Optimized Preparation of *in Situ* Forming Microparticles for the Parenteral Delivery of Vinpocetine

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Received December 23, 2007; accepted March 3, 2008; published online March 14, 2008

A spherical symmetric design-response surface methodology was applied to optimize the preparation of vinpocetine-loaded poly(D,L-lactide-co-glycolide) PLGA *in situ* forming microparticles (ISM system). The influence of the ratio of PLGA to vinpocetine (w/w), the concentration of Tween 80 (w/v) and the volume of propylene glycol on the burst release, medium particle diameter and size distribution was evaluated. Scan electron microscopy of the optimized *in situ* microparticles exhibited spherical shape, and vinpocetine-loading mainly inside the microparticles. The data showed that the release of vinpocetine from *in situ* microparticles *in vitro* and *in vivo* lasted about 40 d. *In vivo* pharmacokinetic characteristics of the optimized *in situ* microparticles was assessed after they were intramuscularly injected into rats. HPLC method was used to determine the plasma concentration of vinpocetine. The absolute bioavailability of vinpocetine in the microparticles was 27.6% in rats, which suggested that PLGA *in situ* microparticles were a valuable system for the delivery of vinpocetine.

Key words formulation optimization; vinpocetine; *in situ* forming microparticle system; bioavailability

Vinpocetine, the chemical structure of which is shown in Fig. 1, is a vincamine derivative used for the treatment of disorders arising from cerebrovascular and cerebral degenerative diseases.[1] Over last several decades, it has been found high clinical value and little adversary effects.[2] Vinpocetine, however, is a poorly water-soluble drug (water solubility value≈5 μg/ml), and is characterized by a short half-life time (*ca.* 2 h) and significant first-pass effect.[3,4] As a consequence, its clinical use is greatly restricted by its low oral bioavailability. Therefore, a kind of controlled release dosage form for parenteral administration is preferred because it may provide enhanced clinical value over conventional oral formulations as a result of possibly promoted bioavailability.[5,6]

Until now, liquid drug-polymer formulations generating (semi-) solid microparticles (*in situ* forming micropartices, ISM) on subcutaneous or intramuscular injection have grown exponentially. The ISM system is based on an emulsion of an internal polymer phase and an external oil phase. The internal polymer phase is a solution of polymer-drug-solvents, and the external oil phase can be peanut oil, soybean oil, or propylene glycol, all of which are much biocompatible. The ISM system is formed by emulsifying the polymer phase into the external phase. The solvents used for the polymer phase can be *N*-methyl-2-pyrrolidont (NMP), triacetin, glycofurol, dimethylsulfoxide (DMSO), benzyl alcohol and benzyl benzoate, which are all water-miscible and acceptably biocompatible.[7—9] As for the polymer, (D,L-lactide) (PLA) and poly(D,L-lactide-*co*-glycolide) (PLGA) are most widely used.

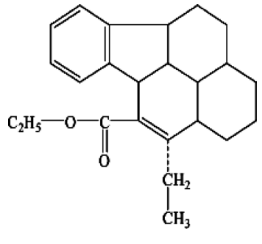

Fig. 1. The Chemical Structure of Vinpocetine

It is due to the fact that they degrade to toxicologically acceptable lactic and glycolic acids that are eventually eliminated from body.[10,11]

Instantly ISM systems are injected into aqueous tissue environment, water miscible solvents dissipate and water penetrates into the organic phase, which leads to phase separation and precipitation of the polymer.[12,13] Consequently, microparticles releasing drugs in a controlled and prolonged fashion form at the site of injection. Objectively, ISM systems have certain advantages over conventional implants or microspheres: less invasive and painful application; much more convenient and easily-controlled preparation; reduced initial release; lower investment and manufacturing costs.[14—16]

In this study, the preparation of vinpocetine-loaded ISM systems was optimized by a spherical symmetric design-response surface methodology and evaluated on the drug release behaviors *in vitro* and bioavailability *in vivo*. The obtained *in situ* microparticles presented good spherical shape. The *in vitro* and *in vivo* experiments showed that vinpocetine in the microparticles released gradually for 40 d, and that the absolute bioavailability largely increased after intramuscular injection in rats. The results indicated that ISM systems were a promising parenteral way to delivery vinpocetine.

