

PHARMACOKINETICS OF GALANTAMINE IN PLASMA AND BRAIN FOR DIFFERENT INTRANASAL FORMULATIONS: AN EXPERIMENTAL IN VIVO STUDY

T'jollyn, H¹; Vercruysse, J²; De Thaye, E¹; Remon, JP²; Vermeulen, A^{1,3}; Van Bocxlaer, J¹; Vervaet, C²

¹ Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium

² Laboratory of Pharmaceutical Technology, Ghent University, Belgium

³ Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium

Introduction

Anti-Alzheimer drugs, such as **galantamine** (Gal), could benefit from intranasal administration in terms of reducing first-pass and gastro-intestinal side effects [1]. An additional advantage is the possibility to directly target the brain via a direct nasal-to-brain (N2B) transportation route [2]. Therefore, different single dose formulations (mainly powders) were administered to New Zealand white rabbits. Plasma samples were collected and used for modelling. Formulations were compared in terms of bioavailability and absorption rate. Then, one formulation was selected for a multiple dosing study. In this study, plasma and brain samples were collected. Subsequently, the Gal brain distribution as well as the pharmacokinetic behavior after multiple doses was determined in the New Zealand white rabbit.

Objectives

The objectives of this study were to:

- Develop a **population PK model** to describe **plasma and brain** pharmacokinetics of galantamine (Gal) in rabbits after intranasal delivery.
- Compare **bioavailability and rate of absorption** between different formulations with varying composition.
- Investigate **direct nasal-to-brain** transport of Gal.

Methods

In vivo experiment

Single dose studies (n= 82 rabbits)

- 1 intravenous and 9 different intranasal formulations
- Blood sampled from ear vein at pre-dose and 8 time points post-dose (n= 513 data points)

Multiple dose study (n= 16 rabbits)

- 1 intranasal formulation administered every hour for 5 doses
- Blood sampled from each rabbit after the 1st dose, then alternately
- Brain data collected at every through level and around T_{max} at the 4th dose (n=138 data points)

Population PK model

A nonlinear mixed-effects pharmacokinetic model was developed in NONMEM 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation. Brain distribution was described using micro-constants from and to the central compartment. The brain's volume was fixed at a wet tissue weight of 12g [3]. The effect of formulation on bioavailability (F₁) and the absorption rate constant (k_a) was retained in the model on the basis of (i) a decrease in objective function value (OFV) of at least 3.84 points (α=0.05), (ii) an improved goodness of fit, (iii) and a condition number not exceeding 1000.

Results & Discussion

Table 1: final parameter estimates from the Gal pop PK model

Parameter	Estimate	RSE	95% CI
CL (mL/min)	240	4%	221-258
V ₂ (mL)	4760	7.80%	4030-5490
V ₃ (mL)	8350	5%	7540-9170
Q (mL/min)	472 (FIX)	-	-
k _a _formA	0.0455	19.60%	0.0280-0.0630
k _a _formB-G	0.107	7.30%	0.0920-0.122
k _a _form H	0.198	13.20%	0.147-0.249
k _a _formI	1.86	17%	1.241-2.479
F ₁ _formA ^a	100% (FIX)	-	-
F ₁ _formB ^b	87.5%	6.50%	76.5-98.5
F ₁ _formC-E ^c	79.7%	4.60%	72.3-87.1
F ₁ _formF ^d	72.3%	7.90%	61.1-83.5
F ₁ _formG ^e	59.3%	14%	43.0-75.6
F ₁ _formH ^f	51.6%	11%	40.5-62.7
F ₁ _formI ^g	92.8%	6.10%	81.9-104
k ₂₄ (min ⁻¹)	0.000655	22.30%	0.0370-0.0940
k ₄₂ (min ⁻¹)	0.116	23%	6.37-16.8

Parameter	Estimate	RSE
IIV CL	18.6%	25.6%
IIV V ₃	22.4%	36.3%
IIV k _a _formA	44.6%	38.3%
IIV k _a _formB-G	23.8%	32.3%

Parameter	Estimate	RSE
Additive error	51.1%	15.8%
Additive error in brain	54.0%	27.0%

^a (A) Amioca®/Carbopol®: GalHBr 90:10

^b (B) Amioca®/Carbopol®: GalHBr 10:90

^c (C) Amioca®/Carbopol®: GalHBr 50:50 ;

(D) Mannitol pH n-adj: GalHBr 10:90 ;

