Study on HPMC Matrix Tablets of Buflomedil Hydrochloride

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ABSTRACT OBJECTIVE: To study the hydroxypropyl methylcellulose (HPMC) matrix tablets of Bufiomedil Hydrochloride (BH) . **METHOD:** The tablets were prepared by the method of wet granule . The effects of the amount , viscosity of HPMC and species of bonding agents on the BH release rate were investigated with orthogonal design . **RESULTS:** The BH release behavior followed Higuchi equation and the amount of HPMC and species of bonding agent could significantly affect the BH release rate from matrix tablets . **CONCLUSION:** The HPMC matrix tablets of BH had a well sustained release .

KEY WORDS Bufiomedil Hydrochloride , orthogonal design , matrix tablet , Hydroxypropyl methylcellulose

盐酸丁咯地尔羟丙基甲基纤维素骨架片的实验研究

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摘要　目的:研制盐酸丁咯地尔 HPMC 缓释骨架片。方法:湿颗粒法压片,正交实验设计考察 HPMC 的用量、粘度及粘和剂对药物体外释放速率的影响。结果:盐酸丁咯地尔骨架片的体外释放行为符合 Higuchi 方程;粘和剂种类和 HPMC 的用量对制剂的释药速率有显著性影响。结论:盐酸丁咯地尔 HPMC 骨架片有良好的缓释性。

关键词　盐酸丁咯地尔;骨架片;正交实验设计;羟丙基甲基纤维素

Introduction

Buflomedil Hydrochloride (BH) is a kind of angiectatic medicine which can improve the blood Supply of ischemic tissues and inhibit the clotting of platelets. It is used in the treatment of peripheral vascular and cerebrovascular diseases and has good effects on cerebrothrombosis and dementia of the old[1]. The half-life of BH *in vivo* is about 2 to 3 hours, so it has a short period of action by taking the common tablets. The drug concentration in blood varies obviously as well. In order to reduce the frequency of taking the drug and the variation of its concentration in blood and make it have a long time of action, we prepared BH matrix tablets with HPMC and studied the factors affecting drug release in this study.

Materials

Medicine and reagents BH control (Qi Lu Pharmaceutical factory); HPMC (K4M, K15M, K100M, supplied by Fei Cheng Rui Tai define Chemical Engineering Ltd); Eudragit III (Jiangsu Lianyungang Iodine Manufactory); ethylcellulose (Shanghai Chemical Reagent Supplying Company).

Instruments U-2000 ultraviolet spectrophotometer (Japan); ZRS-4 Intelligent Dissolution Tester (Tianjing University Radio factory); TA-stamping press (Shandong medical Instrument factory).

Methods and results

Preparation of BH matrix tablets Appropriate amount of BH and HPMC were sift through a sieve with the pore diameter of 172μm and mixed thoroughly. Bonding agent was added and mixed and the mixture were passed through a sieve with the Dore diameter of 950μm to make soft materials and put into an oven at 60℃ to get it dried. The dry materials were sift through a sieve with the pore diameter of 950μm and about 1% of stearate sodium was added before stamping. They were mixed fully and then stamped into tablets.

Content determination of BH in matrix tablets 20 BH matrix tablets were triturated with a mortar. Appropriate amount of powder (about 10mg) was accurately weighed out and put into a 100ml volumetric flask. After 80ml of distilled water was added, the flask was shaken thoroughly to solve the drug. And then water was added to the mark. The solution was filtered with a micropore filter of 0.22μm. 10ml of the filtrate was taken out accurately, put into a 50ml volumetric flask and distilled water was added to the mark. After being shaken extensively, the absorbance was determined by UV spectrometer at 282nm and the content was calculated.