Experimental

Materials Poly(D,L-lactide-*co*-glycolide) (PLGA) (75 : 25, M_w=25700, 0.2 dl/g) was purchased from Boehringer Ingelheim (Ingelheim, Germany). Vinpocetine was donated by Dongbei Pharmaceutical Co. (Shenyang, China). Benzyl benzoate (BB) was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Tween 80 and propylene glycol were supplied by Shenyang Chemical Reagent Factory (Shenyang, China). All other chemicals used were at least of analytical grade.

Phase-Solubility Investigation An excess amount of vinpocetine was added in 15 ml test tubes containing 10 ml different media (PBS, PBS containing SDS (0.1%, 0.3% , 0.5%, w/v), BB, Tween 80, propylene glycol). The tubes were tightly capped and shaken in a horizon shaking incubator water bath (Medical Instrument Factory, Jin Tan, China) at 37 °C. After 48 h, all the tubes were centrifuged and the supernatant was filtered through 0.45 μm membranes. The quantity of vinpocetine in samples was determined by HPLC method modified according to the literature.[17] The HPLC system was composed of a model LC-10AT pump (Shimadzu, Kyoto, Japan)

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and a model SPD-10A UV detector (Shimadzu, Kyoto, Japan). The analytical column was Diamonsil C18 (200 nm×4.6 mm, 5 μm) (Dikma, U.S.A). The injection volume was 20 μl; the mobile phase was methanol–0.1 mol/l ammonium carbonate aqueous solution (90 : 10, v/v) at a flow rate of 1.0 ml/min; the UV detector wavelength was 313 nm; column temperature was 30 °C. All the operations were carried out in triplicate.

Preparation of ISM Systems Vinpocetine and PLGA were dissolved into BB (polymer phase) first, then the ISM systems were prepared by emulsifying the polymer phase into propylene glycol by probe sonication (JY 92-2D, Ningbo Scientz Biotechnology Co., Ltd., Ningbo, China) for 2 min under ice cooling. Tween 80 was contained in propylene glycol as an emulsifier to stabilize the emulsion.

Experimental Design Preliminary experiments indicated that variables, such as polymer to drug ratio, the concentration of Tween 80, and the volume of propylene glycol greatly influenced the burst release (the accumulative release percent at 24 h), particle size (medium particle diameter), and span (particle size distribution). Hence, a spherical symmetric design-response surface methodology was used to systemically investigate the effects of these three critical formulation variables on burst release, particle size and span. The details of the design were outlined in Table 1. For each factor, the experimental range was selected, which was based on the results of preliminary experiments and took into consideration the feasibility of the preparation at extreme values. All the formulations in these experiments were prepared in duplicates.

Optical Microscopy Droplets of the optimized ISM-emulsion were observed under an optical microscope (Micro-Optic Industrial Group Co., Ltd., Xiamen, China) immediately after preparation.

Particle Size and Particle Size Distribution Particle size of the optimized ISM systems was evaluated by dispersing 1 ml ISM emulsion into 50 ml phosphate buffer pH 7.4 and being shaken in a horizontal shaker (Medical Instrument Factory, Jin Tan, China) for approximately 2 h to harden the *in situ* forming microparticles completely. The volume of phosphate buffer pH 7.4 was set to 50 ml in order to diminish the influence on the particle size and span. Then the particle size was determined by a laser particle counter (LS 230, Beckman Coulter, Inc., Fullerton, U.S.A.). The medium particle size (D_{50}, the particle size when cumulative value was 50% by volume in the particle size cumulative distribution profile) and particle size distribution (Span) were measured three times.

Span was calculated by the equation below:

$$\text{Span}=(D_{90}-D_{10})/D_{50}$$

where D_{90}, D_{10} and D_{50} was the particle size when cumulative value was 90%, 10% and 50% respectively. No significant differences between particle size or particle size distribution were observed when shaking ISM systems for between 1 h and 3 h.

Scanning Electron Microscopy (SEM) First, the dried *in situ* forming microparticles were coated for 15 min under an argon atmosphere with a gold-palladium (JFC-1200, JEOL, Japan). Then they were observed with a scanning electron microscope (SSX-550, Shimadzu, Kyoto, Japan) to investigate the surface morphological characteristics.

