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Comparison of the Solubility and Pharmacokinetics of Sildenafil Salts

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To develop sildenafil lactate, a salt form of sildenafil with improved solubility and bioavailability of poorly water-soluble sildenafil base, this salt form was prepared using a spray dryer. Its solubility and pharmacokinetics in rabbits were evaluated compared with sildenafil base and sildenafil citrate. Sildenafil lactate improved the solubility of sildenafil in various solvents including distilled water compared with sildenafil citrate. It provided higher AUC and C_{max} and, shorter $t_{1/2}$ values than did the other materials, indicating that it improved the oral bioavailability of sildenafil in rabbits. Our results suggest that sildenafil lactate would be useful to deliver sildenafil in a pattern that allows fast absorption and late metabolism. Furthermore, the plasma concentration at 0.25 h in sildenafil lactate was similar to the C_{max} value at T_{max} (0.5 h) in sildenafil citrate. Thus, sildenafil lactate might provide a faster onset of action and immediate erection compared with sildenafil citrate, the conventional drug.

Key words: Sildenafil lactate, Solubility, Pharmacokinetics

INTRODUCTION

Sildenafil, (1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)phenylsulphonyl]-4-methyl piperazine, has been used to treat male erectile dysfunction. It is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) (Boolell et al., 1996). However, this drug has low aqueous solubility and high membrane permeability included in class 2 of the Biopharmaceutical Drug Classification system (Amidon et al., 1995). Its bioavailability is relatively low after oral administration since it is practically insoluble in water (Wang et al., 2008; Elshafeey et al., 2009). Thus, the conventional product has been developed with a salt form such as sildenafil citrate, which improves the drug solubility. This commercial product (Viagra®; Pfizer) is a tablet form containing a sildenafil citrate at the equivalent dose of 25, 50 and 100 mg of sildenafil base. It is rapidly absorbed after oral administration, but gives a relatively low absolute bioavailability of about 40% and late onset of action (over 60 min in the presence of sexual stimulation) (Eardly et al., 2002). Thus, a novel commercial product with a fast onset of effect and immediate erection is needed.

In this study, to develop another salt form with an enhanced solubility of the poorly water-soluble sildenafil base, sildenafil lactate was prepared using a spray dryer. Its solubility and pharmacokinetics in rabbits were then evaluated compared with sildenafil base and sildenafil citrate.

MATERIALS AND METHODS

Materials

Sildenafil base and sildenafil citrate were obtained from Hanmi Pharm. Co. Transcutol P was supplied by Gattefosse (Saint-Priest Cedex). Polysorbate 20 (Tween 20) and polyethylene glycol 4000 were purchased from Duksan Chemical Co. Ethanol was of USP grade. All other chemicals were of reagent grade and used without further purification.

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Animals

All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989, revised in 1999 and amended in 2008 by the Society of Toxicology (SOT, 2008). Furthermore, the protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Yeungnam University. Twelve New Zealand albino male rabbits weighing 2.5-3.5 kg were fasted for 24 h prior to the experiments but allowed free access to water at a temperature of 20-24°C and a relative humidity (RH) of 55 ± 10% with a normal 12 h light/dark cycle starting one week before the experiment.

Preparation of sildenafil lactate

A Buchi 190 nozzle type mini spray dryer was used for the preparation of sildenafil lactate. Sildenafil base and lactic acid (1:1, molar ratio) were dissolved in ethanol and delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 mL/min using a peristaltic pump, and spray-dried at 100°C (inlet temperature) and 65-70°C outlet temperature. The pressure of spray air was 4 kg/cm^2. The flow rate of the drying air was maintained at the aspirator setting of 10, which indicated the pressure of the aspirator filter vessel (−25 mbar). The direction of the air flow was the same as that of the sprayed products (Li et al., 2008).

Solubility

An excess of sildenafil base, sildenafil citrate and sildenafil lactate (about 100 mg) was added to 10 mL solvents as shown in Table I. They were shaken in a water bath at 25°C for 24 h, centrifuged at 3000 g for 10 min (Eppendorf) and filtered through a membrane filter (0.45 μm) (Choi et al., 2007). The concentration of sildenafil in the resulting solution was analysed by HPLC as described below.

Pharmacokinetics

Oral administration and blood collecting- All rabbits were kept at 20°C and a 70% RH with a normal 12 h light/dark cycle starting one week before the experiment. Fifteen rabbits were divided into three groups. Sildenafil base, sildenafil citrate and sildenafil lactate were filled into small hard gelatin capsules (#8, Suheung Capsule Co.) and orally administered at an equivalent dose of 25 mg/kg sildenafil in each group. Then, 1 mL of blood samples were obtained at various intervals from the left or right ear vein into heparinised glass tubes, centrifuged at 3000 g for 10 min using a 5415C centrifuge (Eppendorf) and stored at −70°C prior to analysis.