Release rate determination of BH from matrix tablets *in vitro* Release rate was determined according to the method in China Pharmacopoeia of 2000 Year Eddition. 1000ml of distilled water was used as dissolution medium. The revolve rate was 100 r/min, and the medium temperature was (37±0.5)℃. Each time 6 tablets were determined. 5ml of medium was taken out every 1 hour (at the same time the same amount of distilled water with the same temperature was added) and filtered by a 0.22 μm micropore filter. 2ml of the filtrate was taken out accurately, put into a 25ml volumetric flask and distilled water was added to the mark. The absorbance at 282nm was measured and cumulative release percentage was calculated.

Establishment of standard curve About 10mg of BH contrast was weighed accurately out accurately and put into a 100ml volumetric flask. After distilled water was added to the mark, it was shaken extensively. 1.0, 1.5, 2.0, 2.5, 3.0, 3.5ml of the solution were taken out accurately, put into 10ml volumetric flasks respectively and distilled water was added to the marks. The absorbance at 282nm were measured respectively (BH water solution was scanned at the wavelength from 200 to 400nm and it showed the maximum absorbance at 282nm as showed in Figure 1). The absorbance (A) and the corresponding concentration C regress equation was established as follows: $C = 60.205A - 0.1175$, $r = 0.9999$

Determination of recovery 80%, 100%, 120% of the amount of the main medicine in BH matrix tablets were weighed out accurately and other adjuncts were added and then mixed evenly. Appropriate amount of the mixture (about 10 mg BH) was

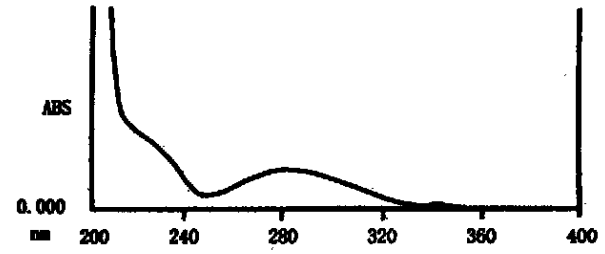

Fig 1. The ultraviolet spectrum of BH water solution.

weighed out accurately, put into a 100 ml volumetric flask and 80 ml of distilled water was added. After it was dissolved, distilled water was added to the mark and then the solution was filtered by a 0.22μm micropore filter. 10 ml of the filtrate was taken out accurately and diluted in a 50 mi volumetric flask. The absorbance at 282nm was measured and the average recovery was calculated to be 101.5%.

Orthogonal design and evaluating formulas According to preliminary experiment, three factors on three levels (see Table 1) were investigated by orthogonal design to prepare BH matrix tablets in the way stated above. The drug release experiments in vitro were studied and formulas were evaluated. The result was showed in Table 2.

Table 1 Experiment factors and levels.

Viscosity of HPMC (cPa□s)(A)	amount of HPMC (mg/tablet)(B)	bonding agent (C)
400	200	Ⅲ
15000	100	ethyl cellulose
100000	50	alcohol

Table 2 Analysis of orthogonal experiment result.

Formula	Factors			cumulative drug release percentage (%)		
	A	*B*	*C*	*F*1	*F*8	*Y* = *F*1 + *F*8
1	1	1	1	47.5	89.9	137.4
2	1	2	2	41.3	91.2	132.5
3	1	3	3	46.6	94.6	141.2
4	2	1	2	33.6	85.4	119.0
5	2	2	3	42.7	90.9	133.6
6	2	3	1	67.8	92.0	159.7
7	3	1	3	34.2	85.6	119.7
8	3	2	1	74.3	89.3	163.6
9	3	3	2	44.7	86.7	131.4
Xl	137.0	*I*25.4	153.6			
*X*2	137.5	143.2	127.6			
*X*3	138.2	144.1	131.5			
K	1.2	18.8	26.0			

F1 and F8 were the cumulative release percentages at the 1st and 8th hour respectively. Xl, X2 and X3 were the average overall release percentages of three experiments under every factors respectively. The result indicated that among the three factors in this experiment bonding agent had the maximum effect and HPMC viscosity had the minimum effect. As indicated in table2, Al Bl C2 was the best formula. The result of drug release in vitro was showed in Figure2. We could conclude from Figure2 that the drug release behavior *in vitro* followed Higuchi equation: $Qt = 3.6367 + 29.4930t^{1/2}$; r = 0.9955(Qt was cumulative drug release percentage).

