Real-time Monitoring Method for Carbon Dioxide and Residual Oxygen in Medical Package

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Abstract: Objective inert gas in vial is commonly used form of packaging which to prevent the drug deterioration. Oxygen and carbon dioxide were remained in vial bottle is an important factor for medicine quality which be strengthened monitoring. Methods The residue amount of carbon dioxide and oxygen were tested in different kinds of vials, respectively. The test method of gas content in pharmaceutical packaging was introduced, and the results were compared and analyzed. Results The results of experiment show that 1# gas contents in sample is consistent with air, 2# and 3# samples are nitrogen-filled packaging, and oxygen and carbon dioxide content in 3# sample changed little after a month. Therefore, 3# sample has the best preservation effect. Conclusion The method with high test efficiency, can quickly and effectively reflect the gas component in samples. According to the changes of gas component along with time in the packaging, preservation effect of 3# sample is the best one in three kinds medicine samples.

1 INTRODUCTION

Most pharmaceutical products are sensitive to oxygen and are easy to be oxidized causing deterioration, discoloration, peculiar smell and the like, which not only affects the curative effect of the products, but also causes toxic and harmful substances generated by oxidation to even endanger life, and drugs containing hydroxide, calcium salt and other components are easy to absorb carbon dioxide to generate carbonate (Zhou, Mei 2011, Ma 2011, Zhou 2008). In order to reduce the amount of oxygen and carbon dioxide contacted by drugs, oxygen and carbon dioxide sensitive drugs are usually packaged in the form of vacuum pumping, inert gas (generally nitrogen) filling and the like.

As common medical packaging, vials are mainly divided into soda-lime glass, borosilicate glass, neutral borosilicate glass, plastic and other material types, which can be used for packaging powder injection, vaccine, lyophilized agent, biological preparation and other drugs, most of which adopt nitrogen-filled packaging form, and are sealed with rubber, metal and plastic combined cover (Huang, Zhu, Chen 2013, WANG, ZHAO 2007). Due to the limitation of inflation equipment and process, the contents of nitrogen, oxygen and carbon dioxide in the finished package of vials may be different from expectations. In addition, under the influence of packaging barrier and sealing (Fan 2014), the gases inside and outside the package may exchange slowly, resulting in the changes of the contents of the above gases with the extension of storage time. Therefore, the timely detection and dynamic monitoring of the gas composition in the nitrogen-filled vials have certain guiding role in preventing the deterioration of drugs and determining the appropriate shelf life.

At present, many enterprises only rely on using barrier packaging materials to hinder gas infiltration /exudation of packaging materials, and cannot eliminate the existing oxygen and other gases in the

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packaging, and also lack real-time monitoring of the internal gas composition. Instead, the monitoring of the gas composition in the packaging should cover any circulation link of the product, including just completed packaging, storage process, transportation process, sales process, expiration of the shelf life and so on. The actual test results will also be used as strong evidence for judging the quality of the goods. (FAN 2012, WU, LIANG 2011) At present, GB/T 6285-2003 Determination of Trace Oxygen in Gases—Electrochemical Method (Fan 2014) is the standard for the test of oxygen content in gas, and no method standard for the test of gas composition content in packaging has been issued. In this paper, according to the general testing methods and testing experience in the industry, the oxygen and carbon dioxide contents in several different packaging forms of vials were tracked and tested.

2 TEST PRINCIPLE

Insert the sampler into the inside of the package to be tested and collect enough sample gas from the top of the package. The sample gas is introduced into the gas analysis sensor, and the test data are recorded after a certain test time interval or the gas concentration output value of the gas analysis sensor is stable.

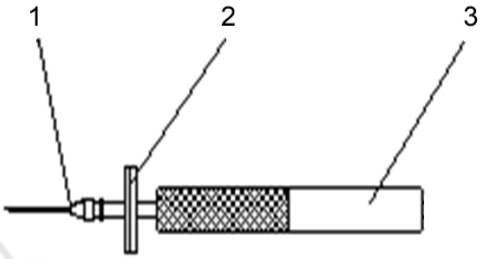
The corresponding gas analysis sensors are needed for the test of different gas contents. When testing the oxygen content in the sample gas, the sample gas needs to be introduced into the oxygen analysis sensor; when testing the carbon dioxide content in the sample gas, the sample gas needs to be introduced into the carbon dioxide analysis sensor. For known packages filled with high purity nitrogen inside, the nitrogen content in the packaging can be obtained by subtracting oxygen content, carbon dioxide content and other known gas content from the total gas content.

3 DETECTION EQUIPMENT AND METHOD

3.1 Test Instruments and Samples

3.1.1 Instruments and Their Performance

The test equipment used in this test is HGA-02 Headspace Gas Analyzer independently developed and produced by Jinan Labthink Electromechanical Technology Co., Ltd., which meets the requirements of GB/T 6285 and is equipped with high-precision oxygen and carbon dioxide sensors, a sliding test head capable of testing samples at any height and a high precision sampling device capable of absorbing small volume gases (Fig.1), and is suitable for rapid and accurate detection and analysis of the content and mixing ratio of oxygen and carbon dioxide in flexible plastic packaging bags and containers in production sites, warehouses, laboratories and other occasions. When the oxygen content is 0~2%, the test accuracy is ±0.3% (absolute value), and ±0.5% (relative value) when the oxygen content is 2~100%; the test range of carbon dioxide is 0~100%, and the test accuracy is ±0.5%.