***In Vitro* Drug Release Studies** Generally, the dialysis bag method is applied in the *in vitro* release experiment of implantable controlled drug delivery system. In this study, the optimized ISM system containing 80 mg vinpocetin was placed into dialysis bags (M_w cut-off 8000—14000) (n=3). The bags were then put into 500 ml phosphate buffer pH 7.4 (0.5% (w/v) SDS was added to maintain the sink condition) in a horizontal shaking incubator water bath (Medical Instrument Factory, Jin Tan, China) at 37 °C at a rate of 30 rpm. At predetermined time intervals, 5 ml samples were withdrawn and replaced by fresh release medium. The vinpocetine content was assayed using the same HPLC method as was described in section 'Phase-Solubility Investigation.'

Table 1. Independent Variables and Correspondent Values for the Optimization of ISM Systems Using the Spherical Symmetric Design-Response Surface Methodology

Independent variables	Levels				
	−1.732	−1	0	1	1.732
X_1	0.5	0.71	1	1.289	1.5
X_2	0.5	1.24	2.25	3.26	4
X_3	1	1.423	2	2.577	3

X_1 represents polymer to drug ratio (w/w), X_2 represents Tween 80 concentration (w/w), X_3 represents the volume of propylene glycol (ml).

Bioavailability Study Bioavailability study of vinpocetine were carried out using male Wistar rats weighing 200—250 g (Animal experimental center of Shenyang Pharmaceutical University). All experiments were conducted abiding by the Principles of Laboratory Animal Care and approved by the Department of Laboratory Animal Research at Shenyang Pharmaceutical University. All the rats were housed in a room with controlled temperature and humidity, fasted overnight but allowed to get free access to water before experiments. Five rats were administrated with vinpocetine-BB solution (2 mg/ml) *via* sublingual vein injection at a single dose of 8 mg/kg. Blood samples were collected at 0, 0.08, 0.17, 0.33, 0.50, 1.0, 1.50, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0 h after administration. Another five rats were orally administrated with vinpocetine-BB solution (2 mg/ml) at a single dose of 8 mg/kg to get the corresponding bioavailability.

Still another five rats were administrated with the optimized ISM system *via* the intramuscular injection in the back legs at a single dose of 80 mg/kg, respectively. Blood samples were collected from suborbital vein at 1, 2, 3, 4, 6, 8, 12 h, 1, 2, 3, 4, 5, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 d after administration. All the samples were centrifuged at 4000×$\boldsymbol{g}$ for 10 min. Plasma were separated and stored at −20 °C until analysis.

The determination of vinpocetine in plasma was carried out using HPLC method.[18] The HPLC system was composed of a model LC-10AT pump (Shimadzu, Kyoto, Japan) and a model SPD-10A UV detector (Shimadzu, Kyoto, Japan). The analytical column was Diamonsil C18 (200 nm×4.6 mm, 5 μm) (Dikma, U.S.A.). The injection volume was 60 μl; the mobile phase was methanol–water–glacial acetic acid (70 : 30 : 0.1, v/v/v); the flow rate was 1.0 ml/min; the UV detector wavelength was 273 nm.

The pharmacokinetic parameters were acquired with the 3p97 program (a practical pharmacokinetic program developed by the Chinese Society of Mathematical Pharmacology). The absolute bioavailability was calculated using the following equation:

$$F_a(\%)=\frac{(AUC/D)A}{(AUC/D)B}\times 100\%$$

Where F_a was the absolute bioavailability, AUC the area under the plasma concentration–time curve, D the dose administrated, A the intramuscular administration of the ISM system or the oral administration of vinpocetine-BB solution, and B the intravenous administration of vinpocetine-BB solution.

Data Analysis Statistical comparisons were made by Student's t-test using a SAS Version 8.0 software during the optimization of the ISM systems. Differences between values were considered significant when p values were less than 0.05.

Results and Discussion

Solubility Study Vinpocetine has been reported to be almost insoluble in water, with an aqueous solubility of about 5 μg/ml at 37 °C.[19] To study the kinetics of *in vitro* release, the aqueous solubility of vinpocetine needed increasing so as to maintain the sink condition. Furthermore, investigating the solubility of vinpocetine in different phases used in this paper would ensure that ISM systems were prepared successfully. The solubility of vinpocetine in various mediums was shown in Table 2. The results indicated that the aqueous solubility of vinpocetine increased from 6.41 to 226.45, 771.74 and 1639.37 μg/ml by corresponding addition of 0.1%, 0.3% and 0.5% SDS. The sink condition was able to be maintained by adding 0.5% SDS into release medium and frequent replacement of fresh buffer during the *in vitro* release experiment. Vinpocetine was of the solubility of 110.38 mg/ml in BB, which meant that enough vinpocetine could be loaded in ISM systems. Comparatively speaking, vinpocetine was much less soluble in propylene glycol (9.11 mg/ml) and Tween 80 (14.62 mg/ml).

