Original Article

The Importance of Filter Integrity Test to Ensure Sterility of Radiophamaceuticals for Using PET Image

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The radiopharmaceuticals are routinely injected to blood vessel for acquiring PET image. For this reason, It is imperative that they undergo strict quality control measures. Especially, Sterility test is more important than any other quality control procedures. According to the FDA guideline, It requires filter integrity test used in the processing of sterile solutions. Among several methods, we can decide to use bubble point test. We usually use vented GS-filters (Millipore co., USA) which are sterilizing-grade (0.22 um pore size) and are placed upper site on product vial. After the synthesis of ^{18}F-FDG, solutions wet the membrane in filter and then go into the product vial. By all synthesis steps have finished, we can observe the presence of the bubbles in the product vial. Since we have started this study, we have never found any bubbles in the product vial. Because the maximum pressure intensity of the filter which has set by manufacturer is up to 5 bars, but helium gas pressure is up to 1 bar in our module system. So, we can make 5 bars pressure using helium gas bombe and increase pressure up to 5 bars step by step. However, it does not happen to anything in vial. **(Korean J Nucl Med Technol 2008;12(1):74-77)**

Key Words : Filter integrity test, Bubble point test, Non-destructive test, Sterility, 0.22 μm pore size

INTRODUCTION

Radiopharmaceuticals which have been using in Nuclear Medicine are used to patients as an intravenous injection. The most part of the radiopharmaceutical for being used to patients in PET Center is ^{18}F-FDG. Due to ^{18}F-FDG is audited by Korea Food and Drug Administration, we can have to check many quality control items to confirm whether this radiopharmaceutical is safe or not. Especially, Radio-pharmaceuticals have more quality control items than conventional drugs have. Because radiopharmaceutical is consist of radio-isotope which can emit a radiation. Most quality control items for radiopharmaceuticals have been performed on a post hoc basis because of radiation exposure and longer test time than half-lives of radio-nuclides. Quality control which is used to radiopharmaceuticals has two main categories: physicochemical tests and biological tests. The physicochemical tests indicate the level of radio-nuclide impurities and radio-chemical impurities and determine the pH, ionic strength, osmolality, and physical state of the sample, particularly if it is a colloid. All radiopharmaceuticals should have an appropriate pH for their stability and integrity. The ideal pH of a radiopharmaceutical should be 7.4 but it is no problem if pH can be between 2 and 9 because capacity of the blood can become the suitable buffer. Also, Other physicochemical tests have proper values so that it can be suitable for human administration. Biological tests have three main categories: sterility, apyrogenicity, and toxi-city. Each main category has several sub-test items. Sterility test indicates the absence of any viable bacteria or microor-ganisms in radiopharmaceutical. To satisfy the absence of bacteria or microorganisms in radiopharmaceutical, prepara-tions and procedures must be sterilized condition. Pyrogens are either polysaccarides or proteins produced by the meta-bolism of microorganisms. They are 0.05 to 1 μm in size and

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they are soluble and heat stable, especially, bacteria products, we can call the endotoxin.

1. Autoclave

Autoclave is to sterilize using heating in steam at 121℃ under a pressure of 18 pounds per square inch (psi) for 15 to 20 minutes. But there are two main reason in this method does not apply to radiopharmaceuticals sterilization. First is that operators can expose to severe radiation risk during they can move radiopharmaceutical from hotcell or synthesis module to autoclave. Second is that radio-isotope has too short half- life to wait for sterilization. Compare to following method: filtration, this method is time and money waste method.

2. Membrane filteration

Membrane filteration method is used to commercial filter which has suitable pore size depend on usage or microorganisms size. These filters can remove various microorganisms by a sieving mechanism. Most common method of sterilization in radiopharmaceutical synthesis is membrane filteration. Normal membrane filter size is 0.45 μm, but we can use a smaller pore size filter: 0.22 μm. because it is necessary for the sterilization of administration for patients and preparations suspected of microorganisms and all the bacteria cannot pass out a 0.22 μm filter completely.

