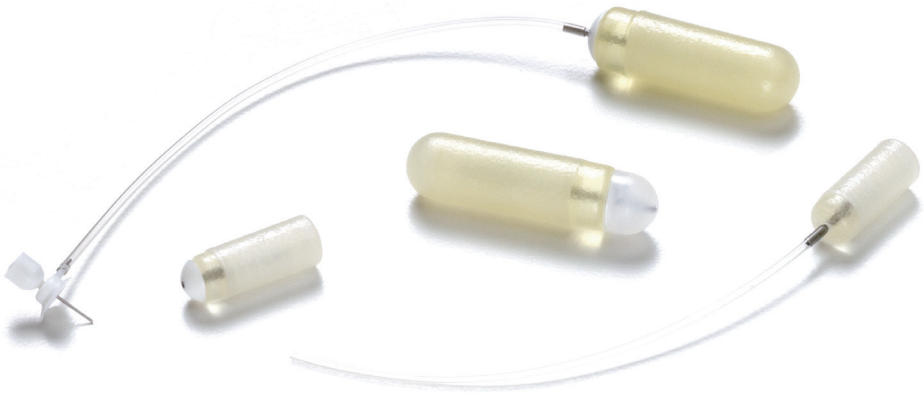
alzet
OSMOTIC PUMPS

NEUROSCIENCE RESEARCH

The blood-brain barrier (BBB) presents an impediment for effective delivery of agents to the central nervous system (CNS). For over 4 decades, ALZET® Osmotic Pumps have been used as a reliable and convenient tool to overcome the BBB and deliver agents directly to their site of action. These small, implantable pumps deliver a precise and continuous dose, without interference in elaborate behavioral testing, and without the stress associated with other methods requiring frequent animal handling.



The ability of ALZET pumps to deliver a compound directly into the brain avoids many of the complications related to bioavailability, side effects, and toxicity inherent with systemic delivery. These pumps are now an integral component in neuroscience research, as evidenced by the thousands of publications describing their use in studies on spinal cord injury, neurodegeneration, ischemia, depression, brain cancer, and more.

ALZET Pump Benefits

- Direct delivery across the blood-brain barrier
- Small size for implantation in mice or larger animals
- Continuous and controlled delivery of neuroactive agents
- Ideal for behavioral studies – no animal handling required during dosing
- Improved bioavailability of short half-life peptides and proteins
- Easy attachment to a catheter for delivery to the brain, spinal cord or peripheral nerves
- Reliable technology with over 21,500 publications
- Reduced drug toxicity and side effects
- Simple design and easy to use
- Convenient and cost-effective for chronic dosing of lab animals
- Automatic nighttime and weekend dosing
- Improved animal welfare

Neuroscience Research Applications

Models of Neurodegenerative disease

ALZET pumps have been used to facilitate the development of animal models of neurodegenerative disease, including Alzheimer's, Parkinson's and Huntington's. Their ability to provide a slow, continuous and chronic dose is favorable for sustaining a stable disease state over prolonged periods. *In vivo* models of Parkinson's have been produced by continuous administration of 6-hydroxydopamine (6-OHDA) into the striatum of rodents, cats, dogs, and monkeys, systemic infusion of the neurotoxin MPTP to mice or monkeys, and systemic rotenone dosing in rats and mice. Alzheimer's can be induced by ICV infusion of β-amyloid peptide to rats and mice using ALZET pumps. Models of Huntington's have been reproduced via continuous infusion of the mitochondrial toxin 3-nitropropionic acid in rodents and nonhuman primates. They have also been reproduced using excitotoxins such as kainic acid and quinolinic acids in rodents and nonhuman primates respectively. These established models display biochemical, behavioral and morphological characteristics of neurodegenerative disease states and facilitate the study of disease mechanisms and potential neuroprotective therapies.

Intrathecal delivery

Targeted delivery via the epidural or intrathecal space circumvents the blood-brain barrier, and can provide a means of delivery for analgesics or other compounds without the side effects associated with systemic administration. ALZET pumps are commonly used for intrathecal infusion of agents at low and constant rates to study axonal regeneration, hyperalgesia, antinociception, and other aspects of pain. A large body of work is also focused on the development of tolerance related to opiate treatment.

