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正交试验优化青防肿痛外敷散纯化工艺 *

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摘要 目的：优选青防肿痛外敷散最佳纯化工艺。**方法：**以干膏率、青藤碱及粉防己碱转移率为指标，设置综合评分。单因素考察筛选直接沉淀法和水沉淀法，正交试验法优选水沉淀法中最佳相对密度、放置时间和加水倍量，将水沉淀法和直接沉淀法及纯化前试验数据对比，并将最佳纯化工艺做三批重复性验证试验。**结果：**水沉淀法最佳工艺为将滤液减压浓缩至相对密度为 1.10～1.15（70 ℃）的稠膏，稠膏加 7 倍量的水搅匀，放置 48 h。单因素试验结果证明水沉淀法优于直接沉淀法。重复性试验验证结果证明工艺稳定可靠。**结论：**此纯化工艺可在保留活性成分的同时，有效的去除杂质，最大程度减少使用剂量，为后期制剂成型和中试放大生产研究奠定了良好基础。

关键词：青防肿痛外敷散；正交试验；纯化工艺；水沉淀法

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Optimization of Purification Technology for Qingfang Zhongtong Powder by Orthogonal Experiment*

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ABSTRACT Objective: To optimize purification technology of Qingfang Zhongtong powder. **Methods:** Used dry extract yielding rate, the content of sinomenine and tetrandrine as indexes, set up comprehensive score, direct-deposition process and water-deposition process was optimized by single factor experiment. The technological parameter of water-deposition process like relative density, placing time and the amount of water were optimized by orthogonal experiment. The results were compared with the ones of direct-deposition process. Three batches of repetitive verification test of the best purification technology were carried out. **Results:** Optimum of purification technology was: concentrating under vacuum to relative density was 1.10～1.15 (70℃), adding 7 times amounts of water then placing 48 hours. Single factor experiment proved that water-deposition was superior to direct-deposition process. Repetitive verification test indicated that the best purification technology was stable and reliable. **Conclusions:** The optimum purification technology can keep active ingredients, remove impurities and reduce the dose, which offer good foundation for later pharmaceutical studies. The technological process was simple and suited for large scale production.

Key words: Qingfang Zhongtong powder; Orthogonal experiment; Purification technology; Water-deposition process

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前言

青防肿痛外敷散来源于《普济方》，方中记载："青藤根三两，防己一两，右㕮咀，酒瓶煮，徐徐服之"，用于治疗风湿痹痛。原方将青风藤与防己两味药用酒进行煎煮后服下。青防肿痛外敷散以此方为基础制备而成，具有祛风除湿，消肿止痛之功效。外敷散剂是将药物加适宜辅料，通过无纺布及纸塑膜压封包装制成，直接贴敷于患处，具有起效快、吸收好等多种优点。

本课题组之前的研究是依据古方中制备要求，将青风藤和防己药材共同提取。采用正交实验设计优化乙醇回流提取工艺，应用多指标综合评分法设置指标的权重，使提取工艺更加合理[1]。但此法提取得到的固形物量较大，达不到成型性要求，必须进行纯化处理，以缩小固形物量，因此为了保证原处方提取物能满足成型技术需求，在不损失有效物质含量的基础上进行提取液纯化工艺研究。

直接沉淀法和水沉淀法是工业生产上对醇提取液进行纯化的常用方法，本试验将直接沉淀法与水沉淀法进行试验对比，以有效成分含量结合干膏率为指标，进行纯化方法筛选。

1 材料与方法

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1.1 材料

U3000 型高效液相色谱仪 (戴安);VWD-3400 MWD 多波长紫外检测器; 色谱柱:Agilent ZORBAX Extend C18 分析柱,规格:4.6× 250 mm,粒径:5 μm;DZF6090 型真空干燥箱(上海恒科技术有限公司);CP225D 型分析天平(德国赛多利斯)等。

工艺考察用青风藤及防己饮片均购自安国市康达中药材有限公司,经黑龙江中医药大学都晓伟老师鉴定为正品。青藤碱对照品(中国药品生物制品检定所,批号:0774 -200206),粉防己碱对照品(中国药品生物制品检定所,批号:110711-200708),甲醇为色谱纯,其他试剂均为分析纯。

1.2 方法

1.2.1 青藤碱及粉防己碱含量测定 (1)色谱条件与系统适用性:以十八烷基硅烷键合硅胶为填充剂;流动相:A:甲醇;B:磷酸盐缓冲液(0.005 mol/L 磷酸氢二钠溶液,以 0.005 mol/L 磷酸二氢钠调节 pH 值至 8.0,再以 1%三乙胺调节 pH 值至 9.0);青藤碱检测波长为 262 nm,粉防己碱检测波长为 280 nm;流速为 1.0 mL/min,理论塔板数按青藤碱峰计算应不低于 2000,按粉防己碱峰计算应不低于 4000[1]。

