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Simultaneous determination of gastrodin and puerarin in rat plasma by HPLC and the application to their interaction on pharmacokinetics

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ABSTRACT

Gastrodin (Gas) and puerarin (Pur) are bioactive substances derived from traditional Chinese medicine *Gastrodia elata* and *Radix Puerariae*, respectively, which were often used together in Chinese clinical prescriptions. Their injections were used in combined way for treatment of some cardiocerebrovascular diseases in clinic, especially for vertigo due to vertebrobasilar ischemia. In this paper, interaction of gastrodin and puerarin in rat plasma pharmacokinetics via intragastic (*i.g.*)/intravenous (*i.v.*) administration was investigated. A reliable HPLC method was developed for simultaneous determination of Gas and Pur in rat plasma with a linear range of 0.101–101 μg/mL for Gas and 0.0500–5.98 μg/mL for Pur ($r^2 > 0.993$). The LLOQ, LOD of Gas and Pur were determined to be 0.101, 0.0486 μg/mL, and 0.05, 0.0245 μg/mL, respectively. The intra-day and inter-day precision were all less than 12.0%, whilst the accuracy were all within 96.4 ± 6.00%. The proposed method has been successfully applied to the pharmacokinetic study of the analytes in rats after *i.g.*/*i.v.* administration of Gas and Pur alone or combined with each other (*i.g.*: 40 mg/kg Gas, 400 mg/kg Pur; *i.v.*: 20 mg/kg Gas, 20 mg/kg Pur). Blood samples were collected from retinal vein plexus of rats at predetermined time points and plasma containing the internal standard tyrosol (IS) were precipitated by methanol and chromatography was carried out on a C_{18} column with a gradient mobile phase of ACN–H_2O with 0.05% phosphoric acid as a modifier. The pharmacokinetic profiles of combined administration were found to be distinct from those of given alone. The C_{max}, T_{max}, $T_{1/2}$, *MRT* of Gas administrated alone or combined with Pur via *i.g.* were 21.7 μg/mL, 0.250 h, 2.81 h, 0.830 h and 18.4 μg/mL, 0.550 h, 0.970 h, 1.37 h, respectively, of Pur administrated alone or combined with Gas via *i.g.* were 0.490 μg/mL, 1.95 h, 1.33 h, 2.10 h and 2.01 μg/mL, 0.570 h, 4.00 h, 5.10 h, respectively. The relative oral bioavailability of Pur in combined administration was 10.7 times as much as that of single administration, whilst 1.52 folds in Gas. These results indicate that co-administration of Gas and Pur is a promising combination to gain higher bioavailability and it is suggested that doctors pay more attention to the dosages of the two when simultaneously using both of them.

1. Introduction

Gastrodin (Fig. 1(A), chemical structure is *p*-hydroxymethylphenyl-β-D-glucopyranoside, Gas), one of the main bioactive components extracted from *Gastrodia elata Blume* (*Orchidaceae*, Tian-ma in Chinese) with multiple beneficial properties. For low toxicity and little side effect, it has been extensively used by Chinese practitioners for treatment of cardiovascular and cerebrovascular diseases, such as vertigo, migraine, headache, hypertension, stroke and epilepsy [1–4].

Puerarin (Fig. 1(B), chemical name is 7,4-dihydroxyisoflavone-8-β-D-glucopyrano-side, daidzein 8-C-glucoside, Pur), the major active ingredient of *Radix Puerariae* (the root of *Pueraria lobata* (*Willd*) *Ohwi*), has a number of pharmacological effects, especially on cardiocerebrovascular and has been used to treat many diseases such as hypertension [5], angina [6], and myocardial infarction [7]. However, due to its poor water-solubility and low oral bioavailability [8], the formulation of puerarin was no other than injection currently, which greatly restricts its clinical application. Furthermore, owing to the short elimination half-life of puerarin in human beings, *i.v.* administration of frequent and high doses may be needed, possibly leading to severe and acute side effects (such as hemolysis [9], acute renal failure [10], anaphylactic shock [11]).

