

Micro infusion pump



Implantable, Programmable and Refillable

Application Examples & Much More



www.iprecio.com

Micro infusion pump

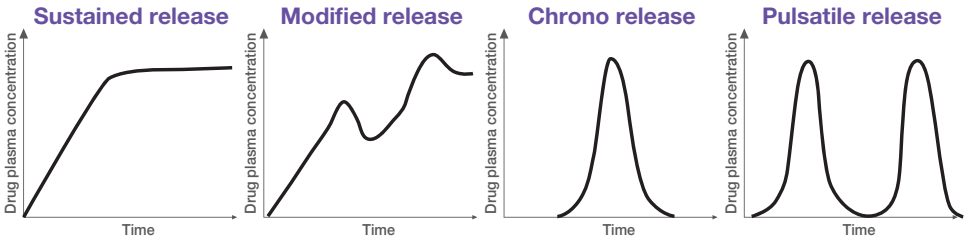


Implantable, Programmable and Refillable

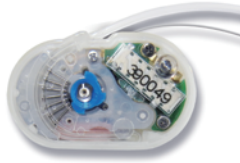
iPRECIO Micro Infusion Pumps

<Off-the-shelf> development tool for use in drug discovery

1. Reduced drug requirements
2. Large selection of compatible solvents used in drug discovery
3. Easy to modulate and time exposure profiles with non-optimized compound
4. Easy to use/program
5. Available since 2007



- Solubility issues and need a higher flow rate?
- Need more control for dosage due to narrow therapeutic index?
- Want to program a drug holiday or maximize efficacy/reduce toxicity with a timed dose during the mornings?
- Want to refill with a different test article/drug (sequential administration)?



SMP-300



SMP-200

The ability to program the device to start, stop and deliver different doses at different time points or just deliver one continuous dose makes iPRECIO ideally suited to the drug discovery and basic research process. All programmed in an easy to use PC based application software.

iPRECIO Micro Infusion Pumps for Drug Delivery

Exposure-enabling technology for advancing early preclinical studies and basic research

- Enables simple and complex dosing regimens at the click of the mouse/keyboard (ubiquitous PC) – several clicks
- Automation which minimizes animal handling
- Reduces stress and behavior anomalies
- Parenteral route which is practical and extremely important

Basic requirements

- Surgical skills/training (important for successful use of iPRECIO Micro Infusion Pumps)
- Basic computer skills/literacy

Resources available from Primetech

- Surgical training videos and step by step Surgical Technical Notes
- User Manual, workflows and step by step programming guide
- Compatible vehicle/solvents and easy to use compatibility test kit

What researchers are saying :

Ease of programming: "I was pleasantly surprised with how easy it was to program, fill, and implant the pumps."

Programmable & implantable pump : "This device enables implementation of infusion protocols to reliably and precisely achieve the desired exposure profiles (shapes and timing) with low degree of invasiveness."

Improved drug delivery: "The infusion pumps enhanced the delivery of the drug and allowed for us to identify a clean behavioral antidepressant effect, devoid of complications due to daily injections."

Improved drug efficacy: "This study demonstrated that an equivalent effect was possible at a much lower dose than was previously studied (25µg/serotonin hydrochloride/kg/min) in the sham and DOCA-salt rat."

Reproducible results: "I have accumulated few more very nice recordings using iPrecio. Few recordings are really breath-taking by reproducibility of responses."

"Your pump is AMAZING in terms of being able to do an intra-animal dose response curve. I absolutely, positively loved this. As a pharmacologist, there is nothing better."

Lead Optimization Study: "...we use them for studies to understand the PK-PD relationship of specific molecules. In terms of the infusion protocol it would be multiple steps to achieve a specific PK concentration in a PD study."

Things went well with the last iPRECIO study. The pumps did a fantastic job as they were programmed to do. iPRECIO data were in line with predicted/ calculated values. As a matter of fact, we are in the process of completing another study using the iPRECIO pumps.

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Program what you need for overcoming:-

 - a. Narrow therapeutic index
 - i. Maximizing efficacy with timed infusion
 - ii. Minimizing toxicity with timed infusions
 - iii. Flexibility to program 101 discreet infusion flow-rates. (SMP-300, 0.0 to 10.0µl/hours)
- 11. Selected Further Reading I : ▶ P.23**
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Timed release of Test Article (TA), β OHB

Rohit Chavan, Céline Feillet, Sara S. Fonseca Costa, James E. Delorme, Takashi Okabe, Jürgen A. Ripperger & Urs Albrecht

Liver-derived ketone bodies are necessary for food anticipation.

Nature Communications 7, Article number: 10580 doi:10.1038/ncomms10580

http://www.nature.com/ncomms/2016/160203/ncomms10580/full/ncomms10580.html?WT.ec_id=NCOMMS-20160205

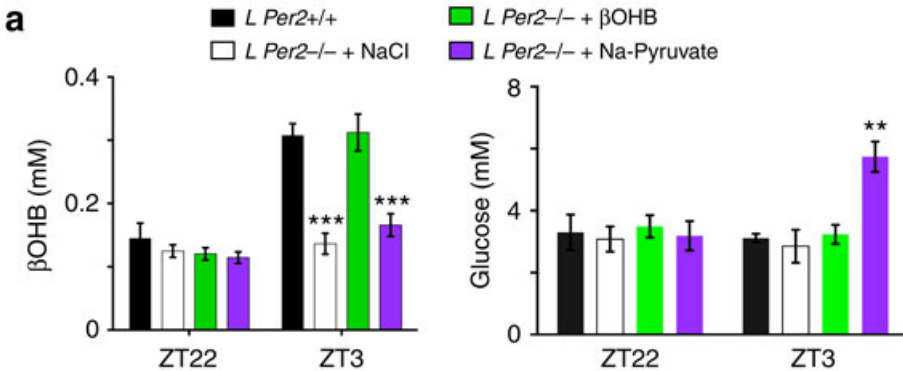


Figure 1 (Figure 4a in Full Article) **Rescue of food anticipation in *L Per2*^{-/-} mice by β -hydroxybutyrate.** (a) Timed release of β OHB (green) but not NaCl (white) or Na-Pyruvate (purple) in *L Per2*^{-/-} mice mimics the β OHB levels in plasma of *L Per2*^{+/+} control animals (black). Measured after 15 days of infusion. Figure reproduced from Chavan et al. in Nature Communications as reference previously.

Figure 1 is reproduced from Liver-derived ketone bodies are necessary for food anticipation. http://www.nature.com/ncomms/2016/160203/ncomms10580/full/ncomms10580.html?WT.ec_id=NCOMMS-20160205 under Creative Common Attribution 4.0 International (CC BY 4.0) <http://creativecommons.org/licenses/by/4.0/>.

No changes were made for reproduction from Figure 4a of Chavan et al.

