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· 药学 ·

桂皮醛亚微乳注射剂中桂皮醛的含量测定研究 *

毕琳琳 杨倩 周暄宣 李骅 赵航 袁佳妮 王四旺[△]

(第四军医大学药理学天然药物学教研室 陕西 西安 710032)

摘要 目的:建立桂皮醛亚微乳注射剂中桂皮醛含量的测定方法。**方法:**采用高效液相色谱法,按照固定相为色谱柱 Diamonsil C18 柱(250 mm× 4.6 mm, 5 μm);流动相为乙腈:0.5%冰乙酸水溶液(60:40),检测波长为 288 nm,流速为 1.0 mL·min⁻¹,柱温为 25 ℃,进样量为 10 μL 的进样条件,测定桂皮醛亚微乳注射剂中桂皮醛的含量。**结果:**桂皮醛在 5~100 μg·mL⁻¹ 浓度范围内呈良好的线性关系,标准曲线方程为 $Y=1703 X -1996$ ($r^2=0.999$, $n=6$)。在低、中、高三个浓度下,一天内连续 3 次和连续 3 天测定样品,测定的 RSD 值均小于 2.0 %,精密度良好。加速试验中,在温度 30 ℃,相对湿度 60 % 的条件下放置 6 个月,样品测定结果与 0 天相比无变化。本实验中 3 批桂皮醛亚微乳注射剂中桂皮醛含量的均值为 19.89 μg·mL⁻¹,平均回收率为 100.98 %,RSD 为 1.45 %。**结论:**本方法操作简便、快速准确,稳定性高,系统重现性良好可有效控制桂皮醛亚微乳注射剂中有效成分含量。

关键词:桂皮醛亚微乳;桂皮醛;HPLC 法;含量测定

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Study on the Determination of Cinnamaldehyde in the Cinnamaldehyde Microemulsion Injection*

BI Lin-lin, YANG Qian, ZHOU Xuan-xuan, LI Hua, ZHAO Hang, YUAN Jia-ni, WANG Si-wang[△]

(Department of Natural Medicine, School of Pharmacy, the Fourth Military Medical University, Xi'an, Shaanxi, 710032, China)

ABSTRACT Objective: To establish the method for determining the content of cinnamaldehyde in the cinnamaldehyde microemulsion injection. **Methods:** Use HPLC method, with stationary phase of Diamonsil C18 column (250 mm× 4.6 mm, 5 μm), mobile phase of acetonitrile-0.5% aqueous solution of glacial acetic acid (60:40), detection wavelength of 288 nm, flow rate of 1.0 mL·min⁻¹, column temperature of 25 ℃, sample quantity of 10 μL, to determine the content of cinnamaldehyde in the cinnamaldehyde microemulsion injection. **Results:** The linear range of cinnamaldehyde is 5~100 μg·mL⁻¹. The standard curve equation is $Y=1703 X -1996$ ($r^2=0.999$, $n=6$). Precision is assessed by analyzing quality-control samples at low, medium and high concentrations in three duplicates a day and in three consecutive days, respectively. The precision (as relative standard deviation, RSD) was less than 2.0%. It shows that the precision is good. The determination results are unchanged to 0 days at a temperature of 30 ℃ and relative humidity of 60% after 6 month. In this experiment, the average contents of cinnamaldehyde are 19.89 μg·mL⁻¹, the average recovery rate is 100.98 %, and RSD is 1.45 %. **Conclusion:** The method is simple, accurate, reliable and reproducible, which can control the quality of cinnamaldehyde microemulsion injection effectively.