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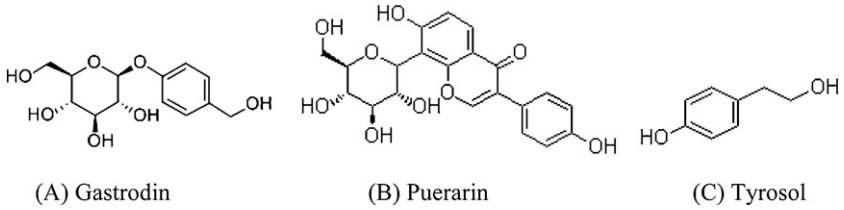

Fig. 1. Chemical structures of gastrodin, puerarin and tyrosol (internal standard).

Thus, oral formulation with improved absorption of puerarin has been one of the research focuses [12–17] and highly desired in the field of pharmaceutics.

Many prescriptions of Traditional Chinese Medicine (TCM) for treatment of some cardiocerebrovascular diseases usually contain Tian-ma and Ge-gen, the bioactive substances of which were Gas and Pur [18–20]. The effect on vasodilatation was close to verapamil but stronger than other combinations when the concentrations of both Gas and Pur were 0.10 g/L with the maximal relaxation being 85.72 ± 1.28% [21]. To our knowledge, there have been some quantitative methods and pharmacokinetic studies with regards to Gas [22,23] or Pur [24,25] in biological samples with relatively fine sensitivity. However, there was no publication describing a simultaneous determination study of Gas and Pur and no research about interplay on pharmacokinetics of Gas and Pur in vivo at present, so it is necessary to investigate the rationality of combined applications and interaction of the two constituents on pharmacokinetics. The major contribution of present HPLC method is developing a simple and accurate analytical HPLC–UV method for simultaneously determination of Gas and Pur in rat plasma using tyrosol (structure was shown in Fig. 1(C)) as an internal standard after protein precipitation with methanol. The HPLC method has been successfully applied to the assay of Gas and Pur in rat plasma after administration of Gas and/or Pur via *i.g.* and *i.v.* routes, the purpose of which is to take a limited view of their interaction pharmacokinetic profiles.

2. Materials and methods

2.1. Chemicals and reagents

Gastrodin (Gas) and puerarin (Pur) with the purity >98% were purchased from Wei Keqi Biotechnology Co., Ltd. (Sichuan, China) qualifying as administration drug and from National Institutes for food and drug control (Beijing, China) as quantitative analytes. Tyrosol (used as internal standard, IS) was obtained from Aladdin reagent Co., Ltd. (Shanghai, China). Methanol and acetonitrile (ACN) of HPLC grade were bought from Thermo Fisher Scientific (Pittsburgh, PA, USA). Phosphoric acid was obtained from Beijing Chemical Co. (Beijing, China). Deionized water was prepared in a Milli-Q water purification system (Millipore, Bedford, MA, USA) and used throughout the entire experiment. All other chemicals and reagents were of analytical grade and commercially available.

2.2. Experimental animals

Male Wistar rats (weight: 240 ± 20 g) were purchased from Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China, Certificate No. SCXK-2006-009). These animals were specifically pathogen-free and acclimated for at least a week in their environmentally controlled quarters (24 ± 1 °C and 12/12-h light/dark cycle) with free access to standard chow and water. The rats were fasted overnight but supplied with water ad libitum before the experiments. All experimental protocols were conducted after being approved by the Animal Ethics Committee of Beijing University of Chinese Medicine.

2.3. Instruments and chromatographic conditions

The analysis was performed using the Shimadzu HPLC system (Chiyoda-Ku, Kyoto, Japan) consisting of a quaternary pump (LC-20AT), a UV detector (SPD-20A), a column thermostat (CTO-10ASVP) and a CBM-20A system controller. Output data from the detector were integrated via LC solution chromatographic workstation.

Analytes were separated on an Agilent ZORBAX SB-Aq C18 column (250 mm × 4.6 mm, 5 μm, Santa Clara, CA, USA) equipped with an Agilent analytical guard column (12.5 mm × 4.6 mm, 5 μm, Santa Clara, CA, USA).

