Coating Process of Paeonol Sustained Release Pills

Chunya ZHOU△, Huimin CHEN△, Liuliu LIU△, Yanlin HUANG, Wenyu LUO, Meijia CAI, Fei HAN*

School of Pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China

Abstract [**Objectives**] To study the coating process of paeonol sustained release pills by extrusion-spheronization method taking ethyl cellulose as the coating material. [**Methods**] Paeonol pills were made by Auari AW-95 Full Automatic Pill Making Machine. Coating of paeonol sustained release pills was prepared by Auari Mini Pill Polishing Machine. The prescription and process factors of paeonol sustained release pills coating were investigated by single factor experiment and orthogonal experiment. The release of paeonol sustained release pills was determined according to the cumulative release curve of paeonol. [**Results**] The prepared paeonol sustained release pills released slowly within 24 h, and the release rate reached 80% in 12 h. [**Conclusions**] The prepared paeonol sustained release pills basically meet the 24 h sustained release standard, and can be further developed and applied.

Key words Paeonol, Sustained release pills, Coating, Ethyl cellulose, Release

1 Introduction

Paeonol (Pae, 2'-Hydroxy-4'-methoxyacetophenone) with chemical formula of $C_9H_{10}O_3$, is a natural phenolic compound. It is isolated from root bark of Ranunculaceae plant peony (*Paeonia suffruticosa*) and whole plant Asclepiadaceae plant *Cynanchum paniculatum*. Due to the unique phenolic and ketone structure of paeonol, modern biological science studies have shown that it has a wide range of biopharmaceutical activities[1-6], such as lowering blood sugar[7], antibacterial and anti-inflammatory[8-12], anti-allergic, antipyretic and analgesic[13], promoting microcirculation, cardiovascular protection[14], anti-atherosclerosis[15-17], anti-tumor[18-19], anti-thrombotic, anti-arrhythmic, anti-liver injury and liver fibrosis[20-21] and other pharmacological effects.

At present, domestic and foreign research on diabetes mainly focuses on chemical drugs, mainly traditional chemical hypoglycemic drugs such as metformin and acarbose. As an active component of traditional Chinese medicine, paeonol can be well absorbed in the intestinal tract. Ha Do Thi *et al.*[22] found that paeonol, an active component of Moutan Cortex, can up-regulate the AMPK signaling pathway and improve glucose uptake and glycogen synthesis in human liver cancer cells (HepG2), and concluded that paeonol can activate the AMPK pathway and has great potential to reverse the metabolic abnormalities associated with type 2 diabetes. Wang Lijing *et al.*[23] found that paeonol could reduce the insulin resistance of rat aortic endothelial cells (RAECs) and promote the uptake of glucose by RAECs.

At present, most of the hypoglycemic drugs on the market are to maintain the body's blood sugar, which requires long-term medication. Therefore, low toxicity, effectiveness and long-term use have become the focus of hypoglycemic drugs. Traditional Chinese medicine has high safety, little toxic and side effects, and can be used for a long time. Therefore, it is of great significance to explore new hypoglycemic drugs that can be taken for a long time from traditional Chinese medicine. Paeonol has significant hypoglycemic effect, and its half-life is short, about 1.03 h, it is very suitable for making sustained release preparations. However, there are no sustained release pills with hypoglycemic effect on the market. Therefore, we used the extrusion-spheronization method to prepare paeonol pills. Then, using hydroxypropyl methylcellulose as the isolation layer, ethyl cellulose as the coating material, and prepared paeonol sustained release pills by coating with Auari Mini Pill Polishing Machine. According to the cumulative release curve of paeonol, we determined whether the release rate of paeonol sustained release pills meets the standard. Therefore, it is of great significance to prepare paeonol sustained release pills to improve the bioavailability and stability of paeonol, so as to exert the new clinical application of paeonol on diabetic cardiomyopathy, and provide a certain reference for the future research on paeonol sustained release pills.

