特非那定片溶出度测定

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摘要：目的　评价市场上 6 个批号的特非那定片的质量。**方法**　采用桨法作为溶出度测定法，HPLC 作为特非那定浓度测定方法，再通过 weibull's 方程获得溶出度参数。**结果**　仅有 2 个批号的特非那定片达到卫生部部颁标准。**结论**　我们应该关注市场上特非那定片的质量。

关键词：特非那定；溶出度；高效液相色谱法

1　Introduction

Terfenadine，a highly selective for H1 receptors，is an antihistamine with little central sedative activity or antimuscarinic activity. It is used to relieve the symptoms of hypersensitivities reactions including urticaria and angioedema、rhinits，and conjunctivitis. Terfenadine is also used to control the pruritus associated with skin disorders such as atopic eczema. There are many factories which product terfenadine in our country，and their clinical effect are not concordence. We determined dissolution of six batch terfenadine tablets in five different factories，in order to evaluate the internal quality of these terfenadine tablets.

2　Experimental

2.1　Materials

Six batch tablets of terfenadine（A1-E）commercially available in China were studied. The tablets contained 60mg of terfenadine. Monopotassium phosphate 、phosphoric acid 、diethylamine、hydrochloric acid and acetic acid glacial were analytical grade . Acetonitrile was HPLC grade and distilled water was further purified.

2.2　Instruments

A ZRS-6 intelligent dissolution tester（Tinjin University radio factory）and A Waters515 liquid chromatograph were used. Analytical separations were carried out on mBondpark C-18 ODS（10mm，300 × 3.9 mm i. d. ）column using a injection valve with a 20mL injection volume.

2.3　Methods

2.3.1　Chromatographic conditions

The samples were eluted with a mixture of Acetonitrile-water-1.0 mol/L phosphate buffer- diethylamine（500:400:100:6）at a constant flow rate of 1.5 mL/min. phosphate buffer was prepared by Monopotassium phosphate 136.1g，phosphoric acid 3.2mL，added water to 1000mL. The mobile phase was filtered under vacuum，through a 0.45 mm membrane filter，and degrassed before use. The column effluent was monitored at 235nm.

2.3.2　Calibration graghs

The stock standard solution of terfenadine was prepaed by dissolving 100 mg terfenadine and 5 mL acetic acid glacial in 0.1mol/L hydrochloric acid（1000 mL）. Working standard solutions of terfenadine（5 ~ 70 mg/L ）were prepared by dilution of the stock standard solutions with 0.1mol/L hydrochloric acid.

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Seven samples (20mL) of each of these solutions were injected into the HPLC column. Calibration graphs were plotted according to the linear regression analysis of the ratios between the peak area of the analytes (A) and that of the standard concentration (C).

2.3.3 Precision and recovery

Dispensing there standard solution in different concentration. These samples(20mL) of each of these solutions were injected into the HPLC column under same Chromatographic conditions. The average recovery 、RSD of inter-day and intra-day were determined according to the linear regression equiation.

2.3.4 Dissolution tests

The release rates of terfenatine were determined according to the rotating paddle method using 900 mL of dissolution medium. Testing were performed using 0.1 mol/L hydrochloric acid. The experiments were carried out at 37 ±0.5℃ at a rotation speed of 50 rpm. At specific times, samples (5mL) of the dissolution medium were removed using a filter syringe, while reintegrating the dissolution medium volume. Quantitative determination was carried out by injecting 20 mL of the samples.

2.3.5 Disintegration time

The disintegration time was determined on six tablets per samples, at 37℃ using distilled water according to the Chinese Pharmacopoeia.

2.3.6 Uniformity of weight

Uniformity of weight was determined on 20 tablets per samples, according to the Chinese Pharmacopoeia.

3 Results and discussion

Disintegration studies in water and weight uniformity tests showed that all tablets met the Pharmacopoeia requirements.

The calibration curves of terfenadine gave excellent linearity showing a correlation coefficient of 0.9997 in the range of injected drug (5 ~ 70 mg/L) with an equation of linear regression curve $C = 1910 + 1.714 \times 10^{-4} A$.

Tab. 1 shows the average recovery is 98.57%, RSD of inter-day and intra-day were 1.63% and 2.45% respectively (n = 6).