Purpose of the study:

Researchers were interested to know where Food Anticipation (FA) signals originate and what role components of the circadian clock might play. To test the potential of β OHB as FA signal, iPRECIO SMP-300 programmable minipumps were used to release β OHB s.c. 6 hours prior to meal time under Restricted Feeding (RF) at ZT22 to reach a concentration normally observed in WT mice under RF preceding feeding time.

iPRECIO SMP-300 pumps were used to test the potential of β OHB as a FA signal.**Short methods or use of the pumps:**

iPRECIO SMP-300 pumps were programmed to infuse saline vehicle at 2 μ l/h, or D- β OHB at 2 μ l/h, or Sodium pyruvate at 5 μ l/h, or coconut oil at 5 μ l/h prior to meal time (6 h, ZT22-ZT4) under Restricted Feeding (RF)

Results/significance:

Liver-derived ketone bodies are necessary for food anticipation.
Timed Release of β OHB partially rescues FA.

Research Need:

Timed Release of β OHB in free moving animal with minimum or no handling to reduce stress and any confounding effects.

Additional information on mini-pump implant

Male and female L Per2^{+/+} and L Per2^{-/-} mice (3-5 months old)
Telemetry transmitter (G2 E-mitter) was i.p. implanted in each mouse under gaseous anaesthesia. At least 10 days after the transmitter implantation an iPRECIO programmable micro infusion pump (SMP/UCD 300; Primetech Corp., Japan) was implanted in subgluteal space(s.c. administration) on the back of each L Per2^{-/-} mouse. Subcutaneous administration.

Related Circadian rhythm Research using iPRECIO SMP-200 in mice

In vivo imaging of clock gene expression in multiple tissues of freely moving mice
Nature Communications 7, Article number: 11705 doi:10.1038/ncomms11705
<http://www.nature.com/ncomms/2016/160610/ncomms11705/full/ncomms11705.html>

Can different dosing (12 hour rectangular exposure profile) and terminating profile (a slow-step down) of Nicotinic Acid (NiAc) prevent/delay tolerance development and attenuate the FFA rebound development respectively.

Tobias Kroon (2016) PhD Thesis,

<Optimizing Nicotinic Acid Delivery for Durable Anti-lipolysis and Improved Metabolic Control>,

<http://pub.epsilon.slu.se/13324/>

http://pub.epsilon.slu.se/13324/1/kroon_t_160429.pdf

Thesis and publications cover Drug Discovery implications

1. Importance of time-series disease model
2. Continuous vs. intermittent drug exposures /Programmable, implantable mini-pump
3. Time exposure to physiology/Shape of exposure
4. Meta-analysis/Rank candidates/Predict designs

Tobias Kroon, Ann Kjellstedt, Pia Thalén, Johan Gabriellsson, Nicholas D. Oakes

Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats

The Journal of Lipid Research, doi: 10.1194/jlr.M058149 , July 13, 2015

<http://www.jlr.org/content/early/2015/07/13/jlr.M058149.abstract>

T. Kroon, J. Gabriellsson, N.D. Oakes

The abruptness of terminating nicotinic acid delivery has a profound effect on free fatty acid and insulin rebound in rats

51st EASD Annual Meeting, Stockholm 2015

<http://www.easdvirtualmeeting.org/resources/the-abruptness-of-terminating-nicotinic-acid-delivery-has-a-profound-effect-on-free-fatty-acid-and-insulin-rebound-in-rats--2>

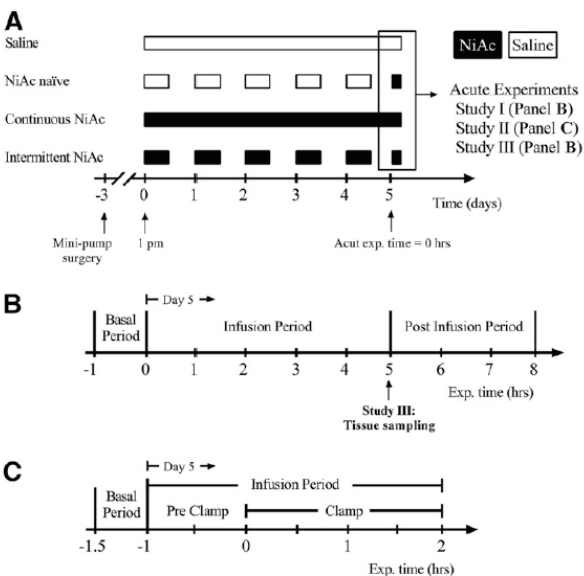


Fig. 2 (Figure 1 in Kroon et al.)
 A: NiAc and saline infusion profiles across studies I–III. Black (NiAc) and open (saline) bars represent time periods of constant rate infusions during days 1–5. B: Terminal protocol for studies I (NiAc-induced FFA lowering) and III (NiAc-induced changes in adipose tissue gene expression). C: Terminal protocol for study II (hyperinsulinemic-isoglycemic clamps).

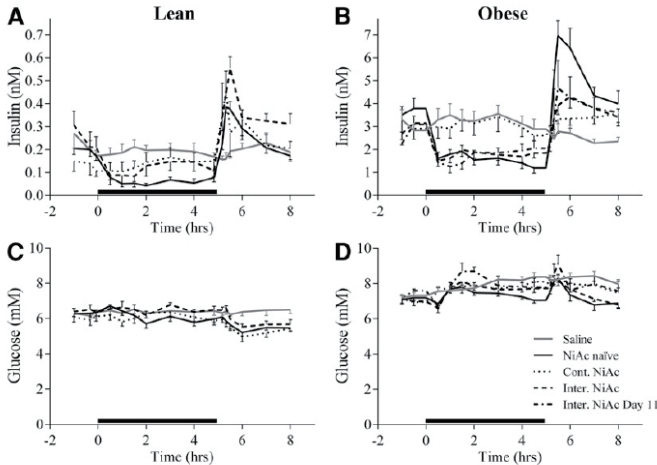


Fig. 3. (Figure 5 in Kroon et al.) Plasma insulin (A, B) and glucose (C, D) concentration in lean (left) and obese (right) following infusion of saline (lean $n = 5$, obese $n = 12$) or NiAc ($0.17 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) given acutely (NiAc naïve, $n = 7/\text{group}$) or following 5 days continuous (Cont. NiAc, lean $n = 4$, obese $n = 8$) or intermittent (Inter. NiAc, lean $n = 4$, obese $n = 9$) or 11 days intermittent (Inter. NiAc Day 11, obese $n = 4$) dosing. The black horizontal bar represents the period of acute NiAc/saline infusion. Data presented as mean \pm SE.

Figures 2 and 3 licensed material. © <2015> The American Society for Biochemistry and Molecular Biology. Warranties: None Publisher makes no representations or warranties with respect to the licensed material and adopt on its own behalf the limitations and disclaimers established by CCC on its behalf in its Billing and Payment terms and conditions for this licensing transaction.

Purpose of the study:

Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats

Researchers wanted to compare the ability of continuous versus intermittent NiAc administration to suppress FFA levels in metabolic healthy and insulin-resistant rats.

