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ALZET Brain Infusion Kits and Present Status and Future Trends of Osmotic Pumps

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Abstract

Many agents do not cross the blood-brain barrier sufficiently to evaluate their effects on the brain without delivering them locally. Cerebral injection is one local delivery method, but it can be challenging to deliver an effective dose in a physiologically-compatible volume. In addition, the agent may not remain in the target location long enough to see an effect. For many compounds, local infusion directly into the brain is the only way to generate reliable data. The ALZET Brain Infusion Kits are designed specifically for use with ALZET pumps for targeted delivery to the central nervous system. They can be used in two ways first Infusion into the cerebral ventricles exposes a wide variety of brain regions to the infusate via the cerebrospinal fluid which bathes the brain second by direct microperfusion of discrete brain structures results in localized distribution of infusate in the target tissue.

Keywords: Microperfusion, Cerebral Injection, ALZET Pumps, Cerebrospinal Fluid.

Introduction

In recent past a relatively new concept of OSMAT has been introduced (Sule and Devarajan, 1994).this novel system exploits the properties of hydrophilic polymers that hydrates and swells in an aqueous environment, thereby providing an intrinsic semi permeable gel barrier across which osmotic ally triggered drug release could occur. Antigen delivery by mini-osmotic pump has been proposed by walduck and opdebeeck, 1997; they showed that continuous delivery of Bovine serum albumin (HSA) stimulated equivalent levels of antibody to delivery by injection over the same time period. Administration of a part of an antigen dose as a bolus injection either after or before zero-order delivery increased antibody levels for only a short period compared to other treatments. They suggested that time period between injections of BSA significantly effects the antibody title. Each ALZET Brain Infusion Kit includes materials for 10 brain infusions: 10 Brain Infusion Cannula, 10 Vinyl Catheter Tubes, and 40 Depth-Adjustment Spacers

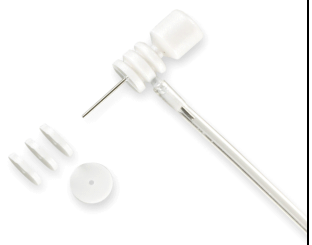
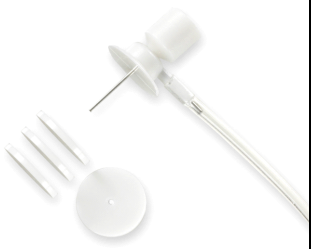
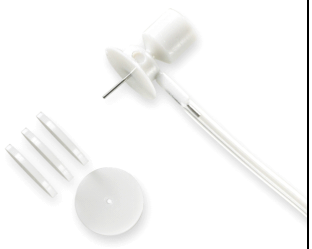
ALZET Brain Infusion Kit 1	ALZET Brain Infusion Kit 2	ALZET Brain Infusion Kit 3
		

