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RESEARCH ARTICLE

Preparation, release and pharmacokinetics of a risperidone elementary osmotic pump system

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Abstract

Preparation and *in vitro*/*in vivo* evaluation of risperidone elementary osmotic pump (RIS-EOP) formulations were investigated. A method for the preparation of RIS-EOP tablets was developed by modulating RIS solubility with citric acid. The influence of osmotic agents and the compositions of semipermeable membrane on drug release profiles was evaluated. The formulation of RIS-EOP was optimized by orthogonal design. The *in vitro* release profile of the optimum formulation achieved to deliver RIS at an approximate zero-order up to 12 h. The pharmacokinetic profiles of RIS-EOP were evaluated compared with immediate release tablets in beagle dogs. The mean t_{max} and mean residence time of RIS-EOP for RIS and its active metabolite, 9-hydroxyrisperidone, were remarkably longer, compared with immediate release tablets. These results corroborated prolonged release of RIS from EOP formulations. Moreover, drug plasma levels with lower fluctuations could be achieved with RIS-EOP tablets. These results suggested that increasing drug solubility by adding or reacting with alkali/acid might be used for the preparation of EOP tablets of certain poorly water-soluble drugs.

Keywords

Controlled release, elementary osmotic pump, risperidone, solubility-modulated

History

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Introduction

Risperidone (RIS) is a slightly soluble (about 0.13 mg/mL in water) benzisoxazole derivate, which is effective in the treatment of psychoses, such as schizophrenia, and other psychiatric illnesses in adults and children, including pervasive developmental disorders (PDD), autism and attention-deficit disorder (ADD)[1]. However, oral side effects and patient compliance is always a problem for schizophrenics[2]. RIS selectively antagonizes dopamine (D2) and serotonin (5HT2) receptor systems in the brain. The main side effect induced by RIS is extrapyramidal symptoms (EPS), which directly correlates with D2 receptor occupancy of RIS[3]. As RIS concentration in plasma increases, D2 receptor occupancy and the likelihood of EPS increase. Therefore, stable drug plasma level will be essential to stable therapeutic activity and reduce risk of side effect. But conventional preparation will lead to large fluctuation in drug plasma concentration resulted in increasing risk of side effect. Constant plasma level can be achieved by controlled drug release system, such as osmotic pumps system.

The first osmotic pumps featuring three compartments were developed by Rose and Nelson in 1955[4]. Distinguished by their ability to release drug substances independently of the medium composition and hydrodynamics, osmotic pumps had many advantages, such as reducing risk of adverse reactions, improving compliance of patients, mitigating the food effect and exhibiting comparable *in vitro*/*in vivo* drug release. Therefore in the past several decades, various osmotic pump systems had been developed for oral drug delivery. Theeuwes introduced oral osmotic pump tablet known as elementary osmotic pump (EOP) in the 1970s[5]. The EOP essentially contained an active agent having suitable osmotic pressure in the core, which was coated with a semipermeable membrane drilled with a delivery orifice. The EOP was very simple in preparation and could deliver water-soluble drugs at an approximately constant rate. But poorly water-soluble drugs could not dissolve adequately in the core of EOP, making release incomplete. Therefore, some specifically designed osmotic pump systems for poorly soluble drugs delivery were developed, such as push-pull osmotic pumps (PPOP)[6,7], sandwiched osmotic pumps (SOP)[8] and swellable elementary osmotic pump (SEOP)[9]. However, a complicated tableting technology was needed for PPOP or SOP. Especially for PPOP, the orifice for drug delivery must be drilled on the surface of the drug layer. The SEOP was simple to prepare and effective for the delivery of poorly water-soluble drug, but there was obvious lag time before drug released from orifice.

In this study, an attempt was made to develop an EOP system for RIS delivery with constant rate. In order to obtain complete release of RIS in EOP tablets, citric acid was used as solubility promoter. The influence of citric acid, osmotic agents and composition of membrane on drug release profile was investigated to determine significant associations of factors based on orthogonal design. Furthermore, the pharmacokinetic profiles of RIS EOP tablets were determined, compared with immediate release tablets in beagle dogs.

