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GAINESVILLE, FLORIDA.

PREPARATION OF AMPULS.*

BY S. L. HILTON.

The object I have in view in discussing this subject is to bring out the main points in connection with the preparation of ampuls. Not that I expect every pharmacist to make them, but I believe every pharmacist should know something very definite about what is required to manufacture ampuls, so that he can talk intelligently about them to physicians and explain what they are, what is necessary to properly prepare them, and at the same time caution them relative to certain things that are liable to occur in ampul medication.

When we handle ampuls, whether in a large or in a small quantity, there are many things that must be taken into consideration. I started in this work because of constant demands from physicians to prepare solutions of all kinds in sterile containers, so that they could have them quickly and be assured that the medications they administered to their patients were sterile and exactly what they wanted.

Ampul medication is more popular than ever before; and one reason is this—there is produced thereby a psychological effect on the patients which they do not receive with the ordinary form of drug administration—they see the physicians take out a little bottle of some kind; that he nicks it, opens it and injects the contents by means of an hypodermic syringe.

Furthermore it is often the case when medicine is administered by mouth, that at once or a little later on it is found that the stomach is in no condition to retain the medicament, and the patient, instead of getting relief, suffers and does not care to continue what has been prescribed. Also ampul medication has become more popular because the patient goes to the physician, the medicine is administered hypodermically, subcutaneously, or intravenously, and the patient goes about his business. He has very little, if any, after-effect, possibly a little pain which passes off quickly, and he requires a dose of medicine only twice or possibly three times a week. This fact has increased the popularity of ampul medication.

QUALITY OF GLASS IMPORTANT.

Ampuls should be tested because they must be of neutral glass. Jena glass, before the war, was neutral glass and very good, but I find that the glass which

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we get from the other side at the present time, supposed to be the same, is different. It is more brittle, more easily broken, it is difficult to seal, and a great deal harder to handle in many other ways. I have been able to locate a firm in this country that does make a glass similar to Jena glass, which seems to stand the tests well and is suitable for practically every solution but one, and that I shall bring to your attention shortly.

The usual method followed in testing ampuls to determine whether or not they are of neutral glass is to fill them with a weak solution of phenolpthalein, seal, put them in a vessel of water and boil for about fifteen minutes. If the ampul is not of neutral glass a reddish color will develop. Probably a better method is to take a number of ampuls, grind them in a mortar and treat them with $N/10$ sulphuric acid and then titrate back to the neutral point with $N/10$ alkali, to determine the alkalinity. For all ordinary purposes the first method is satisfactory and all that is necessary.

There are a few ampuls made of ordinary glass that are not satisfactory for use. The color usually develops in these ampuls within a few minutes. I have here some of the American-made ampuls of non-soluble glass, that have been boiled for two hours, and you cannot see any signs of alkalinity. They are put up by a firm in this country and I am using them at the present time. We, of course, have various sizes of ampuls running from 1-cc. up to 50-cc. capacity.

We also use vaccine vials. Some physicians desire the solutions put up this way; we obtain the vials made of non-soluble glass from the same firm. These vials are kept closed with a rubber cap stopper dipped into a solution of cresol, the top wrapped in cotton, and a glass cap filled with cotton covers the vial.

When the physician is ready to use these vials he removes the cap and cotton, washes the stopper with cresol solution or alcohol to insure sterility, then he punctures the stopper with a sterile hypodermic needle and withdraws the desired dose through the opening in the center and administers it.

STERILIZATION.

As a guide and, probably, for more information with reference to what is required for sterilization, I know of no better authority than the chapter on "Sterilization" of the new edition of the "National Formulary." This chapter has been written and reviewed by a number of pharmacists of large experience in their own laboratories, and the Committee has also had the advantage and coöperation of numerous outside workers.

I have found it is absolutely necessary to obtain glassware in a sterile condition and perfectly dry to use the hot air sterilizer and bringing the temperature up to at least 160° C., sometimes 180° C. I frequently use this temperature on large-sized syringes and glass-stoppered ware, first withdrawing the piston or glass stopper to avoid breakage. At certain times of the year the atmosphere is contaminated by the bacillus of timothy. This bacillus is probably the most troublesome we have to contend with; it requires a temperature of at least 160° C. to destroy it. For all glassware and all containers, the hot air sterilizer should be used, but for solutions you cannot use such temperatures, for the reason that you will decompose them and then the solution will be worthless. Like care must be exercised in sterilizing solutions as in sterilizing glassware.