3. Integrity test method

What we use the commercial filter to sterilize rarely lead to happen a serious problem. Because There is probability that we can use a faulty product. If we could use a faulty product and we should be able to experience the fatal results. To avoid this fatal results, FDA recommend that all the filters which are used to remove the microorganism are tested by filter integrity test method and recommend that all radiopharmaceutical must be tested by this method then, radiopharmaceuticals is injected to patients. There are two categories of filter integrity testing: Destructive testing and Non-Destructive testing.

EXPERIMENTAL

1. Destructive testing

Destructive testing is the best way to determine a sterilizing filter's ability to retain bacteria. This testing provides assurance that the filter membrane can meet the critical performance criteria of a sterilizing filter. During this test, 0.22 μm filter discs and devices are challenged with a solution of culture medium containing bacteria at a minimum challenge of $10^7/cm^2$. The effluent is then passed through a second 0.45 μm assay filter disc that is placed on an agar and incubated.

2. Non-destructive testing

Non-destructive testing may be done on filters before and after use. This testing can detect if the integrity has been compromised during the process and detecting a failed filter alerts operators to a problem immediately. There are three types of non-destructive testing: the bubble point test, the diffusion test and pressure decay test. For this study, We can use the bubble point test during radiopharmaceutical synthesis in module.

3. Bubble point test

The most widely used non-destructive integrity test is the bubble point test. It is based on the fact that liquid is held in the pores of the filter by surface tension and capillary forces.

4. Procedure

1. Wet the filter with the fluid, typically water for hydrophilic membranes or an alcohol such as organic solvent for hydrophobic membranes. 2. We keep monitoring that fluid

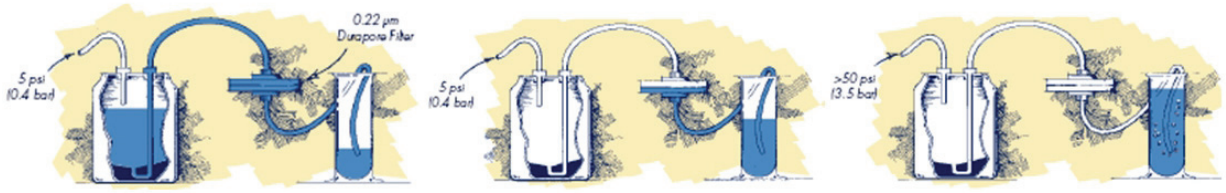

Fig. 1. Bubble point test procedure.

Fig. 2. Normal result (left) and bubble result (right).

pass the membrane filter out completely by remote surveillance camera. 3. After fill fluid with product vial, we can check the bubble in product vial. 4. If bubble would appear in the product vial, using filter must have fatal problem and radiopharmaceutical that has filtered by faulty filter never ever inject to patients. 5. If bubble would not appear in the product vial, All the microorganisms completely remove in the product vial. So, we can inject to patients with this safe radiopharmaceutical.

RESULT AND DISCUSSION

Since we can check bubble in the product vial with remote monitor. We have never confirmed any bubble in the vial. The reason is that we would not find any bubble in it is too lower gas pressure to destroy filter membrane.

Also, we should guess that there are not faulty product we have ever used in synthesis. But we are likely to confirm that how the bubble appear in the product vial using faulty product. We can try to make bubble of purpose making hole in membrane by shape and thin tool such as needle. This is to make a situation that we could use the faulty product in Radiopharmaceuticals synthesis and to confirm a bubble with remote surveillance camera.

CONCLUSION

Filter integrity test is not only most important procedure, but also very simple and very convenience test. This test is imperative to confirm whether Radiopharmaceuticals are safe or not to use for patients. We have to check a monitor which is connected to remote surveillance camera during every synthesis of Radiopharmaceuticals. If bubble could appear in the product vial, the Radiopharmaceuticals have never ever use for patients. If we could synthesize the Radiopharmaceuticals for research, especially for animals, we never ever do again. Until finished sterility test, this test will guarantee that any microorganism is not in the product vial.

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