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Research paper

In vivo evaluation of risperidone-SAIB in situ system as a sustained release delivery system in rats

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Abstract

The objective of this study was to evaluate a sustained release sucrose acetate isobutyrate (SAIB) in situ system formulation of risperidone (RSP) in vivo. The formulation contained SAIB, ethanol, and polylactic acid (PLA) as a release regulator. In vivo pharmacokinetics (PK) studies have shown that PLA is effective in reducing the burst effect. After a 12.5 mg/kg IM injection of a 25 mg/g RSP-SAIB in situ system, the C_{max} was markedly reduced from 944.1 ± 80.2 to 330.4 ± 33.6 ng/ml by increasing PLA from 1% to 10% (w/w), the T_{max} were prolonged from 2 to 4.3 ± 2.0 h, and the area under the curve from day 0 to 2 ($AUC_{0-2\ day}$) was reduced significantly from 16294.8 ± 3946.4 to 7025.3 ± 1979.2 ng h/ml. For the RSP-SAIB in situ system including 10% PLA, the high release rates over a short period allowed therapeutic plasma concentrations to be achieved in the initial stages after activation, and sustained release of the drug led to a stable plasma concentration (by day 25, the plasma concentration was 8% of the C_{max}). These initial in vivo studies suggest that RSP-SAIB in situ system is effective as a sustained delivery system.

Keywords: SAIB; In situ system; Risperidone; Sustained release delivery system; In-vivo pharmacokinetics

1. Introduction

Several oral atypical antipsychotics are available for the management of schizophrenia. Due to their limited availability as oral agents only, their benefits are limited by non-compliance. Therefore, the development of an effective long-acting injectable atypical agent with limited adverse effects and with excellent treatment compliance would make an important contribution to the long-term management of schizophrenia [1]. Risperidone (RSP) is one of the representative atypical antipsychotic drugs which has a potent antagonist effect on serotonin 5-HT2 and dopamine D2 receptors [2,3]. This drug is characterized by its effectiveness against both positive and negative symptoms of schizophrenia [4]. Furthermore, it produces fewer side effects, including extrapyramidal side effects, than conventional antipsychotic drugs [5]. Some authors reported that RSP shows evidence of a curvilinear dose–response relationship over the range 1–16 mg/day for oral therapy, with maximum antipsychotic activity apparently occurring at dosages of 4–8 mg/day [5,6]. An intramuscular formulation of RSP (Risperdal Consta™) has been developed to address the need for a long-acting formulation of an atypical antipsychotic. This long-acting risperidone is an aqueous suspension that contains the drug in a matrix of poly(DL-lactide-co-glycolide) (PLG) [7]. At present, it is recommended that the long-acting risperidone formulation is administered as three separate doses (25, 50, and 75 mg every 2 weeks).

There is an alternative technology – in situ systems for the production of sustained release systems [8–13]. These systems are fluid on injection and rely on a change in the local environment to produce a high viscosity or solid depot at the injection site. The sucrose acetate isobutyrate (SAIB) system is one interesting possibility for developing an injectable sustained release in situ system using a

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polymer-free solution consisting of a small amount of organic solvent, the active ingredient and SAIB [14,15]. SAIB systems have been evaluated in mares when it was found that in vivo estradiol levels similar to poly(DL-lactide) (PLA) microsphere formulations were obtained without any associated scale-up difficulties with regard to the simple "mix and fill" operation [16]. Compared with injectable microspheres, with the polymer, the costs are lower, only a small amount of organic solvent is needed and the method of manufacture is short and simple.

In this study, a SAIB in situ system was used as a sustained release system for RSP. The goal of the current investigation was to study the effect of PLA, injection volume and drug concentration on drug release in vivo.

2. Materials and methods

2.1. Materials

SAIB was provided by Sigma–Aldrich. Poly(DL-lactide) (PLA; MW 9000) was obtained from Southwest Jiaotong University (Chengdu, China). RSP was provided by Xi'an Janssen Pharmaceutica (Xi'an, Chian). 9-OH-RSP was obtained from Toronto Research Chemicals Inc. (North York, Canada) and diphenhydramine hydrochloride was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). All solvents and chemicals were of HPLC grade and obtained from Fisher Scientific (Tustin, CA, USA).