Figure Alzet brain infusion kits

Features of Brain Kits

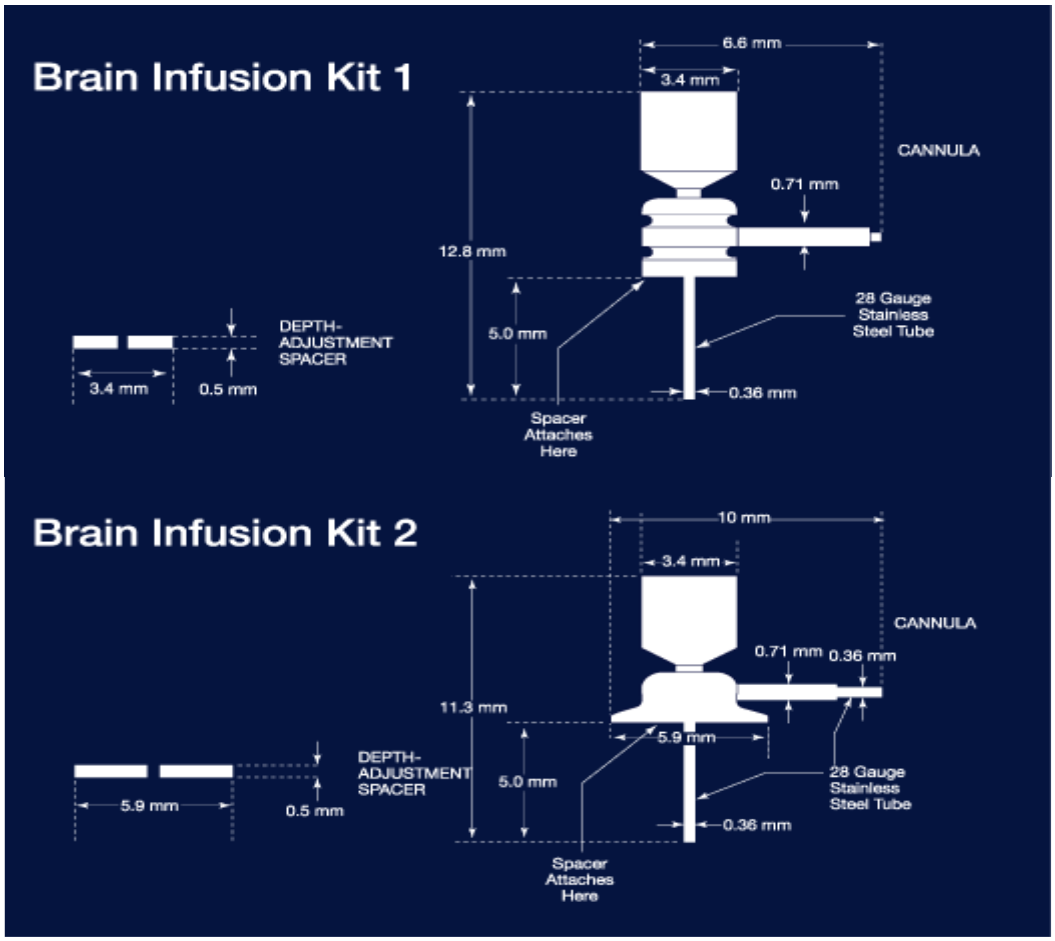
Compatible with all ALZET pumps models Targets lateral ventricles: Without modification, Brain Kits 1 & 2 will penetrate 5 mm below the surface of the skull. When affixed to the skull in the stereotaxically correct location, this will put the tip of the cannula in the region of the cerebral ventricles of a 250-300 g rat. Brain Kit 3 will penetrate 3 mm below the skull surface, which is appropriate for targeting the lateral ventricles in an adult mouse.