2 Materials and methods

2.1 Materials

2.1.1 Instruments. FCR1001-UF-P heat-free ultra-pure water system (Qingdao Flom Technology, China); OTS-800 oil-free air compressor (Taizhou Otus Industry and Trade Co., Ltd., China); BY-300 Auari Mini Pill Polishing Machine (Wenling Aoli Traditional Chinese Medicine Machinery Co., Ltd., China); GZX-9023M electric blast drying oven (Shanghai Boxun Industry & Commerce Co., Ltd. Medical Equipment Factory, China); ZRS-8G intelligent release meter (Tianjin Tianda Tianfa Technology Co., Ltd., China); UV-1800 ultraviolet-visible spectrophotometer (Shanghai Mapada Instrument Co., Ltd., China); EL 20 pH meter (Mettler-Toledo Instrument Co., Ltd., Swiss); Auari AW-

Received: February 16, 2023 Accepted: July 27, 2023

Supported by National Natural Science Foundation of China (81560659); Science and Technology Research Project of Jiangxi Provincial Department of Education (GJJ201219, GJJ2200903); National College Students Innovation and Entrepreneurship Training Program (202210412022); Science and Technology Plan of Jiangxi Provincial Health Commission (202211411).

△These authors contributed equally to this paper.

* Corresponding author. E-mail: hanfei8454871@163.com

95 Full Automatic Pill Making Machine (Wenling Aoli Traditional Chinese Medicine Machinery Co., Ltd., China); SQP analytical balance (Sartorius Scientific Instrument GmbH., Germany).

2.1.2 Reagents. Paeonol Active Pharmaceutical Ingredient (API) (Jinan Biobase Biotech Co., Ltd., batch No.:202102130521); corn starch (Qufu Tianli Pharmaceutical Excipients Co., Ltd., batch No.:20210317); dextrin (Liaoning Dongyuan Pharmaceutical Co., Ltd., batch No.:20210722); microcrystalline cellulose (Huzhou Linghu Xinwang Chemical Co., Ltd., batch No.: GB1886.103-2015); lactose (Tianjin Fuchen Chemical Reagent Factory, batch No.:20210707); hydroxypropyl methyl cellulose (Macklin, batch No.:20210807); ethyl cellulose M70 (Sinopharm Chemical Reagent Co., Ltd., batch No.:20210523); PEG-4000 (Tianjin Fuchen Chemical Reagent Factory, batch No.: 20210419); PVP (K30) (Tianjin Fuchen Chemical Reagent Factory, batch No.: 20210613); triethyl citrate (Shandong Xiya Chemical Technology Co., Ltd., batch No.:20210922); carmine (Shanghai Dyestuff Research Institute Co., Ltd., batch No.: 20210816); lemon yellow (Tianjin Duofuyuan Industrial Co., Ltd., batch No.:20210807); talc powder (Tianjin Kemiou Chemical Reagent Co., Ltd., batch No.:20210711); sodium hydroxide (Tianjin Damao Chemical Reagent Factory, batch No.:20210903); disodium hydrogen phosphate (Tianjin Damao Chemical Reagent Factory, batch No.:20210703); potassium phosphate monobasic (Tianjin Damao Chemical Reagent Factory, batch No.: 20210711); hydrochloric acid (Nanchang Xinguang Fine Chemical Factory, batch No.:20210628); absolute ethanol (Xilong Scientific Co., Ltd., batch No.:20210511); ultrapure water.

2.2 Methods

2.2.1 Preparation of paeonol sustained release pills. First, weighed a certain amount of paeonol according to the prescription amount, added a certain proportion of microcrystalline cellulose, dextrin, lactose and starch and mixed well. Then, added appropriate 10% starch slurry and mixed to make soft material. Put the prepared soft material into the desktop automatic pill making machine, and used the extrusion-spheronization method to make paeonol pills. Finally, put the pills into an oven and dried at 45 ℃ for 6 h to obtain paeonol sustained release pills.

