

Preparation and Quality Control of 0.04% Atropine Sulfate Eye Drops

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The use of atropine sulfate eye drops is one of the most effective methods for preventing and treating myopia in youths and teenagers both in China and abroad. As 1% atropine sulfate has strong mydriatic effects, patients generally are not willing to use it for a long time. Owing to this, 0.04% atropine sulfate eye drops have been prepared by the 4th Affiliated Hospital of Guangxi Medical University, and the clinical application thereof over the years has demonstrated significant effects. The preparation and quality control method of the 0.04% atropine sulfate eye drops are introduced as follows.

1. Materials

LC-10AT High Performance Liquid Chromatograph (HPLC), including SPD-10 Detector, CLASS-VP6.12 SP1 Chromatography Data System and UV-2401PC Spectrophotometer (Shimadzu Corporation, Japan); BP211D Electronic Analytical Balance (Sartorius Stedim Biotech (Beijing) Co., Ltd.).

Atropine sulfate reference substance (Batch No. 715-20001, Chinese National Institute for the Control of Pharmaceutical and Biological Products); atropine sulfate (Batch No. 0406111, Hangzhou Minsheng Pharmaceutical Group Co., Ltd.); chromatographically pure acetonitrile; water for injection; and other reagents of analytically pure grade.

2. Recipe and Preparation

2.1 Recipe

Atropine sulfate 0.4g, sodium chloride 9.0g, ethylparaben (ethyl p-hydrobenzoate) 0.3g, water for injection added to 1,000ml.

2.2 Preparation

Ethylparaben (ethyl p-hydrobenzoate) was weighed and dissolved in 900ml of warm injection water; sodium chloride was added and stirred to dissolve it; the mixture was left to cool; atropine sulfate was added and stirred to dissolve; filtration was performed, and injection water was added from the filter so that the volume increased to 1,000ml; stirring was performed to homogenize; sterilization was performed using 100°C circulating vapor for 30 minutes; sterile packaging was performed to obtain the finished product.

3. Quality Control

3.1 Appearance

The product is a colorless clear solution.

3.2 Identification

A suitable amount of atropine (approximately 5mg of atropine sulfate) was taken and placed on a water bath for evaporation to dryness, and identification reaction of tropane alkaloids (Appendix III to Volume 2 of the “Pharmacopoeia of the People's Republic of China” 2005 edition) was demonstrated by the residues ^[2].

The product demonstrated identification reaction of sulfates ^[2].

3.3 Examination

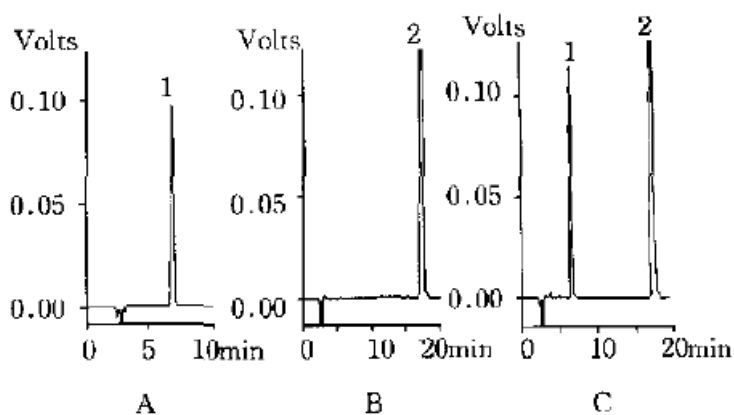
The pH value of the product should be 4.0~6.0. Other characteristics should meet the respective requirements for “Eye Drops” of Appendix II to Volume 2 of the “Pharmacopoeia of the People's Republic of China” 2000 edition ^[2].

3.4 Content determination

3.4.1 Chromatographic conditions. Chromatographic columns: Diamonsil C₁₈ (250mm x 4.6mm, 5μm); mobile phase: acetonitrile-water (containing 0.1% of triethylamine, phosphoric acid used to adjust pH to 5.8) (55: 45); flow rate: 1.0ml•min⁻¹; column temperature: 30°C; detection wavelength: 210nm; sample injection amount: 20μl.