(E) Mannitol pH adj: GalHBr 10:90

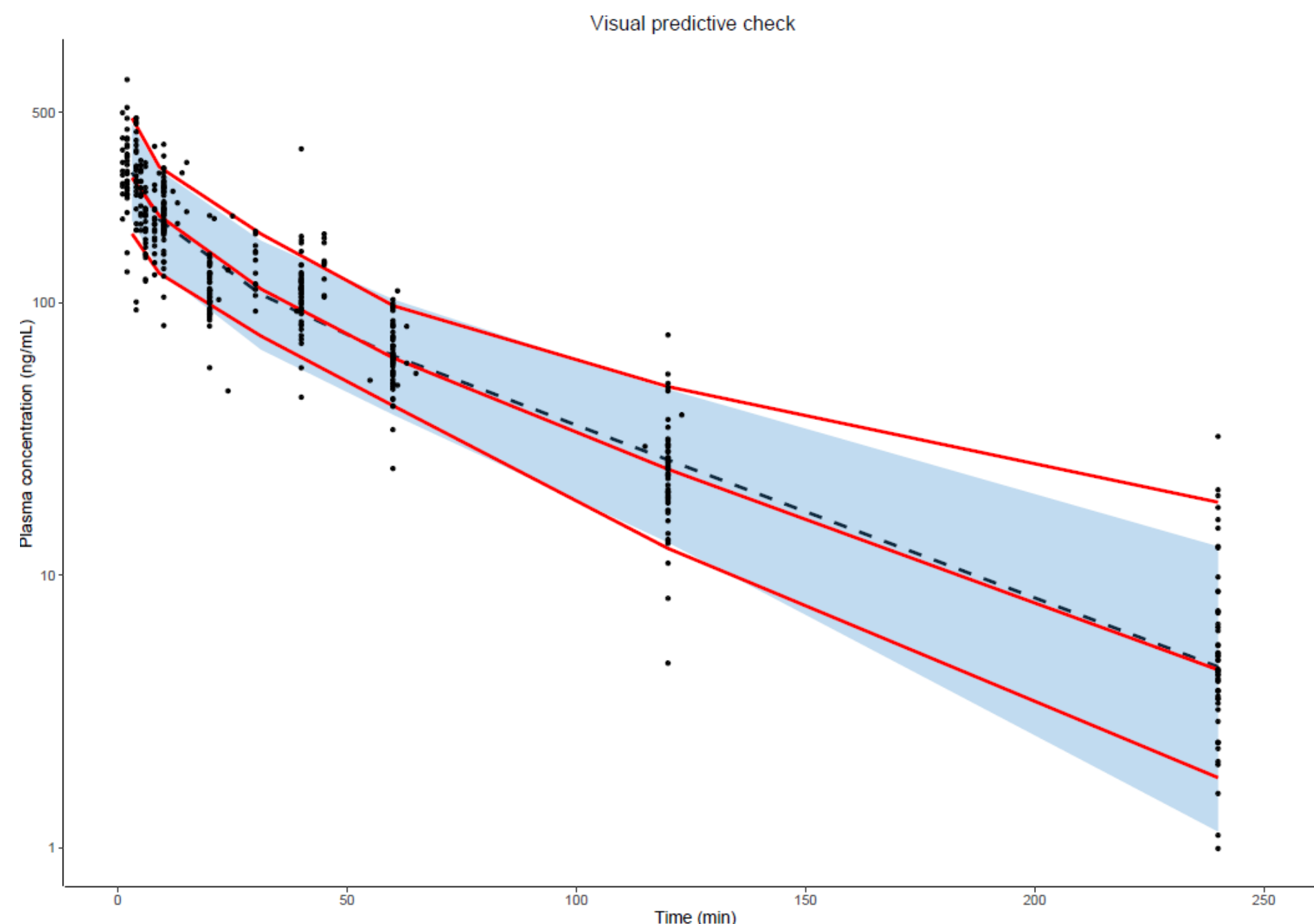
^d (F) GalHBr powder

^e (G) Gal oil suspension

^f (H) GalLac powder

^g (I) GalB powder

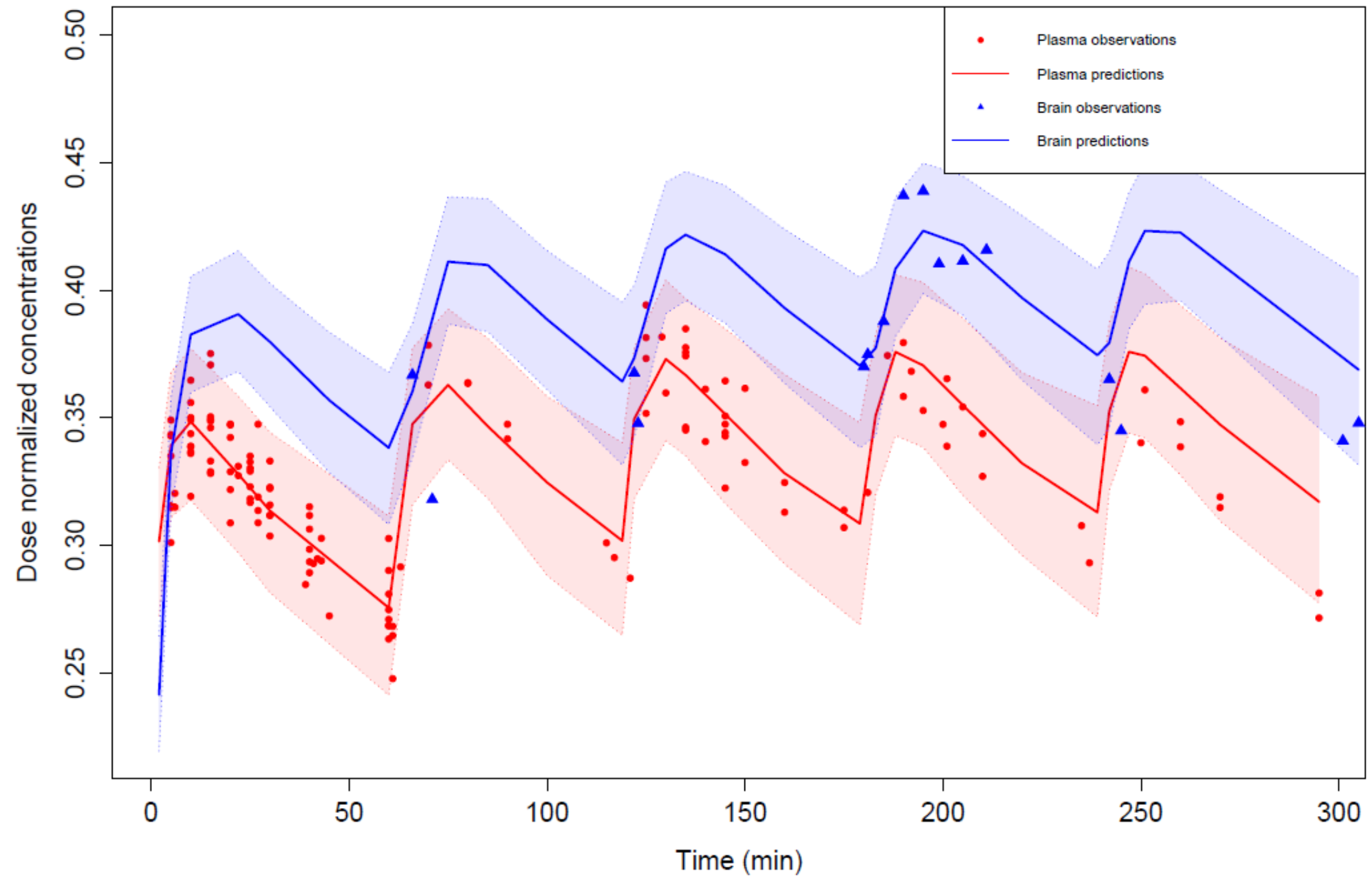
Figure 1: pred-corrected VPC. Red lines represent 5-50-95 percentiles of the observations (black dots). The predicted median (dashed line) and the blue 90% prediction band agree well with the observations.



A 2-compartmental model with first-order absorption and elimination best described the data. Final model parameter estimates are displayed in table 1 with RSE and 95% confidence intervals. The PK parameters related to **iv disposition** (CL, V₂, V₃) are estimated with high precision, and Gal plasma half life seems fast (13.75 min). Concerning Gal intranasal disposition, only k_a and F₁ parameters being significantly different between formulations were retained in the PK model. As indicated by the prediction-corrected VPC plot (figure 1), the model is capable to describe the data over all formulations.

In a multiple dosing study, the **linearity** in plasma and brain PK was investigated. Because of the fast half life of Gal, the steady-sate equilibrium is rapidly achieved (after approximately 1h) in plasma as well as in the brain. In addition, plasma-to-brain transport is the rate limiting step in Gal brain kinetics (table 1).