Targeting Peripheral Nerves

With relative ease, ALZET pumps can be connected to a catheter to enable continuous delivery of solutions directly to a nerve cuff or chamber. The ability to deliver peptides and other compounds to the desired site can amplify their effects, while minimizing widespread systemic side effects. The targeted delivery of tetrodotoxin with ALZET pumps blocks nerve conduction temporarily, which is useful when studying innervations and neuromuscular development. Controlled and localized administration of neurotrophins is also critical when studying nerve regeneration following injury.

Delayed CNS Delivery

ALZET pumps can be adapted to allow for a recovery period following surgery, such as after implantation of brain cannulae. In this application, the pump is filled with drug solution and attached to a length of catheter tubing filled with a vehicle control solution. A spacer substance, such as oil or sterile air, is placed between the control and drug solutions to prevent mixing. Upon implantation, the pump releases drug solution from the pump reservoir into the catheter tubing, displacing control solution from the catheter into the animal. Once all of the control solution is released, the drug solution reaches the end of the catheter and drug dosing begins.

Chronic Delivery

Chronic administration of several months or longer may be necessary to evaluate the long-term effects of test compounds *in vivo*, or to establish a stable animal model of disease. ALZET pumps offer a reliable and convenient alternative to frequent injections for chronic dosing of lab animals. Steady-state levels of therapeutic agents can be maintained in tissues or plasma for up to six weeks with a single pump, and the treatment duration can be extended for multiple months through serial implantation.

Selecting an Optimum Vehicle

Vehicle selection is an important consideration in compound administration to the CNS. Ideally, the vehicle should be biologically inert and have no toxic effect on the animal. Other factors to consider include compound solubility and stability, tissue compatibility, pH, viscosity, and sterility. Artificial cerebrospinal fluid (aCSF) is commonly used for administration of test agents to the CNS. A method for the preparation of aCSF is available on request. This solution closely matches the electrolyte concentrations and physiological compatibility of endogenous CSF.

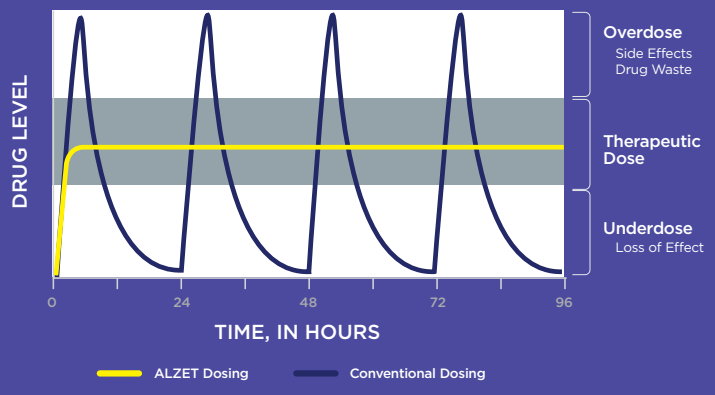
Neuroscience Research Publications

Therapeutic antibodies, enzyme inhibitors, antidepressants, anticonvulsants, dopaminergics, opioids, neuropeptides, neurotrophic factors, and nucleic acids are all examples of agents that have been successfully delivered via ALZET pumps. Below is a list of agents recently used in neuroscience studies.

Agent	Description
Antisense oligonucleotide	Single-stranded deoxyribonucleotide
Oxytocin	Neuropeptide
Letrozole	Aromatase enzyme inhibitor
Wortmannin	PI3K/Akt signaling inhibitor
Brain-derived neurotrophic factor	Growth factor
Fractalkine	Chemokine
QDMgTx	Fluorescent quantum dots bound to margatoxin
Tunicamycin	Endoplasmic reticulum stressor
Tetrodotoxin	Neurotoxin
Gap27	Cx43 mimetic peptide
XPro1595	Biologic mimetic
[D-Tyr^4]-melatonan II	Melanocortin receptor agonist
Pleiotrophin	Cationic glycosaminoglycan-binding cytokine and growth factor

The power of continuous delivery

Injections can result in great variations in serum and tissue concentrations. Immediately after injection, compound concentrations commonly exceed effective levels, resulting in overdosing and toxicity. Rapid clearance causes periods between injections wherein the compound is absent from serum and tissues, resulting in underdosing and lack of drug effect. ALZET pumps deliver compound solutions at controlled and predictable rates, ensuring that constant and optimum levels of test agents are maintained throughout the study duration.