Key words: Cinnamaldehyde microemulsion; Cinnamaldehyde; HPLC; Content determination

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前言

桂皮醛(CA, 3-苯基-2-丙烯酸)是从肉桂树皮中提取到的一种主要活性物质。国内外研究证明,桂皮醛具有多种生物和药理活性,如抗菌^[1-10]、抗肿瘤^[11-19]、抗血栓^[20]、抗炎^[21]、降血糖^[22-24]、降血压和增强胃肠蠕动等作用^[25],其对人体免疫系统和消化系统均具有积极影响。虽然桂皮醛具有诸多肯定的药理学作用,但是由于桂皮醛水溶性差且体内代谢不稳定^[26],进入体内

会迅速氧化,从而使其血药浓度较低。因此,我们将桂皮醛制备成亚微乳的新型药物转运系统进行药物治疗。这种剂型可以使药物选择性地蓄积于肿瘤及炎症部位,在靶区使治疗药物比传统制剂的浓度高出数倍至数百倍,疗效明显提高。并且可延长治疗药物的半衰期,降低治疗药物在其他组织的分布量,减轻不良反应,达到高效低毒的效果^[27-29]。为保障药物质量,本文通过高效液相色谱法对研制的新药桂皮醛亚微乳注射剂进行有效成分质量控制和稳定性评价,对于临床安全用药具有重要意义。

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作者简介:毕琳琳(1979-),女,博士,主管药师,主要研究方向:中药药学及中药药理学,电话:13991132829, E-mail: 89759624@qq.com

[△] 通讯作者:王四旺(1957-),男,教授,029-84772519, E-mail: wangsiw@fmmu.edu.cn

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1 材料与方法

1.1 仪器

高效液相色谱仪(美国 Waters, Alliance 2695 型, 996PDA 检测器), Masslynx 软件系统, 超声波清洗器(昆山超声仪器公司), 电子分析天平(D200 型, 德国 Sartorius 公司)。

1.2 试剂

桂皮醛标准品(中国食品药品检定研究院, 批号 110710-200212)、肉桂醛亚微乳注射剂(西安立邦肇新生物科技有限公司)、超纯水(美国 Millipore 公司纯水器制备)、甲醇(色谱级, 霍尼威尔公司)、乙腈(霍尼威尔公司)、冰醋酸(霍尼威尔公司)。

1.3 对照品溶液的制备

取桂皮醛对照品 10 mg, 精密称定, 置于 10 mL 棕色容量瓶中, 用甲醇溶解, 稀释至刻度, 并摇匀, 即对照品贮备溶液(-20 °C 下保存)。

1.4 供试品溶液的制备

精密量取桂皮醛亚微乳 1 mL, 置 250 mL 棕色容量瓶中, 用甲醇溶解, 稀释至刻度, 摇匀。

1.5 空白对照溶液的制备

按桂皮醛亚微乳处方(肉桂醛、大豆油、维生素 E、卵磷脂、纯净水、甘油、油酸钠)比例(不含桂皮醛)制备空白亚微乳, 精密量取 1 mL, 置 250 mL 容量瓶中, 用甲醇稀释至刻度, 摇匀。

2 结果

2.1 色谱条件

色谱柱: Diamonsil C18(250 mm×4.6 mm, 5 μm); 流动相: 乙腈:0.5%冰乙酸水溶液(60:40); 柱温: 25 °C; 紫外检测波长: 288 nm; 流速: 1.0 mL·min⁻¹; 进样量: 10 μL。

2.2 专属性考察

取桂皮醛对照品溶液、供试品溶液及空白对照溶液, 按“2.1”项下色谱条件分别进样, 并记录色谱图。结果表明: 桂皮醛色谱峰与基线能够完全分离, 其保留时间为 5.37 min, 桂皮醛亚微乳中其他成分不干扰桂皮醛的测定。见图 1。