3.4.2 Blank test. Blank eye drops not containing atropine sulfate was prepared according to recipe, 20μl of which was directly injected, and chromatogram was recorded; sample solution and reference substance solution were separately taken and directly injected, and chromatograms were recorded. Details are as shown in Figure 1.

It can be seen from Figure 1 that no interference was caused by auxiliary materials to the test under these chromatographic conditions.



A. Reference Substance; B. Blank Sample; C. Sample; 1. Atropine sulfate; 2. ethylparaben (ethyl p-hydrobenzoate)

Figure 1 - HPLC Chromatograms

3.4.3 Plotting of standard curve. A suitable amount of atropine sulfate dried at 120°C to constant weight was precisely weighed and taken, and water was added to produce a reference substance stock solution containing atropine sulfate with a concentration of 0.5mg•ml⁻¹. 1ml, 2ml, 3ml, 4ml, 5ml and 6ml volumes of atropine sulfate reference substance stock solution were precisely taken and placed in 50ml volumetric flasks respectively; water was added for dilution to a constant volume; stirrings were performed; 20μl of solution from each volumetric flask was taken and injected into the high performance liquid chromatograph (HPLC), respectively; chromatograms were recorded; linear regression was performed with peak area A versus concentration C and a linear regression equation $A = 14334 + 33928C$ ($r = 0.9999$) was obtained. The results showed that the linear relationship was good when the test concentration of atropine sulfate was within the range of 10~60μg•ml⁻¹.

3.4.4 Precision and stability test. Precisely measured 2ml of atropine sulfate reference substance stock solution was taken from each of the 50ml volumetric flasks and placed in 25ml volumetric flask, respectively; the solution was diluted to volume and shaken to homogenize; sample injections was continuously performed 5 times, and it was determined that the relative standard deviation RSD = 0.86%. The same reference substance solution was placed under room temperature and samples were injected at different times (within 12 hours); peak areas were recorded; and it was determined that the relative standard deviation RSD = 0.81%. The results showed that the solution was basically stable within 12 hours.

3.4.5 Repeatability Test. A suitable amount of the same sample batch was taken and samples were continuously injected 6 times under the same chromatographic conditions defined in section 3.4.1, peak areas were recorded, and it was determined that the relative standard deviation RSD = 0.85%.

3.4.6 Recovery rate test. 24mg, 20mg and 16mg of the reference substance were precisely weighed and taken; the lots were added with earlier prepared ethylparaben-sodium chloride solution respectively according to the proportions as prescribed by recipe for the preparation of high-concentration, medium-concentration and low-concentration (120%, 100% and 80%) simulated sample solutions. 20μl of each solution was injected respectively; atropine sulfate contents were determined and recovery rates calculated. The results were as shown in Table 1.

Table 1 - Recovery Rate Test Results (n=9)					
Serial No.	Amount Added (mg)	Amount Measured (mg)	Recovery Rate (%)	Average Recovery Rate (%)	RSD (%)
1	16.4	16.25	99.1	100.2	0.95
2	16.4	16.66	100.6		
3	16.4	16.49	100.6		
4	19.6	19.65	100.3		
5	19.6	19.82	101.1		
6	19.6	19.45	99.3		
7	24.2	24.42	100.9		
8	24.2	24.33	100.5		
9	24.2	23.93	98.9		

3.4.7 Sample content determination. Suitable amounts of atropine sulfate reference substance were precisely weighed and taken; water was added to dissolve and dilute them to become reference substance solutions with a concentration of $40\mu\text{g}\cdot\text{ml}^{-1}$. 20 μl each of the reference substance solutions and the sample solutions were injected, respectively, to the high-performance liquid chromatograph (HPLC), and chromatograms were recorded; and one-point external standard method was employed to calculate sample concentration based on peak areas, and the results were multiplied by 1.0266. The labeled contents of three (3) lots of samples were 98.5%, 103.4% and 100.2% respectively.