Tab 1 Results of precision and recovery(n = 6)

Concentration(mg·mL^{-1})	Recovery(%)	RSD(%)	
		Inter-day	Intra-day
5	97.10	2.31	4.09
20	98.55	1.85	2.38
50	100.06	0.72	0.88

Using this method, terfenadine release from the 6 commerical products were studied. Fig. 1 shows dissolution profiles and Tab. 2 shows the dissolution parameters.

Tab 2 The accumulative release percentage of four tablets(n = 6)

Time/min	Product (%)					
	A1(961003)	A2(950501)	B(950912)	C(9702182)	D(970102)	E(960901)
3	4.96 ±0.80	4.73 ±0.28	5.07 ±0.30	5.48 ±0.33	39.11 ±2.55	3.62 ±0.26
6	19.02 ±1.35	5.76 ±0.68	7.48 ±0.24	11.47 ±1.35	66.48 ±1.64	4.68 ±0.22
10	35.36 ±2.11	6.90 ±0.07	11.98 ±0.11	21.55 ±1.30	83.62 ±0.32	5.74 ±0.06
20	52.44 ±2.27	7.36 ±0.46	18.61 ±1.03	34.57 ±2.14	93.09 ±1.35	7.45 ±0.04
30	65.00 ±3.26	9.71 ±0.49	22.92 ±1.37	40.96 ±2.05	94.45 ±2.26	9.09 ±0.10
45	75.16 ±5.569	10.14 ±0.75	28.78 ±1.21	48.11 ±2.15	97.29 ±2.08	12.31 ±0.67
60	91.52 ±5.46	11.03 ±0.66	32.65 ±0.99	53.25 ±2.19	98.25 ±1.04	12.97 ±0.15

Note: The experiment were fulfilled in the February, 1997

Tab. 3 shows the main parameters of diffusion:

Tab 3 The main parameters of diffusion of six tablets(min)

T50	18.88	23879	163.5	46.57	1.02	2129.8
Td	30.54	83008	326.0	82.91	2.32	4769.3
m	0.761	0.294	0.531	0.635	0.445	0.454

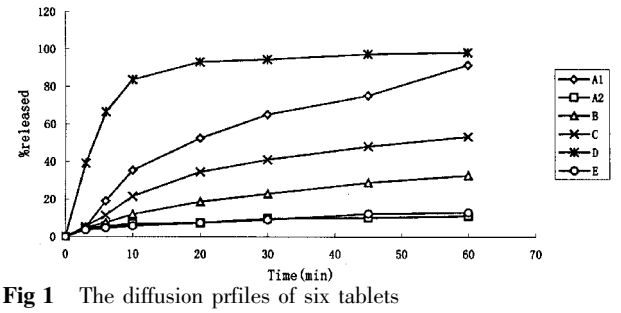

Fig 1 The diffusion prfiles of six tablets

As it can be seen the release rate from the six commercial products were very different. After 20 min from the beginning of the test, Product D had released 93.09% of the drug. Nevertheless, after 60 min, product A2 and E had only released no more than 15% of the drug.. In tab.2 . product A1 and A2 are producted by the same factory . but we can find that the release rate of theses two products are significance different . Maybe the factory change the methods of product or use the different accessories.

According to criterion of Ministry of public health, the accumulative dissolution rate of 45 min should be more than 70%. But we can find only two of six commercial terfenadine tablets are met the criterion of Ministry of public health. We should pay more attention to the quality of the commercial terfenadine tablets.

4 Conclusions

The in vitro dissolution rate of a drug from a dosage form is

very important for the curative effect and for bioequvalence stuies. The different pharmacopoeias in fact request dissolution tests. In particular, terfenadine tablets meet criterion of Ministry of public health only if not less than 70% of the labeled amount of the drug has dissolved in 45 min using 900mL of 0.1 mol/L HCl as a dissolution medium. According to the results obtained in this study, we can conclude that only two batch commercial products met the requirements. We should pay more attention to the quality of terfenadine tablets.

参考文献

[1] 中国药典(二部)2000 版.

[2] 中华人民共和国卫生部。卫生部国家标准(新药试行标准转正式标准)WS1-(X-160)-97Z.

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