Study on the preparation technology of Sanqi Shangyao gels for percutaneous absorption

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Abstract: Objective: To optimize the preparation technology and matrix ratio of Sanqi Shangyao gels. Methods: The effects of carbomer 940, sodium carboxymethyl cellulose and propylene glycol on the formation of gel matrix were investigated by orthogonal test, and the ratio of matrix and preparation process were determined. Results: The orthogonal test results showed that the matrix ratio was carbomer 940 1.5g, carboxymethyl cellulose sodium 2g, propylene glycol 10g, and the gel properties was superior when the proportion of other substrates was fixed. Conclusion: Preparation process and matrix ratio by orthogonal test is even and delicate, easy to be coated and stable.

1. Introduction

Gels belong to transdermal drug system [1], which refer to the semi-solid or thick liquid dosage form with gels characteristics made of traditional Chinese medicine extract and suitable matrix [2]. Clinically, they are mostly water-based gels, which are characterized by easy coating and washing, no greasy feeling. Because of their low viscosity, they are conducive to the release of drugs, especially water-soluble drugs. They are easy to use, the administration can be interrupted at any time, and the safety is higher [2]. Sanqi Shangyao gels are new dosage form based on Sanqi Shangyao tablets. The prescription is composed of Notoginseng radix et rhizoma, Aconiti kusnezoffii radix cocto, Xueshangyizhihao, Borneolum, Drynariae rhizoma, Jiegumu, Carthami flos and Paeoniae radix rubra, which has the effect of relaxing sinews and activating blood, dispersing stasis to relieve pain [3]. However, there is no report on the gels dosage form changed from Sanqi Shangyao tablets, so the research group chose to study it in order to expand its way of drug use.

2. Methods and results

2.1. Prescription Optimization

2.1.1. Single factor test.

Carbomer 940 and sodium carboxymethyl cellulose were dispersed in an appropriate amount of purified water, stirred evenly to make it fully swollen, and then sodium hydroxide was dissolved in proper amount of water and added. After propylene glycol, lauryl azone and Nipagin ethyl ester were added and defoamed by ultrasound. The extract of Sanqi Shangyao extract was dissolved with an appropriate amount of water, then added it to the matrix and mixed it evenly. The amount of lauryl azone and Nipagin ethyl ester was constant, and the ratio of carbomer 940, sodium carboxymethyl cellulose and propylene glycol was investigated. The research group did a large number of single-factor experiments, and the approximate proportion of matrix was Carbomer 940 1-2g, sodium

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carboxymethyl cellulose 2-6g, propylene glycol 8-12g. The orthogonal test was designed according to the pre-test.

2.1.2. Orthogonal test design.

On the basis of pre-test, L_9 (3^3) test is used to design the level table of orthogonal factors. The levels and factors of orthogonal test were shown Table 1.

Table.1. Factors and levels of orthogonal test

Levels	Factors		
	Carbomer 940 (g) A	Sodium carboxymethyl cellulose (g) B	Propylene glycol (g) C
1	1	2	8
2	1.5	4	10
3	2	6	12

2.1.3. Quality evaluation and scoring standards

On the basis of the pre-test, the comprehensive scores of appearance shape, centrifugation, heat resistance test, cold resistance test and PH were taken as the evaluation index[4]. The full score of each index was 20 points (See Table 2), and the comprehensive score was the sum of the scores of each index.

Table.2. Quality evaluation standard of Sanqi Shangyao gels

Inspection index	Quality evaluation standard	Score
Appearance shape	Uniform color, fine and easy to coating, no obvious bubbles, no particles or lumps	20
Centrifugation	No stratification and deposition after centrifugation	20
Heat resistance test	No stratification and even distribution after high temperature	20
Cold resistance test	No delamination and easy to coating after low temperature,	20
PH	PH values are between 4.0 and 11.0	20
Total score		100

2.1.3.1. Appearance shape

The gels are uniform as a whole, fine and easy to coating, no particles or lumps, few or no air bubbles. Score according to the uniformity of the gels, the presence or absence of particles or lumps, and the number of bubbles.

2.1.3.2. Centrifugation

Put proper amount of gels in the centrifuge tube and centrifuge with 3000r/min for 30 minutes to observe whether the gels are delaminated or not. It is graded according to whether or not it is layered or the degree of layering.

2.1.3.3. Heat resistance test

Take appropriate amount of gels and put them in a plug test tube and take a constant temperature water bath at 60 ℃ for 4 hours. It is graded according to whether or not they are layered or the degree of layering.

2.1.3.4. Cold resistance test

Take appropriate amount of gels and put them in a test tube with plug and put them in a refrigerator at 4 ℃ for a week. It is graded according to whether they are layered or the degree of layering and whether they are easy to coat.

2.1.3.4. PH

PH is one of the important factors affecting whether the gels can be formed. Respectively weighed 2 g gels and diluted 10 times with water, and the PH value is measured. Score according to the value of PH.

2.2. Results of orthogonal test

The orthogonal test was designed according to the level and factors of orthogonal test (See Table 3), and analysis of variance was carried out (See Table 4).

Table.3. Results of orthogonal test

Serial number	A	B	C	Total score
1	1	2	8	45
2	1	4	10	66
3	1	6	12	60
4	1.5	2	10	88
5	1.5	4	12	76
6	1.5	6	8	74
7	2	2	12	67
8	2	4	8	50
9	2	6	10	64
K_1	171	200	169	
K_2	238	192	218	
K_3	181	198	203	
k_1	57	66.67	56.33	G=590 CT=38677.78
k_2	79.33	64	72.67	
k_3	60.33	66	67.67	
R	22.33	2.67	16.34	

2.3. Analysis of variance results

Table.4. Analysis of variance results

Source of variance	Sum of squares from mean deviation	Degree of freedom	Variance	F	P
A	870.89	2	435.44	75.34	< 0.05
B	11.56	2	5.78		
C	420.22	2	210.11	36.35	< 0.05
Error (e=B)					

注: $F_{0.05}(2,2)=19.00$ $F_{0.01}(2,2)=99.00$

The results of orthogonal test and analysis of variance showed that the influence of the three factors on gels matrix molding was A > C > B. Among them, factor A and C, that is, the amount of carbomer 940 and propylene glycol, had significant influence on the test results, while factor B, that is, the amount of sodium carboxymethyl cellulose had no significant effect on the test results. From the point of view of cost saving, factor B should choose level 1, that is, the best process combination is $A_2B_1C_2$. This result coincides with the result of orthogonal test, so the best process combination of gels preparation is $A_2B_1C_2$, that is, 1.5g carbomer 940, 2g sodium carboxymethyl cellulose, 10g propylene glycol. Under these conditions, the properties of the gels are stable, easy to coat, uniform and delicate.

3. Verification test

Three batches of samples were prepared according to the optimum matrix ratio, and each index was basically the same as that of orthogonal test.

4. Conclusion

As a new type of preparation, gels have attracted much attention, but at the same time, they also have their own defects, such as poor lubrication of water-based gels, easy to lose water and mildew, and often need to add moisturizing agent and preservative. In addition, only drugs with good permeability are easier to prepare into preparations with stable efficacy, so penetration enhancers are often added to improve drug absorption. Therefore, the research and selection of ideal penetration enhancers is one of the important tasks of the research.

Due to the complexity of the components of traditional Chinese medicine, it is difficult to determine the effective components. At present, most studies only select one of the components as an index for evaluation, which can not reflect the characteristics of traditional Chinese medicine and its compound prescription. In particular, the qualitative and quantitative methods of pharmacokinetic process *in vivo* are more difficult and need to be further studied.

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