Preparation and in Vitro Dissolution of Curcumin Tablets

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Abstract. Objectives: To prepare curcumin tablets, and evaluate their in vitro dissolution. Methods: Curcumin was dissolved in acetone, wet-granulation and tableting. The amount of Poloxamer 188 and Gremophor RH40 were chosen as factors, and the in vitro dissolution at 120 min was used as evaluation index. The best prescription was screened by response surface method of two factors and three levels. UV-visible spectrophotometry was used as detection methods. Results: In this study, the standard curve was in good linearity with the range of 2.5~5.0μg·mL^{-1}, r = 0.9996. The average recovery was 98.08%, RSD = 0.61%. The obtained prescription: Curcumin: Poloxamer 188: Gremophor RH40 = 1: 2.52: 0.40, the in vitro dissolution at 45 min and 120 min were 64.85% and 95.12% respectively. Dissolution of the best prescription of curcumin obtained twice higher than the raw curcumin and physical mixtures, and higher than commercial products. Conclusions:The preparation method of curcumin tablets is simple and reliable, which significantly improves the dissolution of curcumin.

Introduction

Curcumin which was medicinal and edible products was mainly from the root of Curcuma aromatica Salisb, turmeric roots, Curcuma Rhizome, Acorus calamus L roots, etc. In medicine it has antioxidant, anti-inflammatory, anti-proliferative, anti-cancer, anti-bacterial infection, liver damage and other effects protection [1]. In recent years, it has been found to have immunomodulatory effect and a significant effect on the prevention of Alzheimer's disease[2]. Due to its low toxicity (LD50 in mice was greater than 2g. kg^{-1} [3]), the US FDA had evaluated its extensive safety. However, curcumin has some shortcomings such as poorly dissolution in water, sensitive to light, heat and iron ion, easily hydrolyzed in neutral and alkaline environment, content declining sharply under outdoor lighting [4], decreasing after autoclaving, low oral bioavailability [5] etc. Various preparation methods were reported in literature which mainly used polyvinylpyrrolidone (PVP K30), polyethylene glycol (PEG) as carriers to prepare curcumin solid dispersion in order to improve its dissolution [6-8], but the preparation process was complicated and high cost, which was not suitable for large-scale production. In this study, the response surface methodology (RSM) was used to obtain the best preparation of curcumin tablets, thus to increase its dissolution and bioavailability as well as to simplify the production process and facilitate the large-scale production and lower production costs.

Reagent and Instrument

Curcumin substance(Cur, Hebei days Asahi natural pigment Ltd.); Curcumin reference (Guangzhou Qiyun Sheng Technology Co., Ltd., content: HPLC≥98%); Poloxamer 188 (P188, BASF); Gremophor RH40 (Gremophor RH40, BASF); Crosslinked povidone (PVPP, the United States Specialty Products company); Silica powder (SiO_2, Guangzhou Jie Fu trading Co., Ltd.); Low-substituted hydroxypropyl cellulose (L-HPC, Guangzhou Jie Fu trading Co., Ltd.); Lactose (Beijing Feng Jingqiu commercial limited liability company); Microcrystalline cellulose (MCC, Anhui mountains and rivers of medicinal materials Co., Ltd.); Magnesium stearate (MS, Guangzhou Jie Fu trading Co., Ltd.); Curcumin capsules (US Priscilla Pleasant company); Sodium chloride (NaCl, Tianjin Zhiyuan chemical Reagent Co.); Sodium dodecyl sulfate (SDS, Tianjin Zhiyuan Chemicals Limited); Acetone (Tianjin Damao Chemical Reagent Factory).

ZRS-8G Intelligent Dissolution Tester (Tianjin Tianda Tianfa Technology Co., Ltd.); ZKT-18F vacuum degassing device (Tianjin Tianda Tianfa Technology Co., Ltd.); GZX-9246 MBE Digital Blast Oven (Shanghai Bo Xun Industrial Co., Ltd. medical Equipment Factory); UV-1800 UV-visible spectrophotometer (Shimadzu Corporation, Kyoto, Japan); BS 224S electronic balance (Beijing Sartorius instrument systems, Inc.); YP3001N electronic balance (Shanghai precision Scientific instruments Ltd.); ZP-5B rotary tablet machine (Shanghai Tianfeng pharmaceutical Machinery Co.); RCT magnetic stirrer (Germany IKA company); KQ-100 ultrasonic cleaner (Kunshan Ultrasonic instrument Co., Ltd.); TDL-60B desktop centrifuge (Shanghai Anting scientific Instrument Factory); MA35 electronic moisture Analyzer (Guangzhou Great Technology instrument Co., Ltd.).