2.2.2 General procedure of coating process. Coating process generally includes two parts, namely, the coating of the isolation layer and the coating of the slow-release layer. In previous preliminary experiments, we have determined that the optimal process for the isolation layer is 4% HPMC, 3% PEG4000 and 1.5% talc. Based on this, we investigated the process of the sustained-release layer coating. The investigation of the coating process of the sustained-release layer adopted Auari Mini Pill Polishing Machine at 45° and 100 rad/min for coating. Finally, we evaluated whether the cumulative release curve of paeonol within 24 h meets the standard of General Rules 0931 Sustained Release Pills in Volume IV of the *Chinese Pharmacopoeia* (2020 Edition)[26].

2.2.3 Preparation of coating process isolation layer and sustained release layer. First, took4% HPMC aqueous solution, added 3% porogen PEG4000 to swell fully, then added an appropriate amount of lemon yellow and 1.5% talc powder, fully stirred, and used it as a coating solution for the isolation layer[24]. Selected an appropriate ethyl cellulose concentration and porogen concentration, added an appropriate amount of triethyl citrate, used absolute ethanol to prepare a slow-release solution for later use, added an appropriate amount of carmine and 1.5% talc after completely dissolving, and stirred well to make a slow-release layer for later use[25].

2.2.4 Design of *in vitro* release test. In accordance with the General Rules 0931 Dissolution and Release Determination Method 1 (Stirring Basket Method) in Volume IV of the *Chinese Pharmacopoeia* (2020 Edition)[26], took one pill to the stirring basket, separately used hydrochloric acid buffer solution of pH 1.2, the phosphate buffer solution of pH 6.8, the phosphate buffer solution of pH 7.8 – 8.0 and pure water as the dissolution medium, and sampled 5 mL at a volume of 900 mL, a rotational speed of 100 rpm, and a temperature of 37 ℃ at 0.5, 1, 2, 4, 6, 8, 10, and 12 h, and replenished the same amount of release medium in time, then filtered the sample to be tested with a microporous membrane, and used the blank medium to make up the volume in a 25 mL volumetric flask, and determined according to the ultraviolet-visible spectrophotometric method[27].

2.2.5 Preparation of artificial gastric fluid, small intestinal fluid and colonic fluid. These fluids were prepared in accordance with General Rules: Release Rate and Release Medium in Volume IV of the *Chinese Pharmacopoeia* (2020 Edition)[26]. Precisely weighed 8.33 mL of concentrated hydrochloric acid (36%) and diluted with pure water to a constant volume in a 1 000 mL volumetric flask, adjusted the pH with a pH meter to 1.2 to obtain artificial gastric fluid. Precisely weighed 250 mL of 0.2 mol/L potassium phosphate monobasic solution and added 180 mL of 0.2 mol/L sodium hydroxide solution and mixed, diluted with pure water to a constant volume in a 1 000 mL volumetric flask, and adjusted the pH to 6.8 with a pH meter to obtain artificial small intestinal fluid. Precisely weighed 5.5 g of potassium phosphate monobasic and 0.41 g of disodium hydrogen phosphate, dissolved with pure water, then mixed and diluted with pure water to constant volume in a 1 000 mL volumetric flask, and adjusted the pH to 7.8 – 8.0 with a pH meter to obtain artificial colonic fluid.

3 Results and analysis

3.1 Single-factor experimental investigation of the sustained-release layer coating formulation

3.1.1 Selection of coating materials. Based on literature research and preliminary experiments in the early stage, we found that ethyl cellulose has good stability in coating materials, a wide range of viscosity (molecular weight) and good coating performance, can produce a coating layer with good toughness and not easy to wear, which meets the standard of coating material. The characteristics of ethyl cellulose make it widely used in drug sustained and controlled release film coating. Its coating solution is simple to prepare, economical and affordable, the coating process is simple, and the coat-

ing film has low porosity and low strength. Thus, we selected ethyl cellulose as coating material in this experiment.