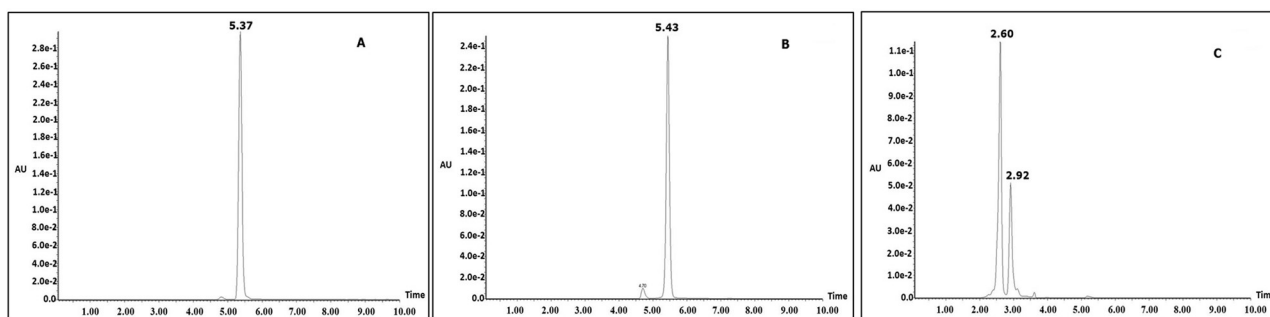


图 1 桂皮醛 HPLC 图

A- 桂皮醛对照品 B- 供试品 C- 空白对照

Fig.1 HPLC figures of cinnamaldehyde from cinnamaldehyde microemulsion injection samples

A- Cinnamaldehyde B-Test samples C-Blank control

2.3 线性关系考察

精密量取桂皮醛对照品溶液 0.05 mL、0.1 mL、0.2 mL、0.3 mL、0.5 mL 和 1 mL, 分别置于 10 mL 棕色容量瓶中, 用甲醇稀释至刻度, 并摇匀, 得到一系列标曲溶液。分别精密吸取上述标曲溶液各 10 μL, 按“2.1”项下色谱条件分别进样, 测定并记录峰面积。以峰面积 A 对浓度作图, 桂皮醛峰面积在 5~100 μg·mL⁻¹ 浓度范围内呈良好的线性关系。回归方程为 $Y = 1703X - 1996$ ($r^2=0.999$, $n=6$)。见图 2。

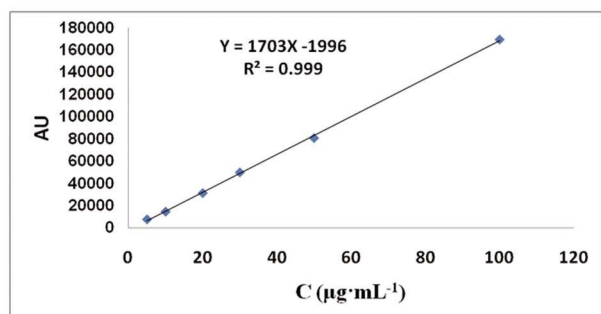


图 2 桂皮醛标准曲线

Fig.2 The standard curve of cinnamaldehyde

2.4 精密度试验

取 10、30、100 μg·mL⁻¹ 浓度的桂皮醛对照品甲醇溶液, 1 日内连续进样 3 次并记录峰面积, 计算桂皮醛的日内 RSD, 分别为 0.43 %、0.65 %、1.93 %。连续 3 天进样 3 次并记录峰面积, 计算桂皮醛的日间 RSD, 分别为 0.88 %、1.15 %、1.85 %。表明在低、中、高三个浓度下, HPLC 测定的 RSD 值均小于 2.0 %。

2.5 重复性试验

精密吸取同一桂皮醛亚微乳注射剂(20140114)各 100 μL, 分别置于 6 个 25 mL 的容量瓶中, 用甲醇定容, 破乳, 过滤, 进行测定。精密吸取供试品溶液各 10 μL, 注入液相色谱仪, 记录肉桂醛峰面积, 计算桂皮醛的 RSD 为 1.62 %。表明本实验所用的方法重复性良好。

2.6 稳定性试验

分别取配置后 1、4、6、8、12 h 的供试品溶液进样分析, 测得桂皮醛峰面积的 RSD 为 0.42 %, 表明桂皮醛在此色谱条件下比较稳定。

2.7 加速试验

取桂皮醛亚微乳注射剂样品置 30 °C, 相对湿度 60 %, 放置 6 个月, 分别于第 1、2、3、6 月月末取样测定, 与 0 天测定结

果相比较。测定结果表明,在温度 30 ℃、相对湿度 60 %条件下放置 6 个月,样品与 0 天测定结果相比较无明显变化。

2.8 回收率试验

取已测定含量的供试品溶液 6 份,分别加入 0、30、100 μg ·

mL^{-1} 三个浓度的桂皮醛对照品甲醇溶液,进样测定,并计算加样回收率。结果:平均回收率为 100.98 %,RSD 为 1.45 %,该方法准确可靠,误差在允许的范围内。见表 1。

