Optimization of Jiawei Qing'e Oral Fast Disintegrating Tablets Based on Response Surface-Central Composite Design

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Abstract: **Objective** To apply the response surface-central composite design to developing and optimizing the oral fast disintegrating tablets (ODT) formulation for Jiawei Qing'e, a kind of prescription of Chinese herbal medicine. **Methods** The bitterness of Jiawei Qing'e was masked using Eudragit E-100 by solvent evaporation technique. Response surface approach was applied to investigating the interaction of formulation parameters in optimizing the formulation. The independent variables were Eudragit E-100/drug ratio (X_1), amount of disintegrants (X_2), and the amount of diluents (X_3). The disintegration time (Y_1), hardness (Y_2), and weight variations of the tablets were characterized. **Results** The models predicted levels of X_1 = 4.63%, X_2 = 5.25%, and X_3 = 34.33%, for the optimal formulation having a hardness of 3.0 kg with the disintegration time of 30 s within experimental region. The observed response of Y_1 = 26.5 s and Y_2 = 3.14 kg reasonably agreed with the predicted response. **Conclusion** Response surface methodology shows the good predictability and reliability in optimizing the formulation. The optimized ODT of Jiawei Qing'e has acceptable taste, rapid disintegrating ability, and good mechanical strength.

Key words: Chinese herbal medicine; oral fast disintegrating tablets; response surface-central composite design; solvent evaporation technique; taste masking

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Introduction

Chinese herbal medicine (CHM) has been used by Chinese people for thousands of years, and it has been widely accepted that CHM has evolved over the millennia, with a battery of herbal materials to preserve health, to treat and prevent illnesses (Lu *et al*, 2004; Matsumoto *et al*, 2008). However, it is true that most Chinese herbal preparations are not pleasant or good in appearance or taste as modern chemical drugs, and the unsatisfied dosage form has greatly limited its clinical application. It may therefore be necessary to develop new dosage forms for improving its patient compliance.

Oral fast disintegrating tablets (ODTs) have been well-known as modern solid fast-release dosage form since the late 1990s (Watanabe, Koizumi, and Zama, 1995; Bi *et al*, 1996; 1999a; 1999b; Ito and Sugihara, 1996; Khankari *et al*, 2000; Jain *et al*, 2001), and the application has become a rapidly growing interest in the pharmaceutical industry. Upon introduction into the mouth, these tablets could be rapidly disintegrated by saliva in the mouth resulting in easy swallowing, and could provide the significant benefits to the pediatric and geriatric population, as well as other patients who prefered the convenience of easily swallowable dosage forms (Zade, Kawtikwar, and Sakarkar, 2009). ODTs have the unique property of disintegrating the tablet in the mouth in seconds, and such a dosage form will definitely enhance the compliance of patients, especially during traveling or in the situations where water is not available (Elnaggar *et al*, 2010; Laitinen *et al*, 2010).

ODTs of CHM are rarely reported because they are extremely bitter and have high drug contents. Taste is an important parameter in administering drugs orally.

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The undesirable taste is one of the important formulation problems encountered with most CHM. The oral administration of bitter drugs with acceptable level of palatability is a key issue in the formulation of ODT. Only the dissolved substances elicit taste sensation and the substances which are completely insoluble in water are tasteless (Freudenberg, Cramer, and Plieninger, 1953). However, the taste masking of water-soluble bitter drugs, especially those with complex composition and a high dose just as CHM, is difficult to achieve by using sweeteners alone (Zelalem *et al*, 2009). In recent years, more efficient techniques such as coating, microencapsulation, and granulation have been used in masking the bitterness and bad smell of the drug (Shah and Mashru, 2008; Bora, Borude, and Bhise, 2008; Patra *et al*, 2010; He *et al*, 2010). Due to the specificness of CHM which is requested high percentage in the formulation of tablets, this efficient technique used in chemical medicine nonselectivly masking water-soluble and water-insoluble drugs and increasing the drug particle size and the amount of the excipients, are usually inapplicable in achieving the taste-masked CHM which is generally used with large dosage in clinic. Solvent evaporation technique, which developed from a preparation method of taste-masked microspheres (Shishu, Kamalpreet, and Kapoor, 2010), may uniformly overlay the Eudragit E-100 on the water-soluble drug with the evaporation of solvent and have little influence on the drug particle size, would be potentially feasible for masking the bitterness of CHM.