3.1.2 Selection of porogen. In the coating solution, the type and concentration of the porogen have a great influence on the release rate of the drug. According to the previous literature research and preliminary experiments, we selected 2% PEG4000, 2% PVP (K30), 2% lactose, and 2% mannitol as porogens for investigation. The results showed that lactose and mannitol were insoluble in absolute ethanol and the coating solution could not be successfully prepared. It can be seen from Fig. 1 that both PEG4000 and PVP (K30) have good sustained-release effects, but because PVP (K30) does not meet the expectations of sustained-release medication, we finally selected PEG4000 as the porogen material.

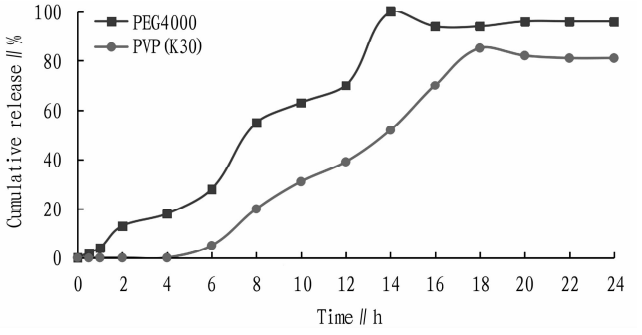

Fig. 1 Selection of porogen

3.2 Single factor experimental investigation of coating process

3.2.1 Concentration of ethyl cellulose. Setting the concentration of ethyl cellulose to 2%, 4%, 6%, 8%, 10%, and 12% to prepare a coating solution, we added a porogen PEG4000 at a concentration of 3%, and coated 10 layers to investigate its effect on drug release. Among them, the coating solution prepared with ethyl cellulose concentration of 2% and 4% was not considered because too low concentration resulted in uneven coating and sticking to the pan; the coating solution prepared with ethyl cellulose concentration of 12% coating solution was not considered because too high concentration resulted in blocking the nozzle of the spray gun. It can be seen from Fig. 2 that there is no significant difference in the release rate of paeonol in the range of 6% to 10% for ethyl cellulose concentration. Under comprehensive consideration, we selected ethyl cellulose with a concentration of 6% as the main material of the coating solution.

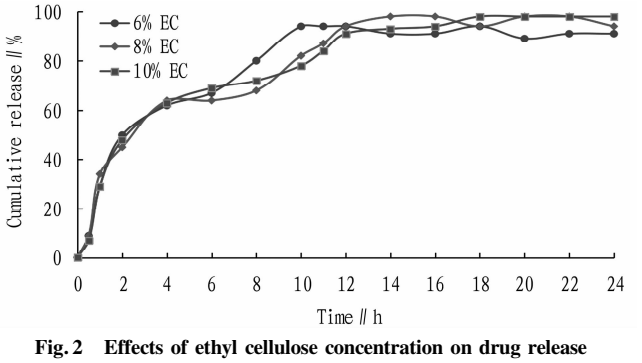

Fig. 2 Effects of ethyl cellulose concentration on drug release

3.2.2 Selection of porogen concentration. Setting the concentration of PEG4000 to 1%, 2%, 3%, 4%, and 5% to prepare the coating solution, we added ethyl cellulose at a concentration of 6%, and coated 10 layers each to investigate its effect on drug release. As shown in Fig. 3, with the increase of porogen concentration, the drug release rate increased.