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Materials and methods

Materials and animals

RIS was provided by Tianheng Pharmaceutical Co., Ltd (Ningbo, China). Polyethylene glycol was purchased from Sasol Germany (Hamburg, Germany). Cellulose acetate (Eastman Chemical Company, Kingsport, TN) was used as a semipermeable membrane. Sodium chloride (NaCl), lactose and mannitol (Nanning Pharmaceutical Co., Ltd, Nanning, China) were applied as osmotic agents. All other chemicals and solvents, which were purchased from Beijing Chemical Agent Co. (Beijing, China), were analytical or high-performance liquid chromatography (HPLC) grade.

Beagle dogs were purchased from Laboratory Animals Center of Academy of Military Medical Sciences (China). All animals were handled according to the code of ethics in research, training and testing of drugs as laid down by the Animal Care and Use Ethics Committee of Academy of Military Medical Sciences.

Preparation of EOP tablets

RIS was mixed with citric acid, lactose and mannitol manually, and then the mixture was granulated through a 250 μm sieve using wet method and dried at 45 °C for 4 h. Then the granules were screened by a 830 μm sieve. The resultant granules were compressed in ZP-5 rotary tablet press (Shanghai Tianhe Pharmaceutical Device Co., Ltd., Shanghai, China) using a 7-mm diameter punch manually. Then the tablet cores were coated in a pan coater (Jiangsu Taizhou Pharmaceutical Device Co., Ltd., Taizhou, China) with coating solution of cellulose acetate (4.5%, w/v) in 95% acetone. Polyethylene glycol was added to the coating solution as a plasticizer. A 350 μm orifice for the delivery of RIS was created by a laser-beam drilling machine (Nanjing Rich Electronic Engineering Technology Industry Co., Ltd., Nanjing, China).

In vitro drug release study

In vitro release test was performed according to USP paddle method using a dissolution apparatus (D-800LS, Precise Apparatus of Tianjin University Co., Ltd, Tianjin, China) in 900 ml dissolution medium at 37 °C. Samples of 10 ml taken at predetermined time intervals were filtered and then determined by HPLC analysis with a Waters HPLC system (Dual λ Absorbance Detector 2487, Binary Pump 1525, Waters, Milford, MA). The HPLC analysis conditions were as follows: reversed phase C_{18} analytical column (Agela Venusil ASB C_{18}, 4.6 × 150 mm, 5 μm, Agela Technologies, Wilmington, DE); wavelength, 280 nm; mobile phase, acetonitrile – 0.4% (v/v) triethylamine (pH4.5, adjusted by acetic acid) (30:70, v/v); flow rate, 1.0 mL/min. The same volume of fresh medium was replaced after sampling.

The similarity of dissolution profiles was analyzed using the similarity factor, f_2 defined in Equation (1)[10].

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum (R_t - T_t)^2\right]^{-0.5} \times 100\right\}. \quad (1)$$

where n was the sample number, R_t the reference assay and T_t the test assay at time point t.

In vivo pharmacokinetic study

Healthy male beagle dogs, having mean weight of 10.9 ± 0.6 kg, were used for *in vivo* study. The dogs were fasted but had free access to water overnight. Dogs were orally administrated with immediate release RIS tablets (RISPERDAL®, Janssen Pharmaceuticals, Inc., Beerse, Belgium) or RIS-EOP tablets at a dose of 4 mg. Blood samples were collected at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 30, 36, 48 h (for RIS-EOP) and 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 16, 20, 24, 36 h (for normal RIS tablets), respectively, after administration. The obtained plasma samples were stored at −20 °C until analysis. The RIS concentrations in dog plasma were determined in an Agilent 1200 HPLC – electrospray ionization – tandem mass spectrometry system (Pump G1312B, UV detector G1316B, Autosampler 1367C, Degasser G1379B, G6410A triple quad mass spectrometer, Agilent Technologies, Santa Clara, CA). The active metabolite of RIS, 9-hydroxyrisperidone (9-OH-RIS), was quantified simultaneously. The separation of RIS, 9-OH-RIS and methylrisperidone (internal standard) was achieved by automated injection of 10 μL samples into a reversed phase C_{18} analytical column (Agilent Zorbax SB C_{18}, 2.1 × 30 mm, 3.5 μm, Agilent Technologies, Santa Clara, CA) under isocratic conditions which contained acetonitrile and water with 0.1% (v/v) formic acid (60:40, v/v) at a flow rate of 0.3 mL/min.

Statistical analysis

Statistical analysis of the pharmacokinetic parameters was performed using Student's *t*-test. An analysis of variance was performed on untransformed and log-transformed data for the pharmacokinetic parameters. All testing was done using the SPSS 16.0 (SPSS Inc., Somers, NY). A p value of ≤ 0.05 was regarded as statistically significant.

