Investigation of the Preparation Process for Pulsatilla Chinensis (Bunge) Regel Total Saponins-Hydroxypropyl-β-Cyclodextrin Inclusion Compound Pellets1

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Keywords: Pulsatilla chinensis (Bunge) Regel total saponins, inclusion compound, pellets, investigation of process.

Abstract. This paper used parallel test of single factor to investigate preparation method, the excipient, the water-soluble filler, the wetting agent and the drug loading for *Pulsatilla Chinensis* (Bunge) Regel total saponins-hydroxypropyl-β-cyclodextrin inclusion compound pellets. The results showed that the best prescription process of inclusion compound pellets was as following: the pellets was prepared by granulation-spheronization method with the drug loading of 20%, 50% MCC as an excipient, mannitol as a water soluble bulking agent, 30% ethanol as a wetting agent. The prepared inclusion compound pellets by the method in this paper had a better legal roundness. Moreover, its preparation process was simple and easy to be industrialized.

1. Introduction

Pulsatilla chinensis (Bunge) Regel, which was used as a traditional Chinese medicine, can clear away heat and detoxicate, cool blood and arrest dysentery, which activities especially in cleaning colon heat and blood toxic heat. Recent pharmacological studies confirmed that *Pulsatilla chinensis* (Bunge) Regel extract had a good effect on anti-ulcer colitis [1]. As a result, it can be developed as an oral colon-targeted preparation for treatment of ulcer colitis.

Pulsatilla chinensis (Bunge) Regel total saponins was *Pulsatilla chinensis* (Bunge) Regel extract separated and purified by Macroporous resin. The preliminary results showed that it had a poor solubility in water [2], and it was difficult to release active components when it was made into pellets directly. However, when it was made into hydroxypropyl-β-cyclodextrin inclusion compound, it can significantly enhance the dissolution rate of the drug [3]. This paper had examined the prescription and process of the pellets for *Pulsatilla chinensis* (Bunge) Regel total saponins-hydroxypropyl-β-cyclodextrin inclusion compound, which can lay the foundation on preparing colon-targeted preparation further.

2. Methods and results

2.1 Instruments and materials

The instruments used together with the suppliers were as follows: Extrusion Rounder (JW-5, Granulating Drying Equipment Ltd. Changzhou Jiafa); Vacuum oven (DZF-6050, Medical Devices Ltd. Emerging Artists, Shanghai); Disintegration instrument (LB-2D, Huanghai Testing Instrument Co., Ltd.，Shanghai).

The main materials used with the suppliers were as follows: Microcrystalline cellulose (MCC,

Pharmaceutical Excipient Ltd., Anhui Sunward); Ethanol (Sinopharm Chemical Reagent Ltd.); Distilled water (Laboratory homemade). All other chemicals were of analytical-reagent.

2.2 Preparation method of pellets

2.2.1 Extrusion-spheronization method

With *Pulsatilla chinensis* (Bunge) Regel total saponins inclusion compound (self-prepared, reported in another paper) as the raw material medicine, MCC as excipient, mannitol as bulking agent and 50% ethanol as wetting agent, the extrusion-spheronization method, which was the common method for making plain pellets in other literatures, was used to prepare *Pulsatilla chinensis* (Bunge) Regel inclusion compound pellets by the extrusion spheronization machine.

2.2.2 Pan-pill method

The mother pills were prepared by pan-pill method with drug loading of 5%. The little mother pills with good roundness were filtered out, and were put into medium coating pan. With 75% ethanol as wetting agent and talc powder as anti-adhesive, the mixed powder of MCC and *Pulsatilla chinensis* (Bunge) Regel total saponins inclusion compound with the weight ratio of 1: 10 was loaded on the mother pills. Then the pellets were removed out when they reached to 24 ~ 40 meshes and were dried as the final required pellets.

2.2.3 Centrifugal-granulation method

The powder of raw materials was all passed through the VI Pharmacopoeia sieve, and the coating granulator was used to form the mother pill from pill core. The mother pills were prepared by putting 50g MCC and lactose mixture with weight ratio of 4: 1 into the coating granulator and taking water as binder. The little mother pills with good roundness was screened out and was put into the granulator. The mixed powder of MCC and *Pulsatilla chinensis* (Bunge) Regel total saponins inclusion compound with weight ratio of 1:10 as powder and water as the binder was put into powder-room of the granulator. The coating granulator parameters were adjusted and the pellets were rounded for 5min when they reached to 24 ~ 40 meshes. The pills were dried when they were taken out.

2.2.4 Granulation-spheronization method

The powder of raw materials was all passed through the VI Pharmacopoeia sieve. The particles were prepared by taking *Pulsatilla chinensis* (Bunge) Regel total saponins inclusion compound as raw materials, MCC as excipient, lactose as bulking agent, 50% ethanol as wetting agent and the feeding amount was 40g. The prepared particles were centrifuged into the cylinder roller to go on centrifuging and rounding. Meanwhile, a small amount of wetting agent was slowly dropped into the cylinder roller. The frequency of the fan speed and the spheronization parameters were adjusted. The pellets were removed out and were dried after they were round molding.