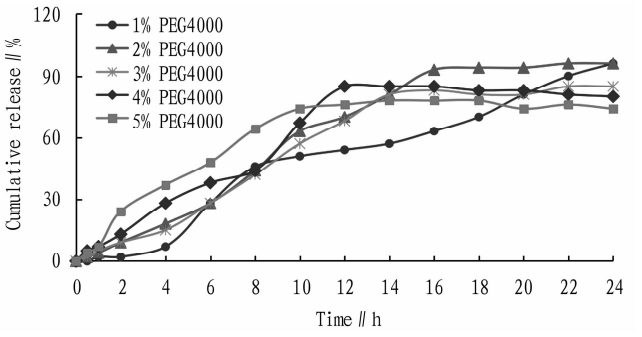

Fig. 3 Effect of porogen concentration on drug release

3.2.3 Coating layers. Setting 4, 7, 10, 13, 16, 19 coating layers, we sprayed each layer of coating for 10 min to investigate its effect on drug release. As shown in Fig. 4, with the increase of the number of coating layers, the release rate of the drug was obviously slowed down.

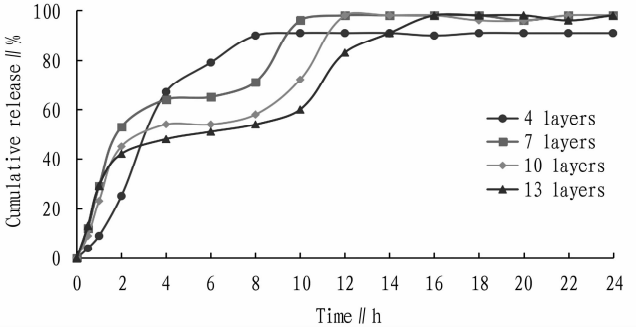

Fig. 4 Effect of coating layers on drug release

3.3 Experimental investigation of orthogonal factors for coating process

3.3.1 Orthogonal experiment. Taking the 8 h drug release rate (90%) and pill weight difference *RSD* (10%) as evaluation indicators, we designed an orthogonal experiment with 3 factors and 3 levels[28] to investigate the significance of the concentration of ethyl cellulose, the concentration of porogen and the number of coating layers on the coating process (Table 1).

Table 1 Factors and levels of orthogonal experiment for coating process

Level	Factor		
	A (EC concentration) // %	B (porogen concentration) // %	C (coating layers)
1	2	1	4
2	6	3	8
3	10	5	12

From the visual analysis of Table 2 and Table 3, it can be seen that the effect of EC concentration (A), porogen concentration (B), and coating layer number (C) on drug-loaded pills is A

> C > B, that is the EC concentration (A) has the greatest effect, and the number of coating layers (C) has the least effect. From Table 3, it can be known that the *Sig* values of the methylcellulose concentration and the number of coating layers are all less than 0.05, so these two factors are significant. Through comprehensively considering the results of range and variance analysis, we selected the paeonol drug-loading layer process as $A_2B_1C_2$, that is, 6% EC, 1% porogen, and 8 coating layers.

Table 2 Results of orthogonal experiment for coating process

Experiment No.	A	B	C	–	*RSD* (10%)	8 h release rate (90%)	Results
1	1	1	1	1	7.2	95	0.86
2	1	2	2	2	6.9	81	0.74
3	1	3	3	3	6.5	88	0.80
4	2	1	2	3	3.5	69	0.62
5	2	2	3	1	3.7	55	0.50
6	2	3	1	2	3.4	95	0.86
7	3	1	3	2	3.7	36	0.32
8	3	2	1	3	3.2	63	0.57
9	3	3	2	1	3.5	57	0.52
K_1	0.800	0.600	0.763	0.627			
K_2	0.660	0.603	0.627	0.640			
K_3	0.470	0.727	0.540	0.663			
R	0.330	0.127	0.223	0.036			

Table 3 Results of variance analysis

	III sums of squares	*Df*	Mean square	*F*	*Sig*
Corrected model	0.266 a	6	0.044	45.214	0.022
Intercept	3.735	1	3.735	3 811.703	0.000
A	0.161	2	0.080	81.924	0.012
B	0.031	2	0.015	15.605	0.060
C	0.075	2	0.037	38.113	0.026
Error	0.002	2	0.001		
Total	4.003	9			
Corrected total	0.268	8			

3.4 Release of paeonol sustained release pills in different release media We set pH 1.2 phosphate buffer solution, pH 6.8 phosphate buffer solution, pH 8.0 phosphate buffer solution and pure water to investigate the drug release medium. From Fig. 5, it can be seen that different release media have no obvious effect on the release of paeonol sustained release pills.