4. Discussions

4.1 Methods for determining atropine sulfate content include the neutralization method^[2], extraction colorimetry^[3] and ultraviolet spectrophotometry^[4, 5]. As the atropine sulfate content of the eye drops is too low, the neutralization method and extraction colorimetry are not suitable for its determination, and due to interference by ethylparaben (ethyl p-hydrobenzoate), ultraviolet spectrophotometry also cannot be used for its direct analysis. After numerous experiments, the author chose to employ high performance liquid chromatography (HPLC) whereby atropine sulfate content can be directly determined without segregation being performed and no interference by ethylparaben (ethyl p-hydrobenzoate) is caused to the analysis of active ingredient (retention time 17.5 minutes).

4.2 As the atropine sulfate reference substance needs to be dried at 120°C to constant weight and transformed into the anhydrous form to be a single ingredient^[3], and since the content of the eye drops is indicated by hydrate, multiplication of a coefficient of 1.0266 needs to be done when calculating the results.

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0.04% 硫酸阿托品滴眼液的制备与质量控制

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摘要 目的:建立0.04%硫酸阿托品滴眼液的制备工艺及其质量控制方法。方法:取硫酸阿托品与辅料制成浓度为0.04%的微量硫酸阿托品滴眼液,以乙腈-水(55:45)为流动相,采用高效液相色谱法测定硫酸阿托品的含量。结果:所得制剂为无色澄明液体;硫酸阿托品检测浓度线性范围为10~60 $\mu\text{g/ml}$ ($r=0.999$),平均回收率为100.2%($\text{RSD}=0.95\%$, $n=9$)。结论:该制剂制备工艺简单,含量测定方法简便、准确,质量可控。

关键词 硫酸阿托品;滴眼液;制备;高效液相色谱法

Preparation and Quality Control of Dilute Atropine Sulfate Eye - drops

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ABSTRACT OBJECTIVE: To establish the preparation process and method of quality control of dilute atropine sulfate eye - drops. METHODS: Mixing atropine sulfate with additives in water to prepare 0.04% atropine sulfate eye - drops. And determined the content of atropine sulfate by HPLC, the system consisted of C_{18} column and mobile phase of acetonitrile - water (55 : 45). RESULTS: The product is colorless and clearing liquid. The linear range of atropine sulfate was 10~60 $\mu\text{g/ml}$ ($r=0.999$). The average recovery rate was 100.2% ($\text{RSD}=0.95\%$, $n=9$). CONCLUSION: The preparation process of dilute atropine sulfate eye - drops is simple and the method of quality control by HPLC is reliable.

KEY WORDS Atropine sulfate; Eye - drops; Preparation; HPLC

以上各项试验结果表明,本品经过强光(4 500Lx) 10d、高温(60℃) 10d、40℃(相对湿度:75%)加速试验 6mo 及室温(5℃~35℃) 12mo 留样考察,测定其含量,体外释放度与开始时比较均无明显变化,表明本品稳定性较好。

5 讨论

组方设计时,考虑应用现代缓释制剂技术把硫酸沙丁胺醇主药与几种缓释材料 HPMC、EC 和 MCC 配制片芯^[3],使主药缓慢逐步溶出;加入的乳糖遇水溶解形成通道,使主药能溶出;加入 DST 吸水溶胀能打开上述几种缓释材料形成的包裹墙。其片芯外另外包肠溶衣,使片剂通过胃时不崩解,进入肠道 pH=6.8 时才崩解。这就延迟 1.5h~2h 崩解释药。

本品按照《中国药典》方法^[1]测定其体外释放度并用市售普通片和缓释片对照测定,测定结果详见表 1。研制品在 3h 前(因胃溶液中 2h 不崩解)很少释放,只有 4.66%,5h 时约有 50% 的硫酸沙丁胺醇释放,6h 时则 80% 以上释放,7h 时则 95% 以上已释放,其释放药高峰在 5h~7h 时(即延迟 5h 定时释药),市售普通片 20min 时主药已溶出过半(58.98%),到 40min 时已基本全部溶出(98.96%);市售缓释片 3h 时主药已释放 40.46%,5h 时则 67.98%,到 12h 时才释放完(97.93%)(详见图 2 及表 1)。

