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Design and Evaluation of Wubei Gastr-Effervescent Tablet

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Abstract

Objective: A new solid preparation with instant effects like powder preparation was developed.

Introduction: Its instant dispersion results from a small amount of alkaline ingredients which would react with gastric acid in stomach to produce gas causing instant disintegration.

Methodology: According to relative specification in Chinese Pharmacopoeia, prescription was optimized.The tablet and the powders were administered to beagle dogs for the double cycle cross experiment. The plasma of the dogs was measured by LC-MS/MS and was compared with each other.

Result: The *in vivo* studies demonstrated that the Wubeigastr-effervescent tablet showed bio-equiavailability with traditional Wubei powder. This formulation could be applied to some liquid preparations without reducing their fastness of effects.

Keywords: Wubei powder; *Endocochasepiae; Thunberg fritillary bulb;* Gastr-effervescent tablet; HPLC-MS/MS

Introduction

In the long history, Traditional Chinese medicines (TCM) had developed dozens of dosage forms, in which oral solutions and powders were main ones. Oral solutions are prepared by extracting crude drugs under appropriate conditions using water or other solvents, and then concentrating or adding antiseptics to obtain liquid preparations. Powders are prepared by crashing and mixing crude drugs with adjuvant to obtain dry powders. The two preparations are beneficial to drugs absorbing and producing the desired effect very fast, while both have bad taste and inconvenience transportation and storage.

How to reform traditional preparations of TCM is an important topic of TCM modernization. This paper would like to design an easy-dispersing solid formulation on the basis of maintaining merits and improving demerits of the two preparations to meet the demand of TCM modernization.

At present, there are three kinds of dispersible solid formulations: dispersible tablet [1], effervescent tablet [2] and soluble tablet [3]. The three were all designed for old people, children and patients with dysphagia to disperse in water before taking medicine. These designs only improved the situation of transportation and storage while bad administration compliance remained. Soluble tablets have specificrequirements for adjuvant and drug so that have narrow application range [4]. Dispersible tablets need special high-performance disintegrant with high price to ensure good disintegration [5]. Effervescent tablets need effervescent and water soluble adjuvant and could not be applied to drugs which could react with acids or alkali. In addition, temperature and humidity must be strictly restrained [6].

This paper aimed to design a new gastr-effervescent tablet which is administered directly in solid form instead of dispersing in water. This new formulation employed the principle of common effervescent tablet that produce gas to promote disintegration. Different to common effervescent tablet, it only contains alkaline ingredients, no acid ingredients so that it would only effervesce at meeting gastric acid in stomach. Its advantages lie in: transportation, storage and administration are all conducted in solid form; produced bulbs make drugs disperse homogeneously in large amount of foams and take effect instantly; relax restrictions to humidity in the process of producing common effervescent tablet and dispersible tablet; superior disintegrants are not needed.

The amount of alkali in the tablet is little so that produced gas should not cause abdominal distention and eructation or break the balance of body. We can find calcium carbonate and aluminium hydroxide tablets in Chinese pharmacopoeia, which just make use of the reaction with gastric acid to exert effects. This formulation is especially suitable for gastropathy drugs because effervesce would form a layer of homogeneous film on gastric wall to protect gastric mucosa against gastric acid. TCM always has unique advantages in recuperating gastrointestinal function[7]. To reform those gastroenteropathy TCM with reliable therapeutic effects into gastr-effervescent tablets maybe bring some unexpected effects thereby maybe become a new direction of TCM modernization.

Wubei powder, a Chinese patent medicine recorded in Chinese Pharmacopeia, consists of *Endocochasepiae* 850g, *thunberg fritillary bulb* 150g, and *pericarpium citrireticulatae volatile oil* 1.5g, exhibiting significant performance in treating for gastropathy resulting from excessive gastric acid. The monarch drug *Endocochasepiae* contains 80~85% calcium carbonate, that could neutralize excessive gastric acid and produce gas. We planned to add appropriate adjuvant into Wubei powder then tablet, employing effervesce to make the tablets disperse in gastric juice within 3min to achieve the performance of powders.

Materials and Methods

Chemicals and reagents

Wubeisan powder, *Endocochasepiae, thunberg fritillary bulb, pericarpium citrireticulatae volatile oil* was purchased from a local

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drug store in Shenyang. Peimine and metronidazole was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Methanol, diethylamine were of chromatographic grade from the Yuwang Chemical Factory (Shandong, China). Deionized water was used and all other reagents were of analytical grade.