表 1 桂皮醛加样平均回收率实验结果(n=9)

Table 1 The average recovery experiment results of Cinnamaldehyde (n=9)

Technical content (μg)	Add the scalar (μg)	Measured the amount (μg)	Recovery(%)	The average recovery(%)	RSD(%)
19.75	16.00	36.22	102.94	100.98	1.45
	16.00	35.87	100.75		
	16.00	35.98	101.44		
	20.00	40.12	101.85		
	20.00	40.09	100.70		
	20.00	39.81	100.30		
	25.00	45.43	102.72		
	25.00	44.31	98.24		
	25.00	44.71	99.84		

2.9 样品含量测定

按照 "1.4" 项下制成供试品溶液,按 "2.1" 项下色谱条件测

定 3 批样品中桂皮醛的含量。结果表明 3 批样品中桂皮醛含量的均值是 19.89 $\mu\text{g}\cdot\text{mL}^{-1}$ (表 2)。

表 2 三批桂皮醛亚微乳样品中桂皮醛含量测定结果(n=3)

Table 2 Three batches of cinnamaldehyde content determination results in the cinnamaldehyde microemulsion (n=3)

Batch number	Cinnamaldehyde content($\mu\text{g}\cdot\text{mL}^{-1}$)	Average ($\mu\text{g}\cdot\text{mL}^{-1}$)
20140114	19.75	19.89
20140411	20.02	
20140606	19.89	

3 讨论

桂皮醛是樟科樟属植物肉桂树皮的提取物挥发油中的主要活性成分,含量可达 80%以上^[30],由于肉桂中桂皮醛的含量高且广泛应用于医药、日化和食品工业中,促使了对桂皮醛的研究。目前,桂皮醛的含量测定多为 HPLC 法^[31,32],也有气质联用的方法^[33]。其由于气质联用仪不能广泛应用于多数实验室,所以,我们采用 HPLC 法对桂皮醛进行含量测定。桂皮醛亚微乳注射剂破乳后,采用高效液相色谱法测定制剂中桂皮醛的含量。采用 2015 版《药典》中肉桂药材有效成分桂皮醛含量测定方法^[34]进行重现测定,无法测定出峰时间,基线不稳。采用文献^[31]中桂皮醛纳米乳的含量检测方法,进行桂皮醛亚微乳注射剂中桂皮醛的检测,结果显示,进样样品种有效成分出峰时间相比文献虽然有所缩短,但是峰形很差且基线不稳定。将流速由 0.25 $\text{mL}\cdot\text{min}^{-1}$ 改为 1 $\text{mL}\cdot\text{min}^{-1}$ 后,出峰时间无改变,但峰形和基线依然很差,说明进样的流速对出峰结果无影响,因此,我们继续选择 1 $\text{mL}\cdot\text{min}^{-1}$ 作为本实验条件下的流速。遂改变流动相比,使乙腈:0.5%冰乙酸水溶液配比由 50:50 调整为 60:40,经重复实验验证得出,出峰时间由文献中的 15 分钟提前至 5 分钟左右并且相对稳定,得到的峰形较好。实验结果表明,提高有机相比,可使出峰时间提前而缩短分析时间,提高效率。全波长(210-400 nm)扫描后,在 288 nm 时吸光度最好,与文献相

近,因此,确定桂皮醛的检测波长为 288 nm。此方法的线性范围(5~100 $\mu\text{g}\cdot\text{mL}^{-1}$)较宽,在此浓度范围内呈良好的线性关系,适用于测定不同规格的制剂。在专属性考察中,此检测条件可以很好地分离制剂中的杂质成分,使色谱峰与基线能够完全分离,保证桂皮醛含量的测定不受其他成分的干扰。由于液体称量比较困难,所以会对实验结果有一定的影响。一般在操作时为了避免较大误差,可以考虑先称取稍大量,然后再进行稀释取样。

综上所述,本研究科学、准确地测定了桂皮醛亚微乳注射剂中桂皮醛的含量,为微乳制剂中桂皮醛的测定提供了新的方法。不仅能够准确、有效地对桂皮醛亚微乳注射剂进行有效成分含量测定,还可以为其质量标准的制定提供可靠的依据。

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