Jiawei Qing'e is a CHM prescription consisting of *Eucommiae Cortex* (*Duzhong*), *Salviae miltiorrhizae Radix* et *Rhizoma* (*Danshen*), *Psoraleae Fructus* (*Buguzhi*), and *Anemarrhenae Rhizoma* (*Zhimu*), and has been certificated that the activity of Qing'e is mediated through estrogenic components and used for the treatment of postmenopausal symptoms (Xu, Zhang, and Geng, 2010). It was chosen to be studied due to its extremely bitter taste and requiring longer time to administer.

The present work is to formulate an ODT of taste-masked Jiawei Qing'e. The crucial aspect in the formulation is to mask the strongly bitter taste and to minimize the disintegration time while maintaining a good mechanical strength of the tablets. In this study, we masked the bitter taste using Eudragit E-100 by solvent evaporation method. Response surface methodology, a collection of mathematical and statistical technique, was used to optimize the formulation as it provided the empirical models that could describe the effect of variables on the response and select the optimized response region from the response surface described by the models. ODTs were made by direct compression method according to a three-factor, three-level face-centered central composite design, which is a widely used method that could fit the experimental results to the non-linear mathematical model and combine the response surface methodology by statistical software (Lin *et al*, 2004). By careful design, the objective of applying response surface-central composite design to optimizing and investigating the main effects and interaction of the formulation parameters was hoped to reach.

Materials and methods

Materials

Powdered extract of Jiawei Qing'e (self-extracted); Eudragit E-100 (Wantai Medicine Material Co., Ltd., Jiangsu, China); polyvinylpolypyrrolidone (PVPP) (XP-10, ISP, America); croscarmellose sodium (CCNa) (CHP Carbohydrate Pirna GmbH + Co. KG, Germany); microcrystalline cellulose (MCC) (PH101, Ahua Medicine Co., Shandong, China); spray-dried lactose (Wasserburg, Germany); magnesium stearate (Ahua Medicine Co., Shandong, China); Mannitol (P200SD, Roquette, Frence). All other reagents and solvents were of analytical grade.

Equipments

Single Punch Tablet Press (DP30, Gylongli Sci. & Tech. Co., Ltd., Beijing, China); Hardness Tester (Huanghai Drug Test Instrument Co., Ltd., Shanghai, China); Rotary Evaparator (RE52C, Yarong Biochemical Instrument Factory, Shanghai, China); Thermostat-controlled Waterbath (W201, Shensheng Biotechnology Co., Ltd., Shanghai, China); Recycle Water Vacuum Pump (SHZ-Ⅲ, Yarong Biochemistry Instrument Factory, Shanghai, China); Dissolution Apparatus (ZRS-8G, Haiyida Tech Co., Ltd., Tianjin, China).

Preparation of taste masked Jiawei Qing'e powdered extract

Varying amounts of Eudragit E-100 were weighed and dissolved in 50 mL anhydrous alcohol, and a

constant amount of powdered extract of Jiawei Qing'e was added in the polymer solution. The Eudragit E-100/drug ratio was taken as 0, 5%, and 10%. Subsequently, the suspension was blended in the rotary evaporator for 10 min, and then the alcohol was evaporated at 50 ℃. After complete evaporation of the solvent, the blend was scraped and dried in vacuum at 40 ℃ for 3 h, and finally passed through a No. 80 mesh screen followed by grinding and stored in desiccator till further use.