2.2. Methods

2.2.1. Preparation of RSP spray dried powders

The drug release rate is obviously effected by the drug particle size in the suspended system. Therefore, RSP needs to be spray dried and the particle size distribution needs to be controlled. Spray dried powders were prepared using an EYELA SD 1000 spray dryer (Tokyo Rikakikai, Japan). Aqueous solutions of RSP containing 1% acetic acid were atomized with a standard 0.5 mm nozzle. The operating conditions used were: inlet temperature, 130 °C, drying air flow rate, 0.6 m^3/min, atomizer pressure, 200 kPa, and a liquid feed, 2.0 ml/min. Operating under these conditions produced an outlet temperature of approximately 80 °C. Powder particles were sized using a Coulter LS 230 counter (Beckman–Coulter, USA) after dispersing excess microparticles in water to form a suspension using an ultrasonicator.

Table 1
Formulations of SAIB solutions

Formulation	SAIB (% w/w)	Ethanol (% w/w)	PLA (% w/w)
I	80	20	0
II	79	20	1
III	75	20	5
IV	70	20	10

2.2.2. Preparation of drug-loaded SAIB in situ systems

RSP-SAIB in situ formulations were prepared by mixing RSP spray dried powders with SAIB solutions (Table 1) followed by sonicating to form a transparent solution or a uniform suspension.

2.2.3. Drug administration and sample collection

Male Wistar rats (7 weeks old, 200 ± 20 g) were supplied by the Lab Animal Center of Shenyang Pharmaceutical University (Grade II, Certificate No. SYXK 2006-0064). The experimental protocol was approved by the University Ethics Committee for the use of experimental animals and conformed to the Guide for Care and Use of Laboratory Animals. Rats were maintained at 22 ± 2 °C and 55 ± 5% relative humidity under a 12-h light–dark cycle. They were fasted for 12 h before drug administration and water was freely available. RSP-SAIB in situ systems and RSP aqueous solution containing 0.625% w/v tartaric acid (Table 2) were administered intramuscularly into the right hind legs of the rats ($n = 6$). Pharmacokinetic (PK) data were generated using non-compartmental analysis.

2.2.4. Sample preparation

Both RSP and 9-OH-RSP were extracted from plasma by a simple one-step liquid–liquid extraction as reported previously [17]. Briefly, to an aliquot of 0.1 ml plasma (including the unknown sample, or quality control (QC) sample, or calibration curve sample) and 0.1 ml methanol in a borosilicate glass tube (7 ml capacity), 20 ng diphenhydramine hydrochloride (I.S., 0.1 ml of 200 ng/ml solution) and 0.5 ml of a saturated solution of sodium carbonate were added (pH ≈ 11, not adjusted). The contents of the tube were mixed and extracted with 3 ml of 20% methylene

Table 2
Groups of RSP-SAIB-ethanol in situ systems

Group	Formulation	Amount of drug loading (mg/g)	Dose (mg/kg)	Injection volume (ml/kg)	Drug state
A	I	25	12.5	0.5	Dissolved
B	II	25	12.5	0.5	Dissolved
C	III	25	12.5	0.5	Dissolved
D	IV	25	12.5	0.5	Dissolved
E	II	25	6.25	0.25	Dissolved
F	II	25	25.0	1.0	Dissolved
G	II	50	25.0	0.5	Dispersed
H	Aqueous solution	2.5	1.25	0.5	Dissolved

Table 3
Mass transitions, cone and collision energy voltages for RSP, 9-OH-RSP and I.S.

Compound	Precursor ion at *m/z*	Product ion at *m/z*	Cone voltage (V)	Collision energy voltage (eV)
RSP	411.3	191.3	40	30
9-OH-RSP	427.4	207.2	40	30
I.S.	256.1	167.0	15	10

chloride in N-hexane by shaking in a test-tube shaker. After centrifugation for 10 min at 4000 rpm, the supernatant organic layer was transferred to an Eppendorf tube (5 ml capacity) and dried at 40 °C in a centrifugal concentrator (Labconco Corporation, Missouri, USA). The residue was reconstituted in 150 μl mobile phase and an aliquot (5 μl) was injected into the UPLC system.