The abruptness of terminating nicotinic acid delivery has a profound effect on free fatty acid and insulin rebound in rats

The aim of this study was to determine whether a slow step-down NiAc infusion protocol (Step-Down group) vs. simply turning infusion off (On/Off group) could attenuate the FFA rebound development.

iPRECIO SMP-200 pumps were programmed to deliver the required exposure profiles of Nicotinic Acid to study impact on tolerance development (see figure 2A) and attenuate the FFA rebound development respectively (not shown)

Results/significance:

An Intermittent NicAc dosing strategy succeeded in retaining FFA lowering and improving insulin sensitivity in obese Zucker rats.

Gradual step-down reduction of NiAc infusion actually degraded the anti-lipolytic effectiveness of NiAc compared to abrupt withdrawal.

Research Need:

Ability to quickly and easily adjust dosing profiles based on PK and PD effects and deliver doses without stressors which could change metabolic activity of animals.

Continuous infusion of PKA and ATP at 1µl/hour for 14 days where solution in pump was changed every 2 days due to stability of PKA and ATP.

Kenji Suehiro, Yuka Nakamura, Shuai Xu, Youichi Uda, Takafumi Matsumura, Yoshiaki Yamaguchi, Hitoshi Okamura, Toshihide Yamashita & Yoshinori Takei

Ecto-domain phosphorylation promotes functional recovery from spinal cord injury

Scientific Reports 4, Article number: 4972 (2014) doi:10.1038/srep04972

<http://www.nature.com/articles/srep04972>

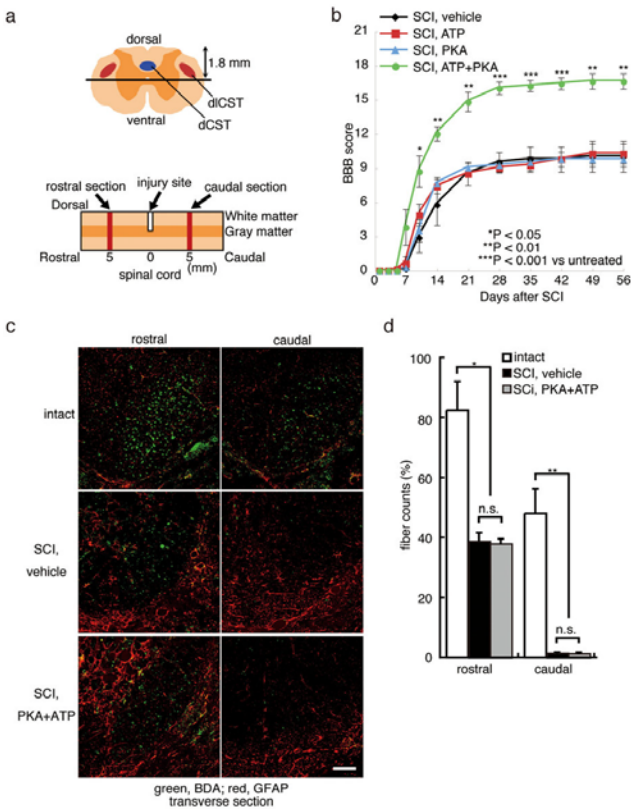


Figure 4 (Figure 1 from Suehiro et al) | Treatment with PKA plus ATP diminishes damage from traumatic SCI. (a) The depth of injury and location of sections used in (c) are illustrated schematically. The dorsal corticospinal tract (dCST) and the dorsolateral corticospinal tract (dlCST) were severed. (b) The BBB scores of vehicle-treated, PKA-treated, ATP-treated and PKA1ATP-treated SCI rats were assessed at the indicated days after SCI. The points on the graph indicate the average BBB score from six independent rats, and the error bars indicate the standard deviation (S.D.) (*p , 0.05, **p , 0.01, ***p , 0.001 vs. vehicle-treated rats, Student' s t-test). (c) The BDA-labelled dCST was visualised. Images are taken from transverse sections at either 5 mm caudal or rostral to the lesion, as shown in (a). The bar indicates 25 mm. (d) The number of BDA-positive axons at T8 or T10 was normalised to the number of BDA positive axons at C1 (intact region of the spinal cord). The average and the S.D. from three independent animals are shown. No significant differences between the vehicle-treated rats and the PKA/ATP-treated rats were observed (*p , 0.05, **p , 0.01,

Figure 4 is reproduced from Ecto-domain phosphorylation promotes functional recovery from spinal cord injury <http://www.nature.com/articles/srep04972> under Creative Common Attribution 4.0 International (CC BY 4.0)

<http://creativecommons.org/licenses/by/4.0/>.

No changes were made for reproduction from Fig. 1 of Suehiro et al.

Purpose of the study:

Investigate if inhibition of Nogo-66 receptor (NgR) via ecto-domain phosphorylation by protein kinase A (PKA), which blocks activation of the receptor can promote recovery following spinal cord injury.

iPRECIO SMP-200 pumps were used to infuse PKA plus ATP for 14 days at 1µl/hour. Solution in reservoir was changed every 2 days.

Results/significance:

Authors found that infusion of PKA plus ATP into the damaged spinal cord can promote recovery of locomotor function.

Research Need:

Ability to replace unstable test articles or drugs easily and rapidly without additional surgeries and stress.

Related publication examples: Refilling to Improve Test Article Stability

Hemoglobin induced lung vascular oxidation, inflammation, and remodeling contributes to the progression of hypoxic pulmonary hypertension and is attenuated in rats with repeat dose haptoglobin administration

Free Radical Biology and Medicine D Irwin et al.
doi:10.1016/j.freeradbiomed.2015.01.012

<http://www.sciencedirect.com/science/article/pii/S0891584915000192>

Free hemoglobin induction of pulmonary vascular disease: evidence for an inflammatory mechanism.

Am J Physiol Lung Cell Mol Physiol. 2012 Aug;303(4):L312-26. Epub 2012 Jun 22.
<http://www.ncbi.nlm.nih.gov/pubmed/22728465>

Excerpt from Mitchell et al. Full reference in box.

Regulatory request to perform an epidural and/or intrathecal animal study to assess degradents associated with a pharmaceutical product that was given epidurally in humans.

Mitchell D., Read, K., Chapman M. and Patten D.

Intrathecal administration using the iPRECIO® implanted pump

Development in Life Sciences, Vol 14, No. 4

http://cdn2.hubspot.net/hubfs/212573/docs/Envigo/Envigo_Pharma_Dils_14.4.4.pdf?t=1460116975327

Purpose of the study:

The customer requested a rat study involving intrathecal infusion for 72-hours of two different degradent mixtures and appropriate controls with acute and delayed endpoints and investigations of local and systemic toxicity. Clinical relevant concentrations of degradents to attain comparable exposure with humans would be necessary.

Developments in LifeSciences Vol. 14 No. 4

Intrathecal administration using the iPRECIO® implanted pump

David Mitchell BSc (Hons) DABT, Senior Toxicologist, Toxicology Operations, Envigo, UK.
Kate Read MA VetMB MRCVS, Veterinary Clinician, Veterinary Services, Envigo, UK.
Melissa Chapman BSc (Hons), Senior Study Director, Toxicology Operations, Envigo, UK.
Duncan Patten FIAT RAnTech, Associate Director, Laboratory Animal Technologies, Envigo, UK.

