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· 药学 ·

治糜灵凝胶剂的薄层色谱鉴别研究*

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摘要 目的:将治糜灵栓剂(《中国药典》2010 版一部)改为治糜灵凝胶剂,建立治糜灵凝胶剂的薄层色谱鉴别方法,为制定其质量控制标准制定依据。**方法:**参照《中国药典》2010 版一部治糜灵栓剂项下黄柏、苦参、儿茶、冰片的薄层色谱鉴别方法,对方中的主要药味进行定性鉴别。黄柏鉴别中以甲苯-乙酸乙酯-异丙醇-水(6:3:1.5:1.5)为展开剂;苦参鉴别中以甲苯-乙酸乙酯-甲醇(8:3:0.5)为展开剂;儿茶鉴别中以正丁醇-醋酸-水(3:2:1)为展开剂;冰片鉴别中以环己烷-三氯甲烷-乙酸乙酯(9:1:2)为展开剂。**结果:**薄层色谱上具有黄柏,苦参,儿茶,冰片的鉴别特征,且阴性对照无干扰。**结论:**色谱斑点清晰,专属性强;该方法操作简便,稳定性、重现性均很好。可作为质量标准的控制依据。证明治糜灵凝胶剂研究的方法可行。

关键词:治糜灵凝胶剂;薄层色谱;黄柏;苦参;儿茶;冰片

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Study on the TLC Identification Method of Zhimiling Gels*

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ABSTRACT Objective: To verify the feasibility that changing Zhimiling suppositories (published in the "Chinese Pharmacopoeia"2010) into Zhimiling gels, and to establish TLC identification method of Zhimiling Gels, and support to set up quality control standard for the product. **Methods:** In accordance with the "Chinese Pharmacopoeia"2010 A, TLC identification method of Cortex Phellodendri, Sophora flavescens, Acacia catechu and Borneol was performed. And a qualitative identification of the main drugs in the prescription was detected. The developer for Cortex Phellodendri was methylbenzene- ethyl acetate- so-Propyl alcohol-water(6:3:1.5:1.5); for Sophora flavescens was methylbenzene- ethyl acetate- methyl alcohol (8:3:0.5); for Acacia catechu was butyl alcohol-AceticAcid -water (3:2:1); for Borneol was cyclohexane- Trichloromethane- ethyl acetate (9:1:2). **Results:** Cortex Sophora flavescens, Acacia catechu and Borneol could be clearly detected by TLC, while the negative control had no interference. **Conclusions:** TLC spots was obvious, and the method was specific, simple, stability and with good reproducibility to be used as quality control guide line for the Zhimiling Gels, which prove the study of Zhimiling gels is feasible.

Key words: Zhimiling Gels; TLC; Cortex Phellodendri; Sophora flavescens; Acacia catechu; Borneol

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前言

宫颈糜烂(cervical erosion)是宫颈炎中最常见病症之一,发病率高,在妇科门诊就诊中占较大比例。大多数育龄妇女都存在宫颈糜烂病症,轻重不等,俗有"十女九带"之称。宫颈糜烂与宫颈癌有极大关联,治疗宫颈糜烂是保障广大妇女身心健康的主要措施之一,也是阻断宫颈癌发生的重要手段。现代医学认为宫颈糜烂主要与细菌、病毒等感染,化学物质损伤、机械刺激损伤、性激素紊乱有关;中医将其归为"带下病"范畴,认

为多因湿毒、热毒下侵,气血郁滞,血瘀肉腐而成。由于病灶部位特殊,临床以局部治疗为主,治疗方法有物理疗法、手术疗法和药物疗法,其中药物疗法因属非创伤性治疗,操作简单方便,对患者要求较低而应用广泛。

阴道给药是宫颈糜烂药物治疗法中的主要治疗方法,也是现代临床治疗宫颈疾病的首选治疗给药途径。随着宫颈疾病患病率的不断增高,阴道给药制剂成为广大医务工作者的研究热点,除传统的洗剂、片剂、膜剂、膏剂之外,相继出现了例如泡腾片、栓剂、凝胶剂等疗效更好、使用更方便的剂型^[1-3]。其中凝

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胶剂是近年国内外医药市场中最活跃的剂型之一,凝胶基质可与粘膜产生良好的生物相容性,提高生物利用度、增强药物疗效,对药物具有缓释、控释作用,使病灶部位的有效浓度增加,且与片剂、栓剂相比较患者使用无油腻感,易清洗,患者使用无异物感,顺应性强,是用于阴道给药治疗宫颈糜烂的一种理想剂型^[4-8]。