A gradient mobile phase system consisting of ACN (A)–H_2O (B) with 0.05% phosphoric acid as a modifier was employed for sample analysis. The gradient elution method was as follows: 0–5 min: 100% B; 5–15 min: 100% B → 98.5% B, 15–25 min: 98.5% B → 90% B; 25–30 min: 90% B → 85% B; 30–40 min: 85% B → 100% B; 40–45 min: 100% B. The wavelength of the UV detector was set at 221 nm for Gas and IS, whilst 250 nm for Pur with a flow rate of 1.0 mL/min and column temperature at 35 °C.

2.4. Preparation of stock and working solutions

Stock solutions of Gas, Pur and IS with concentrations of 1.010, 0.598 and 0.226 mg/mL, respectively, were prepared in methanol and further diluted into 1.01–1010, 0.498–59.800 and 22.600 μg/mL as working solutions.

2.5. Preparation of standard and quality control (QC) samples

The calibration standard samples were prepared by freshly spiking the appropriate working solution into blank plasma yielding the concentration of 0.101, 0.505, 1.01, 2.53, 5.05, 7.58, 10.1,25.2, 50.5, 101 μg/mL for Gas and 0.0500, 0.100, 0.299,0.598, 0.897, 1.50, 2.99, 5.98 μg/mL for Pur, and processed as described in the sample preparation. Quality control (QC) samples used for the intra- and inter-day accuracy and precision, extraction recovery and stability study were prepared in the same way as calibration standard samples at concentrations of 0.505, 5.05 and 101 μg/mL for Gas and 0.100, 1.50, and 5.98 μg/mL for Pur.

2.6. Sample preparation

We followed the published method with slight modification [26,27]. An aliquot of 100 μL thawed plasma sample was transferred into an Eppendorf tube (EP tube), to which 10 μL of IS solution was added. After being vortexed for 15 s, 400 μL of methanol was added to precipitate protein. Subsequently, the mixture was centrifuged at 12,000 × *g* for 10 min following vortex mixing for 60 s. The supernatant was all transferred into another EP tube and evaporated to dryness under the stream of nitrogen in a water bath at 40 °C. The residue was dissolved in 100 μL of

reconstituted solution which consisted of ACN–phosphoric acid–water mixture (20:0.05:80, by volume) and then centrifuged at 12,000 × *g* for 10 min in EP tubes. The supernatant was transferred to an auto-sampler vial, and a 10 μL aliquot was injected into HPLC system for analysis.

2.7. Validation of the method

Chromatogram comparison of blank plasma, blank plasma spiked with IS/analytes and rat plasma samples was conducted to evaluate the specificity and selectivity of the method. Calibration curves were established from peak area ratios (analyte/IS) versus nominal concentrations using linear least-squares regression model ($1/X^2$ weighting). Intra- and inter-day precisions were determined by assessing measured results of QC samples at low, medium and high concentrations. Precisions were expressed by the relative standard deviation (R.S.D, %), while accuracy (%) was evaluated by the percentage difference between the mean measured concentrations and the spiked concentrations. The LLOQ of the assay, defined as the lowest limitation of drug concentration, could be quantified with an acceptable precision (less than 20%) and accuracy (within the range of 80–120%). Extraction recoveries were determined by comparing the ratio of the analytes' peak areas of the extracted QC samples with those of un-extracted standard solutions at the same nominal concentrations. Stability was checked by comparing measured results with those of freshly prepared samples of the same concentration. The short- and long-term stabilities were evaluated by analyzing QC plasma samples kept at room temperature for 4 h and in the freezer (−20 °C) for 30 days, respectively; the freeze–thaw stability was carried out by detecting QC samples undergoing three freeze (−20 °C)–thaw (room temperature) cycles; the post-preparation stability was assessed by determining the extracted QC samples stored under auto-sampler conditions (room temperature) for 24 h.