The background to this project was a regulatory request to perform an epidural and/or intrathecal animal study to assess degradents associated with a pharmaceutical product that was given epidurally in humans. There was a concern that there might be inadvertent intrathecal administration of the product and degradents. The customer requested a rat study involving intrathecal infusion for 72-hours of two different degradent mixtures and appropriate controls, with acute and delayed toxicity endpoints and investigations of local and systemic toxicity. We had

could compromise welfare, in particular for clinical signs associated with increased intrathecal pressure.

The optimal solution was to use the iPRECIO® SMP-200 programmable peristaltic pump implanted subcutaneously and linked to an intrathecal catheter

iPRECIO SMP-200 pumps were used to infuse 1µl/hr of artificial CSF intrathecally following surgery and during the recovery period. Animals recovered well with no adverse clinical signs in the post-operative period. During the treatment period; infusion at 30µl/hr; a small number of animals (5 out of 72) showed hindlimb paresis. Examination of aspirated dose volumes demonstrated accurate pump function.

Results/significance

This method (iPRECIO SMP-200 linked to an intrathecal catheter) is suitable for controlled continuous infusion into the intrathecal space of the rat. The surgical procedure is reproducible and considered to be less invasive than intrathecal access via the cisterna magna. The use of the programmable iPRECIO® pump allows for an ambulatory infusion model without the need to tether the animals. This permits behavioural assessment and is an improvement in animal welfare; animals are able to display normal behaviours post operatively.

Research Need:

A standard method for intrathecal infusion in industry and academia which would not be a confounding factor in the assessment of CNS endpoints (modified Irwin assessment). The infusion system must provide a suitable flow rate over at least 72 hours.

- The pump must allow the flexibility to start infusion immediately following surgery or at a later time.
- The pump must have a reservoir that can be evacuated and refilled, percutaneously, by syringe and needle so there would be the opportunity for a period of recovery from surgery before administration of the degradant mixtures while avoiding the risk of catheter occlusion by administering saline or artificial cerebrospinal fluid.

Aldosterone was continuously infused with SMP-200 programmable infusion pump that delivered aldosterone into the jugular vein. D-Aldosterone was infused into the jugular vein at a dose of $30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ in a solution of 15% ethanol, 50% DMSO, and 35% water at a concentration of 10 mg aldosterone/ml.

Enhanced Resistance to Permeability Transition in Interfibrillar Cardiac Mitochondria in Dogs: Effects of Aging and Long Term Aldosterone Infusion.

Am J Physiol Heart Circ Physiol *ajpheart*.00674.2012;

<http://ajpheart.physiology.org/content/early/2012/12/10/ajpheart.00674.2012.abstract?sid=1c8187a4-b1a5-41e2-9e88-20610af15128>

Purpose of the study:

Effect of aging and long-term aldosterone infusion on respiratory function and resistance to mitochondrial permeability transition (MPT) in subsarcolemmal and interfibrillar cardiac mitochondria (SSM and IFM) from healthy young (1 year) and old (8 year) female beagles.

iPRECIO SMP-200 pumps were used to infuse Aldosterone for 14 weeks at a dose of $30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. The pump reservoir was 900 μl and was refilled percutaneously every 20–30 days through an injection port on the pump. The pump reservoir was evacuated before refilling to ensure the pump had properly discharged its contents and was then refilled using a 26-gauge needle. This procedure was done in conscious animals with no evidence of discomfort.

Results/significance

Authors demonstrated in a large animal model that resistance to MPT is greater in IFM than in SSM in young and old female dogs. When old dogs were stressed with aldosterone infusion, there was selective enlargement of SSM and greater susceptibility to MPT, with no change to IFM.

Research Need:

Long term/chronic 14 week infusions with the ability to refill and check performance of implanted pumps.

Research Applications 6

Brain Administration

Pumps were programmed to instant mode, constant mode and 5µl/hour infusion rate. They were initially loaded with isotone saline or 0.1 mM MTX. Two days later, residual saline or MTX was extracted from the pump reservoirs and refilled with 960µl of 0.3 µg/ml ¹²⁵I-UdR or ¹²⁷I-UdR. See figure 6 below for results obtained. Reproduced with permission from Thisgaard et al. (CC BY-NC-ND 4.0).

Thisgaard et al.

Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced Delivery

Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898

<http://www.thno.org/v06p2278.htm>

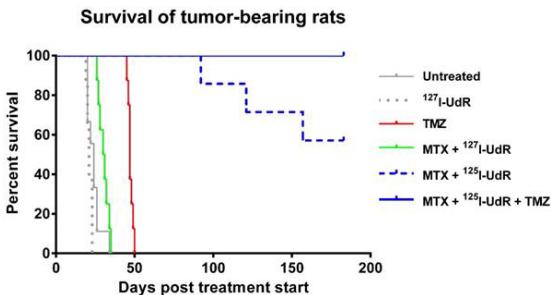


Figure 6. Kaplan-Meier plot showing that the survival benefit of neoadjuvant MTX + ¹²⁵I-UdR as stand-alone Auger-therapy (group 4) or with concomitant, systemic TMZ chemotherapy (group 5) was highly significant compared with the non-radioactive, but chemically identical treatment MTX + ¹²⁷I-UdR (group 3, p=0.0001 and p<0.0001, respectively) or untreated controls (group 1, both p<0.0001). The Auger-therapy was also significantly better than systemic TMZ-chemotherapy alone (group 6, p=0.0001). Reproduced with permission from Thisgaard et al. (CC BY-NC-ND 4.0).

Purpose of the study:

The overall aim of this was to test the effect and safety profile of ¹²⁵I-UdR therapy in vitro and in vivo on immature Glioblastomas (GBMs) spheroid cultures (GSCs) and orthotopic xenografted GBM-bearing rats, respectively. A further objective was to determine if further therapeutic effect was achieved when combining ¹²⁵I-UdR therapy with the currently used first-line chemotherapeutic agent TMZ.

Pumps were initially loaded with isotone saline or 0.1 mM MTX. Two days later, residual saline or MTX was extracted from the pump reservoirs and refilled with 960µl of 0.3 µg/ml ¹²⁵I-UdR or ¹²⁷I-UdR.

Results/significance

The multidrug approach including CED of MTX and the AEE-compound ¹²⁵I-UdR in combination with systematic TMZ was safe and very effective in the orthotopic xenograft GBM model, leading to 100% survival.

Research Need:

The ability to evaluate combinational therapy/multidrug approach easily and rapidly without additional surgeries and stress.

GLP Studies with iPRECIO Pumps

Laura Ringer

The use of the iPRECIO Dual Inlet Infusion Pump in Ambulatory Cardiovascular Dog Studies
 DSI East Coast User Group Meeting, Philadelphia, PA, United States October 29th and 30th 2015

Duncan Patten (Huntingdon Life Sciences, UK)

Use of iPRECIO implantable micro infusion pumps in rats

4th Infusion Technology Organization Meeting, May 8th-9th 2014, Harrogate, UK.