3.5 Verification of coating process of paeonol sustained release pills We prepared 3 batches of paeonol sustained release pills in accordance with the method in Section **2.2.1**, measured the drug release at each time point, and plotted the drug release curve. Fig. 6 shows that the drug is released completely at 12 h and maintains a certain drug concentration within 12 h thereafter, without a significant downward trend, which meets the drug requirements of the *Chinese Pharmacopoeia* (2020 Edition) for sustained-release preparations. Therefore, the final optimal process for paeonol sustained release pills is 6% EC, 1% PEG-4000, 8 coating layers, and a buffer solution with pH 6.8 as the release medium.

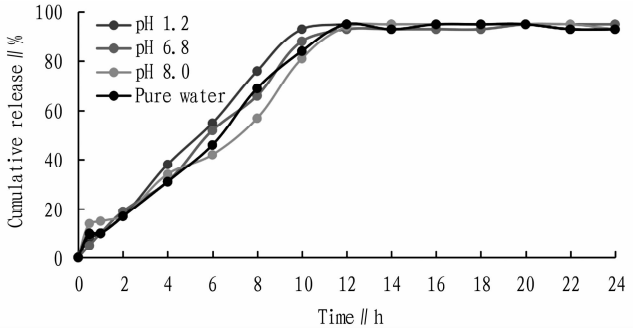

Fig. 5 Effects of different release media on drug release

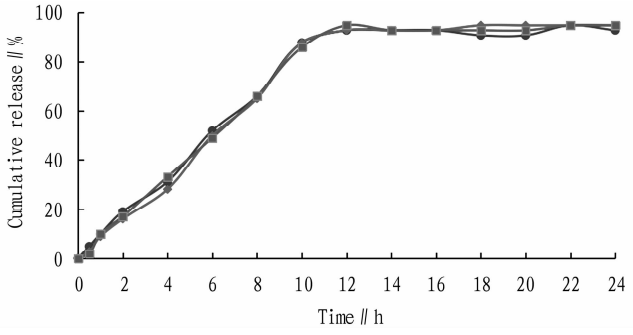

Fig. 6 Verification of optimal process

3.6 Comparison with the 24 h release rate of the market drug Metformin Hydrochloride Sustained Release Tablets Each tablet of Metformin Hydrochloride Sustained Release Tablets weighs 0.5 g. Compared with the 80 mg drug loading per pill in this experiment, it is relatively much larger, and the slightly fluctuating curve has little effect (Fig. 7). The cumulative release curve of paeonol sustained release pills in this experiment is similar to it, which is in line with the *in vitro* release curve of Metformin Hydrochloride Sustained Release Tablets, and can be applied to clinical research.

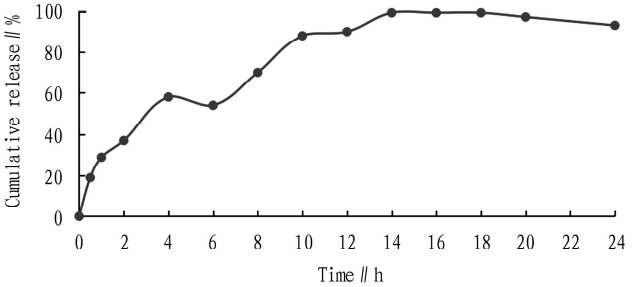

Fig. 7 Cumulative release curve of Metformin Hydrochloride Sustained Release Tablets