2.2.5. UPL-MS/MS method

The UPLC-MS/MS system consisted of an AcQuity™ ultra performance liquid chromatograph (UPLC) and a Quattro Micro Micromass® mass spectrometer (Waters/Micromass, Milford, MA). An AcQuity UPLC™ BEH C_{18} column (1.7 μm, 50 mm × 2.1 mm i.d.), also from Waters, was used for the analysis. The column temperature was maintained at 40 °C. The standard and sample extracts were chromatographed on the UPLC system using a gradient mobile phase consisting of 0.5% formic acid in water as solvent A and acetonitrile (ACN) as solvent B. The gradient conditions of the mobile phase were: 0 min 70% A, 1.50 min 40% A, 1.80 min 10% A, and 3.20 min 70% A. The flow rate was 0.25 ml/min. For all compounds, the MS was operated in positive ion electrospray ionization mode with multiple reaction monitoring (MRM). Source conditions were typically as follows: capillary 3.3 kV, source temperature 110 °C and desolvation temperature 330 °C. The cone and desolvation gas flows were 50 and 400 L/h, respectively. Nitrogen and argon were used as cone and collision gases, respectively. The collision gas was regulated at $3.00e^{-3}$ mbar. Multipliers were set to 500 V and the dwell time for each transition was 0.1 s. The MRM transitions as well as the individual cone and collision energy voltages used for the analysis are summarized in Table 3. Peak areas of the chromatograms were integrated and the peak area ratios of the analyte/I.S. were calculated. A weight $1/x^2$ linear regression was used to obtain a standard calibration curve. The regression equation of the calibration curve was then used to calculate the concentrations of method validation samples and unknown samples.

3. Results and discussion

3.1. Particle size

The character of the drug powders was improved by spray drying. Volume statistics showed that the particle size of 93.5% of the powders was less than 100 μm, and the mean size was 44.77 μm (SD = 30.20 μm). The particle size and distribution could ensure the syringeability and uniformity.

3.2. Method validation of UPLC-MS/MS

Fig. 1 shows the MRM chromatograms of RSP, 9-OH-RSP and I.S. in rat plasma. The retention times for RSP, 9-OH-RSP and I.S. were 0.99, 0.99 and 1.27 min, respectively. The sensitivity (LLOQ) of the assay was confirmed to be 1 ng/ml for the two compounds. The linearity of the calibration curves ranged from 1 to 1000 ng/ml for the two compounds. The accuracy (inter- and intra-batch) was between 85% and 115% of the nominal value over the entire range. The precision was within 15% over the entire range. The overall extraction recovery using the extraction procedure described above was 83%, 72% and 91% for RSP, 9-OH-RSP and I.S., respectively.

3.3. PK study of RSP aqueous solution given intramuscularly

RSP is extensively metabolized to 9-OH-RSP, which is the major circulating metabolite in animals and humans [18–20]. 9-OH-RSP is pharmacologically active and about equipotent with RSP [18,21,22]. Therefore, in vivo, the sum of RSP and 9-OH-RSP constitutes the approximate total active moiety responsible for the pharmacological responses to RSP. The plasma concentration–time curves for RSP and 9-OH-RSP after a single IM dose of 1.25 mg/kg of RSP aqueous solution in rats are shown in Fig. 2. The non-compartmental model pharmacokinetic parameters determined from the concentration–time profiles of RSP, 9-OH-RSP and active moiety (RSP plus 9-OH-RSP) are given in Table 4. After reaching a peak, the plasma levels of 9-OH-RSP declined more gradually than those of the parent drug.

3.4. Influence of PLA on the PK of SAIB in situ systems

The influence of PLA on PK was examined using 20% (w/w) ethanol as a solvent in SAIB solutions with 25 mg/g RSP loading. The plasma concentration–time profile of RSP and 9-OH-RSP after IM administration (dose: 12.5 mg/kg) is shown in Fig. 3. In the initial stage, the plasma concentration of RSP declined quickly. The T_{max} of 9-OH-RSP was 4–8 h, and was longer than that following IM administration of solution. At 24 h after administration of the in situ system, the profile of these two compounds was similar. The plasma concentration–