结果表明,市售硫酸沙丁胺醇缓释片,大都选用本文所述缓释材料及采用各自技术工艺制备而成:选择“2.1”项下材料不同配比,用乙醇或其它有机溶剂混合配制制成湿粒或干燥成干粒压制成片,这类通称为缓释片,其通常在 2h~12h 缓慢释放主药^[4];应用“2.1”项下材料制成缓释片芯,外面包裹一层半透膜,经激光打孔,使其在人体胃肠道内,通过渗透泵定量恒速释放药物,可以在 3h~12h 使血药浓度维持在有效(5ng/ml)水平,

这类称渗透泵控释片^[5];主药与混合粉末(如乳糖或氯化钠等)直接压片,滚转包衣锅内分别包溶胀层(HPMC 等)和控释衣层(如丙烯酸树脂等),形成双层包衣脉冲片,以脉冲形式释放,释药时滞可达 10h~12h,这类称为脉冲控释片^[6];将主药与乳糖、DST 混和,用聚维酮(PVP)5%水溶液制粒压成片芯,其外再用 HPMC、EC、MCC 缓释材料制成的干颗粒干压包成双层片,这类称为延迟释药片^[3],按《中国药典》要求测定其体外释放度,其在 5h 后才明显释放沙丁胺醇,以达到口服后延迟 5h 释药。

本制剂是应用缓释片技术和成熟的包肠溶衣技术制成的硫酸沙丁胺醇延迟释药片。其在胃液中不崩解,进入肠液(pH>6.8)后崩解,以缓释片的方式释放主药,应用并增加了水溶性的乳糖,使缓释片芯较快溶出,其释药高峰在 5h~7h,能延迟 5h 定时释药。

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使用硫酸阿托品滴眼液防治青少年近视是国内、外预防近视眼的有效方法之一。由于1%硫酸阿托品散瞳作用强,一般患者不愿长时间使用。为此,我院配制了浓度为0.04%的微量硫酸阿托品滴眼液,其临床应用多年效果显著^[1]。现将其制备及质量控制方法介绍如下。

1 材料

LC-10AT 高效液相色谱仪,包括SPD-10A检测器、CLASS-VP6.12 SP1 色谱数据系统、UV-2401PC 分光光度计(日本岛津公司);BP211D 电子分析天平(北京赛多利斯公司)。

硫酸阿托品对照品(中国药品生物制品检定所,批号:715-20001);硫酸阿托品(杭州民生制药厂,批号:040611);乙腈为色谱纯,水为注射用水,其余试剂均为分析纯。

2 处方与制备

2.1 处方

硫酸阿托品 0.4 g,氯化钠 9.0g,羟苯乙酯 0.3g,注射用水加至 1 000ml。

2.2 制备

称取羟苯乙酯,溶于 900ml 热注射用水中,加氯化钠搅拌使之溶解,放冷,加入硫酸阿托品,搅拌溶解后,过滤,自滤器上加注射用水使之成 1 000ml,搅匀,100℃流通蒸汽灭菌 30 min,无菌分装,即得。

3 质量控制

3.1 性状

本品为无色澄明液体。

3.2 鉴别

取阿托品适量(约相当于硫酸阿托品 5mg),置于水浴上蒸干,残渣显托烷生物碱类的鉴别反应(2000 年版《中国药典》二部附录Ⅲ)^[2]。

本品显硫酸盐的鉴别反应^[2]。

3.3 检查

本品 pH 值应为 4.0~6.0。其它应符合 2000 年版《中国药典》二部附录Ⅱ“滴眼液”项下的有关规定^[2]。

3.4 含量测定

3.4.1 色谱条件。色谱柱:Diamondsil C₁₈(250 mm×4.6mm, 5μm);流动相:乙腈-水(含 0.1%三乙胺,用磷酸调 pH=5.8)(55:45);流速:1.0ml/min;柱温:30℃;检测波长:210nm;进样量:20μl。