Optimization of Formulation The spherical symmetric design-response surface methodology constitutes an alternative approach because it offers the possibility of investigating

quite a few variables at different levels with only a limited number of experiments.[20,21] So far, it has already displayed much practical importance.

Table 3 displayed the experimental results concerning the tested variables on burst release, particle size and span. The three regressor values ranged from 6.64 to 22.54% by weight, 36 to 125 μm, and 1.131 to 1.604. To investigate the overall influence of the tested variables, the overall desirability (OD) was introduced. The mathematical relationship between factors and parameters was generated by response surface regression analysis in statistical software SAS version 8.0. The three-dimensional response surface plots for the most statistical significant variables on the evaluated regressors were shown in Fig. 2. The response surface diagrams indicated that the bigger the PLGA to vinpocetine ratio or the volume of propylene glycol was, the larger the particle size, the smaller the span and burst release were. On the other hand, higher Tween 80 concentration resulted in smaller particle size, greater span and burst release. To be more specific, PLGA to vinpocetine ratio and Tween 80 concentration significantly influenced the burst release, particle size and span, and all three variables exerted some influence on OD.

The optimized variables showed a good fit to the third-order polynomial equation, with correlation coefficient (r) of 1.000, 0.9998, 0.8973 and 0.8864. The statistical analysis of the results generated the following polynomial equations:

$$\begin{aligned}\text{burst release} = &-8.55311-17.26177\times X_1^2+0.01147\times X_2^2\\ &+0.61742\times X_3^2-2.37854\times X_1X_2+1.17626\times X_2X_3\\ &-4.12643\times X_1X_3+4.629\times X_1^3-0.00192\times X_2^3\\ &-0.13415\times X_3^3+0.2645\times X_1^2X_2-0.065\times X_2^2X_3\\ &+0.516\times X_1^2X_3+26.11836\times X_1\ (r=1.0000,\ p=0.0025)\end{aligned}$$

$$\begin{aligned}\text{particle size} = &-13718-28297\times X_1^2+9.5276\times X_2^2+939.82\times X_3^2\\ &-3454.84296\times X_1X_2+1697\times X_2X_3-6075\times X_1X_3\\ &+7774\times X_1^3-1.742\times X_2^3-202.23\times X_3^3+383.12\times X_1X_2^2\\ &-94.24\times X_2^2X_3+759.15\times X_1^2X_3\ (r=0.9998,\ p=0.0402)\end{aligned}$$

$$\begin{aligned}\text{span} = &\ 13.817-298.55\times X_1^2-7.291\times X_2^2+66.349\times X_1X_2+84.069\times X_1X_3\\ &+561.67\times X_1^3-5.517\times X_2^3-41.74\times X_3^3-14.77\times X_1X_2^2\\ &-33.38\times X_2X_3^2+325.49\times X_1X_3^2-693.30\times X_1^2X_2\\ &+29.667\times X_3X_2^2\ (r=0.8973,\ p=0.478)\end{aligned}$$

$$\begin{aligned}\text{OD} = &\ 0.48628-0.76743\times X_2-1.88424\times X_1^2+1.35736\times X_1X_2\\ &+0.41139\times X_1X_3+0.6619\times X_1^3-0.10889\times X_1X_2^2\\ &-0.09298\times X_1^2X_3\ (r=0.8864,\ p=0.0073)\end{aligned}$$

where X_1, X_2, X_3 represented the values of PLGA-vinpocetine ratio, Tween 80 concentration and the volume of propylene glycol respectively.

According to the three-dimentional response surface plots, the optimized range of the tested variables were listed in Table 4. The best values of the them were 1.2, 2.8 and 2 respectively, and the experimental values of two batches prepared were rather close to the predicted values with low percentage bias, suggesting that the optimized formulation was reliable and reasonable (Table 5).