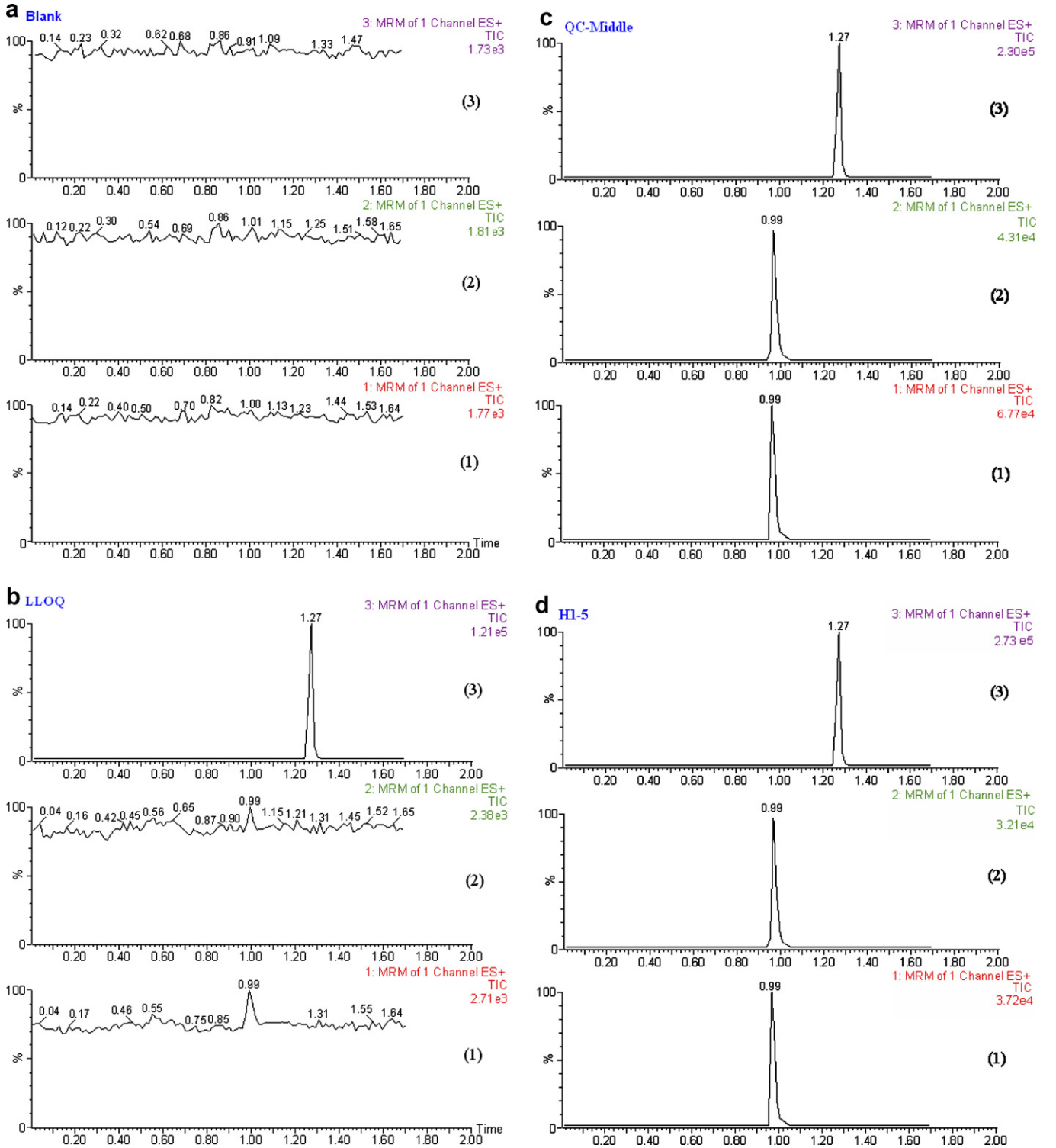

Fig. 1. MRM chromatograms of RSP (1), 9-OH-RSP (2) and I.S. (3) in rat plasma samples, (a) blank plasma; (b) plasma sample spiked with RSP and 9-OH-RSP (1 ng/ml) and I.S. (200 ng/ml); (c) plasma spiked with RSP and 9-OH-RSP (100 ng/ml) and I.S. (200 ng/ml); (d) a rat plasma 4.0 h after IM administration of RSP aqueous solution (1.25 mg/kg).

time profile of the active moiety after IM administration is shown in Fig. 4. The formulation without PLA showed a maximum concentration (C_{max}) at 2 h post-administration, and the concentration decreased rapidly from 2 h to 4 days, and fell below 10 ng/ml. However, the C_{max} was markedly reduced by adding PLA to the formulation. There was significant difference for the C_{max} between each formulation ($P < 0.05$). When the content of PLA was increased from 1% to 10% (w/w), the T_{max} was prolonged from 2 to 4.3 ± 2.0 h, and the area under the curve from day 0 to 2

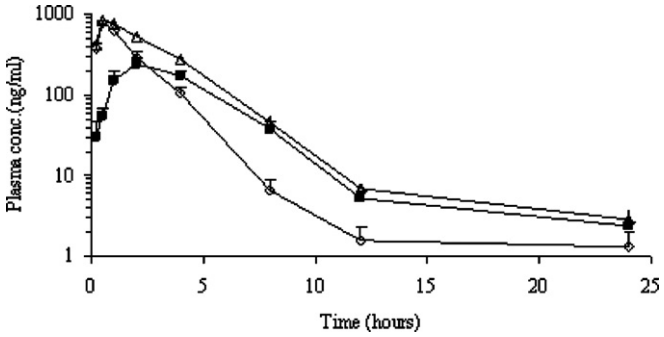

Fig. 2. Plasma concentration–time curve of RSP (◇), 9-OH-RSP (■) and the active moiety (△, RSP plus 9-OH-RSP) in rats after a single IM administration of RSP aqueous solution (1.25 mg/kg) (mean ± SD; $n = 3$).