3.4.2 空白试验。按处方制备不含硫酸阿托品的空白滴眼液,直接进样 20μl,记录色谱;另取样品液及对照品液,直接进样 20μl,记录色谱,均详见图 1。

由图 1 可见,在此色谱条件下,辅料对测定无干扰。

3.4.3 标准曲线的绘制。精密称取于 120℃干燥至恒重的硫酸阿托品对照品适量,加水制成含硫酸阿托品浓度为 0.5mg/ml 的对照品贮备液。分别精密量取硫酸阿托品对照品贮备液 1、2、3、4、5、6ml,置于 50ml 容量瓶中,加水稀释定容至刻度,摇匀,各取 20μl 注入高效液相色谱仪,记录色谱。以峰面积(A)对其浓度(C)进行线性回归,得回归方程 $A = 14\,334 + 33\,928C$ ($r = 0.9999$)。结果,硫酸阿托品检测浓度在 10~60μg/ml 范围内线性关系良好。

3.4.4 精密性及稳定性试验。精密量取硫酸阿托品对照品贮备液各 2ml,置于 25ml 容量瓶中,用水稀释定容,摇匀,连续进

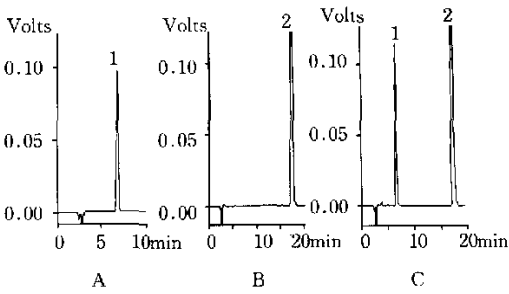


图 1 高效液相色谱

A. 对照品;B. 空白样品;C. 样品;1. 硫酸阿托品;2. 羟苯乙酯

Fig 1 HPLC

a. reference substance; b. blank sample; c. sample; 1. atropine sulfate; 2. ethylparaben

样 5 次,结果 RSD=0.86%。室温放置,于不同时间(12h 内)进样,分别记录峰面积,RSD=0.81%。结果表明,溶液在 12h 内基本稳定。

3.4.5 重现性试验。取同一批样品,按“3.4.1”项下色谱条件连续进样 6 次,分别记录峰面积,结果 RSD=0.85%。

3.4.6 回收率试验。分别取对照品约 24、20、16mg,准确称定,按处方比例加入配好的羟苯乙酯氯化钠溶液,配制成高、中、低(120%、100%、80%)系列浓度模拟样品溶液。各取 20μl 3 份进样,测定含量,计算回收率,结果详见表 1。

表 1 回收率试验结果(n=9)

Tab 1 The results of recovery tests(n=9)

序号	加入量(mg)	测得量(mg)	回收率(%)	平均回收率(%)	RSD(%)
1	16.4	16.25	99.1	100.2	0.95
2	16.4	16.66	101.6		
3	16.4	16.49	100.6		
4	19.6	19.65	100.3		
5	19.6	19.82	101.1		
6	19.6	19.45	99.3		
7	24.2	24.42	100.9		
8	24.2	24.33	100.5		
9	24.2	23.93	98.9		

3.4.7 样品含量测定。准确称取硫酸阿托品对照品适量,加水溶解并稀释成浓度为 40μg/ml 的溶液作为对照品溶液。取对照品溶液和供试品溶液各 20μl,注入高效液相色谱仪,记录色谱,按外标法以峰面积计算,并将结果与系数 1.0 266 相乘。3 批样品标示量分别为 98.5%、103.4%、100.2%。

4 讨论

硫酸阿托品的含量测定方法有中和法^[2]、提取比色法^[3]及紫外分光光度法^[4,5]。由于本品中硫酸阿托品含量太低,故不能采用中和法和提取比色法进行测定,且由于羟苯乙酯的干扰,也不能用紫外分光光度法直接进行测定。笔者经多次试验,最后采用高效液相色谱法,可不经分离直接测定硫酸阿托品的含量,且羟苯乙酯不干扰主药的含量测定(保留时间为 17.5min)。