Results and discussion

Influence of citric acid on drug release profile

To investigate the effect of the amount of citric acid on the release of RIS, osmotic pump tablets with drug/citric acid ratio of 1:0, 1:5, 1:7.5 and 1:10 (w/w) were prepared, respectively. The release rate and extent were remarkably affected by the amount of citric acid (Figure 1). Although RIS was a sparingly soluble drug, its solubility could be modulated by acid. The solubility of RIS in 0.1 M hydrochloric acid was more than 300 folds to that of RIS in water. In this study, citric acid was selected as solubility promoter in RIS-EOP. As a result, the presence of citric acid significantly increased the release rate of RIS, and when the amount of citric acid increased, the release rate of RIS increased. For PPOP, the drug properties may not significantly affect the drug delivery, because the drug release rate was mainly decided by push layer[11]. But for EOP, low drug solubility would result in low and incomplete release. Enhancing the soluble fraction of drugs could increase release rate and decrease lag time[12–14].

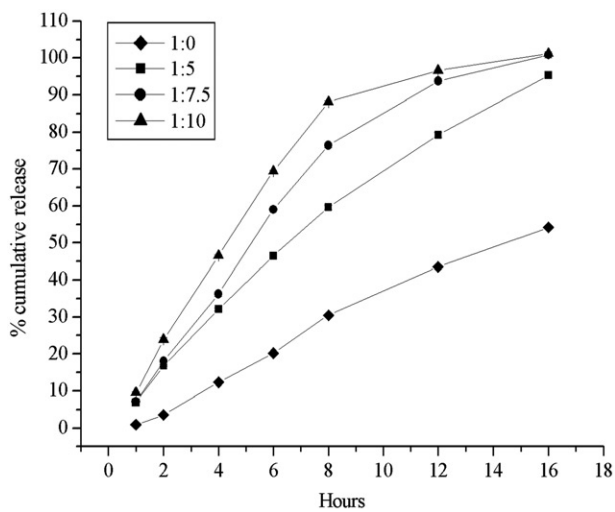

Figure 1. Influence of citric acid on the release of RIS.

Therefore, complete solution of RIS in acid surroundings created by citric acid insured complete release of RIS from EOP tablets.

Influence of osmotic agent on drug release profile

In order to study the influence of osmotic agents on drug release profile, various osmotic agents were investigated, including NaCl, lactose and mannitol (Figure 2A). The onset of drug release took place at the end of a certain time (lag-time); it apparently began after an osmotic pressure built up in the tablet[15]. Besides osmotic pressure created by osmotic agents, the hydrophilicity of osmotic agents also affected the onset of drug release. The tablets with NaCl or mannitol as the osmotic agent had relatively short lag time. According to Van't Hoff equation[16], the same amount of NaCl created the highest osmotic pressure in tablet resulted in quickly release of RIS in the initial stage. The same amount of lactose created relatively high osmotic pressure, but the water hydration rate of tablet core with lactose as the osmotic agent was lower than that of tablet core with mannitol as the osmotic agent. So the time of water diffusion into tablet core increased, which lead to longer lag time. However, the release of RIS from tablets with NaCl as osmotic agent became slow in the later stage. And the hygroscopicity of NaCl was larger compared with other osmotic agents. Thus a mixture of lactose and mannitol was chosen as the osmotic agent finally.

The ratio between lactose and mannitol was also investigated (Figure 2B). When the proportion of lactose increased, the lag time increased and the release rate decreased. But there was no significant difference between the release profiles of tablets with osmotic agent in the ratio of 2:8 and 3:7 lactose/mannitol (w/w). Considering the production cost, lactose/mannitol in the ratio of 3:7 was determined as osmotic agent.