Experiment design

In order to select the suitable excipients and amount to reduce the complexity of optimization, single factor investigation experiments were performed. Considering the high viscosity of CHM, the high level of main drug may increase the difficulty for preparation and disintegration, and the drug content was chosen at 30%. Eudragit E-100 as a taste-masking agent was found benefitial for improving the flowability of the drug, but overdose may affect the disintegration of ODTs. Therefore, the Eudragit E-100/drug ratio was investigated based on the disintegration ability. The results suggest that the ratio between 0—10% performs the best ability. The selecting of disintegrants played an important role in the preparation of ODTs. We found that the combination of two disintegrants could signi-ficantly enhance the performance of the disintergration of the tablets, and the toplimits is 10% after which the disintegration ability will be slow or even declining. In order to achieve the perfect hardness and flowability, we chose MCC and spray-dried lactose as the diluents, and selected the normal amount of 30%—50%.

Experiments were performed using a three-factor, three-level face-centered central composite design created by optimization software MINITAB 14 (Late and Bangal, 2010; Ma *et al*, 2011; Li *et al*, 2010). According to the result of single factor tests, the Eudragit E-100/drug ratio (X_1), amount of super disintegrants (X_2), and amount of diluents (X_3) were taken as the main investigating factors. Table 1 lists the Jiawei Qing'e ODT formulation used in this study. A combination of PVPP and CCNa (1:1) was chosen as the super disintegrant since it has great disintegration capability. MCC and spray-dried lactose (1:1) were chosen as the diluents. Magnesium stearate and SiO_2 were respectively used as lubricant and glidant. Mannitol was used to make up the composition of tablet formulation to 100%. The function of mannitol could also be regarded as diluents or a sweetening agent. It was assumed that any change in the response had no reference to the proportion of the mannitol. The mainly considered responses were disintegration time (Y_1) and hardness (Y_2). The independent factors and dependent responses used in the study are listed in Table 2. The face-centered central composite design generated 20 tests that included six replicaes. All the experiments were carried out in duplicates to obtain the values of the dependent response.

Table 1 ODT formulation of Jiawei Qing'e

No.	Ingredients	Content / %
1	powdered extracts of Jiawei Qing'e treated with Eudragit E-100	30
2	disintegrants (PVPP/CCNa)	0/5/10
3	diluents (MCC/spray-dried lactose)	30/40/50
4	magnesium stearate	1
5	SiO_2	1
6	mannitol	q.s.100

Tablet weight = 300 mg

Table 2 Factors and responses in face-centered central composite design

Factors	Levels / %		
	Low (−1)	Middle (0)	High (1)
X_1	0	5	10
X_2	0	5	10
X_3	30	40	50
Responses			
Y_1 (s)			
Y_2 (kg)			

Preparation of tablets

ODTs were prepared by a direct compression method because of its ease of application and low cost. Formulations were prepared according to test frame work of the face-centered central composite design. The ingredients of formulations are shown in Table 1. The drugs and all the excipients were passed manually through a No. 80 mesh screen before being weighed and mixed through a No. 40 mesh screen for three times without magnesium stearate. Magnesium stearate was added to this blend separately and mixed properly with a spatula. The blend was compressed using 9 mm flat plain face tooling on single punch tablet press at 40 r/min. The pressure was set at a suitable level which could ensure the tablet could bear the pressure during

transport and also have the desired disintegration time. The tablet weight was maintained at 300 mg.