(2)对照品溶液制备:精密称取青藤碱及粉防己碱对照品适量,加甲醇制成每 1 mL 分别含青藤碱 0.5 mg,粉防己碱 0.1 mg 的混合溶液,作为对照品溶液。

(3)供试品溶液制备:取提取液适量蒸干,取蒸干后浸膏适量,精密称定,置 25 mL 容量瓶中,加甲醇至近刻度,超声处理(功率 250 W,频率 20 kHz)20 min,放冷,加甲醇至刻度,摇匀,静置 10 min,取上清液用 0.45 μm 的微孔滤膜滤过,即得。

(4)测定方法:分别精密吸取对照品溶液与供试品溶液各 10 μL,注入液相色谱仪,测定,即得。

表 1 青藤碱及粉防己碱梯度洗脱流动相比例

Table 1 Gradient elution conditions of sinomenine and tetrandrine

t/min	A:B
0 ～ 10	47:53
10 ～ 13	18:82
13 ～ 26	18:82
26 ～ 30	47:53
30 ～ 40	47:53

1.2.2 直接沉淀法 取乙醇回流提取液(相当于 120 g 饮片),回收乙醇至无醇味,静置 48 h,取上清液,测定上清液中青藤碱、粉防己碱的含量、转移率及干膏率。

转移率 = 纯化后青藤碱(粉防己碱)总量÷ 提取出青藤碱(粉防己碱)总量× 100%

1.2.3 水沉淀法 水沉淀法工艺路线设计为:取乙醇回流提取液(相当于 120 g 饮片),回收乙醇至无醇味,减压浓缩至稠膏状,静置,取上清液,降压浓缩至清膏。

为保证水沉淀法能最大限度的除去杂质,对上述工艺中稠膏密度、静置时间、加水量三个因素进行正交试验优化,因素水平见表 2,以静置后上清液中青藤碱、粉防己碱转移率和干膏率差值为考察指标。将青藤碱转移率(X)和粉防己碱转移率(Y)的权重按处方比例分别设为 0.75 和 0.25,以综合值(M)进行统计分析,综合评分公式:

$M = (0.75X + 0.25Y) \times 100\%$

1.3 统计学分析方法

按 L9(3^4)正交试验分析方法,并对结果进行方差分析。

表 2 水沉淀法因素水平表

Table 2 Factor levels table of water-deposition process

Levels	Factors		
	A Relative Density(RD)	B Storage Time(ST)	C Times of Water(WT)
1	The initial density (1.05～1.10)(70℃)	12	3
2	The median density (1.10～1.15)(70℃)	24	5
3	The maximum density (1.15～1.20)(70℃)	48	7

2 结果

2.1 直接沉淀法

直接沉淀法试验结果见表 3。青藤碱含量平均值为 33.33 mg/g,RSD 为 3.7 %; 粉防己碱含量平均值为 12.09 mg/g,RSD 为 4.8 %;干膏率平均值为 8.16 %,RSD 为 7.7 %;青藤碱转移率平均值为 64.16 %,RSD 为 2.2 %;粉防己碱转移率平均值为 55.55 %,RSD 为 4.2%。

表 3 直接沉淀法试验结果

Table 3 The results of direct-deposition process

Sample	Sinomenine Content (mg/g)	Tetrandrine Content (mg/g)	Ratio of Dry Extraction (DER)(%)	Sinomenine Transfer Rate(STR)(%)	Tetrandrine Transfer Rate(TTR)(%)
1	34.7310	12.6402	7.44	63.44	53.09
2	32.3365	12.1471	8.43	63.23	57.76
3	32.9345	11.4861	8.61	65.80	55.81

2.2 水沉淀法

正交试验设计见下表：

表 4 正交试验因素表

Table 4 Orthogonal test table

Factors Num Tests Num	A	B	C	D	D-Value of DER %	STR %	TTR %	Composite Scores %
1	1	1	1	1	0.3267	74.30	66.19	72.27
2	1	2	2	2	0.7017	77.20	62.08	73.42
3	1	3	3	3	0.7850	86.68	69.77	84.45
4	2	1	2	3	0.3017	89.49	76.65	86.28
5	2	2	3	1	0.8267	97.31	85.77	94.42
6	2	3	1	2	0.8850	96.18	80.09	92.16
7	3	1	3	2	1.1183	87.16	74.90	84.10
8	3	2	1	3	2.3600	57.70	48.03	55.28
9	3	3	2	1	2.7933	61.31	53.63	59.39
Ⅰj	76.047	80.883	73.237	75.360				
Ⅱj	90.953	74.373	73.030	83.227				
Ⅲj	66.257	78.000	86.990	74.670				
Sj	24.696	6.510	13.960	8.557				

Note: F0.01(2,2)=99.00 F0.05(2,2)=19.00.