Methods and Results

Study on the Dissolution Method

Preparation of the Solution

Preparation of the Dissolution Medium

Take 11.7ml hydrochloric acid into 50ml volumetric flask, dilute with water to the mark, to obtain hydrochloric acid. Take about 2g NaCl and SDS respectively, with precise metage, adding the above hydrochloric acid 16.4ml, and diluted into 1000ml with water, degassing, then obtain the dissolution medium.

Preparation of the Standard Solution

About 10mg of Cur standard, with precise metage, was placed in a 500ml brown volumetric flask, adding 20ml of 95% ethanol, ultrasonic 5min, then cooled, with dissolution medium to the scale, finally obtained standard solution.

Tested Sample Solution Preparation

Take 20 curcumin tablets, grinded into fine. About 200mg of fine powder, was placed in a 500ml brown volumetric flask, adding proper amount of 95% ethanol, ultrasonic 5min, then cooled ,with dissolution medium to the scale.

UV Absorbance Wavelength Selection

Measured standard solution 5ml and placed it into 20ml brown volumetric flask , with dissolution medium to the scale, filtered, and took successive filtrate, Geometric (V/V) ethanol dissolution medium was used as blank control in the wavelength range of 300-500nm scanning. Cur in 429nm had maximum absorbance, so wavelength of 429nm was selected for Cur maximum absorbance.

Membrane Adsorption Test

According to the method of dissolution determination,one piece of curcumin tablets was taken into the dissolution cup, and the samples were taken for 9 copies, each 10ml. Three of them were placed in the 10ml centrifuge tube, with the rotating speed of 5000r·min^{-1},centrifuged for 15min. The dissolution medium was used as the blank control,and theabsorbance of the supernatant was measured at the wavelength of 429nm. The remaining six copies all passed over 0.8μm micropore filter membrane, three of which were abandoned 2ml of the initial filtrate, while the other three were abandoned 3ml of the initial filtrate. Take the successive filtrate and the dissolution medium as blank control respectively and determine the absorbance at the wavelength of 429nm. Results showed that the average value of 2ml membrane adsorption capacity was 1.96%, and 3ml was 0.03%, which were less than 2%.

Standard Curve

The standard solution was diluted with the dissolution medium to a series concentrations of solutions of 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0μg·ml^{-1}. Filter and take the successive filtrate with geometric ethanol dissolution medium as blank control, determinate the absorbance at the wavelength of 429nm . The concentration C used as y axis on the ceiling light value for X axis for linear regression, the regression equation was as follows C=0.0072A+0.00005, the related coefficient r = 0.9996. The results showed that the linear relationship was good in the range of 2.5 to 5μg·ml^{-1}.

Precision Test

According to the determination method of dissolution, take one piece of curcumin tablet into a dissolution cup, sample 60ml at 45min, filter, take the successive filtrate, the dissolution medium as blank control, determine the absorbance at the wavelength of 429nm 6 times within one day, calculate the concentrations, RSD=0.065%. The results showed that the precision of the instrument was good.

Stability Test

According to the determination method of dissolution, take one piece of curcumin tablet into a dissolution cup, sample 60ml at 45min, filter, take the successive filtrate, and the filtrate was divided into 7 parts. Take the dissolution medium used as the blank control and determinate the absorbance at the wavelength of 429nm at 0, 1, 2, 3, 4, 5 and 6h, respectively,then calculate the concentrations, RSD=0.320%. The results showed that the stability of solution was good within 6 hours.