Characteristics of ISM Systems A photograph of the optimized ISM emulsion was displayed in Fig. 3, where intact droplets could be observed. On injection into PBS pH 7.4, the ISM system solidified and formed microparticles. As was indicated in Fig. 4, the *in situ* microparticles had nearly smooth surface. The reason had something to do with the fact that relatively low solubility of vinpocetine in Tween 80 (14.62 mg/ml) and propylene glycol (9.11 mg/ml) caused it to stay inside rather than the surface during the formation of the microparticles.

Syringeability and injectability problems were associated with *in situ* forming systems which might be of high viscosity, so the ease of the injection into muscular or subcutaneous tissues was a crucial consideration. During our experiments, it was found that all the fifteen ISM systems were able to be injected through 18-gauge needles into tissues with little effort. This was mainly because propylene glycol, the external phase of ISM systems, was of a relatively low viscosity.

The *in vitro* burst release of the optimized ISM system was only 6.64%. As could be observed in Fig. 5, vinpocetine re-

Table 2. Solubility of Vinpocetine in Different Mediums at 37 °C

Medium	Solubility (μg/ml)
PBS	6.41
PBS (0.1%, w/v SDS)	226.45
PBS (0.3%, w/v SDS)	771.74
PBS (0.5%, w/v SDS)	1639.37
BB	110.38×10^3
Propylene glycol	9.11×10^3
Tween 80	14.62×10^3

Table 3. Response Values of Different Variables for the Optimization of ISM Systems Using the Spherical Symmetric Design-Response Surface Methodology

No.	X_1	X_2	X_3	Burst release	Particle size	Span	OD
1	−1	−1	−1	0.1652	85	1.251	0.329212
2	−1	−1	1	0.1468	93	1.202	0.369282
3	−1	1	−1	0.1903	58	1.423	0.175959
4	−1	1	1	0.1825	70	1.338	0.255487
5	1	−1	−1	0.1386	118	1.139	0.173419
6	1	−1	1	0.1196	125	1.131	0
7	1	1	−1	0.1647	83	1.156	0.375294
8	1	1	1	0.1563	90	1.14	0.381501
9	0	0	−1.732	0.1461	68	1.355	0.36295
10	0	0	1.732	0.1292	73	1.256	0.457124
11	0	−1.732	0	0.1308	112	1.604	0
12	0	1.732	0	0.1628	36	1.267	0.440812
13	−1.732	0	0	0.2254	36	1.488	0
14	1.732	0	0	0.0664	89	1.131	0.564406

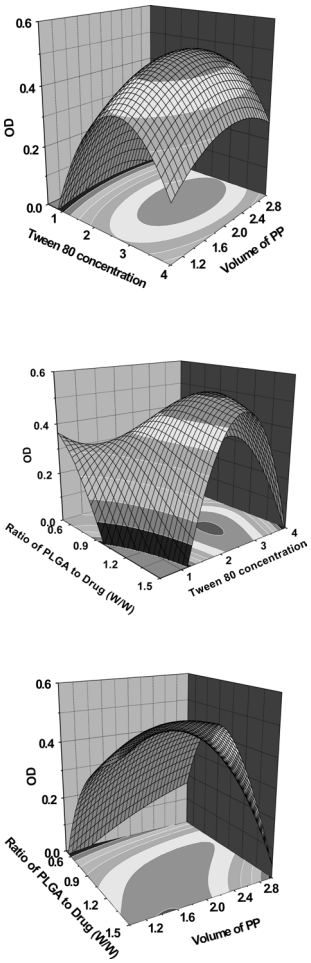

Fig. 2. Three Dimensional Response Plots Showing the Variation in OD with the Changes in the PLGA to Vinpocetine Ratio, Tween 80 Concentration and the Volume of Propylene Glycol

Table 4. The Optimized Range of Tested Variables

Variables	PLGA to vinpocetine ratio (X_1)	Tween 80 concentration (X_2)	Volume of propylene glycol (X_3)
Optimized range	1.1—1.3	2.2—3.2	1.5—2.6

Table 5. Comparison of the Observed Value and the Predicted Value under Predicted Optimum Condition

Observed values				Predicted value	Bias
Burst release (%)	Particle size (μm)	Span	OD		
6.64	59	1.131	0.564	0.534	5.7%

leasing from *in situ* microparticles lasted about 40 d in a uniform and prolonged manner. The polymer phase of ISM systems was emulsified into propylene glycol, which formed a partial barrier between the aqueous medium and the internal polymer solution (Fig. 3). Moreover, another reasonable explanation was that low solubility of vinpocetine in Tween 80 (14.62 mg/ml) and propylene glycol (9.11 mg/ml) caused it to stay in the inner polymer phase as it was encapsulated within