Figure 2: Plot illustrating the dose normalized Gal concentrations, measured in plasma (red circles) and brain (blue triangles) after multiple dose administration. Solid red and blue lines represent the predicted median plasma and brain concentrations, respectively. The 90% prediction band around the median concentration is indicated in red (for plasma) and blue (for brain).



In order to investigate **direct nasal-to-brain** (N2B) transport, 2 other structural models were fitted to the data. A direct N2B process could not be retained in the model. Additionally, brain concentrations were measured after intravenous and intranasal administration. The decline in brain concentrations did not differ, nor did the estimated brain micro-constants alter.

Conclusion

- Gal intranasal absorption differs between formulations in terms of bioavailability and absorption rate constant.
- Absorption was highest and fastest after administration of pure Gal base powder, without excipients
- Extended release times can be obtained by using Amioca®/Carbopol®:API (ratio 90/10)
- After multiple dosing, Gal pharmacokinetics displayed linear pharmacokinetic behavior
- Gal transfer from plasma to brain is the rate limiting step in its brain distribution, with no indications for a direct nasal-to-brain transport

References

[1] Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. International Journal of Pharmaceutics. 2007;337(1-2):1-24.

[2] Illum L. Nasal drug delivery - possibilities, problems and solutions. Journal of Controlled Release. 2003;87(1-3):187-98.

[3] MSTE data archive. MSTE Data Archive: Body and Brain Weights. [cited 05-05-2015]; Available from: <http://mste.illinois.edu/malcz/DATA/BIOLOGY/Animals.html>