Effects of Formulation Parameters on Encapsulation Efficiency and Release Behavior of Risperidone Poly(D, L-lactide-co-glycolide) Microsphere

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A 4-week sustained release risperidone biodegradable poly(D, L-lactide-co-glycolide) (PLGA) microsphere for the therapy of schizophrenia, the effects of formulation parameters on encapsulation efficiency and release behavior were studied. The risperidone PLGA microspheres were prepared by O/W solvent evaporation method and characterized by HPLC, SEM, laser particle size analysis, GC and HPLC-MS. The results indicated that the morphology of the risperidone PLGA microspheres presented a spherical shape with smooth surface, the particle size was distributed from 32 to 92 μm and the drug encapsulation efficiency was influenced by homogeneous rotation speed, intrinsic viscosity, carboxylic terminal group, the polymer concentration in the oil phase and the molecular weight of the polymer. These changes were also reflected in drug release. When the Mw of the polymers increased from *ca.* 28000 to *ca.* 90000, the initial burst release of risperidone PLGA microspheres decreased from 13 to 0.8% and the sustained-release could be extended to 4 weeks. Pharmacokinetic study on beagle dogs showed that the 4-week sustained release profile of the risperidone loaded microspheres prepared with 75253A was verified. The PLGA 75253A and 75255A show the potential as excipients for the monthly sustained release risperidone PLGA microspheres due to higher encapsulation efficiency and almost zero-order release kinetics of release profile.

Key words risperidone; poly(D, L-lactide-co-glycolide); microsphere; formulation parameter; release behavior

Drug therapy is one of the normal treatment methods for schizophrenia. It is important to use drug maintenance therapy to prevent relapse, after an acute psychotic episode has been resolved and the patients are free of overt psychotic symptoms.[1] Long-acting controlled drug delivery systems are presently available as drug maintenance therapy for clinical practice, and long-acting depot dosage therapy has allowed psychiatrists to develop the full therapeutic potential of maintenance medication.[2]

Biodegradable polymer microspheres have been extensively investigated as drug carriers in controlled drug delivery systems,[3] which have several advantages over oral dosage forms: (a) less frequent administration and reduced total dose; (b) improved compliance of patients; (c) the extended duration of drug effect and more predictable absorption; (d) fewer extra pyramidal side-effects and reduced medical workload.[2] Among many biodegradable polymers investigated, poly(D,L-lactide-co-glycolide) (PLGA) has attracted much attention due to its good biodegradable and biocompatible properties. Molecular weight and copolymer types of the polymers could mainly control the drug release rate.[4,5]

Risperidone, an atypical antipsychotic drug, is a benzisoxazole derivative which binds to the serotonin type 2 (5-HT_2), dopamine D_2 and alpha1-adrenergic receptors with high affinity. The chemical name is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido [1,2-*a*]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.[6] It would be beneficial to develop alternative depot delivery systems containing risperidone to treat schizophrenia. The microencapsulation of antipsychotics using biodegradable PLGA polymer for depot controlled release is interesting and attractive.[2] The API (Active Pharmaceutical Ingredient) could be loaded directly into the PLGA microspheres during production. The microspheres could be suspended in an aqueous solution and then readily injected intramuscularly rapidly every two or four weeks.[2] The already marketed product of risperidone encapsulated in poly(D,L-lactide-co-glycolide) (PLG) microspheres (Risperdal Consta by Johnson & Johnson Corp. U.S.A.) were manufactured using a water-based solvent extraction process, its release profile included an initial drug release with about 3.5%, a 3-week initial lag period, and main release between weeks 4—5.[7] The patients who use the Risperdal Consta for the schizophrenia treatment must take some oral antipsychotic supplementation during the first 3 weeks. In order to develop a 4-week steadily sustained release risperidone PLGA microspheres without lag period to reduce extra pyramidal side and less frequent administration, the risperidone PLGA microspheres for monthly sustained release were studied in this paper.