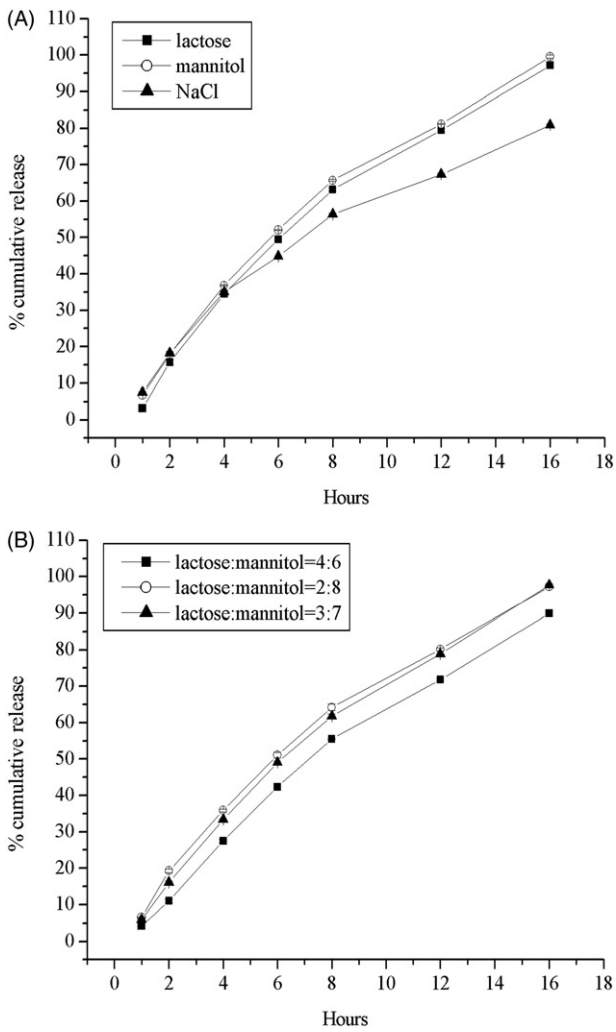

Figure 2. Influence of (A) the osmotic agents, (B) the ratio between lactose and mannitol on the release of RIS.

Influence of PEG 4000 on drug release profile

The tablet cores were coated by coating solution containing various amount of PEG 4000 (0.8, 1.0 and 1.2%, w/v). The role of PEG 4000 in the membrane was studied (Figure 3). The results indicated that there was correlation between the release rate and PEG 4000 amount: the higher the level of PEG 4000 was, the quicker release rate was.

The role of PEG in the membrane had been described in literature with a dual functionality of plasticizer[17] and pore former[18]. Because of the hydrophilic character of PEG, it could be leached easily and left behind porous in the semipermeable membrane of the osmotic pump tablets. Therefore, the water permeability of semipermeable membrane correlated with the leachable agent proportion in the membrane composition[19]. As the proportion of PEG[20] or other hydrophilic plasticizer[9] increased in the membrane composition, more of it dissolved in water. Thus, the membrane permeability and the rate of water ingress increased resulted in higher release rate of drug.

Influence of weight gain of tablet on drug release profile

To investigate the effect of weight gain of tablet on the release of RIS, osmotic pump tablets with weight gain of 4.5%, 6.5% and 8.5%, respectively, were prepared. When the weight gain increased, the release rate decreased (Figure 4). The higher weight gain of tablet induced not only slower release rate but also longer lag time. The drug release rate was directly related to the rate that water entered the tablet core. The rate of water ingress was dependent on the osmotic pressure of the core and the permeability of the coating. The thicker coating layer would result in the decrease of water imbibing through the membrane; thus, the rate of hydration of the drug layer decreased, which resulted in decrease of release rate of drugs[8,21].

Optimization of the formulations

Based on the experiments of individual factor on the drug release, the amount of citric acid, the amount of PEG 4000 and the weight gain of tablet were determined as the key factors for further optimization of the formulations. Osmotic pump tablets with

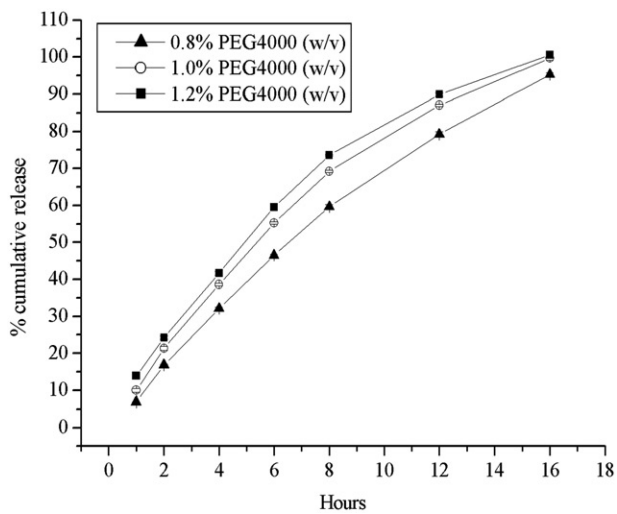

Figure 3. Influence of the amount of PEG 4000 on the release of RIS.