Discussion

The sustained time of oral prolong formulation in gastrointestinal tract is about 9 to 12 hours, in stomach for 2 hours and in intestine for about 4 to 6 hours. According to USP the release percentage of the oral prolong formulation designed to be taken once a day should be as following: releasing 10%-32% in the first hour, 20 ~ 50% in two hours, 35% ~ 80% in four hours, and over 80% in 12 hours. In the release determination, prolong formulation samples were usually extracted three times. The first sample was tested to determine the sustained release of the formulation and see whether the drug would have a sudden release in a short time to ensure the security of the formulation. And it was extracted between 1 and 1.5 hours. The second sample extracted between 4 and 6 hours was to assay the release behavior and see whether the release was stable. The last sample extracted between 8 and 10 hours was to assay whether the drug had been released entirely[2].

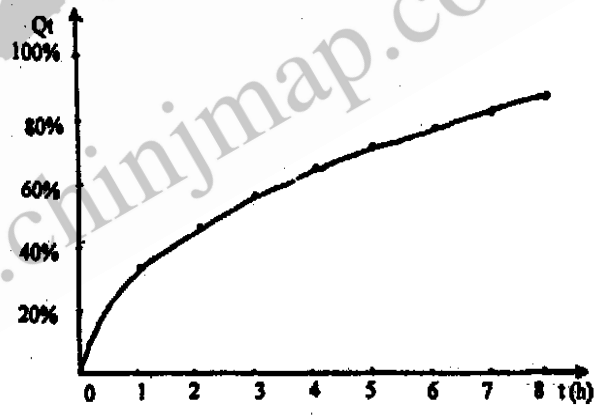

Fig 2. drag release curve in vitro from matrix tablets

The result of the test was that the release percentage in the first hour was irregular and the release percentage between 4 and 8 hours followed above request. So the cumulative release percentages at 1st and 8th hour were used to evaluate the drug release percentages and the release limit was that release percentage in 1 hour was about 30% and in 8 hours was over 80%.

The result of the experiment indicated that bonding agents affected the release rate most significantly and the effect sequence was that: ethyl cellulose > alcohol > Eudragit Ⅲ. Because ethyl cellulose had stronger viscosity, the granules made of it were firm and had good sustained release.

The release of BH in matrix tablets decreased with the increasing of the amount of HPMC. The amount of HPMC had significant difference in changing release rate. The reason was

that the more it was used, the thicker the gel layer was. So the release and dissolution of the matrix tablets slowed down[3,4].

The release rate of 3 kinds of matrix tablets made of HPMC with different viscosity had no significant difference, which indicated that in this experiment viscosity of HPMC had little effect on the release of hydrosoluble BH and this was consistant with the reported result[5].

Reference

1 Xu Wen-Fang. Clinic and pharmacology of buflomedil hydrochloride[J]. Foreign Medical Science-Synthetic medicine, Biochemical medicine and Formulation, 1995, 16(1): 29

2 Ping Qi-Neng. Modern Pharmaceutics[M]. Beijing: Chinese medical science and technology publisher, 1998: 277.

3 Zeng Huan-Xiang, Pan Wei-San. Preparation and release of sustained-release famotidine tablet[J]. Chinese Pharmaceutical Journal, 1997, 32(4): 213

4 Dong Zhi-Chao, Jiang Xue-Tao. Effect of Physico-chemical Properties of Hydroxypropylmethylcellulose on Dissolution from Hydrophilic Matrix Tablets[J]. Acta Pharmaceutical Sinica, 1994, 29(12): 920

5 GuoJiexu, Hisakazu Sundad. Influence of formulation change on drug release kinetics from Hydroxypropylmethylcellulose[J]. Chem Pharm Bull, 1995, 43(3): 483

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