There are several methods to prepare PLGA microspheres, for example, spray-drying method, the emulsion solvent evaporation method and phase-separation method. The O/W solvent evaporation method was chosen to prepare risperidone PLGA microspheres in this study, because risperidone is a lipophilic compound. The effects of a series of formulation parameters of emulsion on the microencapsulation and release behavior of risperidone PLGA microspheres were also investigated.

Experimental

Materials Risperidone 20070603 was supplied by Jiangsu Enhua Pharmaceutical Co., Ltd. Poly(D, L-lactide-co-glycolide) (PLGA) 75252A, 75253A, 75255A, 75257A, 75257E (lactide: glycolide ratio, 75 : 25) were purchased from Lakeshore biomaterials (U.S.A.); properties of commercial PLGAs are listed in Table 1. Poly(vinyl alcohol) (PVA, 87—89% hydrolyzed, Typical Mw 13000—23000) was supplied by Sigma-Aldrich (Stein-

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Table 1. Characteristics of PLGA Polymers (Lactide : Glycolide Ratio, 75 : 25)

PLGA 75 : 25	Intrinsic viscosity (dl/g)	Weight average molecular weight (M_w in D_a)	Polydispersity (M_w/M_n)	End group
7525-2A	0.20	18k	3.0	Uncapped (–COOH)
7525-3A	0.31	28k	1.6	Uncapped (–COOH)
7525-5A	0.52	67k	1.8	Uncapped (–COOH)
7525-7A	0.74	90k	1.7	Uncapped (–COOH)
7525-7E	0.76	110k	1.5	Capped (–ester)

Table 2. Formulations Processing Conditions and Characteristics of Risperidone PLGA Microspheres

Batch	PLGA	PLGA concentration[a)]	DCM (ml)	Homogenization speed (rpm)	PVA concentration	Theoretical drug loading	Actual drug loading	Encapsulation efficiency	Particle size (μm) (n=3)
1	75252A	250	4	2000	0.5%	33.40%	29.31%	87.93%	42.88±0.15
2	75253A	250	4	2000	0.5%	33.40%	30.55%	91.65%	54.14±0.08
3	75255A	250	4	2000	0.5%	33.40%	32.16%	96.48%	63.94±0.22
4	75257A	250	4	2000	0.5%	33.40%	33.04%	99.12%	67.85±0.60
5	75257E	250	4	2000	0.5%	33.40%	30.67%	92.01%	69.78±0.11
6	75253A	125	8	2000	0.5%	33.40%	29.62%	88.86%	40.25±0.31
7	75253A	500	2	2000	0.5%	33.40%	32.34%	97.02%	90.71±0.14
8	75253A	250	4	1000	0.5%	33.40%	31.46%	94.38%	90.34±0.20
9	75253A	250	4	1500	0.5%	33.40%	31.11%	93.33%	80.31±0.23
10	75253A	250	4	2500	0.5%	33.40%	30.03%	90.09%	52.56±0.26
11	75253A	250	4	2000	0.5%	50.00%	44.03%	88.06%	61.58±0.26
12	75253A	250	4	2000	0.5%	25.00%	23.86%	95.44%	42.52±0.17
13	75253A	250	4	2000	0.2%	33.40%	31.40%	94.20%	86.15±0.50
14	75253A	250	4	2000	1.0%	33.40%	30.28%	90.84%	48.51±0.14
15[a)]	75253A	125	8	2000	0.5%	33.40%	22.89%	68.67%	32.10±0.51
16[a)]	75253A	125	8	1000	0.5%	30.00%	28.80%	95.87%	92.07±0.27

a) The ratio of O/W of formulation 15 and 16 was 1 : 187.5, other formulations were 1 : 375. All microspheres were prepared at room temperature.

heim, Germany). Dichloromethane (DCM, Analytical reagent grade) was supplied by Beijing Chemicals Company (Beijing, China). All other chemicals or solvents were of reagent or analytical grade.

