

Injection Liquid Bag Barrier Test Requirements and Prospect

Abstract: the differential pressure method and equal pressure method are both necessary in the injection liquid bag test. As it is a burden to companies and institutions to buy two sets of equipments, Labthink introduced PERME-DM2/330 double methods gas permeation testing instrument, as a better option for medical packaging system and injection liquid bag manufacturers.

Key Words: injection liquid bags, transfusion use film, oxygen permeation rate, nitrogen permeation rate, soft plastic

Fluid containers include glass bottles, soft plastic injection bottle (PP or PE), soft plastic injection bags (PVC and non-PVC). The initial injection liquid was packaged by bottles. Although improvement has been made several times but it could not get rid of the common defects of glasses such as fragileness, poor sealing, crumb and secondary air pollution. Thus in 1960s plastic containers (plastic bottles and PVC injection bags) emerged. In the early 1990s non-PVC composite film injection bag was created. Today, in developed countries such as European countries and the United States, soft plastic containers account for about 96% of the total market. Despite the competition between soft plastic bottles and soft plastic bag, soft plastic packaging is a general trend. Although currently glass bottles still have a large market in China, the trend is soft plastic package.

1 Injection Liquid Bag Needs Material Barrier Tests

New soft plastic injection liquid package has many prominent advantages over traditional glass package, such as environment friendly, cost, sanitary security and convenience. But soft plastic injection bags also have disadvantages such as barrier property, sealing performance and transparency, among which barrier property is the most significant one. Oxygen is the main factor which causes the deterioration of injection liquid. If the oxygen barrier property of injection liquid package cannot perform well, it might cause the medicine to deteriorate before the guarantee date and the outcome is unimaginable. As a result, antioxidant, metal-chelator and inert gases are often employed in order to reduce the oxygen in the packages, postpone and prevent the liquid from oxygenation. Nitrogen is stable and often used with little carbon-dioxide as 'inert gases' to replace the air inside bags. If the barrier property against nitrogen is not strong enough, the nitrogen would permeate through bags. It might reduce the protection effect of inert gases and increase the oxygen in the package. Vapor permeation affects the concentration of medicines especially solute liquid for injection. Such situation will increase the difficulty of medicine concentration and vital risks. As the good barrier property of glass is well known, it can be considered that gases and vapor cannot permeate through glasses. Soft plastic does not have such barrier property thus it is necessary to test the barrier property of soft plastics.

2 Requirements for Barrier Property Test in Medical Packaging Standards

As glass has very excellent barrier property, there is no barrier property test requirement in YBB 00032005 'Na-Ca Injection Fluid Glass Bottle' and YBB 00022005-2 'Neutral Borosilicate Injection Fluid Glass Bottle'. Instead, the sealing performance of rubber plug and container became a focus (in plug standard). However, once the material is soft plastic the barrier property test is very necessary. For example, from 2002 the first version of soft plastic injection fluid bottle standard (YBB 00012002 'Low-density Polyethylene Injection Fluid Bottle' and YBB 00022002 'Polypropylene Injection Fluid Bottle'), it is required to test the vapor permeation rate and

standards are given. In the meantime, other oral liquid soft plastic bottle standards also required vapor permeation rate test. Oxygen and nitrogen barrier properties were not listed in standard tests because the soft plastic injection fluid bottle is too thick (approaching or exceeding the barrier property test instrument's available test thickness up limit, which causes significant error). At that time whole injection fluid bottle oxygen permeation rate test technology was not available. Thickness problem does not exist for injection fluid bags. Thus in 2005 injection fluid film and bag standard (YBB 00102005 'Triple-layer Co-extruded Injection Membrane (I), Bags' and YBB 00112005 'Five-layer Co-extruded Injection Membrane (I), Bag'), barrier property tests are not limited in vapor permeation rate of injection fluid bags. Injection fluid membranes' vapor, oxygen and nitrogen permeation tests are all required. Though the test technology for whole injection fluid bag oxygen permeation rate is ready but there is not national standard thus it is not mentioned in these standards.

3 The Influence of Nitrogen Permeation Rate Test

Injection fluid membrane nitrogen permeation rate test has always been noticeable. How to test the membrane? Currently only differential-pressure testing instrument can test the permeation property of many gases (He、N₂、Air、O₂、CO₂ and so on). If the user can put the gas source under control and deal with the end gas (sometimes flammable, explosive or toxic), the instrument could be used to test the permeation property of some special gases (pay special attention to safety issue). The test process is the same with the test to ordinary oxygen. But equal pressure instrument cannot be used for the common-use gases permeation test. It is determined by the test principle. Though it is ok to use the method to test the carbon dioxide permeation rate of membrane, but equal pressure method cannot test the nitrogen permeation rate of membrane (nitrogen is the carrier gas). Thus regarding to nitrogen permeation test, many institute and injection fluid bag manufacturers will choose the differential pressure test instrument when they are picking gas barrier property test instruments.

However, some people argue that nitrogen and oxygen are both common inorganic gases. There is 'inner relationship' between the permeation rates of same kind of injection fluid membranes. Estimates can be used to calculate the nitrogen permeation rate by a ratio relationship with oxygen permeation rate. This is not a normal method, thus the ratios are often the estimates of users, who read some literatures. The correctness is fairly low. A huge amount of test data also proved that estimates were often with low accuracy. As a matter of fact, there are many factors influencing the gas permeation rate of a membrane. Furthermore, the property of materials and gases are complicated and interactive, not to mention the environmental factors and so on. Thus ratio relationship estimate is a wrong measure. Estimates often cause a wrong decision on material choice. Even it is a right decision there will still be potential risks.

4 Perspectives on Infusion Liquid Bag Standards

The development of standards is often based on resolving current problems of products or methods. The significant problem of infusion liquid bag is that, because of the evenness of bag thickness and the sealing tightness, the gas permeation rate of whole bags is higher (sometimes one time higher) than the gas permeation rate deducted from membrane data. I think there are several factors causing the problem: first of all, the unevenness of material is a fairly common situation to infusion bags and bottles. The unevenness can be the influence of manufacture or be the needs of design. Thus calculations based on thickness average values is often far different from actual tested data. Secondly, the sealing tightness is a key issue. The sealing tightness between infusion bags and infusion tubes has always been a focus. If the tightness is not strong enough, the barrier property of bags will be poor even the barrier property of the membrane is fairly good. Thirdly, the

membrane area of bags is much larger than test membrane, which means defects appear more on bags. As a result, whole bag gas permeation test is the development trend of international barrier property test. However the test can only be performed by equal pressure method. The absence of gas permeation test of infusion bags is mainly because the technology at that moment only allow membrane barrier property test. There was no national standard for container test. Now the standards are getting close to international level and the container oxygen permeation rate test technology is very mature in China. The infusion bag permeation rate is expected to be included in the next standard revision. Consequently some test institutes and infusion bag manufacturers are ready to buy or buying equal pressure instruments.

5 the Development of Test Technology

Generally speaking, the current infusion membrane gas permeation test needs differential pressure instrument. But if it is the oxygen permeation rate test of infusion bags, it needs equal pressure instruments. Two investments to two instruments, it raised the maintenance fee and investment of equipments as well as lower the utilization of all equipments. PERME-DM2/330, double method gas permeation rate test instrument has been introduced by Labthink cooperation, Jinan. It is able to conduct differential pressure and equal pressure tests. Furthermore it can test the oxygen permeation rate of infusion bags and bottles. It is a better test equipment choice to medical packaging industry and infusion bag manufacturers. It can optimize the equipment cost, data accuracy and equipment utilization.