Preparation of drug tablet

Endocochasepiae 85g and *thunberg fritillary bulb* 15g were crashed into fine powder, followed by adding 0.15g *pericarpium citrireticulatae volatile oil* and 0.5g sodium bicarbonate, miscingbene. The mixture were sieved and tableted into 400 pills.

Disintegration time

Placed a tablet into a 250 ml beaker which held 200 ml artificial gastric juice (obtained by mixing dilute hydrochloric acid 16.4 ml with water 800 ml and pepsase 10 g, then adding water to 1000 ml) at 37℃. There should not be granule remained when bulbs stopped emitting from the tablet. The test was conducted in sextuplicate. All of the tablets should disintegrate within 3min and pass through 850 μm sieve.

Drug administration and blood sampling

Study was performed in female beagle dogs (n=6, weight range 9.3 ± 1.0 kg). Six dogs were divided into 2 groups at random and administered orally a dose of 3 g tablets or powders (50 ml water) respectively. Approximately 3ml blood samples were collected in heparinized tubes using an indwelling cannula at 0, 0.5, 0.75, 1.5, 2.5, 3, 4, 5, 6, 8, 10, 12, 24h after administration. The blood samples were centrifuged at 4000 rpm for 10 min, and plasma was separated and kept frozen at -20℃. After a washout period of 7 days, the study was repeated in the same manner to complete the crossover design.

Preparation of plasma samples

Dog plasma 500 μl was mixed with 100 μl ammonia water, 50 μl internal standard solution (100 ng/mL). After vortex-mixing 30s, 4 ml ethyl acetate was added, vortexed 5min, centrifuged at 6000 rpm for 10 min. The supernatant was separated out and blown to dryness with nitrogen at 40℃. Then the residue was reconstituted in 100 μl mobile phase and a 20 μl aliquot of the final testing samples was injected onto the LC/MS/MS system for analysis. The same procedure was used to determine the recovery and precision in plasma.

LC/MS/MS conditions

The HPLC system consists of a LC-10ADvp Pump (Thermo Finnigan, USA) and a SIL-HTA Autosampler (Thermo Finnigan). Chromatographic separation was carried out on a Diamonsil C18 (150×4.6mm I.D., 5μm, Dikma, Beijing) with a Easy Guard C18 Security guard column (8×4.0 mm I.D., Dikma, Beijing) kept at 30℃. The mobile phase consisted of water (containing 1%diethylamine)/ methanol (20:80, v/v), at a flow rate of 0.5ml/min.

Mass spectrometric detection was performed on a Thermo Finnigan TSQ Quantum triple quadrupole mass spectrometer (San Jose, CA, USA) equipped with an ESI source in the positive ionization mode. The MS operating conditions were optimized as follows: the spray voltage: 4200V; the source CID voltage: 10eV; the capillary temperature: 320℃; the sheath gas (nitrogen): 30 psi; the auxiliary gas (nitrogen): 5psi; the collision gas (argon) pressure: 1.2mtorr; the collision energy: 30eV for peimine and peiminine, 20ev for metronidazole. Data acquisition was performed by X calibur 1.4 software (Thermo Finnigan). Peak integration and calibration were performed using LC Quan software (Thermo Finnigan). Quantification was obtained by using SRM mode of the transitions at m/z 432→414 for peimine and at m/z 172→128 for metronidazole (IS) respectively, with a scan time of 0.3s per transition.

Calibration curve

The calibration curves were based on triplicate analyses of each peimine concentration. A linear correlation was found over the entire studied range 0.1~10ng/ml. The mean equation of the calibration curve obtained from three batches in method validation was y=123.58x-4.06(r=0.997), where y represents the peimine peak area to the IS peak area ratio and x represents the peimine concentration. A weighing factor of $1/x^2$ was chosen to achieve homogeneity of variance.

Pharmacokinetics analyses

Pharmacokinetic parameters including area under concentration–time curve(AUC_{0-t}), oral clearance(CL/F), and mean residence time(MRT_{0-t}), apparent elimination half-life($t_{1/2}$) were estimated using a non-compartmental analysis using Drug And Statistics 2.0(DAS 2.0) (Mathematical Pharmacology Professional Committee of China, Shanghai, China). Maximum plasma concentration (C_{max}), time to reach the maximum concentrations (T_{max}), was observed directly from the detected concentration versus time data.