Preparation of Risperidone PLGA Microspheres The preparation formulations of risperidone PLGA microspheres are shown in Table 2. The risperidone PLGA microspheres were prepared using o/w solvent evaporation method which was used widely in the preparation of microspheres.[8)] Briefly, 1.0 g of PLGA polymer and 0.5 g of risperidone were dissolved in DCM to form organic phase (Table 2), and then the organic phase was injected into 1500 ml of 0.5% PVA aqueous solution under homogenization at various rates for 3 min to be emulsified at room temperature (T). Then the risperidone PLGA microspheres were solidified while DCM being extracted for 4 h under stirring at 100 rpm. The solidified microspheres were filtrated with a 154 μm sieve and a 10 μm sieve, washed for 3 times with deionized water to remove PVA and then lyophilized (CHRIST ALPHA 1-4, Germany), and we stored the risperidone PLGA microspheres in a vacuum desicator at 4 °C. Mannitol aqueous solution was added when performing freeze drying to prevent microspheres from aggregation.

Scanning Electron Microscope Analysis Surface morphology of the risperidone PLGA microspheres was investigated by an electron probe microanalyzer (JXA-8100, JEOL Ltd., Tokyo, Japan). Before analyzing the samples, the risperidone PLGA microspheres were coated with platinum under the vacuum condition.

Particle Size Analysis The mean size (volume average particle diameter) and size distribution of all risperidone PLGA microspheres were analyzed by a laser diffraction particle size analyzer (LS 13320, Beckman Coulter Inc., U.S.A.). The powder of the risperidone PLGA microspheres was suspended in water directly, and the amount added was between 8% and 12% in obscuration level. Particle size distribution was described by mean diameter.

Assay of Residual DCM in the Risperidone PLGA Microspheres Gas chromatography (GC-14C, SHIMADZU, Japan) was used to determine the residual DCM in the risperidone PLGA microspheres. Approximately 25 mg of microspheres were dissolved in 1 ml of internal standard. One milliliter *N*,*N*-dimethyl formamide of 0.05 μl of ethyl acetate was used as internal standard. The sample was injected into the GC system for analysis. The condition was: Rtx-17 column of 0.25 μm×30 m (0.25 mm ID, SHIMADZU, Japan); and high purity helium (≥99.99%) as carrier gas with flow rate 30 ml/min; injection temperature at 200 °C, with FLD detector.

Determination of the Encapsulated Risperidone in the Microspheres Microspheres containing risperidone (10 mg) were dissolved in 1 ml of acetone. The resulting solution was then diluted with 0.01 N hydrochloric acid. The media was filtered (Millex-HV, 0.45 μm, Fisher Scientific, Pittsburgh, PA, U.S.A.) and analyzed by a reverse phase HPLC. The HPLC system consists of a Waters 600 pump, and a dual wavelength UV absorbance detector set at 278 nm. The mobile phase consisted of methanol : water : triethylamine (80 : 19.5 : 0.5 (v/v/v), adjusted to pH 10.22 with HAc). The analytical column was a zorbax extend-C18 (4.6 mm×250 mm, pore size 5 μm) (Agilent). The flow rate was set at 1 ml/min. The retention time of risperidone was 4.02 min, and total run time of HPLC analysis was 5 min. The chromatograph was analyzed by Waters Chromatography System (Model 203, software). The risperidone content was calculated with external standard method.

$$\text{drug loading (\%)} = (\text{weight of drug in microspheres} / \text{weight of microspheres}) \times 100\%$$

$$\text{entrapment efficiency (\%)} = (\text{drug loading (\%)} / \text{theoretical drug loading (\%)}) \times 100\%$$