4 Discussion

Taking ethyl cellulose as coating material, we used Auari Mini Pill Polishing Machine to prepare paeonol sustained release pills. The paeonol release test also well proves that the prepared paeonol sustained release pills have a certain sustained-release effect, no ob-

vious burst release phenomenon, and meet the drug efficacy requirements of sustained-release preparations. It is found that adding a small amount of talcum powder in the ethyl cellulose solution can well prevent the adhesion between the coated pills. Through multiple release experiments, we found that the cumulative release curve sometimes has a downward trend. Using market drug Metformin Hydrochloride Sustained Release Tablets, we carried out a release experiment for comparison. It can be seen that even commercially available products will have a decrease in concentration. Therefore, it is inferred that this phenomenon is an uncontrollable phenomenon and has no effect on the experimental results. In addition, the cumulative release curves of paeonol sustained release pills and Metformin Hydrochloride Sustained Release Tablets showed a similar trend. Therefore, the study of paeonol sustained release pills has certain clinical significance. This study is expected to provide a certain reference for the future study of paeonol sustained release pills, and also to provide some reference and basis for the development of new antidiabetic preparations of traditional Chinese medicine.

References

[1] LIU YC, BAI YP, WANG L. Research progress on pharmacological action of paeonol and its application of skin diseases[J]. Journal of New Chinese Medicine, 2021, 53(23): 18 - 22. (in Chinese).

[2] YANG SJ, LI LJ. Pharmacological effects and application of paeonol[J]. Pharmacology and Clinics of Chinese Materia Medica, 2022(5): 237 - 241. (in Chinese).

[3] YANG JM, CHEN GQ, TIAN YE, *et al.* Research progress in paeonol compounds and their biological activities[J]. Chemistry, 2021,84(8): 776 - 786. (in Chinese).

[4] LIU YX, ZHAO F, KANG BT, *et al.* Advances in pharmacological research of paeonol[J]. Shaanxi Journal of Traditional Chinese Medicine, 2020, 41(4): 550 - 552. (in Chinese).

[5] WU CC, GUO XH, LIU X, *et al.* Advances in modern pharmaceutical action of Moutan Cortex in recent five years[J]. Chinese Journal of New Drugs, 2020, 29(3): 281 - 284. (in Chinese).

[6] ZHAI CM, MENG XY, FU JJ, *et al.* Research progress of peony bark in modern pharmacy [J]. Information on Traditional Chinese Medicine, 2020, 37(1): 109 - 114. (in Chinese).

[7] ZHAI KF, DUAN H, LUO L, *et al.* Protective effects of paeonol on inflammatory response in IL-1β-induced human fibroblast-like synoviocytes and rheumatoid arthritis progression via modulating NF-κB pathway[J]. Inflammopharmacology, 2017(25): 523 - 532.

[8] WANG LJ, SUN H. Paeonol improves insulin resistance and oxidative stress induced by PA in rat aortic endothelial cells[J]. Journal of Toxicology, 2020, 34(2): 150 - 154, 175. (in Chinese).

[9] JIN X, WANG J, XIA ZM, *et al.* Anti-inflammatory and anti-oxidative activities of paeonol and its metabolites through blocking MAPK/ERK/p38 signaling pathway[J]. Inflammation, 2016(39): 434 - 446.

[10] QI JH, DONG FX, WANG XL. Exploring targets and signaling pathways of paeonol involved in relieving inflammation based on modern technology[J]. Molecular Diversity, 2021, 26(3): 1731 - 1742.

[11] CAI YW. Study on the pathogenesis of PMDD liver-qi adverse syndrome and the mechanism of paeonol intervention based on progesterone and tetrahydroprogesterone anabolic transduction pathway[D]. Jinan: Shandong University of Traditional Chinese Medicine, 2020. (in Chinese).

[12] LIU YR, SHAO Q, ZHANG HH, *et al.* Inhibitory effect of paeonol on aortic endothelial inflammation in atherosclerotic rats by up-regulation of caveolin-1 expression and suppression of NF-κB pathway[J]. China Journal of Chinese Materia Medica, 2020, 45(11): 2578 - 2585. (in Chinese).