Disintegration test

The ODTs disintegrate in mouth by limited saliva within 1 min. There is no standard on simulated tablet disintegration test in *Chinese Pharmacopeia*. The method of tablet disintegration test for common tablets could not exactly simulate the conditions of oral cavity. Researchers made a wide exploration about disintegration test for ODTs and designed adaptive methods according to the different properties (Su, Ma, and Jiao, 2010; Chen and Zhu, 2008; Zhou, Xu, and Lu, 2006; Zhai *et al*, 2007). Since it is difficult to apply general disintegration test to reflecting the real conditions, a paddle method for the measurement of the disintegration time of ODTs in good correlation with *in vivo* evaluation was applied to this study (Li *et al*, 2006). The paddle method originally proposed by Bi *et al* (1996; 1999a; 1999b) was modified according to USP regulations and employed to determine the disintegration time of rapid disintegrating tablets. A dissolution apparatus was used instead of a disintegration tester. The disintegration fluid was 900 mL of water thermostatically maintained at 37 ℃ and stirred at 100 r/min. The dimension of the sinker was 5 cm in height and 2 cm in diameter, and the openings of the sinker screen were 1.98 mm in diameter. The disintegration time was determined as the time between the immersion of the tablet in water and the time at which the tablet disintegrated and passed through the screen of the sinker completely. Six tablets were chosen randomly from each of the tableting runs and the average disintegration time was calculated.

Hardness test

The hardness of the tablets was measured by a hardness tester. Six tablets were chosen randomly from each of the tableting runs, and the average hardness was calculated.

Results

Data analysis methods

Table 3 summarized the values for the responses Y_1 and Y_2. The data were analyzed using MINITAB 14 statistical software. This software could respectively fit the data to linear, interaction effect between two factors, second-order regression models and even higher order models, and exactly locate the response optimum. The model was judged by multiple correlation coefficient (R^2) and confidence interval (P) of the adjusted model (Ma *et al*, 2011). Second-order regression models were developed based on the regression of statistically significant variables. Results of multiple regression analysis for each response variable were as follows.

Table 3 Matrix of face-centered central composite design and results for each test ($\bar{x} \pm s$)

No.	X_1	X_2	X_3	Y_1 / s	Y_2 / kg	Weight / mg
1	0	0	1	55 ± 0.86	3.31 ± 0.37	299.8 ± 5.2
2	0	0	−1	50 ± 1.14	3.21 ± 0.95	304.9 ± 7.6
3	1	0	0	62 ± 3.82	3.25 ± 0.23	300.2 ± 4.6
4	0	0	0	50 ± 2.82	3.06 ± 0.20	296.1 ± 6.3
5	−1	0	0	38 ± 5.89	2.40 ± 0.57	298.6 ± 10.1
6	0	−1	0	702 ± 2.11	3.16 ± 0.73	297.5 ± 6.4
7	0	0	0	48 ± 0.82	3.07 ± 0.30	295.6 ± 6.2
8	0	1	0	33 ± 4.18	3.02 ± 0.39	301.8 ± 6.1
9	−1	1	1	38 ± 2.40	2.64 ± 0.29	311.7 ± 7.6
10	−1	−1	−1	668 ± 0.89	2.52 ± 0.32	288.5 ± 12.3
11	0	0	0	45 ± 2.18	2.96 ± 0.80	299.3 ± 5.9
12	1	−1	−1	746 ± 1.88	3.30 ± 0.37	297.7 ± 5.8
13	0	0	0	46 ± 1.88	3.01 ± 0.30	304.8 ± 6.0
14	1	1	−1	26 ± 0.06	3.33 ± 0.26	306.9 ± 5.2
15	1	−1	1	754 ± 1.60	3.63 ± 0.21	308.6 ± 4.4
16	1	1	1	33 ± 0.40	3.70 ± 0.14	301.3 ± 4.7
17	0	0	0	47 ± 0.18	2.99 ± 0.50	305.4 ± 5.6
18	−1	1	−1	36 ± 2.12	2.39 ± 0.29	291.6 ± 10.7
19	−1	−1	1	675 ± 0.48	2.66 ± 0.24	304.3 ± 6.8
20	0	0	0	43 ± 4.18	3.06 ± 0.20	306.6 ± 5.7

$Y_1 = 47.18 + 16.86X_1 — 337.64X_2 — 21.18X_1X_2 + 319.29X_2^2$ ($R^2 = 0.9999$, $P < 0.0001$)

$Y_2 = 30.4 + 4.65X_1 + 1.16X_3 — 2.32X_1^2 + 1.90X_3^2$ ($R^2 = 0.9847$, $P = 0.0003$)