Excipients Interference Test

According to the preparation process and the amount of the prescription, make blank tablets without drugs. Take 20mg of blank tablet and grind them into fine, take about 10mg of fine powder, with precise metage, place it in a 25ml brown volumetric flask, with 95% ethanol and diluted to the scale, ultrasonic 5min, chilling, take 2ml into a 10ml volumetric flask, diluted to the scale with dissolution medium, shake, filter, take the successive filtrate. Take dissolution medium containing geometric ethanol (V/V) as blank control and determine the absorbance at the wavelength of 429nm, and scan in the wavelength range of 300~500nm. The results showed no absorption peak at 429nm, which indicated no interference from excipients.

Recovery Test

Take 3 copies of standard solutions of 2.5, 4, 5ml respectively into 10ml brown volumetric flask, add fine powder of the blank tablets with amount of prescription, dilute with dissolution medium to the sample solutions containing 50%,80%,100% Cur, Filter the above solution, take successive filtrate, and use dissolution medium of corresponding concentration of ethanol as blank control to determinate the absorbance at the wavelength of 429nm. Result showed that the average recovery rate was 98.08%, RSD=0.610%, which was in line with the requirements.

In Vitro Dissolution Test

Take this product, according to the dissolution test method (Appendix X C second), with hydrochloric acid solution (containing 0.2% SDS and 0.2% NaCl, w/v) as the dissolution medium at the speeding rate of 50, According to the operation, sample 10ml at 45, 60, 90 and 120min, then supplement fresh medium of the same temperature and volume, filter, take successive filtrate, take precisely moderate amount of successive filtrate, diluted quantitatively with dissolution medium to obtain the Cur concentration of 3μg.ml^{-1}. According to UV-VIS spectrophotometry (Appendix IV A), the absorbance is determinated at the wavelength of 429nm. And then take another Cur standard solution, dilute it to 3μg•ml^{-1}. The absorbance was determined by the same method, and the dissolution amount of each table was calculated.

Preparation of Curcumin Tablets

Prescription amount of L-HPC, lactose and MCC were weighed and screened through No.5 mesh sieve respectively, and then mixed equably and standby. Prescribed amount of Poloxamer 188 was added into an appropriate amount of acetone, stirred until completely dissolved. Add prescriptions amount of Cur, and mix well. Then add Gremophor RH40, stir until Cur was completely dissolved. Prescription amount of PVPP and SiO_2 were added to the above solution with stirring. The backup mixture flour was added to the system, and soft material was prepared and screened a No.2 mesh sieve to granulate. The granules were dried at 40 ℃ to a control the moisture content at 3~6%, over a NO.2 mesh sieve. a prescription amount of lubricant (0.4% MS calculated by particles (W / W), 0.6% SiO_2 calculated by particles (W / W)) was added and mixed well. Measure content and prepare tablets. The weight of every tablet is about 200mg.

Preparation Process Optimization of Curcumin Tablets

Previous studies found that a certain amount of Poloxamer 188 and Gremophor RH40 caused tableting process sticking phenomenon, and affected the disintegration and dissolution of the tablets.

Therefore, Poloxamer 188 and Gremophor RH40 were as main factors to the dissolution of the indexes, selecting the best prescription with RSM.

Gremophor RH40 Single Factor

Based on the of preliminary experiments tablet were granulated and prepared followed by the method under ”3.2” using the ratio of Cur: Poloxamer 188: Gremophor RH40 with 1: 5: 0.5, 1: 5: 1 and 1: 5: 1.5, respectively. When the amount of Gremophor RH40 was 0.5 times of Cur, the granules could be screened, but still caused tablets sticking phenomenon. When the amount of Gremophor RH40 was 1.0 and 1.5 times of Cur, it sieves difficultly and sticks seriously. The results showed that with the increase of the proportion of Gremophor RH40, it was more difficult to screen and illustrated more serious to stick. The amount of Gremophor RH40 in this preparation should be less than half of Cur.