由于硫酸阿托品对照品需在 120℃干燥至恒重,全部转化为无水物后才是单一成分^[3],而滴眼液含量是以水合物来标示,故在结果计算时需乘上系数 1.0 266。

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3 种抗组胺药治疗慢性特发性荨麻疹的最小成本分析

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摘 要 目的: 评价 3 种抗组胺药治疗慢性特发性荨麻疹的疗效和经济学效果。方法: 96 例慢性特发性荨麻疹患者随机分成 A、B、C 3 组, 分别给予咪唑斯汀、西替利嗪、氯雷他定治疗 28d, 观察疗效及停药 7d 内的复发率, 并运用最小成本分析法进行研究。结果: A、B、C 组的有效率分别为 96.7%、94.1%、93.8%, 停药 7d 内的复发率分别为 40.0%、35.3%、28.1%, 药品成本分别为 116.76 元、45.64 元、128.80 元。结论: 西替利嗪为最佳治疗方案。

关键词 慢性特发性荨麻疹; 咪唑斯汀; 西替利嗪; 氯雷他定; 最小成本分析

Cost - minimization Analysis on 3 Varieties of Antihistamines for Chronic Idiopathic Urticaria

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ABSTRACT OBJECTIVE: To evaluate the therapeutic efficacy and pharmacoeconomic results of 3 varieties antihistamines in the treatment of chronic idiopathic urticaria. METHODS: 96 patients with idiopathic urticaria were randomly divided into Group A, B and C, treated with mizolastine, cetirizine and loratadine for 28 days, respectively. The therapeutic effects and recurrence within 7 days after drug withdrawal were observed, and the results were analyzed using cost - minimization analysis. RESULTS: The effective rates in Group A, B, and C were 96.7%, 94.1% and 93.8%, respectively. The recurrent rates within 7 days after discontinuation of the treatment were 40.0%, 35.3% and 28.1%, respectively. The cost of drugs were 116.76 yuan, 45.64 yuan and 128.8 yuan, respectively. CONCLUSION: Cetirizine is the preferable treatment prescription for idiopathic urticaria

KEY WORDS Chronic idiopathic urticaria; Mizolastine; Cetirizine; Loratadine; Cost - minimization analysis

慢性荨麻疹是一种病因不明、病程长、治疗困难的皮肤病, 其中慢性特发性荨麻疹 (CIU) 是一种严重影响患者生活质量的类型。在美国和欧洲, CIU 患病率为 0.1%~3%, 40% 以上患者超过 6mo 仍有风团, 更有长达 10y 者^[1]。研究表明, 很大比例的 CIU 患者系自身免疫所致^[2]。咪唑斯汀、西替利嗪、氯雷他定是新型第 2 代 H₁ 受体拮抗药, 具有起效迅速、抗组胺作用强、持续时间长, 能有效阻滞变态反应炎症递质生成的特点, 被视为治疗 CIU 的一线药物。笔者对以上 3 种抗组胺药治疗 CIU 方案进行药物经济学分析, 以期临床合理用药提供参考。

1 资料与方法

1.1 病例选择

96 例患者均为我院皮肤科诊断的 CIU 患者, 根据预先采用 SAS 统计软件包随机产生的用药编号分组, 其中 A 组 30 例, 男性 18 例, 女性 12 例, 年龄 18a~72a, 病程 (20.98±

37.50)mo; B 组 34 例, 男性 20 例, 女性 14 例, 年龄 15a~58a, 病程 (25.15±9.54)mo; C 组 32 例, 男性 20 例, 女性 12 例, 年龄 15a~62a, 病程 (27.46±11.29)mo。3 组年龄、性别、病程等均无显著性差异, 具有可比性。

1.2 治疗方案

A、B、C 组分别给予咪唑斯汀 (Mizolastine, 皿治林, 西安杨森制药有限公司)、西替利嗪 (Cetirizine, 苏州东瑞制药厂)、氯雷他定 (Loratadine, 开瑞坦, 上海先灵葆雅制药有限公司), 每次 10mg, 1 次/d, 每组定时服药, 连续服用 28d。受试者至少 1mo 内未服用长效皮质类固醇及抗组胺药, 试验期间不使用大环内酯类抗生素、抗真菌药及皮质类固醇等药。

1.3 疗效评估

按 4 级评分法 (0 分~3 分) 记录受试者治疗前和治疗后瘙痒、风团大小和数量的症状总积分。瘙痒采用 10mm 视觉模拟标尺法 (Visual analogue scale, VAS) 评分: 0 分为无痒感,

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