2.8. Drug administration

The rats were randomly divided into 6 groups with at least 6 rats per group: group A (*i.g.* administration of Gas at the dose of 40 mg/kg, single-*i.g.* Gas); group B (*i.g.* administration of Pur at the dose of 400 mg/kg, single-*i.g.*-Pur); group C (*i.g.* administration of Gas with the dose of 40 mg/kg and Pur 400 mg/kg, unite-*i.g.* Gas & Pur); group D (*i.v.* administration of Gas at the dose of 20 mg/kg, single-*i.v.* Gas); group E (*i.v.* administration of Pur at the dose of 20 mg/kg, single-*i.v.* Pur); group F (*i.v.* administration of Gas and Pur together at the dose of 20 mg/kg, unite-*i.v.* Gas &Pur). The administered dosages were converted according to the reported literature [13,28–30].

After dosing, the rats were anesthetized by small amounts of diethyl ether and approximately 0.3 mL of blood was collected from retinal vein plexus of rats at predetermined time points (0, 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 12, 24 h for *i.g.* administration or 0, 0.033, 0.083, 0.167, 0.333, 0.666, 1, 1.5, 2, 3, 4, 6, 12 h for *i.v.* delivery) and put into clean heparinzed EP tubes. Subsequently, more than 100 μL plasma was obtained by centrifugation at 7800 × *g* for 10 min and storaged at −20 °C until assay.

2.9. Pharmacokinetic study and data analysis

The pharmacokinetic parameters, such as area under the plasma concentration–time curve (*AUC*), maximum plasma concentration (C_{max}), corresponding time (T_{max}) and half-life ($T_{1/2}$), plasma clearance (*CL*), mean residence time (*MRT*) as well as initial plasma concentration (C_0) for *i.v.* dose were performed on each individual set using the software of WinNonlin (Version 5.2, Pharsight Corp., Mountain View, CA, USA) by the non-compartmental model.

The relative bioavailabilities (F_{re}) of Gas and Pur in the plasma were calculated as the ratio of $AUC_{G\&P}/AUC_G$ and $AUC_{P\&G}/AUC_P$, respectively. ("G&P" meant administration of Gas combined with Pur; "G" meant administration of Gas alone; "P&G" meant administration of Pur combined with Gas; "P" meant administration of Pur alone). The absolute oral bioavailability (F_{ab}) of Gas was calculated as the ratio of $(AUC_{i.g.}/X_{i.g.})/(AUC_{i.v.}/X_{i.v.})$, and the algorithm of F_{ab} for Pur was the same as Gas.

Data are presented as mean ± SD. Comparisons of the pharmacokinetic data were performed by Student's *t*-test and the statistically significant difference was set at a value of $P < 0.05$ (SPSS statistical software package, Version 17.0, SPSS Inc., Chicago, IL, USA).

3. Results and discussion

3.1. Chromatography condition and selectivity

Because of the good water-solubility for Gas and bad for Pur, they couldn't be separated by isocratic elution procedure with high percent of organic mobile phase. So the gradient elution procedure which consisting of 100% phosphoric acid solution initially, then slowly drop to 85% was chosen. It can not only wash out the polar endogenous substances in plasma but also obtain better separation of the analytes and gain a smooth baseline in present mobile condition with the entire analysis time of only 45 min. Typical chromatograms of rat plasma samples after administration of Gas and Pur are shown in Fig. 2. There was little interference peak close to the retention positions of the analytes and IS in the blank plasma. LOD of Gas and Pur were determined to be 0.0486 μg/mL and 0.0245 μg/mL, respectively.

3.2. Recovery

The extraction efficiency for Gas, Pur and IS in rat plasma with methanol as precipitant in sample preparation was consistent, precise and reproducible. The results showed the extraction recovery (absolute recovery) of Gas and Pur were all more than 75% with the RSD values being less than 10% at each QC level by comparing the peak areas of analytes and IS spiked in pre-extracted blank plasma with those in standard solutions at equivalent concentrations.

3.3. Precision and accuracy

The intra-day and inter-day precision R.S.D. values of Gas and Pur were all less than 12%, whilst the accuracy deviation values were all within 96.4 ± 6.0% of the actual values at each QC level. The results suggested that the accuracy and precision in the present assay are acceptable for the analysis.