治糜灵凝胶剂由黄柏、苦参、儿茶、枯矾、冰片五味中药组成,是在治糜灵栓的基础上研制的现代中成药,来源于《中药部颁标准》第十一册中成药制剂治糜灵栓,现已收录于《中国药典》2010 版一部^[9]。用于宫颈糜烂、感染性阴道炎、滴虫性阴道炎等,具有明显的抗炎消肿、抑菌作用。但栓剂易变形、不易保存,使用不方便且有异物感,且与凝胶剂相比较,栓剂的粘膜粘附性较差,滞留时间较短,无法充盈整个阴道。而治糜灵凝胶剂采用水溶性高分子材料西黄蓍胶为基质,药物在凝胶内呈分子水平扩散,对提高药物的生物利用度有很大意义,避免了原栓剂的应用受到限制。

在中药新药研制中,几乎所有的新药都必须提供薄层层析谱。为此,本研究决定在给药途径相同情况下,将治糜灵栓剂改为凝胶剂,从新药研究角度出发,参照《中国药典》2010 版一部治糜灵栓项下的规定,采用薄层色谱法对治糜灵凝胶剂处方中主要药味进行鉴别。薄层色谱技术在中药成药的定性鉴别中应该是最常用的方法之一,具有良好的专属性强、可比性及较高的灵敏度,依据薄层色谱上板斑点的有无、颜色、位置来判定中成药所含原料药物的真伪,同时其斑点的大小、颜色的深浅亦可在一定程度上直接反映出所用原料药材的优劣。采用薄层色谱分析与其他色谱分析相比,其显著不同之一是得到的图谱是直观性很强的图像。我们的实验结果表明,该方法简便可行,重现性好,薄层图谱清晰,阴性对照无干扰,可作为治糜灵凝胶剂质量标准的控制依据。现报道如下。

1 材料与方法

1.1 实验材料

黄柏对照药材;盐酸小檗碱对照品;苦参对照药材;苦参碱对照品;儿茶素对照品;儿茶素对照药材;冰片对照品,均购于中国药品生物制品鉴定所。治糜灵凝胶剂(自制)。实验所用的试剂均为分析纯^[10,11]。

1.2 薄层色谱鉴别

1.2.1 黄柏的 TLC 鉴别 取本品 5 g,加甲醇 50 mL,加热回流 40 分钟,滤过,滤液蒸干,加甲醇溶解至 5 mL,作为供试品溶液。同时依原处方,去掉黄柏,同法制备阴性对照溶液。另取黄柏对照药材 0.1 g,加甲醇 10 mL 同法制成对照药材溶液。照薄层色谱法试验,吸取上述供试品及阴性对照溶液各 5 μ L,对照药材溶液 1 μ L,分别点于同一硅胶 G 薄层板上,以甲苯-乙酸乙酯-异丙醇-水(6:3:1.5:1.5)为展开剂加入双槽展开缸中,另一槽内加入等体积的浓氨试液,预平衡 15 分钟,展开 8 cm,取出,晾干,置紫外光灯(365 nm)下检视。供试品色谱中,在与对照药材色谱相应的位置上,显相同颜色的荧光斑点,阴性对照无干扰^[12]。

1.2.2 苦参 TLC 定性鉴别 取本品 5 g,加浓氨溶液 1.5 mL,加三氯甲烷 25 mL,超声处理 30 分钟,滤过,滤液蒸干,加三氯

甲烷 0.5 mL 使溶解,作为供试品溶液。取苦参对照药材 0.5 g,同法制成对照药材溶液。另取苦参碱对照品,加乙醇制成每 1 mL 含 0.2 mg 的溶液,作为对照品溶液。按此方比例,同法制成苦参阴性对照品溶液。照薄层色谱法试验,吸取上述四种溶液各 2 μ L,分别点于同一硅胶 G 薄层板上,以甲苯-乙酸乙酯-甲醇(8:3:0.5)为展开剂,展开,展距为 8 cm,晾干,再以甲苯-乙酸乙酯-甲醇-水(2:4:2:1)10 $^{\circ}$ C 以下放置的上层溶液为展开剂,展开,取出,晾干,依次喷以碘化铋钾和亚硝酸钠乙醇试液,日光下检视,供试品色谱中,分别在对照药材、对照品色谱相应的位置上,显相同颜色的斑点,阴性对照品无干扰^[13]。