As shown in Table 1, among these four methods, the pellets prepared by granulation-spheronization method had the best roundness and fast disintegration and the situation of preparation was acceptable.

Table 1: Investigation of the preparation for inclusion compound pellets

Method of Preparation	Pellets roundness	Situation of disintegrating	Situation of preparation
extrusion-spheronization	bad, multi-rod	not disintegrating	not easy to round , multi-rod, and multi-material waste
pan-pill	general, rough surface, not round	fast	Low-efficient, easy to bond together

centrifugal-granulation	general	general	easily rounded, multi-material waste
granulation-spheronization	good	fast	easy to prepare, less adhesion, efficient

2.3 Investigation of MCC amount

The granulation-spheronization method was used to prepare pellets with the drug loading of 15%, of which the amount of inclusion compound was 30%, with lactose as filler and 50% ethanol as wetting agent, and the amount of MCC was respectively investigated for the influence on the preparation of pellets at 40%, 45%, 50%, 55% and 60%. The results which were shown in Table 2 showed that the greater amount of MCC was added, the better shape of pellets and the higher of the yield was get. But considering the proper lever of disintegration time, the final selection for the prescriptions amount of MCC was 50%.

Table 2: Investigation of MCC amount

MCC addition	Roundness of pellets	Yield (40-65 meshes)	Disintegration time
40%	bad	55.4%	20 min
45%	general	68.3%	25 min
50%	good	80.7%	28 min
55%	good	81.2%	33 min
60%	good	85.6%	40 min

2.4 Selection of water-soluble bulking agent

With the drug loading of 15%, MCC of 50%, the water-soluble filler of 20%, 50% ethanol as wetting agent, the different kinds of water-soluble filler including lactose, mannitol, soluble starch and sucrose were respectively investigated for the influence on the preparation of pellets. The results were shown in Table 3. The experimental results showed that mannitol as a filler for the pellets had good roundness and the highest yield.

Table 3: Selection of water-soluble bulking agent

Filler types	Roundness of pellets	Yield (40-65 meshes)	Situation of preparation
lactose	very good	76.2%	materials had little stickiness
mannitol	good	80.3%	materials had no stickiness
soluble starch	general	76.2%	materials had little stickiness
sucrose	general	72.1%	materials had great stickiness

2.5 Selection of wetting agent

With the drug loading of 15%, MCC of 50%, mannitol of 20%, and the wetting agent including water, 10% ethanol, 30% ethanol, 50% ethanol, 70% ethanol, etc, were respectively investigated for the influence on the preparation of pellets. The results were shown in Table 4. Among these five

kinds of wetting agents, ethanol of 30% was turned out to be the easiest one for the preparation of pellets and had the highest yield.

Table 4: Selection of wetting agent

Wetting agent types	Roundness of pellets	Yield (40-65 meshes)	Situation of preparation
water	good	62.8%	materials had little stickiness and had a phenomenon of sticky wall
10% ethanol	good	71.6%	materials had little stickiness and had a phenomenon of a little sticky wall
30% ethanol	good	79.5%	materials were easy to be rounded
50% ethanol	good	64.6%	materials were loose and need a little more wetting agent
70% ethanol	general	51.8%	materials were loose, had a poor shape and need a little more wetting agent

2.6 Investigation of the drug loading

With MCC of 50% as excipient, mannitol as bulking agent and 30% ethanol as wetting agent, the granulation-spheronization method was used to prepared the pellets and the drug loading was investigated for the influence on the preparation of pellets, respectively at the lever of 10%, 15%, 20%, and 25%. The results which were shown in Table 5 indicated that the fewer drug loading, the better forming of pellets and the higher of yield. Moreover, it was difficult to prepare the pellets and had poor shape when the drug loading was too high. Taking all factors into consideration, the optimal drug loading of 20% for the inclusion compound pellets was determined.

Table 5: Investigation results of the drug loading

Drug loading	Roundness of pellets	Yield (40-65 mesh)	Situation of preparation
10%	good	82.6	easy to prepare, good shape
15%	good	79.2	easy to prepare, good shape
20%	good	75.8	easy to prepare, good shape
25%	general	61.5	difficult to prepare, poor shape

3. Conclusion

The prepared inclusion compound pellets by the method in this paper had a better legal roundness, so it will be well coated in the further research to get colon-targeted preparation. Moreover, the preparation process in this paper was simple and the drug dissolution was well improved.

The process of preparation for the inclusion pellets had many impact factors and mutual influences. Therefore, there were no fixed parameters that could be controlled during the actual operation, so that the equipment parameters should be adjusted according to the actual situation.

Acknowledgment

This work was supported by a grant from the Doctoral Scientific Research Foundation of Jiangxi Science and Technology Normal University (3000990117), the Key Laboratory of Drug Design and Optimization of Jiangxi Science and Technology Normal University (300098010306), the 8th session of Undergraduate Research Fund Project of Jiangxi Science and Technology Normal University (20140801012) and partially by National Scientific and Technology Major Special Project for Significant New Drug Creation (2013ZX09103002-001).

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