***In Vitro* Release of the Risperidone PLGA Microspheres** Approximate 10 mg of risperidone PLGA microspheres were quantitatively transferred to a 15 ml screw-cap centrifuge tube and incubated with 6 ml of 50 mM phosphate buffer (pH 7.4) containing 0.02% Tween 80 and 0.05% sodium azide at 37 °C in water bath oscillator (100 rpm). At predetermined intervals, the samples were centrifuged, and 4 ml of the supernatant was extracted, and replaced with fresh buffer to maintain sink conditions. The risperidone PLGA microspheres were vortexed for resuspension and put back into the incubator to agitate the suspension continuously throughout the release experiment, in order to prohibit microspheres from aggregation and sedimentation. The risperidone concentration in the supernatant was detected by HPLC analysis using the same method.

***In Vivo* Release Studies in the Risperidone PLGA Microspheres** Animal experiments were conducted according to protocols approved by the Animal Care and Use Committee of Jilin University. The beagle dogs

(10±1.0 kg) were supplied by Experiment Animal Center of Jilin Tianyao Science and Technology Co., Ltd. *In vivo* study of risperidone loaded microspheres prepared with 75253A was carried out on beagle dogs (n=3). Each animal was injected intramuscularly (i.m.) with the risperidone PLGA microspheres (Batch 16), the doses administered to beagle dogs were designed according to 4.35 mg/kg ([893 μg (dose of risperidone per day 12.5 mg Risperdal Consta for 2 weeks)/60 kg (body weight)/28.80% (actual drug loading of the microspheres)×28 d (4 weeks)]$_{human}$×3 (the dose conversion factors of body weight between dog and human)).[9,10]

The risperidone PLGA microspheres were suspended in the viscosity solution containing sterile carboxymethylcellulose sodium (0.5%), NaCl (0.9%) and Tween 80 (0.1%), and then 2 ml of the microspheres were injected intramuscularly (i.m.). Before and during the sampling time, the animals had free food and water. The blood samples were collected at preset time intervals 0.125, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36 and 38 d into heparinized tubes after drug administration. Plasma was separated by centrifugation at 15000 rpm and 4 °C for 5 min. The serum samples were frozen and stored at −70 °C until analysis. The drug content of microspheres *in vivo* was determined by a HPLC-MS (SCIEX API4000 triple–quadrupole mass spectrometer) and conducted as concentration of risperidone obtained in ng/ml and cumulative release percentage of plasma at various time points.[11]

Results and Discussion

Morphological Studies, Particle Size and Residual DCM Analysis in the Risperidone PLGA Microspheres The morphology of the risperidone PLGA microspheres prepared with PLGA 75253A showed spherical and smooth characteristics as visualized in SEM images, with nonporous surface (Fig. 1).

Particle size is one of the important characteristics of microspheres, because of its effects on degradation rate, drug loading and initial burst release of microspheres.[12] The average particle diameters of risperidone PLGA microspheres were from 32 to 92 μm with a good dispersibility in Table 2.

The residual DCM contents in all risperidone PLGA microspheres were below 600 ppm, which was in accord with the requirements of the ICH standard.

Effects of Formulation Parameters on Encapsulation Efficiency The encapsulation efficiency is highly influenced by various parameters, such as the polymer concentration in the oil phase, intrinsic viscosity, carboxylic terminal group and molecular weight of polymers.[13] The encapsulation efficiency increased significantly from 87.93% for PLGA 75252A (Mw *ca.* 28000) microspheres to 99.12% for PLGA 75257A (Mw *ca.* 90000) microspheres (Table 2), a higher Mw, a higher drug encapsulation. But PLGA 75255A and 75257E microspheres gave different results. Although the molecular weight of PLGA 75257E was higher than that of PLGA 75255A and the microspheres were prepared under the same condition, the encapsulation efficiency (92.01%) of the PLGA 75257E microspheres is lower than that of 96.48% in the PLGA 75255A microspheres. The lower content of carboxylic terminal group in the case of PLGA 75257E, which is ester terminated, may lead to a less compatible with amino group-contained risperidone than that of 75255A. The nature of the terminal groups of polymer is particularly important to the polymer–drug compatibility.[14]