Poloxamer188 Single Factor Test

On the basis of preliminary experiments, according to the method under “3.2” to granulate and prepare tablets, when Cur: Poloxamer188: Gremophor RH40 ratio were 1: 1: 0.4, 1: 3: 0.4, 1: 5: 0.4 and 1: 7: 0.4, respectively. The dissolution was used as the indicator and tablet sticking situation was compared. When the amount of Poloxamer188 was 3, 5 and 7 times of prescription amount of Cur, the dissolution at 45min were 69.40%, 64.63%, 87.43% and 97.86% , respectively; While at 120min, the *in vitro* dissolution was 85.34%, 80.22%, 89.71 % and 99.43%, respectively. Dissolution of the ratio 1: 5 and 1: 7 indicated better, but the phenomenon of sticking became more serious with the increase of the amount of Poloxamer188. Therefore, through the prescription optimization the amount of Poloxamer188 should be less than five times of Cur's.

Response Surface Methodology

Design-Expert 8 software is used to statistically optimize the formulation to improve in vitro dissolution with RSM. According to the principle of 3-Level design, ratio of P188 to Cur (x_1) and Gremophor RH40 to Cur (x_2) were selected as the variables and in vitro dissolution at 120min (y) as the dependent variable tested in a 13-run experiment to determine the optimum levels (As shown in Table 1). As shown in Figure 1, response surfaces at 45, 60, 90 and 120min were obtained， which reflected the increasing of y as x_1 and x_2 were growing. Because of the hydrotropy of P188 and Gremophor RH40, as x_1 and x_2 increased, y increased accordingly, but when the amount of the two came to a certain value, it would affect the viscosity of the tablets, which affected the disintegration and dissolution. The analysis of variance in 120min was shown in Table 2. The variance analysis results of Table 2 showed that experimental models had significant differences, quadratic term x_1^2 has a significant influence on dissolution. The least squares method was used to calculate the optimum ratio of Cur: P188: Gremophor RH40= 1: 2.52: 0.4.

Table 1 Response Surface Methodology Analysis

Experiment No.	*P188/Cur*	*Gremophor RH40/Cur*	*Dissolution(%) at 120[min]*
	(x_1)	*(x_2)*	*(y)*
1	4.0	0.4	59.79
2	2.5	0.4	94.04
3	2.5	0.4	96.84
4	2.5	0.3	87.36
5	2.5	0.4	90.78
6	4.0	0.5	71.17
7	2.5	0.5	72.80
8	1.0	0.3	56.37
9	1.0	0.4	74.60
10	1.0	0.5	65.61
11	2.5	0.4	90.53
12	2.5	0.4	90.53
13	4.0	0.3	68.94