1. Sampling needle, 2. Filter, 3. Handle

Figure 1: Diagram of the Structure of High Precision Sampling Device.

3.1.2 Samples

In this test, three kinds of vial powder injection samples were used, numbered 1#, 2# and 3# respectively, one of which was in ordinary air packaging, and the other two were in nitrogen-filled packaging. The number of samples for each kind of sample should be sufficient to complete the entire test, at least five, and take the average test as the test result. The samples should be placed in the dryer for more than 48 h under the sample condition adjustment and standard environment specified in GB / T 2918.

3.2 Test Method

(1) Determine the appropriate test parameters according to different equipments before verification. The main factors affecting the stability and reliability of the test results are sample gas extraction and sample gas flow through the sensor. When the sample gas extraction speed and the sample gas flow rate in the instrument are constant, the sample gas extraction and the sample gas flow through the sensor are related to the sample gas extraction time and the sample gas analysis time respectively. Therefore, it is necessary to determine the optimal sample gas extraction time

and sample gas analysis time to prevent its impact on the test results. Set the sampling time, analysis time and other test parameters on the control panel of Headspace Gas Analyzer, and the sampling time and analysis time of this test are set to 12 s.

(2) Place the finished packing sample of vial in the gas collection device, carefully remove the stopper of the vial, and the gas in the bottle will be collected in the gas collection device. Stably place the sample, then insert the sampling needle into the inside of the package through the middle part of the sealing gasket. The puncturing force shall be appropriate to prevent the sampling needle from sticking into the contents of the package, causing the needle to become blocked or broken.

(3) Carefully insert the sampling needle into the gas collection device (Fig.2). Click the test button to start the test. The sampling needle shall not be pulled out from the gas collection device. The sample gas to be tested in the sampler shall be introduced into the detection device through the sample injection port. The sample gas will enter the gas analysis sensor through the sample injection port and pipeline. The instrument collects the sample gas in the gas collection device and analyzes it. After the test, the test results, i.e. oxygen content and carbon dioxide gas content, are automatically displayed. Five specimens of each sample were tested in parallel.

1. Samples, 2. Sealing gasket

Figure 2: Schematic diagram of gas sampling with gas collection device.

4 RESULTS AND DISCUSSION

4.1 Gas Sampling Time

The analysis time of sample gas is fixed at 12 s. The optimum time of gas sampling time is determined by measuring the gas content in three kinds of samples with the sampling time changed in the range of 4s - 12s. The test results are shown in Table 1.

The data in Table 1 show that when the sampling time is 8 s - 12 s, the oxygen content test results of the three samples are stable and independent of the sampling time, with the maximum error <2% and standard deviation RSD <0.5%. Therefore, the sampling time of this equipment is fixed at 12 s to ensure that sufficient sample gas is drawn.

4.2 Gas Analysis Time

The gas sampling time is fixed at 12 s. The optimal analysis time of sample gas is obtained by testing the gas content in three kinds of samples with the gas analysis time varied within the time range of 8 s - 18 s. The test results are shown in Table 2.

The data in Table 2 show that when the analysis time of the three kinds of sample gases exceeds 11 s, the oxygen content test results are stable regardless of the change of analysis time, with maximum error <3% and standard deviation RSD <0.5%. In order to ensure the stability of the test results and reduce the test time, the preferred gas analysis time of this equipment is set to be 12 s.

4.3 Sample Testing and Analysis

In this test, the oxygen and carbon dioxide contents of the three samples before and after the interval of 1 month are tested respectively. The test results are shown in Table 3.

Table 1: Gas Content Analysis Results for Different Gas Sampling Times

Sampling time (s)	Sample	4	5	6	7	8	9	10	11	12
Oxygen content (%)	1#	19.31	19.57	21.17	20.49	20.36	20.47	20.35	20.38	20.41
	2#	1.83	1.96	1.81	1.92	2.09	2.11	2.09	2.10	2.12
	3#	0.85	0.92	1.09	0.95	1.19	1.19	1.20	1.18	1.20
Carbon dioxide content (%)	1#	0.02	0.02	0.03	0.02	0.02	0.02	0.02	0.03	0.02
	2#	0.01	0.00	0.01	0.02	0.01	0.00	0.00	0.01	0.01
	3#	0.00	0.01	0.00	0.01	0.00	0.00	0.00	0.01	0.00

Table 2: Gas Content Analysis Results for Different Gas Analysis Times.