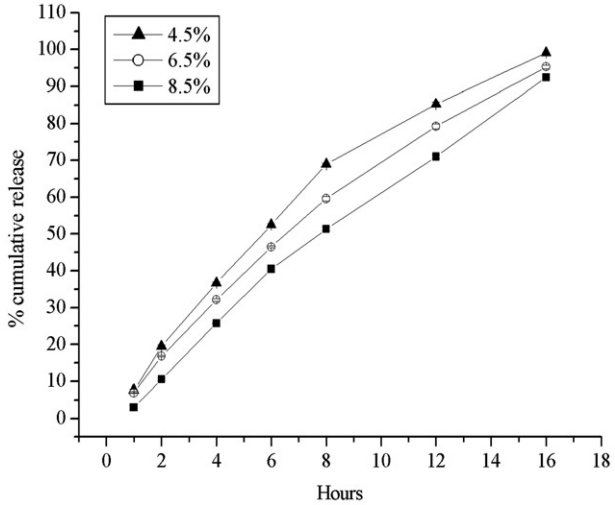

Figure 4. Influence of the weight gain of tablet on the release of RIS.

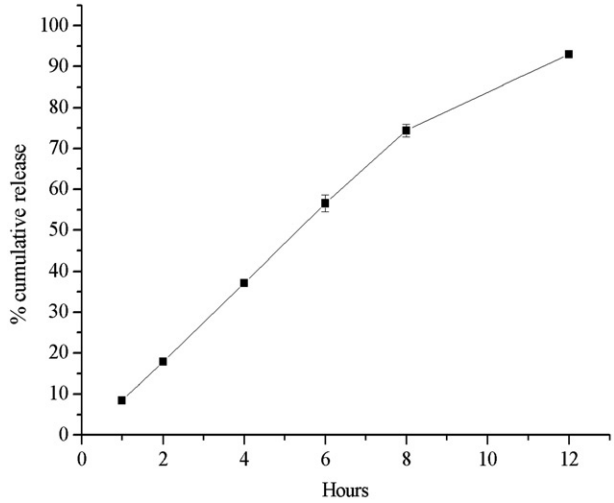

Figure 5. *In vitro* cumulative release profile of the optimized formulation.

Table 1. Results of orthogonal design (L_9 (3^4)).

	Factors			
	Drug: citric acid	PEG 4000 (%)	Weight gain (%)	*S*
1	1:5	0.8	7	22.33
2	1:5	1.0	9	18.69
3	1:5	1.2	11	21.47
4	1:7.5	0.8	11	19.84
5	1:7.5	1.0	7	18.12
6	1:7.5	1.2	9	16.84
7	1:10	0.8	9	38.15
8	1:10	1.0	11	50.40
9	1:10	1.2	7	19.61
k1	20.83	26.77	29.86	
k2	18.27	29.07	19.38	
k3	36.05	19.31	25.91	
Δk	15.22	9.76	10.48	

k1, k2 and k3 are the average sum scores of Level 1, Level 2 and Level 3 for each factor; Δk is the range among the average sum scores of Level 1, Level 2 and Level 3 for each factor.

various formulations were prepared according to L_9 (3^4) orthogonal design (Table 1). Comprehensive grading method was employed to evaluate the release profiles of various formulations compared with the ideal release profile. The score of various formulations was calculated by the following Equation (2):

$$S = (|t_1 - 10\%| + |t_2 - 18\%| + |t_4 - 35\%| + |t_8 - 70\%| + |t_{12} - 95\%|) \times 100 \quad (2)$$

where *S* was total score of the formulations, t_1, t_2, t_4, t_8 and t_{12} were the cumulative released percentage at 1, 2, 4, 8 and 12 h, respectively. The ideal cumulative released percentages at 1, 2, 4, 8 and 12 h were supposed to be 10, 18, 35, 70 and 95%, respectively. Apparently, the smaller the total score was, the closer to the ideal release profile was. The level which got the smallest score was chosen as the optimal level of each factor. The optimal formulation was found to be in the ratio of 1:7.5 drug/citric acid, 1.2% (w/v) PEG 4000 and 9% weight gain of tablet.