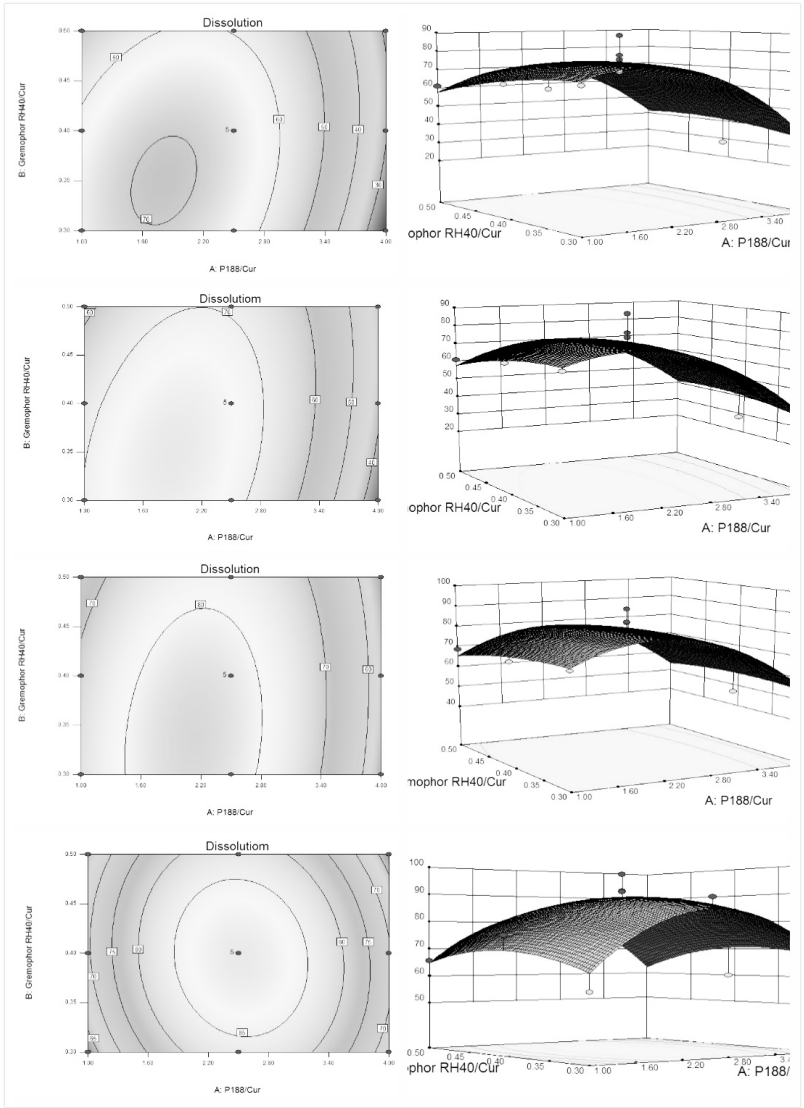

Fig. 1. Response surface renderings (top to bottom are 45, 60, 90 and 120min response surface map)

Table 2 ANALYSIS of VARIANCE IN 120[min]

Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	*p-value >F*
Modle	1521.81	5	304.36	4.11	0.0462
x_1	1.84	1	1.84	0.025	0.8792
x_2	1.59	1	1.59	0.021	0.8876
x_1x_2	12.31	1	12.31	0.17	0.6956
x_1^2	965.66	1	965.66	13.04	0.0086
x_2^2	93.233	1	93.23	1.26	0.2989
Residual	518.38	7	74.05		
Lack of Fit	371.46	3	123.82	3.37	0.1355
Pure Error	146.93	4	36.73		
Cor Total	2040.19	12			

Verification Test

Press optimal formulation, In accordance with the method under "3.2", three batches of curcumin tablets were prepared. The in vitro dissolution results remained the same, the average dissolution was 64.85% at 45min and 95.12% at 120min.

The Dissolution of Different Formulations

Cur pharmaceutical raw materials by count of 10mg/cup, prescriptions Cur raw materials mixture with the 200mg, capsules of Cur powders and a commercial operator by 10mg Cur were accurately weighed respectively. The dissolution was measured according to the dissolution procedure. The dissolution of Cur substance, raw materials and accessories prescriptions Cur mixture, capsule powder were 28.31%, 29.30%, 77.49% at 45min and 46.88%, 41.92%, 89.21% at 120min. The dissolution of Cur tablets by the response surface design of optimal prescription obtained was 64.85% at 45min, and 95.12% at 120min. The results showed that the tablets prepared along the optimal prescription had higher dissolution compared with raw Cur and physical mixtures, capsule powder.

Conclusions

Microporous membranes used in this experiment is a polyether sulfone material, curcumin has certain adsorption, membrane adsorption in the experiment, and the filtrate was discarded early 2ml~3ml, membrane adsorption amount is less than the average 2%, but the beginning of the filtrate was discarded 3mL adsorption filters less experimental error is smaller, so this was chosen 3ml beginning of the filtrate was discarded.

The study found Gremophor RH40 sample order of dissolution Cur sheet impact, will Gremophor RH40 was adjusted to Cur added prepared curcumin tablets dissolution repeatable, and the corresponding dissolution also increased. Another of the experiment the amount of PVPP screening results show that, PVPP dosage of curcumin on in vitro dissolution of little effect.

Curcumin poorly soluble drugs, for poorly soluble drugs, its dissolution time than the body of drug absorption time, and the dissolution rate is the rate-limiting step of drug absorption. So, dissolution rate and bioavailability have a high correlation [9]. This insoluble drug Cur solubility is not high in ethanol, and much higher in acetone. Thus, acetone was used in the experiment. In order to improve the bioavailability of the drug, this experiment optimized formulation and technology to improve dissolution in vitro of Cur. The preparation process for equipment less demanding, simple operation, eliminating the solid dispersion is heated to melt and freeze-dried preparation to join the cumbersome extra step adhesives and the like, easy to implement industrial production.

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