Results and Discussion

Preparation

Calcium carbonate in *Endocochasepiae* is mingled together with other ingredients so that could not produce gas vigorously enough to make the tablet disintegrate instantly and completely. Extra alkali, such as sodium bicarbonate is necessary to promote effervesce. The tendency of disintegration time changing with the amount of sodium bicarbonate was shown as Figure 1. After the fraction of sodium bicarbonate added up to 0.5%, the disintegration time didn't decrease significantly any more. Since the less the amount of extra alkali is, the less effect to body it would cause, we chose 0.5% as the amount of sodium bicarbonate.

It was interesting to notice that the crude drugs could be shaped using direct tablet compressing without adding any other adjuvant, such as disintegrant or cohesives, and the resulted tablets were

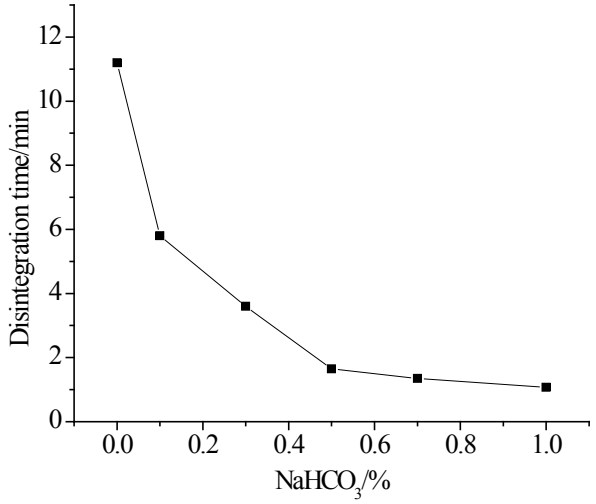

Figure 1: The disintegration time changed with the fraction of sodium bicarbonate.

satisfactory for the specification about friability, disperse homogeneity, weight variation in Chinese Pharmacopoeia. Probably it was the good compactibility of calcium carbonate that should take the responsibility [8,9].

HPLC and MS/MS chromatograms

The product ion spectra of the substances can be seen in Figure 2. The SRM transitions at *m/z* 432→414, at *m/z*172→128, were selected to analyze peimine and IS, respectively. Figure 3 shows the typical chromatograms of a plasma sample peimine and IS where no significant interfering peaks were observed.

Determination of peimine in plasma

As the chemical constituents of the formula are complex, pharmacokinetic studies usually focus on the main active constituents. According to Chinese pharmacopoeia [10], peimine can be used as a marker compound to characterize Wubei formulations. The plasma concentration versus time profiles of peimine in beagle dogs are shown in Figure 4, after oral administration of effervescent tablet and powders. The main pharmacokinetic parameters for peimine are presented in Table 1.

The main pharmacokinetic parameters were evaluated with analysis of variance (ANOVA) and two one-sided test. The 90% confidence interval of $AUC_{0\text{-}t}$ of tablet fell in the 80~125% range of powder; the 90% confidence interval of C_{max} of tablet fell in the 70~145% range of powder, that showed no significant difference (P>0.05). A nonparametric method test (Wilcoxon method) proved there was no significant difference between t_{max} of the two preparations. The statistical results suggested the two preparations were bioequivalent.

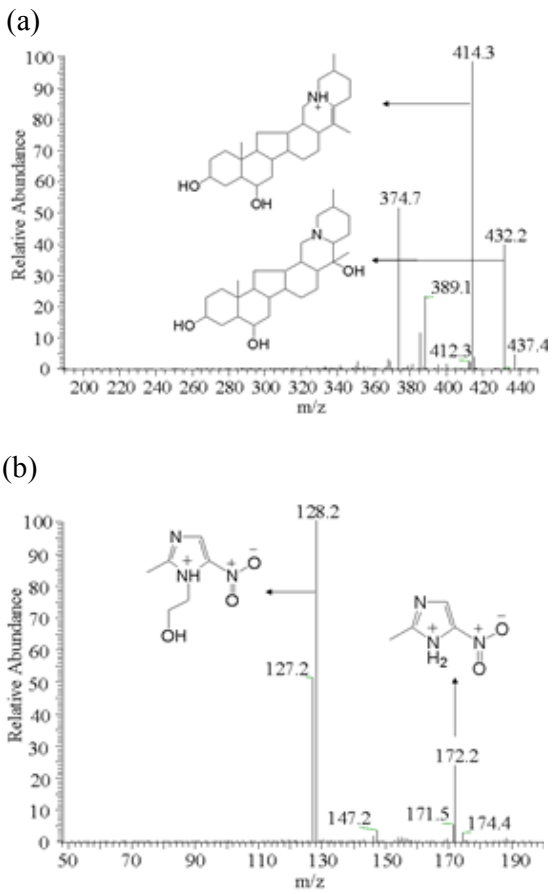

Figure 2: Product ion mass spectra of [M+H]+ ions of(A) peimine (B) metronidazole (IS).