Table 4
The non-compartmental model pharmacokinetic parameters of RSP, 9-OH-RSP and active moiety after a single IM administration of RSP aqueous solution (1.25 mg/kg)

	RSP	9-OH-RSP	Active moiety
$AUC_{0-24\ h}$ (ng h/ml)	1594.0 ± 153.6	1232.9 ± 198.6	2826.8 ± 252.5
T_{max} (h)	0.5	2.0	0.5
C_{max} (ng/ml)	777.6 ± 51.3	239.6 ± 45.6	831.8 ± 55.9
$t_{1/2}$ (h)	1.27 ± 0.06	3.41 ± 0.26	1.57 ± 0.06

($AUC_{0-2\ day}$) was reduced significantly from 16294.8 ± 3946.4 to 7025.3 ± 1979.2 ng h/ml, although the area under the curve from day 2 to 25 ($AUC_{2-25\ day}$) was increased

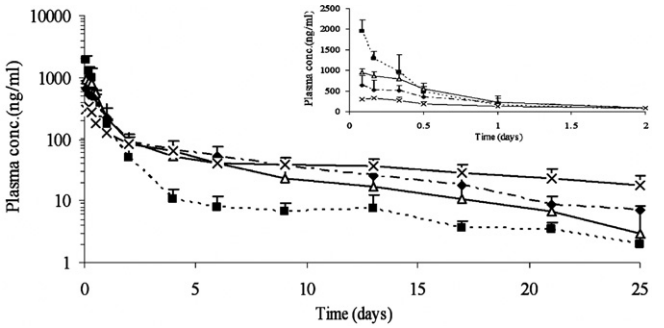

Fig. 4. Plasma concentration–time curve for the active moiety after IM injection (dose = 12.5 mg/kg, injection volume = 0.5 ml/kg) of 25 mg/g RSP-SAIB in situ systems with different contents of PLA (mean ± SD; $n = 3$). 0% PLA (■); 1% PLA (△); 5% PLA (♦); 10% PLA (×). Concentration–time curve from 0 to 2 days was scaled up and inserted in the right top of the figure.

from 12623.3 ± 5330.2 to 20202.8 ± 3877.2 ng h/ml (Table 5). The $AUC_{0-25\ day}$ of the formulation without PLA was lower than the formulations containing PLA. The steady-state concentration (C_s) was the average value of the plasma concentration from 9 to 21 day, and the C_{max}/C_s was remarkably reduced due to the increased PLA ($P < 0.05$). From day 2 to 25, a slope was fitted by plotting log (plasma concentration) against time. When the content of PLA was increased, the absolute value of the slope was reduced indicating that the plasma concentration was more stable for the 10% PLA formulation.