Either higher Mw of PLGA or higher concentration of polymer in oil phase increases the drug encapsulation of PLGA microspheres, because an increase in the viscosity of the oil phase prevents API from diffusion (Table 2). However, an increase in the concentration of PVA in the external phase leads to a decrease in the encapsulation efficiency. It might be explained by that the solubility of risperidone is increased in aqueous PVA solution.[15]

The particle size has an impact on encapsulation efficiency of risperidone PLGA microspheres (Table 2). Smaller microspheres show a low drug encapsulation due to the higher surface/volume ratio, so the drugs have more potential to be solved in PVA aqueous external phase during the solidification of the droplet.[6] Other preparation parameters which have significant influence on encapsulation efficiency are shown in Table 2.

Effects of Formulation Parameters on *in Vitro* Release of Risperidone from Microspheres As reported in an earlier research, the drug release of PLGA microspheres is impacted by numerous parameters, such as the polymer molecular weight, the physicochemical properties of drug, particle size of microspheres, preparation process, *etc.*[15] To investigate the effects of formulation parameters on *in vitro* release of risperidone from microspheres, a series of formulation of risperidone PLGA microspheres were designed and prepared by the O/W solvent evaporation method (Table 2). Results showed that the parameters during the preparation of the microspheres had significant influence on the *in vitro* release behavior of risperidone PLGA microspheres.

The releases of five types of risperidone PLGA microspheres prepared with the same polymer concentration of 250 mg ml^{-1} were investigated (Fig. 2). The drug release rate of PLGA 75252A (Mw *ca.* 28000) microspheres was the fastest among all the risperidone PLGA microspheres prepared. The low molecular weight of PLGA 75252A may increase water permeation and the diffusion of the drug, and also accelerate the erosion of PLGA.[15] Drug loading also showed significant influence on the drug release; a higher drug loading leads to a faster release due to low ratio of polymer/drug (Fig. 3).

Effect of the particle size on *in-vitro* release behavior of risperidone PLGA 75253A microspheres was investigated (Fig. 4). The release of smaller particle size of microspheres was significantly faster, because smaller particle size has much larger ratio of surface/volume, which increases the diffusion of drug to the release medium. Many other preparation parameters which have significant influence on the particle size of risperidone PLGA microspheres can also affect

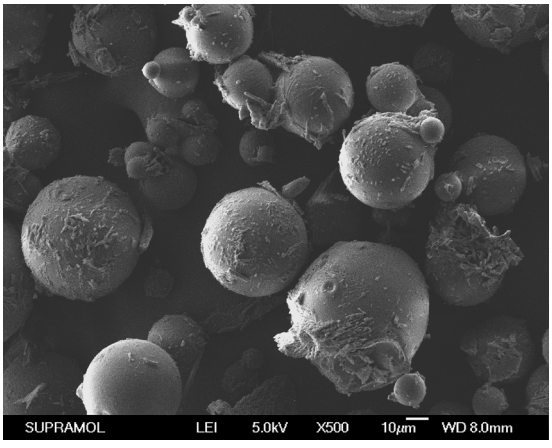

Fig. 1. Scanning Electron Microscopy (SEM) of Different Risperidone PLGA Microspheres Prepared with PLGA 75253A

Surface and surrounding of the microspheres are covered and isolated by the powder of mannitol which can prevent microspheres from aggregation.

the *in vitro* release behavior, such as the homogenization speed, the PVA concentration in the external water phase and the polymer concentration in the oil phase.