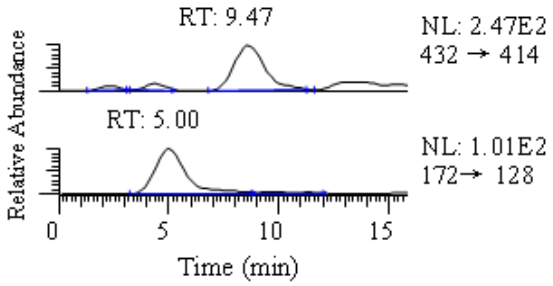

Figure 3: Representative SRM chromatograms for peimine and IS in dog plasma.

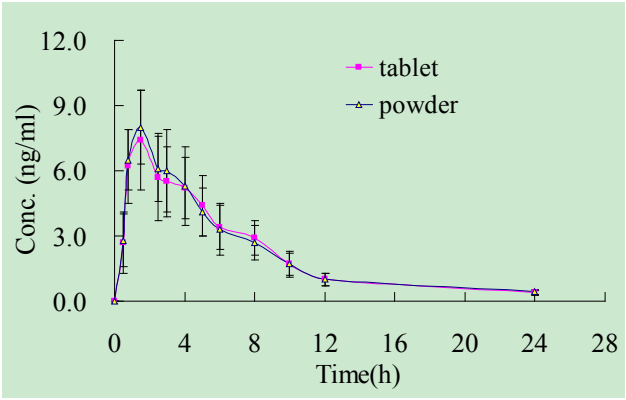

Figure 4: Plasma concentration-time profile of peimine in beagle dogs after oral administration of two Wubei formulations. Each Point represents the mean ± SD (n=6).

Parameters	Powder	Tablet
$AUC_{0\text{-}t}$(ng/ml·h)	68.78 ± 16.27	59.13 ± 15.25
$t_{1/2}$(h)	9.05 ± 3.57	8.73 ± 2.97
t_{max}(h)	1.5 ± 0	1.5 ± 0
C_{max}(ng/ml)	8.0 ± 1.7	7.4 ± 2.3

Table 1: Pharmacokinetic parameters of peimine in beagle dogs after oral administration of two Wubei formulations.

Conclusion

In vivo studies demonstrated that the gastr-effervescent tablet had identical effects to the powder meanwhile showed more convenience in practice. This formulation doesn't involve any complex craft to impede further spread. Although the gastr-effervescent tablet was designed basing on TCM powders originally, its principles could be applied to liquid preparations obviously. It has both instant effects like liquid preparations and convenience, stability and good taste like solid preparations.

Reference

1. Bi YX, Sunada H, Yonezawa Y, Danjo K (1999) Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Dev Ind Pharm 25: 571-581.

2. Goel H, Rai P, Rana V, Tiwary AK (2008) Orally disintegrating systems:

innovations in formulation and technology. Recent Pat Drug Deliv Formul 2: 258-274.

3. Risheng W, Xia C (2000) Studies on the stability of nasal drip analgin soluble tablet. China Pharmaceuticals 9: 17-18.
4. Dvorackova K, Rabiskova M, Masteikova R, Muselik J, Krejcova K (2009) Soluble filler as a dissolution profile modulator for slightly soluble drugs in matrix tablets. Drug Dev Ind Pharm 35: 930-940.
5. Ishikawa T, Mukai B, Shiraishi S, Utoguchi N, Fujii M (2001) Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules. Chem Pharm bull (Tokyo) 49: 134-139.
6. Jacob S, Shirwaikar A, Nair A (2009) Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. Drug Dev Ind Pharm 35: 321-328.
7. Fangyan D (2005) Modern practical new preparations and new technologies of TCM (2nd Edn). Peoples Medical Press, Beijing: 85-87.
8. Chi-Ming C, Jing-Shen W, Jian-Xiong L, Ying-Kit C (2002). Polypropylene/calcium carbonate nanocomposites. Polymer 43: 2981-2992.
9. Xiang L, Xiang Y, Wang ZG, Jin Y (2002) Influence of chemical additives on the formation of super-fine calcium carbonate. Powder Technology 126: 129-133.
10. The State Pharmacopoeia Commission of PR China (2010) Pharmacopoeia of PR China, Chemical Industry Press, Beijing 1.