The above equations indicate the effect of independent factors (X_1, X_2, and X_3) and their interactions on the responses Y_1 and Y_2. The values of coefficients X_1 to X_3 are associated with the effect of these variables on the responses. The interaction term (e.g., X_1X_2) shows how the response changes when two factors simultaneously changed, while the quadratic terms (X_n^2) denoting nonlinearity relationships suggest that there is a curvature in the response and there are optimal values for these variables. Only statistically significant coefficients ($P < 0.05$) were retained in the equations. The lack-of-fit test ($P > 0.05$) and the square of the correlation coefficients ($R^2 \approx 1$) indicated that models were fitted sufficiently to the measured data.

The standard errors of estimate for Y_1 and Y_2 were 3.530 and 0.6077, respectively.

Data analysis on disintegration time of tablets

Response surface plots (Fig. 2) were used to illustrate the relationship between the dependent and independent variables. Response surface plot in Fig. 1 described the effects of X_1, X_2, and their interaction on Y_1. It could be clearly seen that Y_1 was strongly affected by X_2, since Y_1 decreased sharply with the increase of X_2. At low level of X_1, Y_1 decreased rapidly from 668 to 26 s as X_2 increased from 0 to 6.2%. Above 6.2% of X_2, Y_1 increased from 26 to 36 s. At high level of X_1, Y_1 decreased rapidly from 754 to 28 s as X_2 increased from 0 to 6.5%. Above 6.5% of X_2, Y_1 increased from 28 to 33 s. From the figure it could be seen that X_1 has little effect on Y_1 since it increased slightly from 668 to 746 s with the increased X_1 from 0 to 10% at low level of X_2. At high level of X_2, the trend of Y_1 was similar to that at low level of X_2. On the whole, X_2 was the key factor affecting Y_1. The effect of X_1 was negligible contrasted with the strong disintegrating ability of disintegrants.

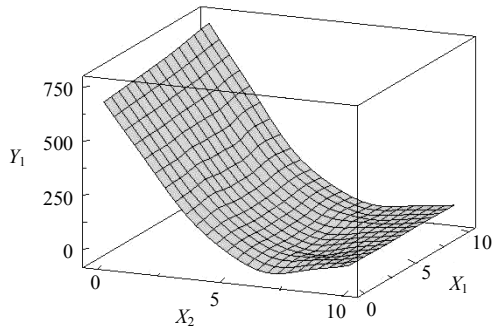

Fig. 1 Response surface plot for effects of X_1 and X_2 on Y_1

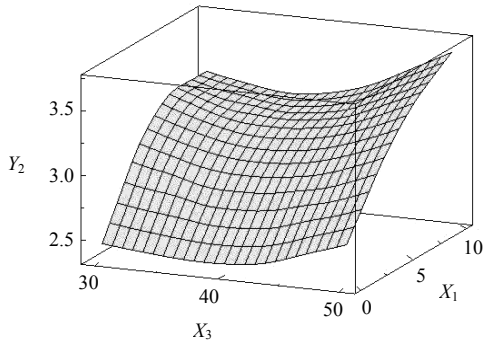

Fig. 2 Response surface plot for effects of X_1 and X_3 on Y_2

Analysis on hardness of tablets

Response surface plots (Fig. 2) described the effects of X_1, X_3, and their interaction on Y_2. It indicated that X_1 had a desirable effect on Y_2. It showed that Y_2 increased with the increase of X_1. At the low level of X_3, Y_2 increased from 2.5 to 3.3 kg with the increase of X_1 from 0 to 10%. At the high level of X_3, Y_2 increased from 2.6 to 3.6 kg as X_1 increased from 0 to 10%. At the low level of X_1, Y_2 decreased from 2.5 to 2.1 kg as X_3 increased from 30% to 40%, and then increased above 40%. At the high level of X_1, Y_2 decreased from 3.3 to 3.1 kg as X_3 increased from 30% to 40%, and then increased above 40%. The positive effect of X_1 was a determinant factor of increased X_2; This made it possible to achieve tablets with adequate mechanical strength under minimum press.