Table: Material used in brain infusion kits

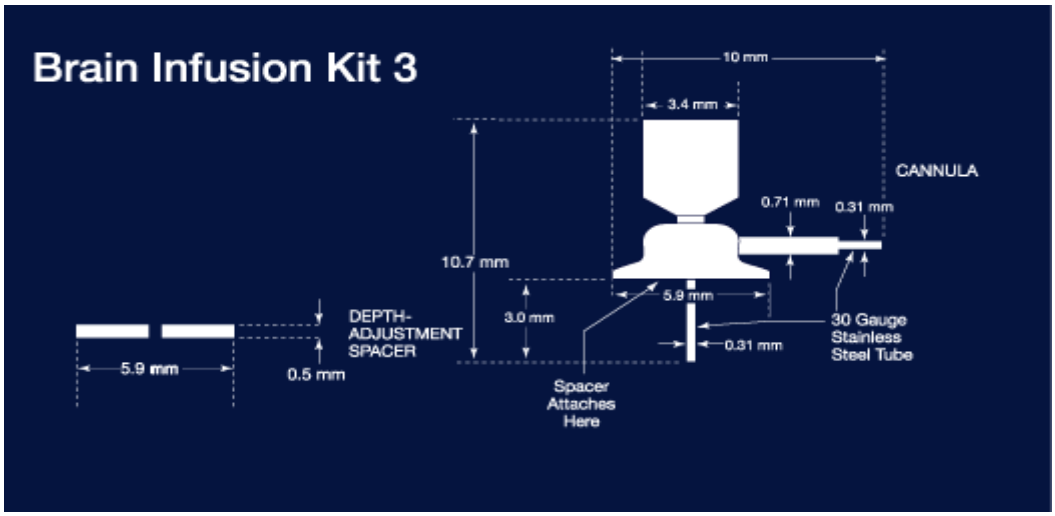
Brain Infusion Cannula	Brain Kit 1	Brain Kit 2
Material (tube)	Stainless steel	
Gauge (tube)	28 gauge	30 gauge
Dimensions (steel tube)	ID = 0.18 mm; OD = 0.36 mm; length below pedestal = 5 mm	ID = 0.16 mm; OD = 0.31 mm; length below pedestal = 3 mm
Penetration depths (adjust using spacers)	3-5 mm (from skull surface)	1-3 mm (from skull surface)
Material (elbow stop, flange)	Polycarbonate	
Side Connector (for catheter attachment)	0.71 mm (21 gauge)	
Cannula Design	Narrow diameter with suture grooves	Low profile and wide base for skin closure and stability
Volume inside tube	0.32 µl	0.23µl
Height Adjustment Spacers		
Material	Polycarbonate	
Dimensions (height)	0.5 mm	
Catheter Tubing		
Material	Polyvinylchloride (Medical grade)	
Length	15 cm (approx.)	
Inside diameter	0.69 mm (± 0.08)	
Outside diameter	1.14 mm (± 0.08)	
Volume per 15 cm	56 µl (3.7 µl/cm)	

Easily customized to target different brain regions or adjust for differences in animal size. Uniquely designed depth adjustment spacers allow the depth of the cannula tip within the

brain to be adjusted in 0.5 mm increments. Note that the cannula can easily be cut to target more superficial structures. Two specialized cannula designs: The original Brain Infusion Kit 1 has a taller base with a narrower diameter and grooves which are ideal for anchoring sutures in certain applications. The Brain Infusion Kits 2 and 3 feature a wide base pedestal which have been designed for greater stability, and may obviate the need for anchor screws. The Brain Kits 2 and 3 have a lower profile pedestal, which facilitates closure of the skin after placement. Design minimizes local trauma: Fine gauge stainless steel cannula minimizes trauma to the brain during cannula placement. (Brain Kits 1 & 2 is 28 gauges. Brain Kit 3 is 30 gauges). Flexible vinyl tubing that is well-suited for brain infusion. All components are provided sterile. Biocompatible: All materials in the Kits meet U.S. Pharmacopoeia (USP) Class VI standards for the biocompatibility of medical plastics.



Implantation & Explantation [2,3,4,5,6] ALZET osmotic pumps can be implanted subcutaneously or intraperitoneally following the animal size guidelines. ALZET pumps may also be connected to a catheter to deliver the pump contents directly into the venous or arterial systems, the brain, or into any organ or tissue. Subcutaneous (SC) implantation is technically the easiest and least invasive procedure. Volatile inhalation anesthetics are best for most indications in most species as induction and recovery times are shorter and the surgical plane can be maintained for a short or long duration. Injectable anesthetics are an option in some instances.



Subcutaneous Implantation The usual site for subcutaneous implantation of ALZET pumps in mice and rats is on the back, slightly posterior to the scapulae. Other regions may be used, provided that the pump does not put pressure on vital organs or impede respiration. Absorption of the compound by local capillaries results in systemic administration. With compounds that are absorbed very slowly by the capillaries, a direct vascular connection from the pump may be required

Intraperitoneal Implantation ALZET pumps can be implanted intraperitoneally in animals with sufficiently large peritoneal cavities Depending on the size of the animal relative to the pump, Allow 24 to 48 hours for the animal to recover after intraperitoneal implantation. With any substance administered intraperitoneally, whether by injection or by infusion, a majority of the dose may be absorbed via the hepatic portal circulation rather than by the capillaries. For substances which are extensively metabolized by the liver (i.e., have a high “first pass effect”), the intraperitoneal route of administration may produce highly variable concentrations of agent in plasma and consequently highly variable effects. Therefore, the intraperitoneal route should probably be avoided with agents that have a significant first-pass effect.