Release Kinetics of Different Types of Risperidone PLGA Microspheres To study the mechanism of risperidone release, the cumulative release percent of risperidone PLGA microspheres *versus* time profiles were fitted to different mathematical models as follows[16,17]:

Zero-order kinetics model: $M_t/M_\infty = kt$

First-order kinetics model: $\ln(1-M_t/M_\infty) = -kt$

Higuchi model: $M_t/M_\infty = kt^{1/2}$

Ritger and Peppas's empirical equation model: $M_t/M_\infty = kt^n$

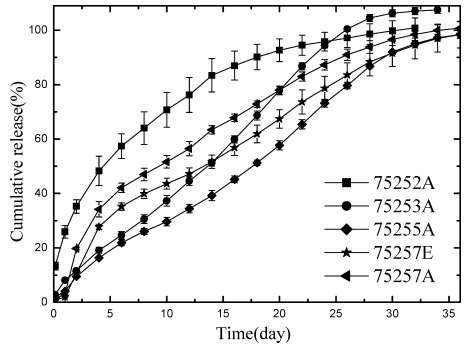

Fig. 2. Effect of the Types of Polymers on *in Vitro* Release Behavior of Risperidone PLGA Microspheres Facilitated at the Same Polymer Concentration of 250 mg·ml^{-1} in the Oil Phase

Each point represents mean±S.D. (n=3).

Where M_t is % drug cumulative released at the time t, M_∞ is % drug cumulative release at the time ∞, M_t/M_∞ is the fraction of drug released at the time point t, k is a kinetic rate constant and n is the exponent characterizing the mechanism of drug release.[16,17] When n=0.5 in the Ritger and Peppas's empirical equation model, the mechanism of drug release is considered as higuchi model; that is the drug diffusion and release from the polymer matrix following a fickian diffusion. While n<0.5, drug diffusion and release from the polymer matrix also follow a fickian diffusion, if 0.5<n<0.89, anomalous or non-fickian type diffusion occurs. If n>0.89, the mechanism of drug release belongs to bulk erosion. If n=1, it belongs to zero-order release kinetics and which is prevalent, the mechanism is considered as bulk erosion.[16]

Correlation coefficients of risperidone cumulative release *vs.* time profiles were fitted to different mathematical models shown in Table 3 obtained using the software developed by Microsoft office Excel.[18] Among the different PLGAs formulations, the microspheres prepared with PLGA 75253A and PLGA 75255A were optimized by a low initial burst phase with a secondary zero-order release phase until 28 d, and the correlation coefficients (r) were 0.9982 and 0.9962 (Fig. 5). It shows that the mechanisms of drug release of the PLGA 75253A and PLGA 75255A microspheres are bulk erosion. Risperidone cumulative release of the PLGA 75252A microspheres *vs.* time profile is fitted to Ritger and Peppas's empirical equation model, and the correlation coefficient (r) is 0.9975, the drug release mechanism of which is

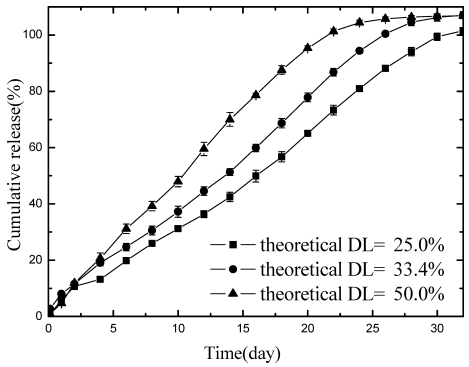

Fig. 3. Effect of the Theoretical Drug Loading on *in Vitro* Release Behavior of Risperidone PLGA 75253A Microspheres

Each point represents mean±S.D. (n=3).

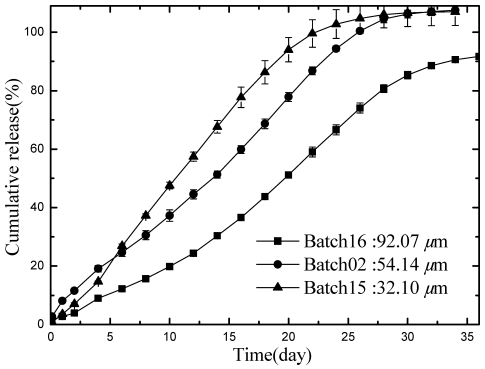

Fig. 4. Effect of the Particle Size on *in Vitro* Release Behavior of Risperidone PLGA 75253A Microspheres

Each point represents mean±S.D. (n=3).