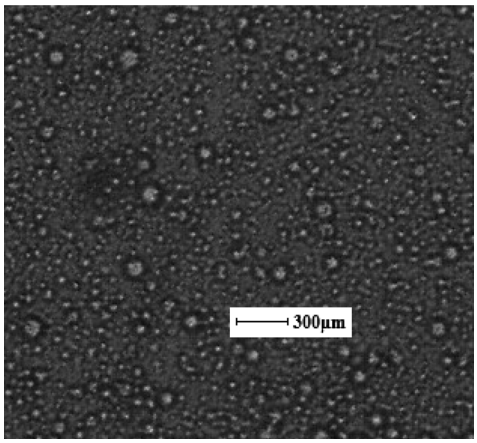

Fig. 3. The Photograph of the Optimized ISM Emulsion

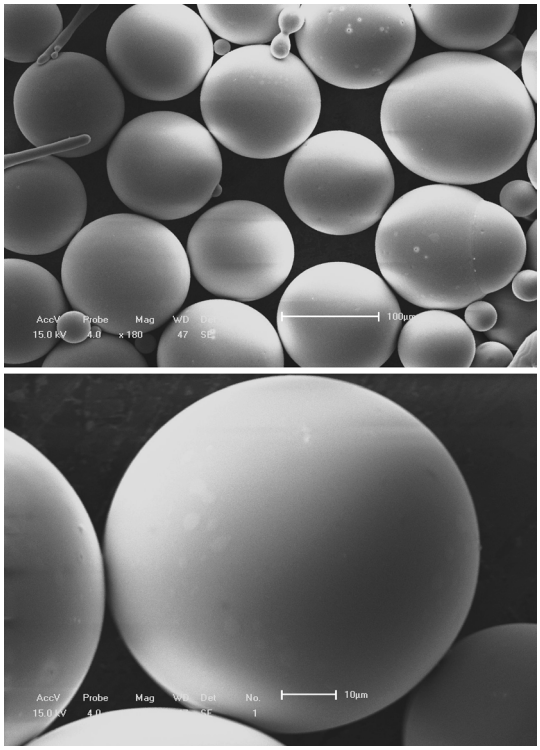

Fig. 4. Scanning Electron Micrographs of Microparticles (×180) Originating from Optimized ISM System in PBS pH 7.4

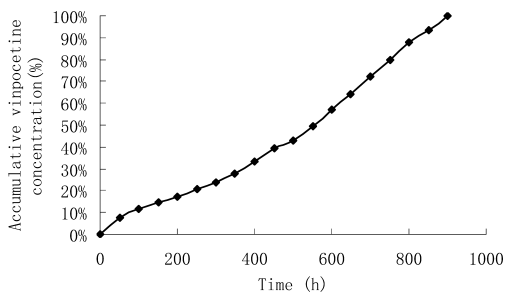

Fig. 5. *In Vitro* Release of Vinpocetine from the Optimized ISM System in pH 7.4 PBS Containing 0.5% SDS

the precipitated microparticles (Fig. 4). One thing still worth mentioning was that BB also contributed to the reduction of initial drug release owing to low solvent/water affinity.[22)]

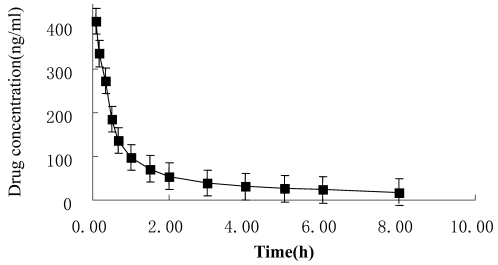

Fig. 6. The Mean Plasma Concentration–Time Profile of Vinpocetine after Intravenous Administration of the Vinpocetine-BB Solution ($n=5$)

Table 6. Pharmacokinetic Parameters for Vinpocetine-BB Solution in Rats after Intravenous Injection (Mean±S.D., $n=5$)