Intravenous Infusion (via the External Jugular Vein) in Rats Via a catheter, ALZET pumps can deliver directly into the venous or arterial circulation. ALZET pumps have been shown to pump successfully against arterial pressure with no alteration in flow. The following procedure details placement of a catheter in the external jugular vein. In many cases, this site is preferable because of its size and ease of access. Other sites may also be used.

Explanting ALZET Pumps Surgical removal of the ALZET pumps is accomplished in the anesthetized animal via a simple skin incision. If the pump has been in place longer than a couple of weeks, or the infusate is an irritant, it may be necessary to free the pump from surrounding connective tissue in order to remove it. The pump should be removed in the following circumstances: To verify delivery by measuring residual volume. To verify stability & bioactivity of the test agent in solution. No later than the recommended “explants by” date.

Schedule for Removing Spent ALZET Osmotic Pumps After its pumping lifetime has ended, an ALZET osmotic pump becomes an inert object for a period of time lasting about half

again as long as the pump's specified pumping duration. After that time, because of the continued osmotic attraction of water into the pump, it may swell and begin to leak a concentrated salt solution, resulting in local irritation of tissues around the pump. Therefore, DURECT advises explanting spent ALZET osmotic pumps according to the following schedule.

Table: Explant of Alzet osmotic pump

ALZET Pump Model No.	Explant Pump By
1003D	Day 5
1007D	Day 10
1002	Day 21
1004	Day 42
2001D	Day 1.5
2001	Day 10
2002	Day 21
2004	Day 42
2006	Day 63
2ML1	Day 10
2ML2	Day 21
2ML4	Day 42

Table Marketed products [7, 8]

Product Name	**Chemical Name**	**Marketer**	**Indication**
Acutrim	Phenyl propanolamine	Alza/Heritage	Appetite suppressant
Alpres LP	Prazosin	Alza/pfizer	Hypertention
Calan SR	Verapamil	Alza /GD Searle&co.	Hypertention
Cardara XL	Doxazosin mesylate	Alza/pfizwe(germany)	Hypertention
Conserta	Methyl penidate	Alza	Attention deficiency,hypersensitivity disorder
Coveralts	Verapamil	Alza /GD Searle&co	Hypertention
Ditropan	Oxybutirine chloride	Alza/UCB pharma	Overactive bladder

Dynacire CR	Isradipine	Alza/novartis	Hypertention
Efidac 24	Pseudoephedrine	Alza/novartis	Cold medication
Efidac 24 chlorpheniramin e	Chlorpheniramine	Alza/novartis	Antiallergic
Efidac 24	Pseudoephedrine	Alza/novartis	Cold medication
Chlorfeniramine	Chlorfeniramine	Alza/novartis	Antiallergic
Efidac 24	Pseudoephedrine brompheniramine	Alza/novartis	Antiallergic, cold treatment
Glucotrol XL	Glypizide	Alza/pfizer	Antidiabetic
Minipress XL	Prazosine	Alza/pfizer	Hypertation
Procordia XL	Nifedipine	Alza/pfizer	Hypertation, angina
Sudafed 24 hrs	Pseudoephedrine	Alza/warner/lambert	Nasal /decongestant
teczem	Analapril diltiazen	Merck/Aventis	Hypertation
Tiamet	Diltiazen	Merck/Aventis	Hypertation
Volmax	Albuterol	Alza/micro pharmaceautical	Bronchospasm

***Present Status and Future Trends*:** Osmotic drug delivery devices possess potential application in all vistas. The versatility of osmotic drug delivery system is presented in table