Blood sample analysis- Plasma (0.1 mL) was thoroughly mixed with 0.05 mL of 0.1 N borax, 1 mL of ether and 0.05 mL of acetonitrile solution containing nifedipine (200 μg/mL) as an internal standard. This mixture was vortexed for 2 min and centrifuged at 10,000 g for 10 min to precipitate the proteins. The supernatant layer (0.5 mL) was evaporated under N_2 (g). The residue was reconstituted in 50 μL for the mobile phase. The resulting solution (20 μL) was analysed by HPLC (Jasco UV-975) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 25 cm × 0.46 cm *i.d.*) and UV detector (Model L-7450). The mobile phase consisted of 20 mM KH_2PO_4 and acetonitrile (70:30, v/v). The eluent was monitored at 292 nm with a flow rate of 1.0 mL/min (Gratz et al., 2004; Quintero et al., 2009).

Pharmacokinetic data analysis and statistical analysis- The area under the drug concentration-time curve from zero to infinity (AUC), the elimination constant (K_{el}) and half-life ($t_{1/2}$) were calculated using a non-compartmental anaylsis (WinNonlin; professional edition, version 2.1; Pharsight). The maximum plasma concentration of the drug (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were obtained directly from the plasma data (Gibaldi and Perrier, 1982). Levels of statistical significance ($p < 0.05$) were assessed using the Student's-*t*-test between two means for unpaired data. All data were expressed as mean ± S.D. or as the median (ranges) for T_{max}.

Table I. Solubility in various solvents

Solvent	Solubility (mg/mL)		
	Sildenafil base	Sildenafil citrate	Sildenafil lactate
Distilled water	0.0 ± 0.0	4.1 ± 1.3	92.5 ± 10.5
Ethanol	5.2 ± 1.2	1.3 ± 0.2	17.1 ± 3.3
Polyethylene glycol 4000	2.0 ± 0.4	4.9 ± 0.3	17.3 ± 4.7
Transcutol	24.7 ± 4.7	3.4 ± 0.7	38.3 ± 2.6
Tween 20	12.0 ± 3.8	5.6 ± 0.9	19.8 ± 3.2

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

RESULTS AND DISCUSSION

Sildenafil lactate was prepared easily by spray-drying sildenafil base and lactic acid (1:1, molar ratio). In preliminary study, other sildenafil salts prepared with tartaric acid or hydrochloric acid using spray-drying technique could not improve the aqueous solubility of sildenafil base (data not shown). The aqueous solubility of sildenafil base was about 14.5 μg/mL, which indicated that this drug was poorly water-soluble (Wang et al., 2008; Elshafeey et al., 2009). As shown

in Table I, the aqueous solubility of sildenafil salts was in the order of sildenafil base < sildenafil citrate < sildenafil lactate. In particular, the aqueous solubility of sildenafil lactate was about 25-fold higher than sildenafil citrate, the conventional drug (92.5 ± 10.5 *vs* 4.1 ± 1.3 mg/mL). Compared with sildenafil base, sildenafil citrate reduced the drug solubility in other solvents such as ethanol, Transcutol and Tween 20, but sildenafil lactate increased it further. Thus, sildenafil lactate was a salt form that provided an improved solubility of sildenafil.

Fig. 1 shows the changes in mean plasma concentration of sildenafil after the oral administration of the preparations in rabbits. Sildenafil citrate gave higher total plasma concentrations than sildenafil base. Furthermore, it showed significantly higher initial plasma concentrations of the drug than did sildenafil base. The total plasma concentrations of drug obtained from sildenafil lactate were higher than those in sildenafil base and sildenafil citrate. In particular, the initial plasma concentrations of drug from sildenafil lactate, until 1 h, were significantly higher than those of other preparations ($p < 0.05$). Our results suggest that the higher initial plasma concentrations of drug in sildenafil lactate in rabbits were due to the increased solubility of the drug from sildenafil lactate (Choi et al., 1998; Yong et al., 2004).