[13] FENG YB. Simultaneous determination of four target ingredients in Xiao'er Tuire Koufuye by HPLC[J]. China Health Standard Management, 2018, 9(24): 73 - 77. (in Chinese).

[14] YANG HX. Effects of paeonol on renovascular hypertension in rats[D]. Shijiazhuang: Hebei Medical University, 2018. (in Chinese).

[15] HE H. Study on the mechanism of paeonol's anti-atherosclerosis effect through bile acid metabolism based on intestinal flora[D]. Hefei: Anhui University of Chinese Medicine, 2021. (in Chinese).

[16] SUN Y, LIU YR, WU HF, *et al.* Effect and mechanism of paeonol on atherosclerosis-related cells[J]. Journal of Anhui University of Chinese Medicine, 2020, 39(3): 92 - 96. (in Chinese).

[17] GE YZ. Study on the mechanism of paeonol in alleviating DSS-induced ulcerative colitis under Candida albicans colonization based on Dectin-1/TLRs/NF-κB pathway[D]. Hefei: Anhui University of Chinese Medicine, 2021. (in Chinese).

[18] WU Q, CHEN YZ, WU GM. Effects of paeonol combined with cisplatin on the proliferation and apoptosis of human osteosarcoma MG-63 cells as well as PI3K/Akt/mTOR signaling pathway[J]. China Phmarcy, 2021, 32(4): 438 - 442. (in Chinese).

[19] FU DH, FU YJ, ZHANG DD, *et al.* Advances in research on the antitumor effect of paeonol [J]. The Medical Forum, 2019, 23(35): 5159 - 5160. (in Chinese).

[20] WU JD. Mechanism of paeonol in preventing inflammatory injury in alcoholic liver disease based on the intestinal fungal flora and its mediated Dectin-1/IL-1β pathway[D]. Hefei: Anhui University of Chinese Medicine, 2020. (in Chinese).

[21] LIU B. Mechanism of paeonol in alleviating colitis-associated colorectal cancer based on STAT-3/NF-κB/ICAM-1 pathway[D]. Hefei: Anhui University of Chinese Medicine, 2021. (in Chinese).

[22] HA DT, TRUNG TN, HIEN TT, *et al.* Selected compounds derived from Moutan Cortex stimulated glucose uptake and glycogen synthesis via AMPK activation in human HepG2 cells[J]. Journal of Ethnopharmacology, 2010. 131(2): 417 - 424.

[23] WANG LJ, SUN H. Paeonol improves insulin resistance and oxidative stress induced by PA in rat aortic endothelial cells[J]. Journal of Toxicology, 2020, 34(2): 69 - 73,94. (in Chinese).

[24] BIAN YY. Preparation of Gualou sustained-release pills and study on antithrombotic effect and mechanism[D]. Wuhu: Wannan Medical College, 2020. (in Chinese).

[25] BIAN YY, YAN HY, ZOU CC. Preparation and *in vitro* release rate of Trichosanthes sustained-release pellets [J]. Journal of International Pharmaceutical Research, 2019, 46(6): 461 - 466. (in Chinese).

[26] Chinese Pharmacopoeia Committee. Chinese Pharmacopoeia (2020 Edition)[M]. Beijing: China Medical Science and Technology Press, 2020: 160 - 176. (in Chinese).

[27] ZHENG H, SONG LQ, FANG DY. Preparation of levofloxacin hydrochloride sustained-release tablets and influence factors of drug release [J]. Central South Pharmacy, 2021, 19(8): 1575 - 1580. (in Chinese).

[28] LI GX, ZHANG ZZ, SUN WD, *et al.* *In vitro* and *in vivo* consistency study of acetazolamide sustained-release capsules [J]. The Chinese Journal of Clinical Pharmacology, 2021, 37(19): 2547 - 2552. (in Chinese).