Perron J., Frenette V., and Copeman C.

Validation and use of the iPRECIO® Micro Infusion Pump on GLP studies

Society of Toxicology Annual Meeting, San Francisco, United States, March 11th to 14th 2012.

<http://www.criver.com/about-us/eureka/podcasts/july-2012/micro-infusion>

Validation and use of the iPRECIO® micro-infusion pump on GLP studies
 Perron J., Frenette V., Copeman C.
 Charles River Laboratories Preclinical Services Montreal Inc., 25522 Taschereau Avenue, Brossard, Quebec, Canada J4W 3P3

Introduction:
 Low infusion rates are generally required for conduct of preclinical studies using long-term infusions of pharmaceuticals such as oncology, neurology, and cardiovascular. The use of iPRECIO® micro-infusion pumps in the pre-clinical setting allows for the use of low infusion rates in a wide range of studies. The pump is designed to deliver a precise volume of fluid over a defined period of time. The pump is designed to deliver a precise volume of fluid over a defined period of time. The pump is designed to deliver a precise volume of fluid over a defined period of time.

Materials and Methods:
Micro infusion pump:
 The iPRECIO® micro-infusion pump is designed to deliver a precise volume of fluid over a defined period of time. The pump is designed to deliver a precise volume of fluid over a defined period of time. The pump is designed to deliver a precise volume of fluid over a defined period of time.

Pump delivery accuracy:
 The pump's delivery accuracy was evaluated in order to allow its use in a wide range of studies. The pump's delivery accuracy was evaluated in order to allow its use in a wide range of studies. The pump's delivery accuracy was evaluated in order to allow its use in a wide range of studies.

Results and Conclusions:
 Our studies have demonstrated the successful integration of the iPRECIO® pump with other components in pre-clinical studies. The pump is designed to deliver a precise volume of fluid over a defined period of time. The pump is designed to deliver a precise volume of fluid over a defined period of time.

Study ID	Species	Volume (µl)	Rate (µl/hr)	Duration (hr)	Actual Volume (µl)	% Error
1	Rat	100	10	10	98	-2%
2	Rat	200	20	10	195	-2.5%
3	Rat	500	50	10	490	-2%
4	Rat	1000	100	10	980	-2%
5	Rat	2000	200	10	1950	-2.5%
6	Rat	5000	500	10	4900	-2%
7	Rat	10000	1000	10	9800	-2%
8	Rat	20000	2000	10	19500	-2.5%
9	Rat	50000	5000	10	49000	-2%
10	Rat	100000	10000	10	98000	-2%

References:
 iPRECIO® user manual ver. 8.5.14

Toxicology Studies with iPRECIO Pumps

Masaru Tsuboi, Yoshihide Ueda, Yasufumi Ota, Hiroshi Takehara, Takuya Aoshima, Fukutaro Mizuhashi

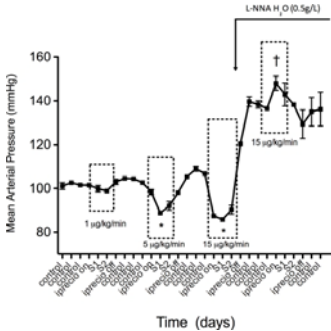
Physiological conditions in iPRECIO® -implanted rats

Fundamental Toxicological Sciences Vol.3 (2016) No.1 p.1-8

https://www.jstage.jst.go.jp/article/fts/3/1/3_1/_article

Application Examples

5-HT dose response with control period : 5-25 greater sensitivity

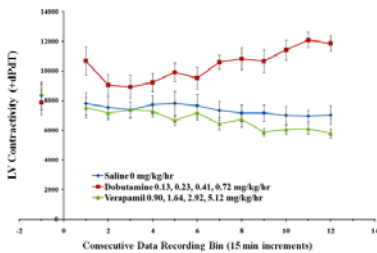


Drug Delivery: Enabling Technology for Drug Discovery and Development. iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable

Tsung Tan, Stephanie W. Watts, and Robert Patrick Davis
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29.
doi: 10.3389/fphar. 2011.00044

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/?tool=pmcentrez>

Dose response: Dobutamine, verapamil & saline 3 test articles per animal (pump)

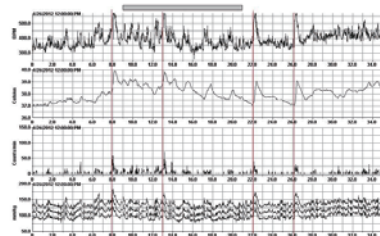


Drug Delivery: Enabling Technology for Drug Discovery and Development. iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable

Tsung Tan, Stephanie W. Watts, and Robert Patrick Davis
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29.
doi: 10.3389/fphar. 2011.00044

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/?tool=pmcentrez>

100nl bicuculline methiodide (BMI) bolus injections



Zaretsky D.V., Zaretskaia M.V., Durant P.J., Rusyniak D.E.

The use of microinfusion pump to perform intrahypothalamic injections in conscious rats.

Neuroscience 2012, New Orleans, USA.,
October 13th - 17 2012

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2964&sKey=87d8b951-316f-466a-9eb7-4b154d0bbd2c&cKey=b4b8338f-9bd2-44e2-bcf4-6e05a36cbbcb&mKey=%7b70007181-01C9-4DE9-A0A2-EEBFA14CD9F1%7d>

Comparison of arterial pressure and plasma ANG II responses to three methods of subcutaneous ANG II administration

Comparison of arterial pressure and plasma AngII responses to three methods of subcutaneous AngII administration
Kuroki M.T. , Gregory D. Fink , John W. Osborn
American Journal of Physiology - Heart and Circulatory Physiology Jul 2014, DOI: 10.1152/ajpheart.00922.2013
<http://ajpheart.physiology.org/content/early/2014/06/30/ajpheart.00922.2013>

Webinar

Gold Standard Physiological Measurements and Novel Drug Delivery Methods

Session 1: The harmony of gold standard physiological monitoring with novel infusion technology: Better quality of science in preclinical models ranging from mice to marmosets.

Session 2: Vitamin B12 Conjugation of Peptide YY3-16 Decreases Food Intake Compared to Native Peptide-YY3-36 Upon Subcutaneous Administration in Male Rats.



Watch the video



Access the slides



Download
the Q&A Report

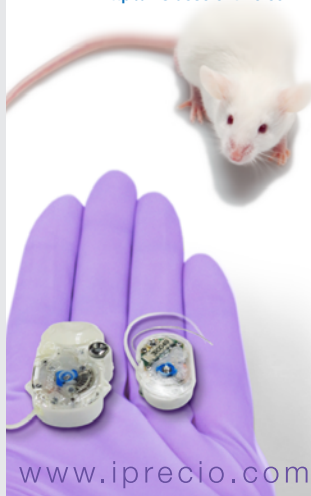


Download
the iPRECIO Resources

Learn how iPRECIO Micro Infusion Pumps will help you with your research needs. Webinar recordings, slide decks, iPRECIO resources (Bibliography of Scientific publications by product features) and Q&A report are now all < Open Access >

Webinar

<http://insidescientific.com>



www.iprecio.com



Dr Christian Schnell

Want to see objective data which lead Dr Schnell to the following conclusions?