3.4. Stability

The stability results illustrate that Gas and Pur are stable in rat plasma for at least 30 days when stored at −20 °C for three freeze–thaw cycles and in the reconstituted solutions when stored under auto-sampler condition for 24 h.

3.5. In vivo application of the method

The mean plasma concentration–time profiles of Gas and Pur are illustrated in Fig. 3 and their estimated pharmacokinetic parameters are presented in Table 1 and Table 2. The pharmacokinetic profiles of combined administration were found to be significantly different from those of given alone ($P < 0.05$).

We found that Gas in rat plasma reached the C_{max} at 0.25 h and was rapidly eliminated from the plasma. T_{max} value of single

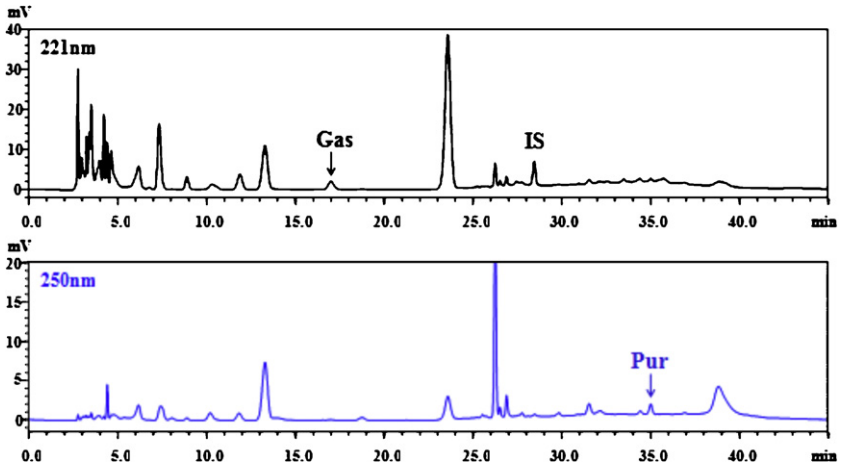

Fig. 2. Representative HPLC chromatograms of gastrodin (Gas), puerarin (Pur), and internal standard (IS) in rat plasma sample collected at 90 min after *i.g.* administration of Gas together with Pur.

Table 1
Pharmacokinetic parameters of gas in rats following intragastric and intravenous administration (mean ± SD, $n = 5$).

Parameters	Group A (single-*i.g.*-Gas)	Group C (unite-*i.g.*-Gas & Pur)	Group D (single-i.v.-Gas)	Group F (unite-i.v.-Gas &Pur)
C_{max} (μg/mL)	21.7 ± 6.90	18.4 ± 5.56	75.6 ± 6.63	70.0 ± 10.8
T_{max} (h)	0.250	0.550 ± 0.270[a]	0	0
$T_{1/2}$ (h)	2.81 ± 2.25	0.970 ± 0.400[a]	1.14 ± 0.380	1.70 ± 1.44
AUC_{0-t} (μg h/mL)	17.3 ± 5.19	27.2 ± 4.02[a]	22.1 ± 2.58	27.2 ± 2.91[b]
$AUC_{0-\infty}$ (μg h/mL)	18.1 ± 5.63	27.6 ± 3.82[a]	22.3 ± 2.57	27.6 ± 3.05[b]
CL (mL/h/kg)	(2.42 ± 0.907) × 10^3	(1.47 ± 0.212) × 10^3	(9.08 ± 0.994) × 10^2	(7.32 ± 0.859) × $10^{2,b}$
MRT (h)	0.830 ± 0.100	1.37 ± 0.520[a]	0.360 ± 0.060	0.460 ± 0.090
C_0 (μg/mL)	NA	NA	94.59 ± 57.63	82.73 ± 22.07
AUC_{0-t}/D (g h/mL)	0.433 ± 0.130	0.679 ± 0.101[a]	1.103 ± 0.129	1.362 ± 0.146[b]
C_{max}/D (g/mL)	0.544 ± 0.173	0.461 ± 0.139	3.783 ± 0.332	3.50 ± 0.538
F_{ab} (%)	40.8 ± 12.6	62.0 ± 8.59[a]	NA	NA
F_{re} (%)	NA	152	NA	124