In my experience the only satisfactory glassware that I have had success with for containers, other than the ampuls, is Pyrex ware. While Pyrex ware will give a positive test for boric acid, in small quantities, such a small amount, even if it does enter into the solution, has no deleterious effect whatever. Consequently, you will be sure you are giving the physician a solution that will prove satisfactory.

It is necessary to determine what temperature to use. If you are using the autoclave and the temperature is raised to above 100° C., in the majority of cases you will partially decompose the solution; if it should happen to be a cacodylate, the odor of garlic will be immediately recognized, showing that the organic arsenic compound has been broken up and the arsenic liberated. This is likewise true of all organic mercury salts if you raise the temperature above 100° C., mercury being precipitated as a black oxide.

MERCURY SALTS.

We are called upon constantly to put up suspensions of mercury salts in various forms. We use glass-stoppered bottles and sterilize in the Arnold sterilizer for one hour, with satisfactory results. If, however, you are tempted to use the autoclave with steam under pressure, the temperature is raised above 100° C., and decomposition takes place, and a heavy gray deposit will occur, showing that the mercury salt has been broken up, as I previously mentioned.

All glassware is sterilized, as pointed out, at a temperature of 160° to 180° C., for one hour in the hot air sterilizer. Solutions are sterilized in the Arnold sterilizer for one hour. In cases where we can use the autoclave, 15 pounds' pressure for twenty minutes suffices; the work is accomplished much more quickly.

AMPULS OF DISTILLED WATER.

I put up a great many ampuls of various sizes of distilled water. Here we use the autoclave. If the larger ampuls are sealed before placing them in the sterilizer the loss by breakage is very heavy, reaching sometimes 85 per cent. To overcome this I place the ampuls in wire gauze baskets made for the purpose, and each ampul is covered with a cap made of parchment paper that fits over the stem of the ampul and is held in place with a rubber band. These caps are covered with gauze so that they will not come off, and autoclaved at 15 pounds' pressure for twenty minutes. When they are cold they are sealed by using a Meeker burner which gives a very high temperature. The cap is removed, and the flame of the burner is at once applied until the ampul is sealed, thereby avoiding any contamination. By this method, the loss is reduced to practically nil. The ampuls I spoke of a few minutes ago that must be watched more carefully than any others are ampuls of distilled water. This may seem peculiar, but we have more trouble with them than any other ampuls. Inquiries have elicited the same condition with large manufacturers. What is the cause I do not know. I have turned over to the Research Committee a number of specimens, in an attempt to solve the problem, and I have several here that I want to show you.

After the water has been in the ampul, sometimes for a day only or for weeks, a condition develops which shows fine needle-shaped crystals of pure silicon. Ampuls out of the same lot will often stand for weeks without this condition

developing. Consequently, it is necessary to examine ampuls of distilled water very closely before sending them out. Here is a specimen and there are two others in which the silicon from the glass has been thrown out. Examine them and notice the needle-shaped crystals.

There are some other substances we are called upon to put in ampuls with which we cannot follow the usual methods of sterilization or pasteurization. One in particular is a 1-per cent solution of tartar emetic. You have a condition confronting you here that requires certain technique and the greatest care. If you attempt to heat the solution, a basic salt will form which will not redissolve and will appear in fine needle-shaped crystals. It, therefore, becomes necessary to resort to the Berkefeld filter and vacuum filtration. Before using the filter it must be taken apart to separate rubber washers prior to sterilizing the filter. The rubber washers are sterilized in the Arnold sterilizer, while the filter candle is sterilized in the hot air sterilizer.

In using the Berkefeld filter for the smaller size, after it has been set up, the filter candle is covered with a small beaker, and the larger size with a large test-tube, to prevent the drawing in of air until the solution has reached the bottom of the container. In handling the Berkefeld filter it is necessary to make up more of the solution than is required for the number of ampuls to be filled because you have not only a loss by reason of the filter candle holding some but also the container; as the cost of the solution is only a trifle, this amounts to little.

The simplest method for vacuum filtration is with a Bunsen pump, using two filtering flasks. The Bunsen pump is attached to an ordinary water spigot and connected with the second flask, which is then connected to the first flask to which the Berkefeld filter has been properly connected. The purpose of the second flask is for a safety flask to prevent any of the solution from becoming contaminated if somewhere in the same building the water may be turned on, which would, by reason of the vacuum, suck some of the tap water into the first flask.

The Berkefeld filter is also used in preparing sterile glucose solutions for intravenous use. I make a 50-per cent solution of glucose and put these up in 50-cc. ampuls which are now largely used in several of our local hospitals in connection with the administration of Insulin. In these ampuls we have never had any precipitate and they can be used by adding the contents of the ampul to enough sterile water, which the hospitals always have on hand, to make 500 cc. of a 10-per cent solution which they desire. I have really been surprised at the number of times I have received rush calls for these ampuls. The hospitals will not keep them on hand, and that, I find, is the trouble with the majority of hospitals in Washington. Their supplies are miserably low to meet emergencies, and the drug stock very short, yet they constantly need them. Is it not a wonder they do not learn by experience?