1.2.3 儿茶 TLC 鉴别 取本品 5 g,加乙醚 30 mL,超声处理 10 分钟,滤过,滤液蒸干,残渣加甲醇 5 mL 使溶解,作为供试品溶液。另取儿茶对照药材 0.5 g,同法制成对照药材溶液,另取儿茶素对照品,加甲醇制成每 1 mL 含 0.2 mg 的溶液,作为对照品溶液。按处方比例,同法制成儿茶阴性对照溶液。照薄层色谱法试验,吸取供试品溶液及阴性对照溶液各 5 μ L、对照药材溶液及对照品溶液各 2 μ L,分别点于同一硅胶 G 薄层板上,以正丁醇-醋酸-水(3:2:1)为展开剂,展开,取出,晾干,喷以 10%硫酸乙醇溶液,加热至斑点显色清晰。供试品色谱中,分别在对照药材、对照品色谱相应的位置上,显相同颜色的斑点,阴性对照品无干扰^[14-16]。

1.2.4 冰片 TLC 鉴别 取本品 5 g,放置于一培养皿中,其上盖一玻璃板,使培养皿与玻璃板间有一定空隙。加热培养皿,使冰片升华。升华完成,用三氯甲烷溶解玻璃板上升华物于一蒸发皿中,作为供试品溶液。另取冰片对照品,加三氯甲烷制成每 1 mL 含 5 mg 的溶液,作为对照品溶液。按处方比例,同法制成冰片阴性对照品溶液。照薄层色谱法试验,吸取供试品,阴性对照品溶液各 8 μ L 及对照品溶液 1-2 μ L 分别点于同一硅胶 G 薄层板上,以环己烷-三氯甲烷-乙酸乙酯(9:1:2)为展开剂,展开,取出,晾干,喷以 1%香草醛硫酸溶液,在 105 $^{\circ}$ C 加热至斑点显色清晰,日光检视,供试品色谱中,在与对照品色谱相应的位置上,显相同颜色斑点,阴性对照无干扰^[17,18]。

2 结果

参照《中国药典》2010 版一部治糜灵栓剂的鉴别实验,对治糜灵凝胶剂成品中主要成分黄柏、苦参、儿茶、冰片进行了薄层色谱鉴别研究,均采用了阴性对照试验,见图 1,2,3,4。结果表明,薄层色谱上具有黄柏、苦参、儿茶、冰片的鉴别特征,各检出成分不受处方中其他药的干扰,方法稳定,斑点清晰,可作为治糜灵凝胶剂的有效鉴别方法。

3 讨论

随着生活节奏的加快、饮食结构的变化、自然生态的破坏、工作压力的增大等原因,现代女性被越来越多的妇科疾病所困扰,宫颈糜烂属首要难题,中药和西药在宫颈糜烂治疗中的应用,各有特点,西药多为抗生素类化学合成药品,成分明确,疗效良好,但许多药物都有明显的毒副作用,易产生抗药性及药源性疾病。中药相对西药而言,长期使用毒副作用小或无毒副作用,不易产生抗药性及药源性疾病;复方制剂中各味药严格遵循中医辨证论治理论,发挥协同作用,达到标本兼治的效果。随着现代药物分析技术、药理学、毒理学、药代动力学的不断发

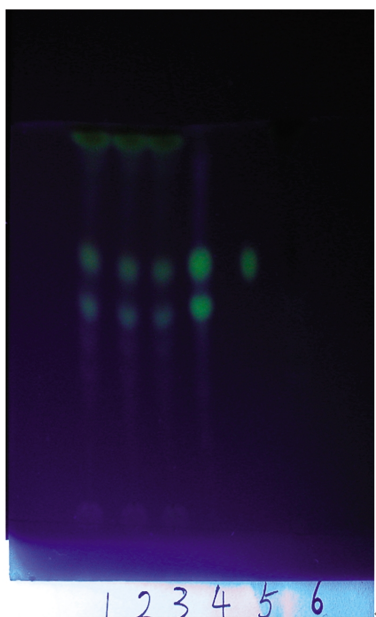


图1 黄柏 TLC

Fig.1 TLC chromatograms of Cortex Phellodendri

注:1、2、3 供试品,4 对照药材,5 对照品,6 阴性对照。

Note:1, 2, 3 test samples, 4 referenced crude material, 5 referenced crude material, 6 negative control.