The osmotic pump tablets with the optimal formulation were prepared and *in vitro* release was tested. To study the release kinetics, data obtained from *in vitro* drug release (Figure 5) were plotted in various kinetic models including zero-order model, first-order model and Higuchi model. The kinetic pattern was fit for zero-order equation according to the coefficient. The regression release equation for the release of the optimized formulation was $Y = 7.9278t + 4.2824$, with a regression coefficient 0.9964, which was higher compared with first-order and Higuchi equation. Therefore, the optimal osmotic pump tablet was able to deliver RIS at an approximate zero-order up to 12 h. Furthermore, the release profiles of RIS-EOP tablets in different release media were investigated (Figure 6). The results showed RIS-EOP exhibited a media-independent release. Thus, it might be expected that the gastrointestinal fluid scarcely affected RIS release.

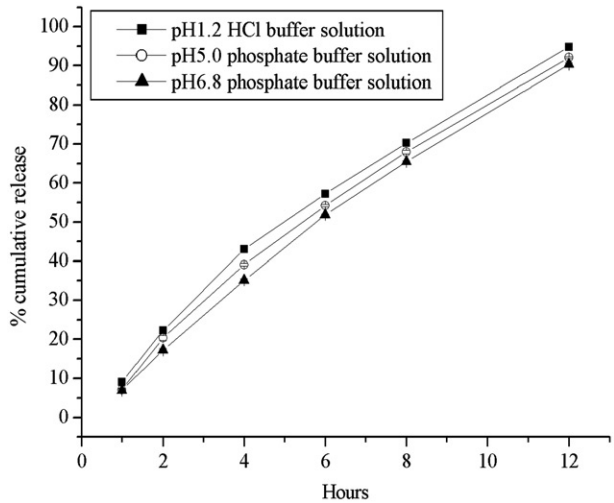

Figure 6. Influence of release media on the release of RIS.

In vivo pharmacokinetic study

The mean plasma concentration of RIS and 9-OH-RIS versus time following single dose oral administration of RIS-EOP and immediate release tablets in beagle dogs were shown as Figures 7 and 8, respectively. The pharmacokinetic parameters results (Table 2) showed that the mean t_{max} of RIS-EOP for RIS and its active metabolite, 9-OH-RIS, were 3.42 ± 1.86 h and 8.17 ± 2.71 h, respectively, which were remarkably longer than that of immediate release tablets for RIS and 9-OH-RIS (0.96 ± 0.56 h and 2.83 ± 1.33 h, respectively). Similarly, the mean residence time (MRT) of RIS-EOP for RIS and 9-OH-RIS were significantly longer, compared with immediate release tablets. These results corroborated prolonged release of RIS from EOP formulations. Meanwhile, the mean C_{max} of RIS-EOP

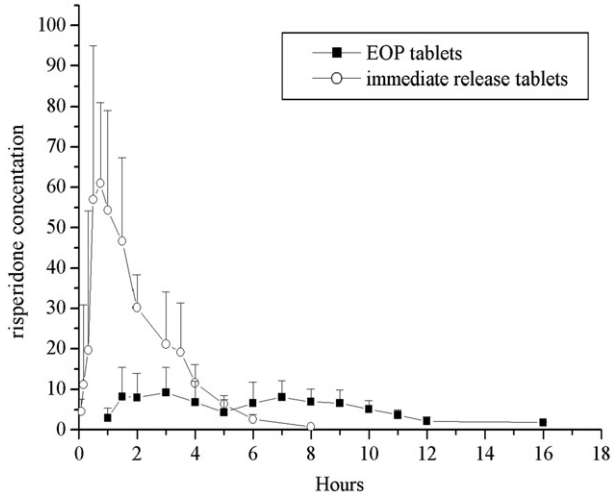

Figure 7. Mean RIS plasma concentration versus time for EOP tablets versus immediate release tablets.

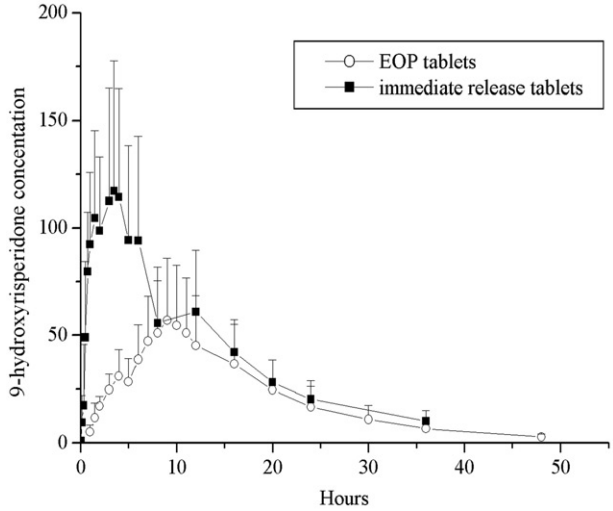

Figure 8. Mean 9-OH-RIS plasma concentration versus time for EOP tablets versus immediate release tablets.