SD, standard deviation; NA, not applicable; *D*, administered dose; F_{ab}, absolute bioavailability; F_{re}, relative bioavailability (compared with single administration).
[a] Significantly different from group A, $P < 0.05$.
[b] Significantly different from group D, $P < 0.05$.

administration group in our studies (15 min) was found to be similar to that reported (16.6 min) [23]. C_{max} and AUC_{0-t} were 21.7 μg/mL, 17.3 μg h/mL, respectively, which were close to the results previously reported [26]. The absorption rate of Gas was obviously slowed down to 0.55 h, and *MRT* and *AUC* were increased by 1.65-fold and 1.52-time, respectively, when co-administrated with Pur via *i.g* (group A and C).

Compared with Pur administrated alone, Pur co-administrated with Gas has markedly higher C_{max}, increased *AUC*, and longer $T_{1/2}$, *MRT* ($P < 0.01$), which account for the higher bioavailability of Pur in group C. In single administration of Pur group, $T_{1/2}$ of puerarin in our studies (1.33 h) was found to be similar to that reported (0.861 h, 1.70 h) [31,32]. The mean T_{max} of puerarin in our study was in close agreement with the published report [33].

Table 2
Pharmacokinetic parameters of Pur in rats following intragastric and intravenous administration (mean ± SD, $n = 5$).

Parameters	Group B (single-*i.g.*-Pur)	Group C (unite-*i.g.*-Gas & Pur)	Group E (single-i.v.-Pur)	Group F (unite-i.v.-Gas & Pur)
C_{max} (μg/mL)	0.490 ± 0.150	2.01 ± 0.380[b]	71.4 ± 6.50	65.8 ± 9.73
T_{max} (h)	1.95 ± 1.15	0.570 ± 0.340[a]	0	0
$T_{1/2}$ (h)	1.33 ± 0.350	4.00 ± 1.16[b]	1.44 ± 0.990	2.22 ± 0.780
AUC_{0-t} (μg h/mL)	0.940 ± 0.280	9.46 ± 0.650[b]	21.1 ± 1.77	23.8 ± 3.85
$AUC_{0-\infty}$ (μg h/mL)	1.16 ± 0.320	12.4 ± 1.51[b]	21.2 ± 1.83	24.1 ± 3.88
CL (mL/h/kg)	(3.65 ± 1.00) × 10^5	(3.27 ± 0.447) × $10^{4,b}$	(9.47 ± 0.872) × 10^2	(8.50 ± 1.48) × 10^2
MRT (h)	2.10 ± 0.430	5.10 ± 0.570[b]	0.350 ± 0.0300	0.570 ± 0.140[c]
C_0 (μg/mL)	NA	NA	89.6 ± 15.0	81.6 ± 18.1
AUC_{0-t}/D (g h/mL)	0.00235 ± 0.000700	0.0236 ± 0.00162[b]	1.05 ± 0.0885	1.19 ± 0.192
C_{max}/D (g/mL)	0.00122 ± 0.000375	0.00502 ± 0.000950[b]	3.57 ± 0.325	3.29 ± 0.486
F_{ab} (%)	0.270 ± 0.0700	2.92 ± 0.350[b]	NA	NA
F_{re} (%)	NA	1.07 × 10^3	NA	113

SD, standard deviation; NA, not applicable; *D*, administered dose; F_{ab}, absolute bioavailability; F_{re}, relative bioavailability (compared with single administration).
[a] Significantly different from group B, $P < 0.05$.
[b] Significantly different from group B, $P < 0.01$.
[c] Significantly different from group E, $P < 0.05$.