Optimization of formulation and verification

Contour plots (not shown) were obtained by the statistical software according to each independent variables and responses. Contour plots were used to determine the optimum formulation parameters. Each contour plot had its own optimal area which represented the optimal formula condition for ideal response. Overlaping the optimal area of each contour plot gave the optimal formulation. Models predicted the levels of X_1 = 4.63%, X_2 = 5.25%, and X_3 = 34.33%, for the optimal formulation with 3.0 kg hardness and 30 s disintegration time within test region. A verification test was performed on the basis of this optimal level, and the observed responses Y_1 = 26.5 s, Y_2 = 3.14 kg reasonably agreed with the predicted response. The variances of Y_1 and Y_2 were 3.5 and 1.4, respectively. The predicted values and test data of the optimized formulation showed the good correlation, which validated prognostic ability of response surface methodology in optimizing ODTs using Eudragit E-100 for taste masking.

Discussion

The taste masking technology played an important role in the preparation and optimization of ODT for Jiawei Qing'e. The taste buds of human contain very sensitive nerve endings, which could transmit bitter taste sensation to the brain when molecules of water-soluble drug come in contact with the taste receptor on the tongue. Therefore, the bitter taste may be effectively

masked if the drug couldn't dissolve in the oral cavity. Eudragit E-100 is such a material that insoluble in water as well as saliva but soluble in the gastric fluid. In the solvent evaporation technique, Eudragit E-100 and water-insoluble ingredients of the drug were dissolved in the alcohol, while the water-soluble ingredients suspended in it. Eudragit E-100 uniformly dispersed in the water-soluble ingredients without raising the particle size of the drug during the evaporation of solvent, and taste masked the bitterness by preventing or slowing down the dissolution of water-soluble ingredients of the drug in oral cavity. It was confirmed that the bitterness was reduced and acceptable with the ratio of Eudragit E-100/drug above 4%. Thus, Eudragit E-100 showed a good taste masking ability on ODTs, but it may also have negative influence. It had been reported that the disintegration time of tablets in the mouth is related to the penetration rate of water into the tablets (Sugimoto *et al*, 2001). The lag time of water uptake could play a great role in evaluating the disintegration characteristic of ODTs (Li, Yi, and Guo, 2006). Eudragit E-100 which is water insoluble material flocculated in water may lead to reduce water uptake by disintegrants. This may be the probable explanation for the behavior of slightly increased disintegration time of the tablets due to the increased ratio of Eudragit E-100/drug. However, the weak influence of Eudragit E-100 could be sufficiently nullified by the disintegrants which was the main determining factor to have the required disintegration time for ODTs. Moreover, the hardness of tablets increased with the increased ratio of Eudragit E-100/drug. This was a desired effect during the process of tablets making because of its contribution in achieving adequate mechanical strength to bear the pressure during handling and transport. In this work, it was observed that the flowability of the medicine powder treated with Eudragit E-100 was better than that of untreated one. This may help reduce the variation of the tablets weight during the formulation (Table 3), which is especially suitable for the direct compression method.

Conclusion

ODTs of Jiawei Qing'e were successfully optimized by response surface methodology. The highly significant mathematical model showed good correlation between the predicted values and test data of the optimized formulation in optimizing the formulation of ODTs for Jiawei Qing'e. The optimum formulation was 4.63% Eudragit E-100/drug ratio, 5.25% disintegrants and 34.33% diluents. And the measured disintegration time and hardness were 26.5 s and 3.14 kg, respectively. The optimized ODTs of Jiawei Qing'e have acceptable taste, rapid disintergrating ability, and good mechanical strength. Therefore, the response surface methodology showed the good predictability and reliability in optimizing the formulation of ODTs for Jiawei Qing'e using solvent evaporation technique as a taste masking method.

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