Table 2. Pharmacokinetic parameters of risperidone (RIS) and 9-hydroxyrisperidone (9-OH-RIS) in beagle dog after a single dose oral administration of risperidone elementary osmotic pump tablets (RIS-EOP) and immediate release tablets ($n = 6$).

	RIS-EOP		RIS immediate release tablets	
Parameter	RIS	9-OH-RIS	RIS	9-OH-RIS
C_{max} (ng/mL)	12.33 ± 6.92*	59.33 ± 26.76*	71.59 ± 25.79	130.92 ± 51.51
t_{max} (h)	3.42 ± 1.86*	8.17 ± 2.71*	0.96 ± 0.56	2.83 ± 1.33
$t_{1/2}$ (h)	1.89 ± 0.84	7.84 ± 1.22	1.01 ± 0.20	7.88 ± 1.24
AUC_{0-t} (ng·h/mL)	79.48 ± 39.68*	988.69 ± 468.20	138.51 ± 46.15	1650.06 ± 715.41
$AUC_{0-\infty}$ (ng·h/mL)	83.21 ± 39.21*	1019.96 ± 480.33	142.73 ± 44.22	1767.47 ± 775.40
MRT (h)	8.49 ± 2.35*	16.98 ± 0.99*	2.04 ± 0.30	13.49 ± 0.47

AUC, area under the curve; MRT, mean residence time; $t_{1/2}$, half-life. The asterisk ''*'' indicates $p < 0.05$ versus RIS immediate release tablets.

for RIS and 9-OH-RIS (12.33 ± 6.92 ng/mL and 59.33 ± 26.76 ng/mL, respectively) were remarkably lower compared with immediate release tablets (71.59 ± 25.79 ng/mL and 130.92 ± 51.51 ng/mL, respectively). The immediate release oral formulation exhibited plasma concentration profiles characterized by peaks and troughs, which, over time, may lead to over- or under- D2-receptor occupancy in striatum[22,23]. Remarkably, the fluctuation of plasma concentration for RIS-EOP was significantly smaller compared with normal tablets. Therefore, it may be desirable to achieve a stable plasma profile and, consequently, consistent D2-receptor occupancy throughout the day, as well as a reduced risk of EPS[24,25]. However, the area under the plasma concentration–time curve (AUC) after oral administration of RIS-EOP tablets was lower than that of immediate release tablets. The relative bioavailability (active moiety including RIS and 9-OH-RIS) of the RIS-EOP tablets compared to immediate release tablets was on average about 60%. Because of the physiological difference of the gastrointestinal tract between dogs and humans, drug absorption was likely to be more variable and less complete in dogs[26]. The length and transit time of dog intestines were less than those of human intestines. Moreover, osmotic pump tablet was a rigid structure and could keep integrity in gastrointestinal tract. Therefore, a fraction of drug might be residual in the tablet and excreted resulted in the loss of AUC.

Conclusion

A method for the preparation of RIS-EOP tablets was developed by modulating RIS solubility with citric acid. The compositions of RIS-EOP tablets were screened and optimized. The *in vitro* release profile of the optimum formulation achieved to release RIS at an approximate zero-order up to 12 h. The pharmacokinetic profiles of RIS-EOP and immediate release tablets were evaluated in beagle dogs. Compared with immediate release tablets, the mean t_{max} and MRT of RIS-EOP for RIS and its active metabolite, 9-hydroxyrisperidone, were remarkably longer. These results corroborated prolonged release of RIS from EOP formulations. Moreover, drug plasma levels with lower fluctuations could be achieved with RIS-EOP tablets. These results suggested that increasing drug solubility by adding or reacting with alkali/acid might be used for the preparation of EOP tablets of certain poorly water-soluble drugs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. Financial support was provided by the Important National Science & Technology Specific Projects (Grant No. 2012ZX09301003-001-009).

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