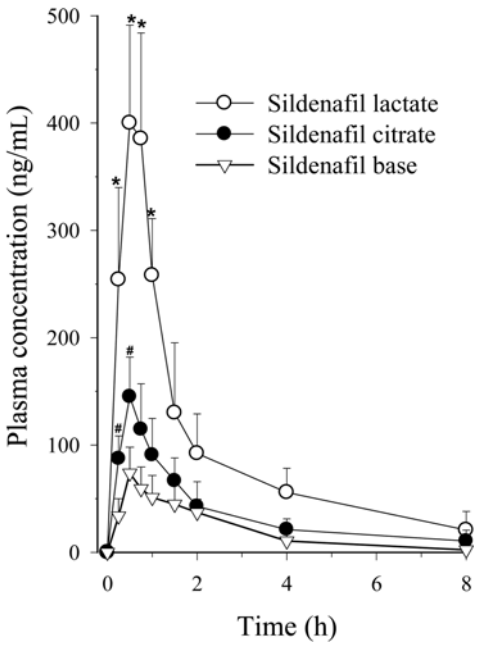

Fig. 1. Plasma concentration-time profiles of the drug after the oral administration of sildenafil base, sildenafil citrate and sildenafil lactate to rabbits. Each value represents the mean ± S.D. (n = 5). $^{\#}p < 0.05$ compared with sildenafil base. $^{*}p < 0.05$ compared with sildenafil base and sildenafil citrate.

The pharmacokinetic parameters are shown in Table II. Sildenafil citrate showed a significantly higher AUC and C_{max} of the drug than did sildenafil base ($p < 0.05$). However, there were no significant differences between the T_{max} and $t_{1/2}$ values. Thus, sildenafil citrate, the conventional drug, could improve sildenafil. By contrast, sildenafil lactate gave a significantly higher AUC and C_{max} of the drug than did the other materials ($p < 0.05$). In particular, the AUC of the drug from sildenafil lactate was about 2.5- and 5.5-fold higher than that from sildenafil base and sildenafil citrate, respectively. The enhanced oral bioavailability of the drug in sildenafil lactate was contributed by the marked increase in the absorption rate of sildenafil in rabbits because of the increased solubility (Gupta et al., 2005; Elshafeey et al., 2009). Moreover, sildenafil lactate showed a significantly shorter $t_{1/2}$ of the drug than did the other materials ($p < 0.05$). Our results suggest that sildenafil lactate is useful to deliver sildenafil in a pattern that allows fast absorption and late metabolism. The T_{max} value of the drug from sildenafil lactate was not significantly different from that from sildenafil citrate. The plasma concentration at 0.25 h in sildenafil lactate (145 ng/mL) was similar to the C_{max} value (about 145 ng/mL) at T_{max} (about 0.5 h) in sildenafil citrate (Fig. 1). Thus, sildenafil lactate might provide a faster onset of action and immediate erection compared with sildenafil citrate, the conventional drug. However, in this study, the reason for more improved solubility, faster absorption and later

Table II. Pharmacokinetic parameters

Parameters	Sildenafil base	Sildenafil citrate	Sildenafil lactate
C_{max} (ng/mL)	73.81 ± 24.20	145.04 ± 36.84$^{\#}$	399.98 ± 91.34*
T_{max} (h)	0.52 ± 0.09	0.56 ± 0.03	0.51 ± 0.05
AUC (h·ng/mL)	164.95 ± 16.87	353.64 ± 111.51$^{\#}$	873.37 ± 236.14*
$t_{1/2}$ (h)	1.41 ± 0.22	1.35 ± 0.18	0.57 ± 0.22*
K_{el} (h^{-1})	0.49 ± 0.30	0.52 ± 0.23	1.22 ± 0.24*

Each value represents the mean ± S.D. (n = 5).
$^{\#}p < 0.05$ compared with sildenafil base.
$^{*}p < 0.05$ compared with sildenafil base and sildenafil citrate.

metabolism of sildenafil lactate compared to sildenafil citrate could not be discussed. Thus, further study on their experimental evidence will be carried out.

Sildenafil lactate improved the solubility of sildenafil in solvents including distilled water compared with sildenafil base and sildenafil citrate. It gave higher AUC, and C_{max}, and shorter $t_{1/2}$ values than did sildenafil citrate, indicating that it improved the oral bioavailability of sildenafil in rabbits compared with sildenafil citrate. Our results suggest that sildenafil lactate is useful to deliver sildenafil in a pattern that allows fast absorption and late metabolism. Furthermore, the plasma concentration at 0.25 h in sildenafil lactate was similar to the C_{max} value at T_{max} (0.5 h) in sildenafil citrate. Thus, sildenafil lactate might provide a faster onset of action and immediate erection compared with sildenafil citrate, the conventional drug.

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