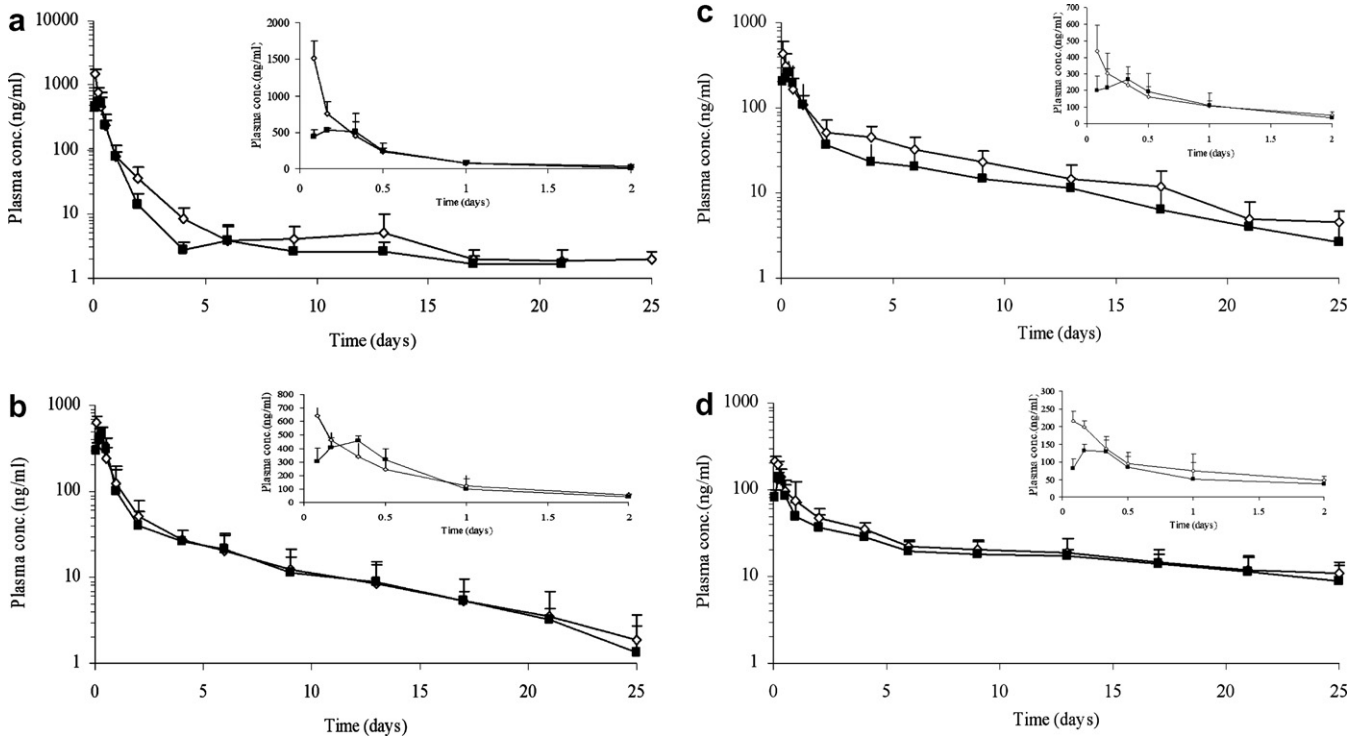

Fig. 3. Plasma concentration–time curve for RSP (◇) and 9-OH-RSP (■) after IM injection (dose = 12.5 mg/kg, injection volume = 0.5 ml/kg) of 25 mg/g RSP-SAIB in situ systems with different contents of PLA (mean ± SD; $n = 3$). (a) 0% PLA; (b) 1% PLA; (c) 5% PLA; (d) 10% PLA. Each concentration–time curve from 0 to 2 days was scaled up and inserted in the right top of the corresponding figure.

Table 5
The non-compartmental model pharmacokinetic parameters of the active moiety after IM injection (dose = 12.5 mg/kg, injection volume = 0.5 ml/kg) of 25 mg/g RSP-SAIB in situ systems with different contents of PLA

PLA content (%)	0	1	5	10
$AUC_{0-2\ day}$ (ng h/ml)	16879 ± 3828	16295 ± 3946	12086 ± 4496	7025 ± 1979
$AUC_{2-25\ day}$ (ng h/ml)	4192 ± 1268	12623 ± 5330	17150 ± 5483	20203 ± 3877
$AUC_{0-25\ day}$ (ng h/ml)	21071 ± 4845	28918 ± 7028	29236 ± 8981	27228 ± 5209
T_{max} (h)	2.0	2.0	3.2 ± 2.7	4.3 ± 2.0
C_{max} (ng/ml)	1951 ± 268	944 ± 80	640 ± 238	330 ± 34
C_{max}/C_s[a]	416 ± 176	83 ± 47	31 ± 15	11 ± 4
Slope (2–25 day)	−0.045	−0.059	−0.049	−0.027

[a] C_s was the average value of the plasma concentration from 9 to 21 day.

The SAIB in situ systems are based on the mechanism of nonsolvent induced phase separation (NIPS). The basic NIPS concept requires a material that does not dissolve in body fluids, and a material solvent that is fully or partially miscible with body fluids. Burst release is observed in these systems because the depot does not set immediately, causing some drug not to be successfully encapsulated, thus allowing free drug to be released in a burst. The dissolving of PLA in the formulation probably alters the initial release of the drug by forming a diffusional membrane around the depot after contact with the aqueous buffer. This membrane would be formed when the solvent composition at the aqueous interface changed as the solvents diffused away from the SAIB and water diffused in, causing the dissolved PLA to precipitate [23]. Therefore, PLA avoids burst release efficiently in the case of SAIB in situ systems. In the drug delivery system, SAIB was a matrix used to reserve the drug, and the membrane formed by PLA enclosed the matrix, and upon activation, the drug diffused through the membrane at a finite, controllable rate. Thus, the SAIB in situ system appears to be similar to a coated matrix preparation after administration. For coated surfaces, it has been shown that increasing the polymer concentration reduced the burst effect, and produced a more sustained release profile [24]. For higher PLA concentrations, the smaller pores of the polymer membrane formed a more compact barrier for preventing drug burst release. Besides the degradation rate of PLA was slower, causing the drug release to be more sustained. Therefore, with the help of 10% (w/w) PLA the plasma concentration was stable.