表 5 正交试验方差分析表

Table 5 Variance analysis of orthogonal experiment

Source of Variation	Sum of squares Degree of freedom Mean squares			F-value(P-value)	Significance
	SS	DOF	MS		
A	927.978	2	463.989	6.845(0.127)	Non-significant
B	63.846	2	32.923	0.471(0.680)	Non-significant
C	384.078	2	192.039	2.833(0.261)	Non-significant
D	135.580	2	67.790		

结果分析：通过对表 4 的直观分析表明，在所选因素水平范围内，各因素作用主次顺序为 A>C>B。方差分析(表 5)表明，各因素均无显著性影响(P＞0.05)。最佳工艺条件为 A2B1C3，即浓缩至相对密度为 1.10～1.15(70 ℃)，加 7 倍量水，放置 12 h。由干膏率差值可以看出，放置 12 h 后，干膏率差值较小，证明杂质不能沉淀完全，达不到纯化的目的，故选择放置 48 h。最终确定生产工艺为滤液减压浓缩至相对密度为 1.10～1.15(70 ℃)的稠膏，放置至室温，加稠膏 7 倍量的水搅匀，放置 48 h，取上清液，滤过。滤液减压浓缩至相对密度为 1.10～1.20(70 ℃)的清膏，保存。

2.3 直接沉淀法、水沉淀法试验结果比较

将上述两种纯化方法三批验证结果的平均值作比较，数据如表 6 所示。水沉淀法中青藤碱和粉防己碱含量明显高于直接沉淀法，故选择水沉淀法作为纯化方法。此外，纯化后与纯化前相比，含量相差不大，杂质明显降低，达到纯化要求。

表 6 纯化试验结果

Table 6 The results of purification tests

Purification Methods	Sinomenine (mg/g)	Tetrandrine (mg/g)	Ratio of Dry Extraction (%)	Sinomenine Transfer Rate(%)	Tetrandrine Transfer Rate(%)
Before-purification	45.94	17.17	9.03		
Direct-deposition	33.33	12.09	8.16	64.16	55.55
Water-deposition	45.49	15.26	8.26	83.90	85.16

2.4 工艺验证试验

按确定的最优纯化工艺进行三批重复性验证试验。

试验过程：按处方比例称取饮片 120 g 三份，加 8 倍量 70%乙醇，浸泡 2 h，加热回流提取 1.5 h，滤过，滤液保存；药渣加

6倍量70 %乙醇,加热回流提取1.5 h,滤过,合并滤液,减压浓缩至相对密度为1.10 ～1.15(70 ℃)的稠膏,放至室温,加稠膏7倍量的水搅匀,放置48 h,取上清液,滤过,合并滤液,按含量测定方法测定。测定结果见表7。

表7 纯化工艺验证性试验结果

Table 7 Certification tests results of purification process

Samples	Sinomenine (mg/g)	Tetrandrine (mg/g)	Ratio of Dry Extraction (%)	Sinomenine Transfer Rate(%)	Tetrandrine Transfer Rate(%)
1	44.22	14.90	8.42	83.21	84.81
2	46.50	15.50	7.92	82.31	82.97
3	45.76	15.40	8.43	86.20	87.71

三批验证结果为青藤碱含量平均值为45.49 mg/g,RSD 2.6 %;青藤碱转移率平均值为83.90 %,RSD 2.4 %;粉防己碱含量平均值为15.26 mg/g,RSD 2.1 %;粉防己碱转移率平均值为85.16 %,RSD 2.8 %;干膏率平均值为8.26 %,RSD 3.5 %。结果表明此工艺稳定,可有效去除杂质,达到纯化效果。

3 讨论

青防肿痛外敷散主要由青风藤和防己两味药组成,青风藤是防己科植物青藤及毛青藤的干燥藤茎[2]。目前已报道文献中青风藤的茎和根中分离提取化合物有41种，主要为生物碱成分。其中青藤碱是青风藤中的主要成分,总量高达2 %[3]。青风藤提取物青藤碱具有镇痛、抗炎、免疫抑制[4,5]等多种药理作用[6,7],近年已用于风湿性关节炎的治疗[8-11]。防己中的代表性成分为粉防己碱和防己诺林碱[12],在临床中常用来作为抗高血压、抗风湿及镇痛药等[13,14]。青风藤和防己在口服和注射应用时均表现出明显的毒副作用[15],改变其给药途径,进行经皮制剂的开发,可有效避免药物直接进入体循环所带来的不良反应。

纯化工艺中，出膏率是评价工艺合理性的重要指标参数,本文中直接沉淀法出膏率和水沉淀法相差不大,但其代表性成分青藤碱和粉防己碱的转移率相差较大。证明水沉淀法与直接沉淀法相比能更好的保留活性成分。本文中药材经提取精制后,制备成外敷散剂,在工艺研究过程中去除杂质、使药效活性成分高效富集,可为药物有效性提供物质基础。

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