1. The best situation is to get rid of stress because training is not really a solution.
2. An implantable pump is the only way to deliver the compound without interfering at the moment of delivery.

The open access on-demand webinar, resources, and Q&A are available 24/7.



Dr Robert Doyle

How are we going to know that if we do SC or Oral administration that we are not inducing a stress response which essentially negates the data we collect at the back end in terms of food intake and body weight as they pertain to our study?

Q: What were the best resources for learning how to program the iPRECIO mini pumps? Was it relatively simple?

Ans. [R. Doyle]:

Highly skilled technician used iPRECIO for the first time and did not have any difficulties and expect that similar skilled technicians to be fine. Medicinal chemists with only basic husbandry have been trained by technician (Monday–Friday week), to program and implant (surgery). Never lost a pump and never had a student screw-up.

What drug delivery concerns did Dr. Robert Doyle have and how did he solve it?

The open access on-demand webinar, slide deck, iPRECIO resources and Q&A are available 24/7. See also publication in Endocrinology.

1. We have to be particularly conscious of the fact that when looking at <Food Intake> and <Body Weight Reduction>, the handling of the animals is particularly confounding because inducing stress or inducing fight-or-flight response etc. is going to play havoc with our data collection.
2. And if we are dealing with subtle changes that can be the reason we lose out on seeing something we wouldn't otherwise and obviously that's something we were really really conscious of and concerned about when we began to do this project.
3. How are we going to know that if we do SC or Oral administration that we are not inducing a stress response which essentially negates the data we collect at the back end in terms of food intake and body weight as they pertain to our study?

Endocrinology Publication

Vitamin B₁₂ Conjugation of Peptide-YY₃₋₃₆ Decreases Food Intake Compared to Native Peptide-YY₃₋₃₆ Upon Subcutaneous Administration in Male Rats

Endocrinology February 6, 2015 doi: 10.1210/en.2014-1825

<http://press.endocrine.org/doi/abs/10.1210/en.2014-1825>

SMP-200 iPRECIO Use

- Recovery period after surgery of 7 days and 5 day baseline period (2µl/hr of saline)
- Treatments were delivered sc with five pulses per day; three 1 hour pulses of 10 nmol.kg⁻¹.h⁻¹ (20 µl.h⁻¹) with three hours between pulses and two 1 hour pulses of 5 nmol.kg⁻¹.h⁻¹ (10 µl.h⁻¹) with five hours between pulses.

The Ultimate Choice for Neuroscience

iPRECIO Micro Infusion Pumps for Drug Delivery Implantable Programmable Refillable

- The only way to deliver compound without interfering at the moment of delivery
- Paired data sets: Program a recovery/baseline period prior to drug delivery for control period for comparison.
 - Recovery period after surgery (pump stop or saline infusion)
 - Baseline period (pump stop or saline infusion)
 - Drug delivery /Treatment period (start pump or exchange from saline to drug)
 - Continuous
 - Intermittent
 - Dose escalation / de-escalation
 - Circadian
 - Reversibility (pump stop or exchange to saline)
- Infuse directly to brain
- Infuse directly to intrathecal space
- SC, IP and IV administration

Example Drug Delivery Regimen (Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0))
Schedule what you require : program and/or exchange infusate as per study requirements

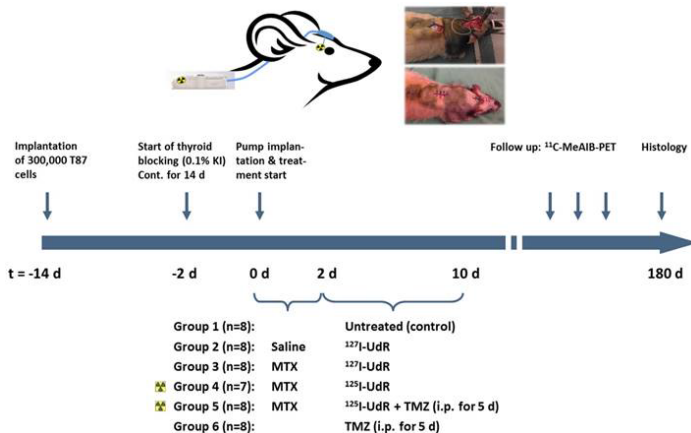


Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)

Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced Delivery
Thisgaard et al. Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898

<http://www.thno.org/v06p2278.pdf> Attribution-Non Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0)

<https://creativecommons.org/licenses/by-nc-nd/4.0/>

Brain Infusion (Selected Publications)

Keisuke Shinohara, Toshimichi Hata

Memory forgetting and NMDA receptor : Post-acquisition chronic micro infusion of NVP-AAM077 into dorsal hippocampus subsequently impairs the performance at reversal learning task in Morris water maze in rats

The 39th Annual Meeting of the Japan Neuroscience Society, Oral Session Learning and Cognition: Hippocampus [O2-H-2-2] July 21, 2016.

http://www.jnss.org/abstract/neuro2016/meeting_planner/sessiondetail.php?st_id=2016000289&u=1469585803&yz=0

Gey et al.

Continuous bilateral infusion of vigabatrin into the subthalamic nucleus : Effects on seizure threshold and GABA metabolism in two rat models

Neurobiology of Disease Volume 91, July 2016, Pages 194–208 doi:10.1016/j.nbd.2016.03.012.

<http://www.sciencedirect.com/science/article/pii/S0969996116300560>

Yamato et al.

Brain Interleukin-1 β and the Intrinsic Receptor Antagonist Control Peripheral Toll-Like Receptor 3-Mediated Suppression of Spontaneous Activity in Rats

Published: March 12, 2014 DOI: 10.1371/journal.pone.0090950 PLOS ONE Volume 9 Issue 3

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0090950>

Intrathecal Infusions (Selected Publications)

Matsubara et al.

Secreted Ectodomain of Sialic Acid-Binding Ig-Like Lectin-9 and Monocyte Chemoattractant Protein-1 Promote Recovery after Rat Spinal Cord Injury by Altering Macrophage Polarity

The Journal of Neuroscience, February 11, 2015 • 35(6):2452–2464

<http://www.jneurosci.org/content/35/6/2452.short>

Yamamoto et al.

Analysis of the Neuroregenerative Activities of Mesenchymal Stem Cells in Functional Recovery after Rat Spinal Cord Injury

Animal Models for Stem Cell Therapy

Methods in Molecular Biology Volume 1213, 2014, pp 321-328 Chapter 26 , 04 Aug 2014

http://link.springer.com/protocol/10.1007/978-1-4939-1453-1_26

Pain Research

Imai et al.