Why neuroscience researchers use ALZET pumps in their studies

ALZET Benefit	Article Quote
Improve efficacy Reduce toxicity	"In our C9BAC mice, we were not able to safely perform ICV bolus injections with more than 10 nmol of LNA-modified ASO3 due to induction of severe motor phenotypes. To overcome this limitation, we used osmotic pumps to compare the potency of ASO3 and ASO5." *Tran et al. Nature Medicine 2022:28(1), 119.*
Bypass the BBB Reduce toxicity	"The mini-osmotic pump provides drug treatment directly to the brain and also bypasses the liver, thereby achieving the desired drug concentration in the glioma microenvironment while avoiding the use of high drug doses." *Wang et al. Journal of Neurosurgery 2018:128(3), 699*
Chronic treatment Constant drug levels Reduce stress	"We used micro-osmotic pump and ICV administration for chronic delivery of aCSF or AraC, which provided good control of drug concentration and continuous delivery without disturbing animals. This method also reduced the likelihood that treatment effects on sleep–wake function could be due to stress of daily or multiple IP injections or mechanical or inflammatory responses of the sites examined in this study due to local manipulation." *Kostin et al. Neuroscience 2019:404, 552.*
Targeted delivery Chronic treatment	"Collectively, these data support the utility of long-term CNO delivery in indwelling osmotic minipumps to activate DREADDs in vivo...Importantly, percentage theta power was further reduced in EC-Tau/hAPP mice following chronic hM4D$_i$ DREADDs activation." *Rodriguez et al. PLoS Biology 2020:18(8):e3000851, 17*

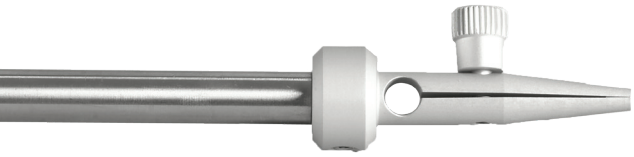
ALZET Products for Neuroscientists

ALZET Osmotic Pumps

Twelve pump models available in 3 different sizes, durations ranging from 1 day to 6 weeks, and various release rates.

Brain Infusion Kits

Designed for use with ALZET pumps, they are ideal for delivery to lateral ventricles and other brain regions in rats (BIK1 & 2) and mice (BIK3).



Cannula Holders

Designed to hold the removable tab on all ALZET brain cannulae, they facilitate stereotaxic placement of brain cannula to the skull of lab animals.

Rat & Mouse Intrathecal Catheters

These are constructed with high quality materials for increased patency and reduced tissue trauma. Useful features include: flexible and secure catheter junctions to minimize kinking and leaking; teflon-coated, stainless steel wire to facilitate placement.

Wound Closure Systems

The AutoClip & Reflex wound closure systems provide a fast and effective alternative to sutures for closing incisions.

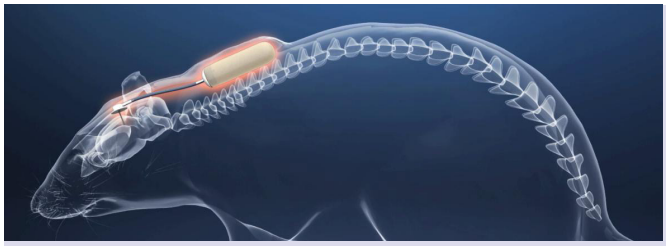
Loctite 454 Cyanoacrylate Adhesive

Loctite 454 is an instant adhesive gel for securing cannulae to the skull.

CSF Volumes and Production Rates in Mice & Rats

Species	Volume	Production Rate
Mouse	35 µl	18 µl/hr
Rat	150 µl	180 µl/hr

Source: Pardridge WM (1991) Transnasal and intraventricular delivery. In "Peptide Drug Delivery to the Brain", p. 112 (Table 4.2) Raven Press, NY.



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alzet® OSMOTIC PUMPS

Customer Service
toll-free: 877.922.5938
phone: 408.761.4542
alzetcs@durect.com

Technical Support
toll-free: 800.692.2990
phone: 408.761.3630
alzet@durect.com

Mailing
10260 Bubb Road
Cupertino, CA 95014
www.alzet.com

durect