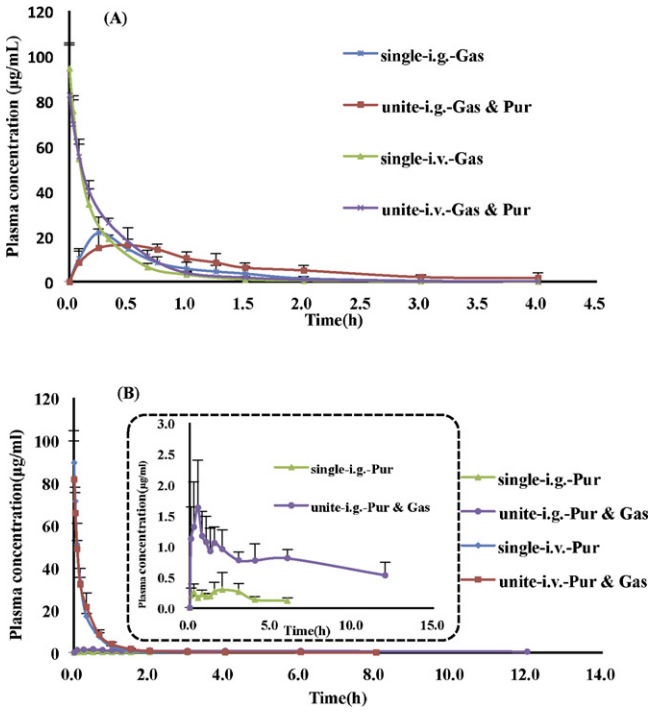

Fig. 3. (Mean ± SD, $n = 5$) rats plasma concentration of Gas (A) and Pur (B) following *i.g./i.v.* administrations of either Gas alone or together with Pur and administrations of either Pur alone or together with Gas, respectively. Insert shows the pharmacokinetic curves of Pur alone or co-administrated with Gas via *i.g.* route.

On the whole, compared with Gas administrated alone, Gas co-administrated with Pur could have higher bioavailability (*F*) and lower clearance rate (*CL*), as well as longer mean residence time (*MRT*) both through *i.g.* and *i.v.* routes, particularly notable via *i.g.* administration, and the pharmacokinetic profiles of Pur were analogous to Gas but more remarkable (the relative oral bioavailability of Pur in combined administration is 10.7-time as much as that of single administration, while 1.52-fold in Gas).

It was unclear concerned the mechanism of enhanced absorption between Gas and Pur. On one hand, few people studied the mechanism of absorption for Gas mainly because it has relatively good absorption. On the other, the research on Pur in-depth was rare and the conclusions of previous studies were inconsistent. Cui [34] reported that the transport of Pur across Caco-2 cell monolayer was directional and the direction could be suppressed by verapamil, the P-glycoprotein inhibitor, while Li [35] obtained a different result that there was no obvious direction from 50 μg/mL to 200 μg/mL of Pur, and the rate of transport was almost constant, suggesting that the absorption of Pur was passive transport process.

In addition, there were a few explanations on low bioavailability of Pur, such as P-glycoprotein-mediated drug-efflux [34], cytochrome P_{450} on drug metabolism [35] and low intestinal permeability of Pur [36]. We speculate that Gas plays the role of inhibitor of P-glycoprotein or cytochrome P_{450}, all of which would account for the increased absorbtion of Pur, so may the interpretation for higher bioavailability of Gas.

In a word, further studies are needed to understand the precise mechanism of the mutual promotion effect on absorption between Gas and Pur.

4. Conclusions

A reversed-phase HPLC method which is simple, highly accurate and appropriate to the bioanalytical requirements was successfully applied to characterize the pharmacokinetic interaction of Gas and Pur in rat plasma. The results of the present study showed that there were significant differences on pharmacokinetic parameters of Gas given alone and co-administrated with Pur, and of Pur administrated alone and combined with Gas. The combination of Gas and Pur increased drug absorption, reduced elimination rates, and proloned mean residence time, indicating the interactions between Gas and Pur could lead to an improvement in the bioavalibility of each other. These results might lay a foundation for explaining the combination of traditional Chinese medicine in prescriptions containing Gas and Pur and provide an important basis in clinical practice with these two components, especially in the treatment of vertebrobasilar ischemia.

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