Study on the preparation technology of Sanqi Shangyao smeared films for percutaneous absorption

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Abstract. Objective: The dosage form of Sanqi Shangyao tablets was reformed and made smeared films. Methods: PVA-124 was used as film forming material, glycerol as plasticizer, Twain 80 as surfactant and azone as penetration enhancer. On the basis of the single factor test, the orthogonal test L9(34) was used to screen the matrix prescription, and the optimum matrix ratio was obtained by investigating the fluidity, color, flexibility, film forming time and the appearance uniformity of the coating agent. Results: The best substrate ratio was Twain 80 0.5 g, PVA-124 4.0 g, glycerol 2.0 g, azone 0.3 g. Conclusion: The proportion of the smeared films prepared by orthogonal test is stable. The film forming time is short, and the preparation process is simple and feasible.

1. Introduction
The smeared film is a percutaneous absorption preparation [1], which refers to a liquid preparation made of raw materials and film-forming materials for external use and can form a film [2]. The smeared film can avoid the first-pass effect of the liver [3]. Its preparation process is simple, does not need backing material, does not need special equipment, and has a good effect on the prevention and treatment of some skin diseases.

Sanqi Shangyao tablet has the effect of relieving menstruation and activating blood circulation, dispelling blood stasis and relieving pain. At present, there are tablets, granules and capsules [4], and there are no literature reports on the smeared films, so the research group reformed the dosage form of Sanqi Shangyao tablet to make the smeared films, which not only avoids the first-pass effect of oral administration, but also can be administered in many directions. The curative effect is safe, which provides a certain basis for industrial production.
2. Methods and results

2.1. Prescription Optimization

2.1.1. Single factor test. In order to determine the dosage range of each matrix in the orthogonal test, the research group did several groups of single factor experiments. The amount of PVA-124 is taken as a variable, and the dosage of Tween 80, glycerol and azone remains unchanged. It is found that the greater the proportion of film-forming materials, the worse the fluidity, but too little is not easy to smear. When the amount of water is 10 times, the fluidity is better and the film-forming time is less. Taking glycerol as a variable and other substrates as quantitative, it was found that the greater the content of the film, the more greasy the skin, but when the content was low, it was not easy to tear off, and the effect was better at 4 g. The situation of Tween 80 is similar to that of glycerol, the more azone, the worse the color of the matrix, and the better effect is at 0.6 g. The research group determined the dosage range of each matrix in the orthogonal test according to the results of single factor test.

2.1.2. Orthogonal test design. On the basis of pre-test, L$_9$ (3$^4$) test is used to design the level table of orthogonal factors. The levels and factors of orthogonal test were shown Table 1.

| Levels | (A) Twain 80 /g | (B) PVA-124/g | (C) Glycerol/g | (D) Azone/g |
|--------|----------------|---------------|---------------|-------------|
| 1      | 0.5            | 2.0(20mL water) | 2.0           | 0.3         |
| 2      | 1.0            | 3.0(30mL water) | 3.0           | 0.6         |
| 3      | 1.5            | 4.0(40mL water) | 4.0           | 0.9         |

2.1.3. Appearance evaluation and scoring standards [5-6]. Flowability: The smeared film prepared by 1 mL was poured into the inclined glass plate under the same conditions, and the fluidity was observed. The smaller the fluidity, the higher the score, and the total score was 20.

Color and lustre: Observe the color transparency of the smeared film substrate, the better the transparency, the higher the score, and the total score was 20.

Flexibility: Observe the stretchable shape of the matrix after smearing, the more difficult it is to break, the higher the score, and the total score was 20.

Film forming time: Pour 2 mL of matrix onto the glass plate and observe the time it takes to form the film. The shorter the time is, the higher the score is, with a total score of 20.

Uniformity: Smear on the glass plate, observe the uniformity of the film, the more uniform, the higher the score, and the total score was 20.

The score is calculated on the basis of the average score of 10 students.
2.2. Results of orthogonal test

Table 2. Results of orthogonal test

| Serial number | A | B | C | D | Total score |
|---------------|---|---|---|---|-------------|
| 1             | 1 | 1 | 1 | 1 | 58.4        |
| 2             | 1 | 2 | 3 | 2 | 64.6        |
| 3             | 1 | 2 | 3 | 3 | 73.6        |
| 4             | 2 | 1 | 2 | 3 | 62.2        |
| 5             | 2 | 2 | 1 | 4 | 64.7        |
| 6             | 2 | 3 | 1 | 2 | 68.5        |
| 7             | 3 | 1 | 3 | 2 | 59.4        |
| 8             | 3 | 2 | 1 | 3 | 63.5        |
| 9             | 3 | 3 | 2 | 1 | 80.4        |
| K1            | 196.6 | 180 | 190.4 | 203.5 |         |
| K2            | 195.4 | 192.8 | 207.2 | 192.5 |         |
| K3            | 203.3 | 222.5 | 197.7 | 199.3 | G=595.30 |
| K1/3          | 65.533 | 60.000 | 63.467 | 67.833 | CT=39375.79 |
| K2/3          | 65.133 | 64.267 | 69.067 | 64.167 |         |
| K3/3          | 67.767 | 74.167 | 65.900 | 66.433 |         |
| R             | 2.634 | 14.167 | 5.600 | 3.666 |         |

2.3. Analysis of variance results

Table 3. Analysis of variance results

| Source of variance | Sum of squares from mean deviation | Degree of freedom | Variance | F | P  |
|--------------------|-----------------------------------|------------------|----------|---|----|
| A                  | 12.082                            | 2                | 6.041    |   |    |
| B                  | 316.909                           | 2                | 158.455  | 26.230 | <0.05 |
| C                  | 47.309                            | 2                | 23.655   | 3.916  |    |
| D                  | 20.542                            | 2                | 10.271   | 1.700  |    |
| Error (e=A)        |                                   |                  |          |     |    |

Note: \( F_{0.05} (2, 2) = 19.00 \) \( F_{0.01} (2, 2) = 99.00 \)

The comparison of the variance between the range R in Table 2 and the variance in Table 3 showed that the best matrix prescription was A\(_3\)B\(_3\)C\(_2\)D\(_1\). The influence of the four factors on the test was B\( > C\) \( > D\) \( > A\), the influence of factor B on the test results is significant \( (P < 0.05)\), and A, C and D had no significant effect on the test results. Therefore, the dosage of A, C and D factors can be prepared according to the minimum amount, that is, A\(_1\)B\(_3\)C\(_1\)D\(_1\), Tween 80 0.5 g, PVA124 4.0 g, glycerol 2.0 g, azone 0.3 g.

3. Verification test

Three batches of samples were prepared after the best matrix ratio obtained from the orthogonal test was mixed with 0.5g Sanqi Shangyao extract, and 10 students were asked to make a comprehensive score, and the results showed that the score of each batch was more than 80, indicating that the preparation process of the orthogonal test was feasible and repeatable.

4. Conclusion

The research group conducted an orthogonal experiment on the basis of the results of single factor pre-test, and optimized the dosage of Tween 80, PVA124, glycerol and azone by the method of appearance evaluation, and prepared Sanqi Shangyao smeared films after adding the Sanqi Shangyao extract. The
experiment can provide some help to the development of the smeared films agent, but the mechanism of transdermal absorption is not clear, and needs to be further tested.

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