Table 3. Results of Correlation Coefficient (r) Fitted from Mathematical Models

Batches	Zero-order kinetics model	First-order kinetics model	Higuchi model	Ritger and Peppas's empirical equation model
1	y=0.0322x+0.3066	y=−0.1237x−0.1058	y=0.1783x+0.1148	y=0.2828$x^{0.3904}$
	r=0.9510	r=0.9970	r=0.9908	*r=0.9975
2	y=0.0372x+0.0237	y=−0.0949x+0.2536	y=0.2013x−0.1733	y=0.0865$x^{0.6847}$
	*r=0.9982	r=0.9153	r=0.9635	r=0.9878
3	y=0.0291x+0.0172	y=−0.0475x+0.0529	y=0.1908x−0.2135	y=0.0599$x^{0.731}$
	*r=0.9962	r=0.970567	r=0.9707	r=0.9896
4	y=0.0307x+0.0822	y=−0.0582x−0.0004	y=0.1743x−0.1053	y=0.046$x^{0.9365}$
	r=0.9764	r=0.9875	*r=0.9921	r=0.9751
5	y=0.0337x+0.1272	y=−0.0777x+0.0003	y=0.1935x−0.0851	y=0.0685$x^{0.852}$
	r=0.9688	r=0.9893	*r=0.9949	r=0.9720

x represents the time of drug release from risperidone PLGA microspheres, y represents the cumulative percentage of drug release at the time point x. *r represents the highest one fitted from different mathematical models.

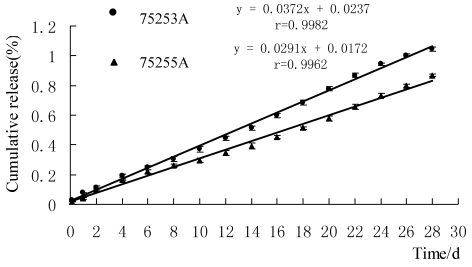

Fig. 5. Cumulative Released *vs.* Time Profiles of the PLGA 75253A and PLGA 75255A Microspheres Fitted by Zero-Order Kinetics Model

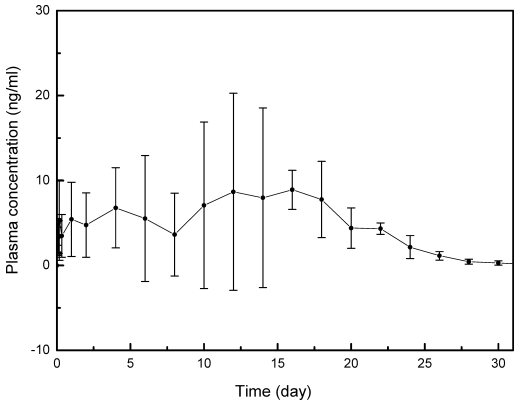

Fig. 6. Plasma Concentration *versus* Time Curve for Drugs (Risperidone and 9-Hydroxyrisperidone) after i.m. Administration of the Risperidone PLGA microspheres (Table 2, Batch 16)

Each point represents mean±S.D. (n=3).