3.5. Influence of dose on PK of SAIB in situ systems

The influence of dose on PK was studied at doses of 6.25, 12.5 and 25 mg/kg using SAIB/ethanol/PLA (79:20:1, w/w) with an RSP loading of 25 mg/g. The plasma drug concentration–time curve of the active moiety is shown in Fig. 5, and the pharmacokinetic parameters are summarized in Table 6. The drug release of the 6.25 mg/kg dose was the fastest, and the plasma concentration was below the limit of detection after day 17. There was significant difference for the T_{max} between 25 mg/kg dose and the other two doses ($P < 0.05$). The T_{max} of the 25 mg/kg dose was prolonged to 4.4 ± 2.2 h, and the drug release was relatively slower than for the other two doses. The C_{max}/C_s of the 6.25 mg/kg dose was over 3-fold higher than that for the other dose ($P < 0.05$). From day 2 to 25, the slope of log (plasma concentration) against time was similar for the 6.25 and 12.5 mg/kg doses, and the absolute value was clearly less than for the 25 mg/kg dose.

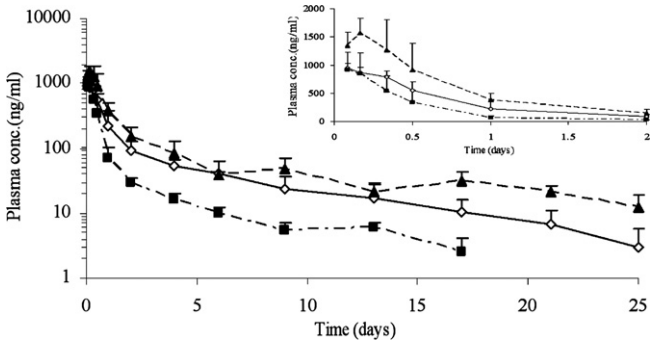

Fig. 5. Plasma concentration–time curve for active moiety after IM injection of 25 mg/g RSP-SAIB in situ systems at 6.25 mg/kg (injection volume = 0.25 ml/kg, ■), 12.5 mg/kg (injection volume = 0.5 ml/kg, ◇) and 25 mg/kg (injection volume = 1.0 ml/kg, ▲) (mean ± SD; $n = 3$). Concentration–time curve from 0 to 2 days was scaled up and inserted in the right top of the figure.

Non-linear PK was found for the SAIB in situ system after IM administration and this non-linearity was more significant for the smaller dose. Because a small volume offers a relatively larger surface area across which the dissolved drug can be released into the interstitial fluid, the absorption rates were higher. RSP was dispersed in SAIB depot similar to that which was formulated in oily vehicles.

Table 6
The non-compartmental model pharmacokinetic parameters of active moiety after IM injection of 25 mg/g RSP-SAIB in situ systems at different doses

Dose (mg/kg)	6.25	12.5	25
$AUC_{0-2\ day}$ (ng h/ml)	10026 ± 4634	16295 ± 3946	27233 ± 7633
$AUC_{2-25\ day}$ (ng h/ml)	3327 ± 502	12623 ± 5330	21302 ± 5733
$AUC_{0-25\ day}$ (ng h/ml)	13353 ± 4399	28918 ± 7028	48535 ± 10912
T_{max} (h)	2.0	2.0	4.4 ± 2.2
C_{max} (ng/ml)	918 ± 314	944 ± 80	1573 ± 253
C_{max}/C_s[a]	285 ± 118	83 ± 47	64 ± 25
Slope (2–25 day)	−0.060	−0.059	−0.037

[a] C_s was the average value of the plasma concentration from 9 to 21 day.

For the oily formulation, it was assumed that the oil droplets were spheroidal in shape after injection, and it has been found that the absorption rate constant of the oil solutions was inversely proportional to the cube root of the injection volume [25]. For the 6.25 mg/kg dose, the larger surface area led to rapid drug release and degradation of PLA and SAIB [23]. It was found that the plasma concentration of the small dose was higher in the initial stage, and decreased rapidly in the later stage, falling below 1 ng/ml after day 17. For the 25 mg/kg dose, the plasma concentration was more stable than the small dose after day 2.

3.6. Influence of drug concentration on PK of SAIB in situ systems

To study the effect of drug concentration on PK, SAIB/Ethanol/PLA (79:20:1, w/w) system was injected into rats with an RSP loading of 25 and 50 mg/g (both 0.5 ml/kg injection volume). The shape of the two plasma drug concentration–time curves was similar. However, for the 50 mg/g drug loading, the plasma level was slightly higher, and this became significant at later stage (Fig. 6). This could also be observed for the C_{max}, $AUC_{0-2\ day}$ and $AUC_{2-25\ day}$ in Table 7, and no disparity was found in the T_{max} of these two formulations. The results showed that there was significant difference for the C_{max}/C_s of two formulations ($P < 0.05$). The ratio of C_{max}/C_s for the 25 and 50 mg/g drug loading was 2.4. The smaller absolute value of the slope was reviewed with the 50 mg/g drug loading.