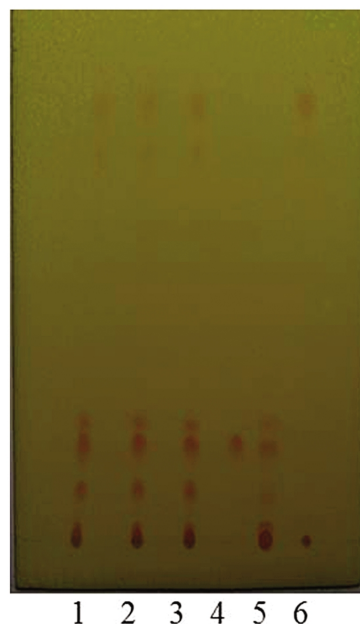


图2 苦参 TLC

Fig.2 TLC chromatograms of Sophora flavescens

注:1、2、3 供试品,4 对照品,5 对照药材,6 阴性对照。

Note:1, 2, 3 test samples, 4 reference substance, 5 referenced crude material, 6 negative control.



图3 儿茶 TLC

Fig. 3 TLC chromatograms of Acacia catechu

注:1、2、3 供试品,4 对照品,5 对照药材,6 阴性对照。

Note:1, 2, 3 test samples, 4 reference substance, 5 referenced crude material, 6 negative control.

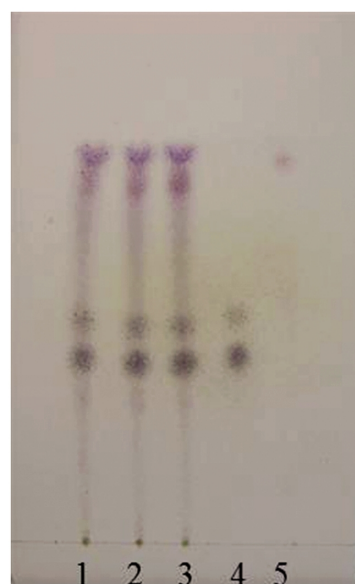


图4 冰片 TLC

Fig.4 TLC chromatograms of Borneol

注:1、2、3 供试品,4 对照品,5 阴性对照。

Note: 1, 2, 3 test samples, 4 reference substance, 5 negative control.

展, 传统中医理论结合现代分析技术全面阐述中药的药理药效,使中药越来越被人们认可和肯定。近年来,中医外治法运用在宫颈糜烂治疗中,取得了较好的临床效果。用于宫颈糜烂治疗的复方制剂,剂型较多,口服剂型如汤剂、片剂、丸剂、口服液等,外用制剂如洗剂、散剂、膏剂、栓剂等。随着制剂技术的发展和新材料的不断问世,许多新剂型也开始应用于中药阴道给药,由于阴道的特殊生理结构,药物经阴道给药能够发挥更好

的局部治疗作用,是治疗宫颈疾病的首选给药途径。其中中药凝胶剂是一种新型中药外用制剂,可容纳中药细粉及提取药膏,生物相容性好,使用方便、舒适,工艺条件不苛刻,适合中药复方制剂的生产现状,便于推广应用,是中药传统制剂改进的良好选择^[19,20]。这使得中药在妇科宫颈疾病治疗中的应用更加广泛,疗效更加确切。

随着中药的广泛应用,中药原药材及其制剂质量定性鉴别

所采用的方法、操作技术和理论依据,经历了一个从形成、到发展、再到不断完善与不断提高的全过程。定性鉴别研究是保证中成药所用原药材与制剂成品质量可靠依据,也是中药现代化研究的重要环节。文献表明,色谱法在鉴别研究实验中的应用比例迅速上升。其中薄层色谱法因快速、经济、可靠、操作简单、适用范围广、重现性好等优点,被为国内外学者广为接受和认可。在中药天然药物新药研制中的质量标准制定及已上市中药天然药物提高质量标准,几乎所有必须提供薄层色谱定性鉴别,同时一定要附有标准品及阴阳药材对照的彩色照片^[21]。

本研究在初步药效学研究的基础上,对治糜灵凝胶剂中的主要成分进行了薄层色谱定性鉴别研究,证实了治糜灵凝胶剂制剂对宫颈糜烂有治疗作用。本研究对治糜灵凝胶剂进行了提取工艺、制备工艺、质量标准、初步稳定性以及药效学的实验研究。对提取工艺采用正交试验法,以总生物碱含量和出膏率为指标,采用超微粉碎技术代替常规粉碎;对制备工艺的研究以产品的成型性、细腻性、稳定性为指标进行凝胶基质筛查。结果表明,黄柏,苦参,儿茶,冰片薄层鉴别特征与原治糜灵栓(《中国药典》2010年版一部)项下的规定一致,色谱斑点清晰,阴性对照无干扰,专属性强。该方法操作简便,稳定性、重现性良好,可作为治糜灵凝胶剂质量标准的控制依据。本实验着重研究质量标准,对处方中黄柏、苦参、儿茶、冰片薄层色谱定性鉴别,充分考查了新药研究的相关问题,进行了可行性试验,可作为方法学考察的依据。

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