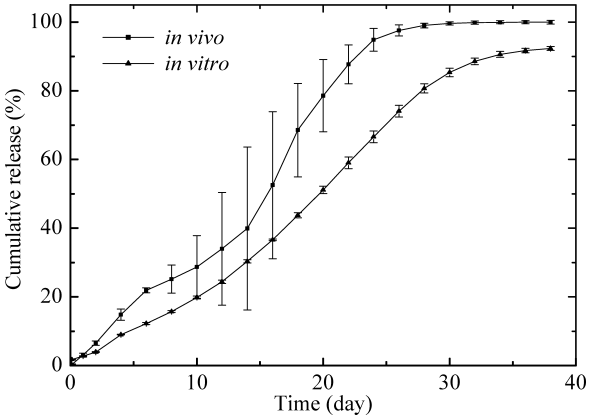

Fig. 7. Cumulative Released Curves of the *in Vitro* and *in Vivo* Release of the Risperidone PLGA Microspheres (Table 2, Batch 16)

Each point represents mean±S.D. (n=3).

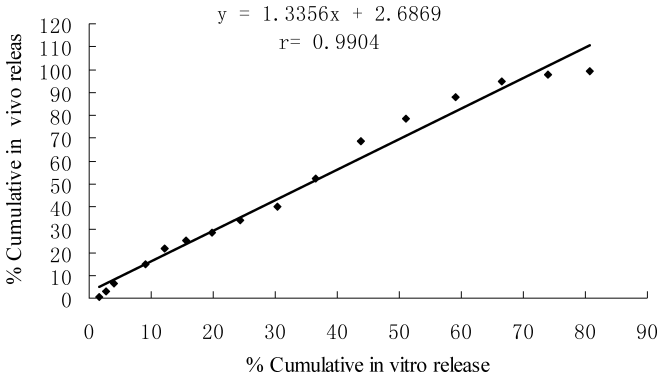

Fig. 8. An *in Vitro–in Vivo* Relationship for the Risperidone PLGA Microspheres (Table 2, Batch 16)

% released *in vivo* was plotted against % released *in vitro* for 28 d.

also considered as bulk erosion. Cumulative releases *vs.* time profiles of the PLGA 75257A and PLGA 75257E microspheres are fitted to higuchi model which means the drug diffusion and release from the polymer matrix follow a fickian diffusion, and the correlation coefficients (r) are 0.9949 and 0.9921 respectively. These results indicate that drug release of the risperidone PLGA microspheres are best characterized by zero-order release kinetics, which suggests that the drug release rate of the microspheres is uniformly sustained release and not influenced by time and drug concentration in the microspheres.

***In vivo* Release Studies of the Risperidone PLGA Microspheres** After intramuscularly (i.m.) administration of the microspheres, the plasma concentration of microsphere formulation (Table 2, batch 16) was detected at various time points (Fig. 6). The plasma concentration was reached rapidly 5.34±4.73 ng/ml at 4 h and then sustained-released until to 28 d, a C_{max} of 8.90±2.31 ng/ml was detected at the 16th day in beagle dogs.

The cumulative release curves of *in vitro* release and *in vivo* release of the risperidone PLGA microspheres are shown in Fig. 7. The *in vivo* release of the drug is similar with the *in vitro* release but a little faster. The drug is eventually eliminated until the 30th day. A good linear regression relationship is fitted between the *in vitro* and *in vivo* releases of the risperidone PLGA microspheres: % cumulative *in vivo* release=1.34 (% cumulative *in vitro* release)+2.69, with a correlation coefficient of 0.9904 (Fig. 8).

Conclusion

Risperidone PLGA microspheres were designed and prepared successfully through the o/w emulsion solvent evaporation method. The formulations described in this study released risperidone constantly for 4 weeks. The encapsulation efficiency is highly depended on polymer concentration in the oil phase, intrinsic viscosity, terminal groups and molecular weight of the polymers. Higher drug encapsulation efficiency can be obtained by increasing the concentration of the PLGA in inner oil phase, decreasing the PVA concentration in the external phase, and lowering the homogenization speed during the preparation process. The properties of PLGAs and the parameters of the preparation show significant influence on *in-vitro* release of the drug. *In vivo* and *in vitro* studies demonstrate that the microspheres prepared with PLGA 75253A can release the drug steadily within 28 d which is a potential candidate for the monthly sustained release risperidone PLGA microspheres.

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