Inhibition of P2X4 receptor on spinal microglia attenuates mechanical allodynia in experimental autoimmune neuritis rats

Pain Research, Vol. 26 2011, O-59

https://www.jstage.jst.go.jp/article/pain/27/1/27_4/_pdf

Suggested Reading: EEG with iPRECIO Micro Infusion Pumps (Selected Publications)

Wood S.K., McFadden D.V., Grigoriadis D., Bhatnagar S. and Valentino R.J.

Depressive and cardiovascular disease co-morbidity in a rat model of social stress: a putative role for corticotropin-releasing factor

Psychopharmacology 2012 Feb 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22322324>

Andreas Lundt, Carola Wormuth, Magdalena Elisabeth Siwek, Ralf Müller, Dan Ehninger, Christina Henseler, Karl Broich, Anna Papazoglou, and Marco Weiergräber

EEG radiotelemetry in small laboratory rodents - a powerful state-of-the art approach in neuropsychiatric, neurodegenerative and epilepsy research -

Neural Plasticity

<https://www.hindawi.com/journals/np/2016/8213878/>

Selected CNS Applications with iPRECIO Micro Infusion Pumps

Addiction/ Drug abuse liability

Examples

- Adversive effects of drug withdrawal in rats and mice
- Withdrawal Test
 - Test potential compounds which may have similar effects in the same animals or reduce the signs of withdrawal
 - Abrupt cessation

Spinal Cord Injury Research

Tolerance

Pain Research

Program exposure profiles

- to study impact on tolerance development (example: continuous v intermittent)
Program exposure profiles to study impact of increasing or decreasing dose
Verify reversibility (start and stop of drug delivery)

iPRECIO Micro Infusion Pumps for Cancer Research

Solubility
&
precipitation
issues?

More difficult to
dose correctly
and need more
control?

Program what you require

- Solubility issues and need a higher infusion flow-rate to reduce drug concentration and precipitation risk
- Difficult to dose correctly and need to be able to have accurate flow-rates/dose groups
- Suited for intermittent dosing of onco substances – daily for 1 hour or every 2 days for 2 hours.
- Would like to allow tumor size to grow to a certain size before drug infusion
- Want to program a drug holiday
- Want to evaluate chrono release for maximum efficacy and minimize toxicity

Cancer Research Publications

Establishment of an orthotopic bladder cancer model to evaluate continuous intravesical delivery of small molecule inhibitors in the nude rat

AACR 106th Annual Meeting 2015; April 18-22, 2015; Philadelphia, PA
http://cancerres.aacrjournals.org/content/75/15_Supplement/5146.short

Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: a proof of concept.

Journal of Neuro-Oncology 2015 Oct 1.
<http://link.springer.com/article/10.1007%2Fs11060-015-1947-2>
<http://www.ncbi.nlm.nih.gov/pubmed/26428358>



Schnell C. and Ferrat T.,
Use of novel programmable pump for intracranial administration in an orthotopic glioblastoma tumor model in rats.

DSI User Group Meeting, Paris, France;
 March 17th 18th 2011



Christian R. Schnell (Oncology Research, Novartis, Switzerland)

Use of iPRECIO implantable micro infusion pumps in rats

4th Infusion Technology Organization Meeting, May 8th-9th 2014, Harrogate, UK.

Selected Further Reading I

► **For More detailed Background iPRECIO and Drug Discovery, see**

**Drug Delivery: Enabling Technology for Drug Discovery and Development. iPRECIO®
Micro Infusion Pump: Programmable, Refillable, and Implantable**

Front Pharmacol. 2011; 2: 44. Published online 2011 July 29. doi:10.3389/fphar.2011.00044
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/?tool=pmcentrez>

Discovering and Developing Molecules with Optimal Drug-Like Properties

Editors: Allen C Templeton, Stephen R. Byrn, Roy J Haskell, Thomas E. Prisinzano
ISBN: 978-1-4939-1398-5 (Print) 978-1-4939-1399-2 (Online) 27 Sep 2014
<http://link.springer.com/book/10.1007/978-1-4939-1399-2>

► **For More Trends, see**

Dosing-Time Makes the Poison: Circadian Regulation and Pharmacotherapy

Dallmann, Robert et al.

Trends in Molecular Medicine , Volume 22 , Issue 5 , 430 – 445
[http://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914\(16\)00056-3](http://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(16)00056-3)

The right dose for every patient: a key step for precision medicine

Richard W. Peck

Nature Reviews Drug Discovery 15, 145–146 (2016) doi:10.1038/nrd.2015.22
<http://www.nature.com/nrd/journal/v15/n3/full/nrd.2015.22.html>

Animal-based studies will be essential for precision medicine

K. C. Kent Lloyd, Peter N. Robinson and Calum A. MacRae
Science Translational Medicine 17 Aug 2016:

Vol. 8, Issue 352, pp. 352ed12, DOI: 10.1126/scitranslmed.aaf5474
<http://stm.sciencemag.org/content/8/352/352ed12>

Can formulation and drug delivery reduce attrition during drug discovery and development—review of feasibility, benefits and challenges

S Basavaraj, Guru V. Betageri,

Acta Pharmaceutica Sinica B

Volume 4, Issue 1, February 2014, Pages 3–17

SI: Drug Delivery System and Pharmaceutical Technology

<http://www.sciencedirect.com/science/article/pii/S2211383513001081>

Circadian Timing in Cancer Treatments

Annual Review of Pharmacology and Toxicology

Vol. 50: 377-421 (Volume publication date February 2010)

DOI: 10.1146/annurev.pharmtox.48.113006.094626

<http://www.annualreviews.org/doi/abs/10.1146/annurev.pharmtox.48.113006.094626?journalCode=pharmtox>

Selected Further Reading II

(Miscellaneous Application Research Areas)

For comprehensive list, go to www.iprecio.com or contract Primetech Corporation.

► Drug Discovery: iPRECIO Micro infusion pumps referenced

Discovering and Developing Molecules with Optimal Drug-Like Properties

AAPS Advances in the Pharmaceutical Sciences Series, 2015

Editors: Templeton, A.C., Byrn, S.R., Haskell, R.J., Prinszano, Th.E. (Eds.)

http://www.springer.com/jp/book/9781493913985?wt_mc=ThirdParty.SpringerLink.3.EPR653>About_eBook

Enabling Discovery Through Leveraging and Miniaturizing Pharmaceutical Principles and Processes

Discovering and Developing Molecules with Optimal Drug-Like Properties

AAPS Advances in the Pharmaceutical Sciences Series Volume 15, 2015,

pp 95-140 Chapter 3, 27 Sep 2014,

http://link.springer.com/chapter/10.1007/978-1-4939-1399-2_3

Discovery Formulations: Approaches and Practices in Early Preclinical Development

Discovering and Developing Molecules with Optimal Drug-Like Properties

AAPS Advances in the Pharmaceutical Sciences Series Volume 15, 2015,

pp 49-94 Chapter 2, 27 Sep 2014

http://link.springer.com/chapter/10.1007/978-1-4939-1399-2_2

Optimising in vivo pharmacology studies-Practical PKPD considerations

Journal of Pharmacological and Toxicological Methods Volume 61, Issue 2,

March-April 2010, Pages 146-156, Troubleshooting methods in pharmacology and toxicology

<http://www.sciencedirect.com/science/article/pii/S1056871910000183>

► Drug Discovery PK/PD

Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of Biomedical Research

Front. Pharmacol., 28 July 2014 | <http://dx.doi.org/10.3389/fphar.2014.00174>

<http://journal.frontiersin.org/article/10.3389/fphar.2014.00174/abstract>

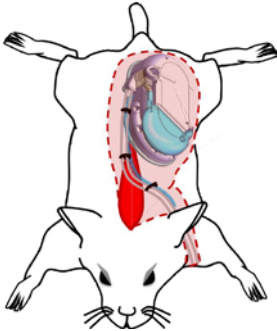
Pharmacokinetics in Drug Discovery: An Exposure-Centred Approach to Optimising and Predicting Drug Efficacy and Safety.