Sampling time (s)	Sample	8	9	10	11	12	13	14	15	16	17	18
Oxygen content (%)	1#	19.05	21.00	20.46	20.53	20.49	20.39	20.46	20.37	20.41	20.50	20.47
	2#	1.73	1.80	1.91	2.07	2.09	2.09	2.11	2.10	2.12	2.10	2.09
	3#	1.05	1.12	1.07	1.20	1.19	1.17	1.19	1.21	1.18	1.20	1.20
Carbon dioxide content (%)	1#	0.03	0.02	0.03	0.03	0.02	0.02	0.02	0.02	0.03	0.02	0.02
	2#	0.01	0.01	0.02	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00
	3#	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.00

Table 3: Test results of oxygen and carbon dioxide content in three samples.

Gas content/%		1# sample		2# sample		3# sample	
		Before 1 month	After 1 month	Before 1 month	After 1 month	Before 1 month	After 1 month
Oxygen content	1	20.31	20.76	2.16	16.31	1.26	2.99
	2	20.56	20.23	2.03	16.49	1.18	3.04
	3	19.70	20.31	2.07	16.08	1.20	3.09
	4	20.64	20.51	2.11	15.94	1.21	3.13
	5	20.11	20.57	2.17	16.18	1.17	3.06
	Average	20.26	20.48	2.11	16.20	1.20	3.06
	Standard deviation	0.38	0.21	0.059	0.21	0.035	0.052
Carbon dioxide content	1	0.03	0.02	0.01	0.01	0.00	0.00
	2	0.02	0.02	0.01	0.02	0.00	0.01
	3	0.03	0.03	0.00	0.02	0.00	0.01
	4	0.02	0.02	0.02	0.02	0.00	0.00
	5	0.02	0.02	0.00	0.01	0.00	0.00
	Average	0.02	0.02	0.01	0.02	0.00	0.004
	Standard deviation	0.0055	0.0045	0.0084	0.0055	0.00	0.0055

As can be seen from Table 1, the standard deviation of the 12 groups of data is low, indicating that the dispersion degree between the test data of each group is small, and the test method for testing the oxygen and carbon dioxide content in the package adopted in this paper has good stability and repeatability.

The detection data of the three samples before one month showed that the contents of oxygen and carbon dioxide in 1# sample bottle were high, which were basically the same as those in air, indicating that the gas in 1# sample was ordinary air. The contents of oxygen and carbon dioxide in 2#and 3# samples are obviously lower than those in 1# sample, which are nitrogen-filled packaging, and the contents of oxygen and carbon dioxide in 3# sample are the lowest. The difference of oxygen and carbon dioxide content in the nitrogen-filled packaging is related to the nitrogen filling process and the purity of the filled nitrogen. In order to ensure the quality guarantee effect of the nitrogen-filled packaging, the content of nitrogen in the package should be increased, and the contents of oxygen and carbon dioxide in contact with the medicine should be reduced. Therefore, the air in the package should be removed as far as possible before nitrogen filling, the volume of residual gas should be reduced, and the purity of the filled nitrogen should be ensured.

After a comprehensive analysis of the test data of the three samples before and after one month's interval, the oxygen and carbon dioxide contents in 1# sample did not change significantly; the content of both gases in the 2# sample increased after being placed for one month, and the oxygen content increased by about 7 times; the oxygen and carbon dioxide contents of 3# sample only increased slightly. This shows that among the three samples, 3# sample has good barrier property and sealing property, which can effectively prevent the gas exchange inside and outside the bottle; 2# sample has poor barrier property or sealing property, and the gas in the environment permeates into the sample at a high speed, while 1# sample is ordinary air, so it is impossible to infer the barrier property or sealing effect from the change of oxygen and carbon dioxide content. From the point of view of the preservation effect of the sample on the internal gas, if the same drug is packaged, the quality guarantee effect of 3#

sample on the packaged drug is better, and the quality guarantee period can be relatively prolonged.

5 CONCLUSIONS

The content of oxygen and carbon dioxide in packaging is an important factor affecting the quality of pharmaceuticals, and the residual oxygen is one of the basic requirements of GMP for inert gas packaging of sterile drugs. In this paper, the contents of oxygen and carbon dioxide in three kinds of vial powder injection samples were measured by Headspace Gas Analyzer, and the contents of residual oxygen and carbon dioxide in 3# sample were the lowest and the gas preservation effect was the best. From the test process, the test method used in this paper is simple, short-time, high-efficiency, and can quickly and effectively reflect the gas content in the samples, also reduce the number of defective products with unqualified internal gas composition in the production line, effectively control the proportion of oxygen and carbon dioxide in the gas-modulated packaging of drugs, promote the overall quality of domestic packaging products to pursue the goal of high standards and high quality, and accelerate the large-scale use of innovative and convenient modern test equipment in domestic drugs and other industries.

At present, the testing technology both at home and abroad have no uniform standard test methods, but the test principle, test structure, test indicators and other specific content has been initially formed. Due to the lack of standard support, versatility and data comparability are not high. Therefore, there is an urgent need for the development and publication of relevant standards in the industry, and only with testing standard specification can this method and quantitative indicators be effective in product standards.

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