Parameters	Value	Parameters	Value
A (ng/ml)	408.93±7.56	V_c (mg/(ng/ml))	0.004±0.0001
B (ng/ml)	93.00±0.98	K_{21} (1/h)	0.70±0.003
α (1/h)	2.75±0.04	K_{10} (1/h)	1.05±0.01
β (1/h)	0.26±0.002	K_{12} (1/h)	1.26±0.01
$t_{1/2\alpha}$ (h)	0.28±0.002	AUC (ng/h·ml)	535.94±10.6
$t_{1/2\beta}$ (h)	2.97±0.03	C_L (l h/kg)	0.004±0.0001

Bioavailability Evaluation The mean plasma concentration–time profile of vinpocetine-BB solution after intravaneous injection was shown in Fig. 6. The Pharmacokinetic parameters were listed in Table 6. According to the data obtained, vinpocetine plasma concentration declined rapidly in the first 2 h. And the distribution half-life time was very short whilst the elimination half-life was comparatively long, which indicated that vinpocetine was rapidly transported to tissues or organs from blood, and cleared slowly from blood.

The plasma concentration data of vinpocetine were best fitted to two-compartment model. Figure 7 showed the plasma vinpocetine concentration–time profile of the optimized ISM system after intramuscular injection. The total vinpocetine concentration fluctuated and lasted over 40 d, which meant that frequent administration of vinpocetine was able to be avoided. The absolute bioavailability of the optimized ISM system was 27.6%, while that of orally administrated vinpocetine-BB solution at a dose of 8 mg/kg was just 8.9%.

It was reported that the absolute bioavailability (F_a) of vinpocetine tablets after oral administration in humans was around 7%.[23—25] As could be easily observed, the absolute bioavailability of the optimized ISM system after intramuscular administration was much higher. The optimized ISM system also overwhelmingly outweighed vinpocetine-BB solution in absolute bioavailability that was orally administrated.

Reducing particle size is one of the key ways of promoting the *in vivo* performance of poorly water soluble drugs. The hardened *in situ* microparticles were of particle size of 59 μm. Due to their small size, there would surely be increase in surface area and saturation solubility, then in release and dissolution rate. Subsequently, higher plasma concentration would be achieved. Besides, parenteral administration could avoid first-pass effect which would be extensively experienced by oral routine.

Another advantage of ISM system is the protection of vinpocetine from chemicals as well as enzymatic degradation,

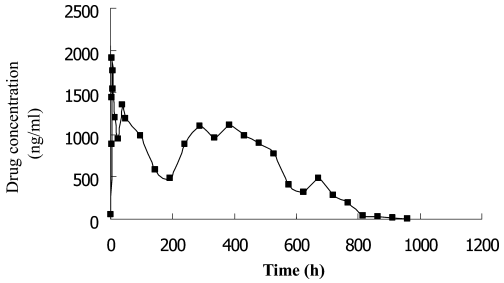

Fig. 7. The Mean Plasma Concentration–Time Profile of Vinpocetine after Intramuscular Administration of the Optimized ISM ($n=5$)

thereby delaying *in vivo* metabolism. It is reported that different cytochrome P450 (CYP) isozymes are able to catalyse the apovincaminic acid, the main pathway of vinpocetine metabolism.[26,27] Incorporated into *in situ* microparticles which are solid matrixes, vinpocetine can reduce its exposure to enzymatic degradation following absorption. In addition, the surfactant Tween 80 may also slightly inhibit CYP, which elevates vinpocetine absorption to some degree.[28]

From the *in vivo* pharmacokinetic data, it could be safely concluded that the optimized ISM system significantly improved the absolute bioavailability compared with vinpocetien-BB solution and conventional formulations. Such a kind of system opened up new perspectives for the formulation of vinpocetine. The poor aqueous solubility of vinpocetine makes it difficult to prepare parenteral formulations. To date, only a transfusion parenteral formulation is available for clinical use, but it needs multiple administrations. So, the ISM systems can not only be formulated for parenteral use, but also enhance the absorption of vinpocetine.

Conclusion

The vinpocetine-loaded ISM system was optimized using the spherical symmetric design-response surface methodology by fitting a third-order model to the response data. The experimental value of the *in situ* microparticles prepared under the optimum condition was significantly close to the predicted value with low percentage bias. The release of vinpocetine in *in situ* microparticles *in vitro* and *in vivo* lasted about 40 d. And the intramuscular injection of the optimized ISM system enhanced the absolute bioavailability of vinpocetine to a large extent, which indicated that such a kind of systems were an attractive alternative to the conventional formulations.

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