Type of Device	**Application**	**Disease**	**Drug**
Osmotic pump	Clinical studies	Cancer pain	Hydromorphone
GITS	Clinical studies	Better plasma profile	Nifedipine
Osmotic pump	Research	Neovascularisation	VEGF
OROS	Clinical studies	B2 recepter	Metoprolol
Osmotic pump	Research	Decrease oedema	Dexamethasone
Mini Osmotic pump	Research	Leukemia	Doxorubicin and verapamil
Osmotic pump	Clinical studies	Hypertensive asthma	Metoprplol
MOTS	Research	Fungal infection	Nystatin

OROS	Veterinary use	Parasitic infestation	Milbemycin
Osmotic pump	Research	Cancer	5-bromo-2-deoxy uridine
Osmotic pump	Research	CV disorders	CV drugs
Osmotic pump	Research	Depression	Fluoxamine
Osmotic pump	Clinical studies	Hypertension	verapamil
Osmotic pump	Research	Hyperplasia	EGF
OROS	Research	Neuroleptic	Chloropromazine
Mini-Osmotic pump	Research	Vaccine development	Antigen (BSA)

Implantable osmotic pumps and polymer disks bearing hydromorphone have utilized for pharmacodynamic studies related to drug and comparison of pharmacokinetic drug release with intravenous administration. Implantable opioid delivery device could provide a sustained subcutaneous infusion of hydromorphone to patient with cancer pain and improve compliance vis avis reduce the concern regarding illicit diversion of opiods. A swellable matrix tablet partially coated with cellulose acetate (CA) has been described by catellani *et al* coating permeability was modified by using different ratio of PEG to CA and admitted the reduced dependence of swellable matrix tablet release on environmental condition. Osmotically controlled delivery device have been employed for vascular endothelial growth factor (VEGF) delivery. Controlled delivery of VEGF eventually promotes neovascular ization and maintained function in a rabbit model of ischemia.[9-11].

Controlled delivery of dexamethasone by osmotic pump has been suggested, which reduces peritumoural oedema vis-à-vis suppresses tumor growth and prolongs the survival. Cochlear delivery of drugs presents several technical problems; Brown et al. developed continuous long term delivery of experimental drugs to the cochlea of small animals like guinea pig by utilizing osmotic device. Co-administration of doxorubicine and verapamil has been successfully attempted using mini-osmotic pump. This combination in alzet mini-osmotic pump increased the survival of B6D2F1 mice bearing the multi-drug resistant P388/ADR leukaemia.[12-14]. Relatively new mucosal oral therapeutics system (MOTS) has been developed for nystatin to attain high concentration of drug in oral mucosa. The milbemycins, novel broad- spectrum anathematic chemicals have been delivered using osmotic devices (Mckeller, 1994) orally for veterinary use. Consistent delivery of drug provides an effective means of veterinary parasite eradication. Implantable osmotic delivery system of 5-bromo-2-deoxyuridine (BRDU) has been formulated for rats with induced thyroid carcinoma. A significant reduction in plasma concentration of thyroid hormones and testosterone was observed.

Nocturnal administration of verapamil has been attempted by utilizing osmotic devices to evaluate the efficacy and safety-in-patients with stage 1 and 2 hypertension. Treatment was found to be remarkably effective. Osmotic pumps loaded with Epidermal Growth Factor (EGF have been utilized for studies on neointimal hyperplasia; controlled delivery of EGF

effectively inhibits the neointimal hyperplasia in vivo. Controlled release by osmotic drug delivery system significantly affects the pharmacotherapy of cardiovascular diseases. Calcium channel blocking agents, clonidine and nicotinic acid can be administered by these means, which have greatly influenced the application of these drugs in clinical practice [15-19].

Conclusion

Osmotic system technology has been extended to allow rate controls, constant drug delivery over a wide range of water solubility delivery rates & duration can be designed to limits imposed by GI Transit time & absorption capacity. The development of once duty formulation successfully can be achieved by osmotic systems for short half life drugs. The development of controlled porosity pumps & asymmetric cover drilling of the systems. The present status & future trends of osmotic technology in drug delivery is bright.

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