Handb Exp Pharmacol. 2016;232:235-60. doi: 10.1007/164_2015_26.

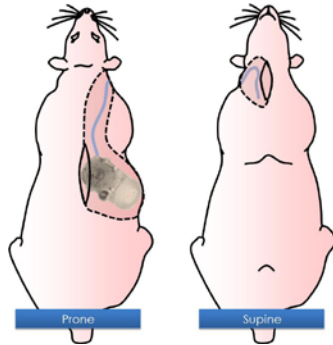
http://link.springer.com/chapter/10.1007%2F164_2015_26

Example Pump implantation site and drug administration site

Intravenous Administration

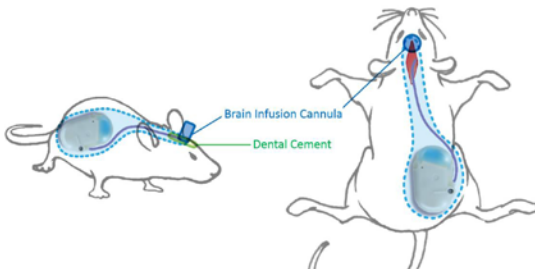


SMP-300

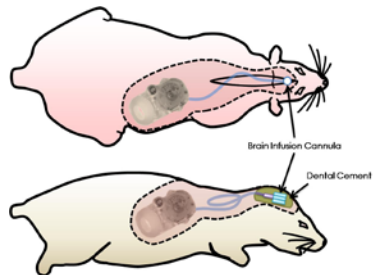


SMP-200

Intracerebral Administration



SMP-300



SMP-200

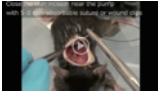
Support Materials

Technical Note/Surgical Protocol :

- Recommendation for Intravenous Administration.
- Recommendations for Subcutaneous Administration.
- Recommendations for Intraperitoneal Administration.
- Recommendations for Intracerebral Administration.
- Recommendations for Intrathecal Administration.

Surgical Videos

Mouse Surgeries (SMP-300)



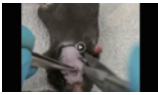
SMP-300 with SC administration and general preparation video

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSVFBSVVAzTIZHaWc&usp=sharing>



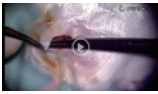
SMP-300 with IP administration

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSd1BNdDVZeEFQUWM&usp=sharing>



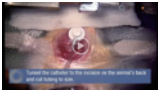
SMP-300 with IV Jugular administration

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSbEnyQ21nY2REcHM&usp=sharing>



SMP-300 with IV femoral administration

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSdIFtVfDJMFFncWM&usp=sharing>



SMP-300 with ICV administration

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSUGxHWkdLTXMwSEk&usp=sharing>



Refilling Video and Refilling FAQ

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSX203d114bGsx0G8&usp=sharing>

Rat Surgeries (SMP-200)



Surgery Training Videos

<https://drive.google.com/folderview?id=0B0pySJ1uXUqSR2kzLVIMbWtRNUE&usp=sharing>





We have been working on surgical videos which we hope will help our users. These are for the SMP-200 pumps you have been using

- ▶ We have been working surgical videos unfortunately, they are not complete yet.
- ▶ Feedback on the videos were provided by other surgeons (word document attached)
- ▶ We have been working with Vetbiotech, www.vetbiotech.com to complete them.

Support

From both Distributor and direct with Manufacturer (any way you want)

- Phone
- E-mail or fax
- Web meeting and training

Model	IMS/SMP-300	IMS/SMP-200
Appearance of the pump		
Type	Implantable SC	Implantable SC
Volume / Weight	2.15cc / 3.3g	7.20cc / 7.9g
Animal Species	Mouse or larger	Rats or larger
Reservoir Volume	130 µL	900 µL
Flow Rate (Setting Resolution)	0.0 – 10.0 µL/hr (0.1µL/hr)	0.0, 0.2, 0.5 & 1.0 – 30.0 µL/hr (0.1µL/hr)
Flow Steps / Repeat	15 / Yes	10 / Yes
Battery Life	0 & 0.1 ul/hr for 46 days 1 µL/hour up to 33 days 10 µL/hour up to 9 days	0, 0.2, 0.5, 1 µL/hour - 6 mths 2.5 µL/hour - 86 days 30 µL/hour - 8 days
Programmable	 Wireless Preprogrammable	 Preprogrammed prior to implantation

Compatible solvents for SMP-300 and SMP-200

* Tested for both SMP-200 & SMP-300

* Tested in SMP-200 Pump Only

(same materials and manufacturing process) and expected to be compatible when compatible. Also, not compatible when not compatible.

Compatible Solvents

Acids, with pH 2 or weaker *

Bases, with pH less than 13 *

Buffered Phosphate Saline (PBS) *

Culture Media (1% benzyl alcohol) *

Cyclodextrin *

Dextrose, up to 5% in water or saline *

N,N-Dimethyl formamide (DMF), up to 25% in water *

DMSO 50% and water or saline 50% *

DMSO, up to 50% in ethanol (≤15%) and water *

DMSO 5% and PEG400 95% *

50% DMSO + 50% Propylene Glycol *

DMSO 50% and water 50% *

DMSO 50% + 15% ethanol and 35% water *

Dulbecco's Modified Eagle Medium (D-MEM) (1X), liquid *

Ethanol, up to 50% in water *

Glycerin, up to 75% in water *

Glycerol 100% *

1-Methyl-2-Pyrrolidone, up to 12.5% in water *

Propylene Glycol *

Ringer's solution (without lactate) *

Saline, 0.9% (or other aqueous salt solution) *

Triacetin, up to 5% in water *

Tween 80, up to 2% in water *

Water, distilled *

PEG200 100% *

Solutol® 15% in water *

Viscosity up to 20 cp is ok.

(Higher viscosity not tested due to the use of 27G needles.

Difficulty to aspirate solution with 27G needle)

Short term use only (1 - 2month)

PEG300 100% * (< 45 days)

PEG400 100% *

Crephophor EL 25% in water * (< 30 days)

PEG400/Propylene Glycol/Water 30 : 50 : 20 * (< 30 days)