For the 25 mg/g drug concentration, the SAIB systems were uniform solutions, and RSP existed as molecular state in the vehicle. However, for the 50 mg/g drug concentration, RSP was not completely dissolved in the SAIB in situ system, and a part of the drug was suspended in the vehicle. Therefore, in the initial stage, the drug release rate was similar for the two formulations. However, the suspended particles acted as a drug reservoir, continuously dissolving to replenish what was being lost. This could explain why the difference in plasma concentration was more significant in the later stage.

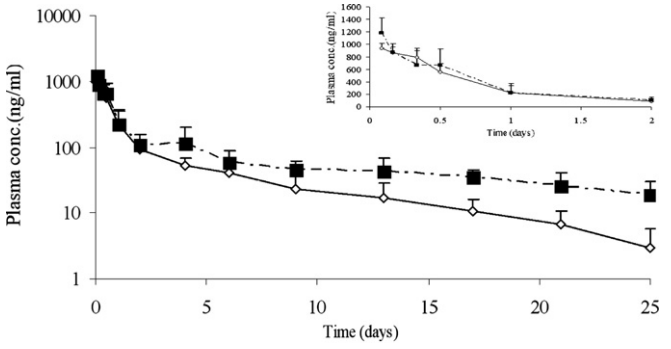

Fig. 6. Plasma concentration–time curve for active moiety after a 0.5 ml/kg IM injection of SAIB in situ systems with 25 mg/g (◇) and 50 mg/g RSP (■) loading (mean ± SD; $n = 3$). Concentration–time curve from 0 to 2 days was scaled up and inserted in the right top of the figure.

Table 7
The non-compartmental model pharmacokinetic parameters of active moiety after 0.5 ml/kg IM injection of SAIB in situ systems with different drug loading

Drug loading (mg/g)	25	50
$AUC_{0-2\ day}$ (ng h/ml)	16295 ± 3946	17207 ± 5902
$AUC_{2-25\ day}$ (ng h/ml)	12623 ± 5330	25835 ± 6488
$AUC_{0-25\ day}$ (ng h/ml)	28918 ± 7028	43041 ± 12016
T_{max} (h)	2.0	2.0
C_{max} (ng/ml)	944 ± 80	1185 ± 239
C_{max}/C_s [a]	83 ± 47	34 ± 11
Slope (2–25 day)	−0.059	−0.032

[a] C_s was the average value of the plasma concentration from 9 to 21 day.

4. Conclusions

This study was aimed at evaluating the release rate of RSP from SAIB in situ systems. The PK studies have shown that PLA can be used efficiently to reduce the burst effect. It was found that the plasma concentration was rendered stable by adding 10% (w/w) PLA. For the low dose injection, the larger surface area of depot led to rapid drug release and degradation of PLA and SAIB, the plasma concentration was higher in the initial stage, and then decreased rapidly due to vehicle degradation. In the suspended SAIB in situ system, the continuously dissolving drug particles gave a more sustained drug release.

At present, there is a long-acting formulation of RSP (Risperdal Consta™), which is encapsulated into a matrix of glycolic acid-lactate copolymer prepared as an aqueous suspension. There is gradual hydrolysis of the copolymer in the naturally occurring glycolic acid and lactic acid at the site of injection. After a single injection of Risperdal Consta™ into the gluteal muscle, the release involves a lag time of about 3 weeks, during which little drug is released from the depot. Therapeutic plasma concentrations of RSP and 9-OH-RSP are reached beginning 3–4 weeks after injection, and are maintained for an additional 2 weeks (up to 6 weeks after injection), and then fall 7 weeks after injection [26]. Therefore, it needs oral supplementation regimen to ensure a smooth transition and oral RSP has to be continued at the same dose for the first 3 weeks. However, for the RSP-SAIB in situ system including 10% PLA, high release rates in a short time can lead to therapeutic plasma concentrations in the initial stages after activation, and the sustained release of drug can lead to a stable plasma concentration (C_{max}/C_s: 11.3 ± 3.6). Furthermore, the plasma concentration will be more stable in human due to the longer half-life of 9-OH-RSP. These initial in vivo studies suggest that RSP-SAIB in situ system is a promising carrier for the sustained release of risperidone.

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