In making a glucose ampul we use the very highest of anhydrous glucose obtainable—it is put up by a company in Detroit, and costs over $3 per pound; I can rely upon this product to obtain a solution absolutely pure and almost colorless. The same glucose ampul can be made by sterilizing in the autoclave. Here you will find there is a difficulty. When you prepare the solution and it is filtered, and this takes considerable time to filter through paper, and you auto-

clave it, you will find when you remove it from the autoclave the solution has not only darkened, but there is considerable of a precipitate which will again require another filtration through paper, and be again autoclaved to obtain a solution free from foreign particles and one that is suitable for intravenous use.

That was my trouble when I first started to prepare this ampul. I worked out the process just spoken of, using the autoclave, and the following week after getting good results, the *Journal of the American Medical Association* contained an article along the same line by two physicians who had the same trouble and solved it in the same manner. This then led me to the Berkefeld filter which is much more rapid, far easier to handle, and gives me a better solution and one that is thoroughly sterile.

FILLING AMPULS.

There are many methods for filling ampuls. I believe, on a large scale, a number of manufacturing plants use the vacuum method with which they fill a large number of ampuls at one time. That may be all right, but it has its disadvantages. I have tried it and have abandoned it. Ampuls put up by this method are held in a certain position, the stems are dipped into the solution, a vacuum is created and the solution drawn up into the ampul. Not only will some of the solution remain in the stem of the ampul but the outside of the stem has become wet with the solution, so that when you seal it you carbonize what remains on the stem; if you will notice, a lot of ampuls have black spots on the stem which are due to this method of filling.

The plan I find best and the one I now use and have tried hundreds of times is by use of the separatory funnel. These, of course, are of various sizes according to the amount of solution required. Burettes can be used, but they are too small, too clumsy and more apt to be broken. For this reason, the separatory funnel is best. For small amounts of solutions you can use a 250-cc. funnel, for larger quantities 1000-cc. funnel. Your funnel is stoppered with a plug of cotton wrapped in a double thickness of gauze and then flamed, to burn off loose particles of cotton so that they will not fall into the solution. This same method of using cotton and gauze, and flaming must be followed in plugging flasks or any other container; otherwise, in intravenous injections these particles will be carried by the blood stream to the heart and are apt to get caught in the valves of the heart, thereby producing embolism.

I examine all solutions with a magnifying glass and numerous samples of the ampuls, after filling, for foreign particles before boxing, and if they contain any they must be rejected. The plug of cotton in the gauze of the separatory funnel acts as an air filter excluding bacteria when filling the ampul. In filling, a short piece of sterile rubber tubing is attached to the separatory funnel and a hypodermic needle made of platinum for the small ampuls, and for the larger ampuls a glass filler is easily provided by heating and drawing out the glass so that the opening is larger than that obtained with a needle, and the flow of the liquid much faster.

The reason for using a platinum needle is that many solutions will act on the ordinary steel needle, as, for instance, a solution of mercury iodide with sodium iodide. This is evidenced at once by the solution getting dark; you will have to use either the platinum needle or a glass filter.

All solutions for ampuls must be as near the neutral point to litmus as can be contained without decomposing the solution. If they are perceptibly alkaline the patient suffers pain; if they are acid to any extent the patient likewise suffers pain. A solution of iron arsenite, iron citrate and several others are always very, very acid and will cause considerable pain. If, however, you will bring the solutions as close to the neutral point as possible, the patient can take them and will not have any pain or but very little, which will not last long.

IRON ARSENITE REQUIRES CAREFUL MANIPULATION.

Ampuls of iron arsenite require careful manipulation. A Washington physician had tried every ampul obtainable of iron arsenite, for use in treating a lady of prominence who was very cranky and one who must have what she wanted. He came to me for help. After numerous attempts, I succeeded in furnishing this ampul which proved not only satisfactory, but brought me many more customers for the same ampul and made me new customers for other business.

In filling and sealing ampuls two dispensers work together. With a little practice you can hold five of the ordinary-sized ampuls in your hand, and fill them very quickly. They are placed in holders with a capacity for ten ampuls, one dispenser works on one side of a glass-top hospital table, filling, and another on the other side, who seals the ampuls as fast as the holder is filled. Here I also use a Meeker burner because a high temperature can be obtained—1700° C.—thereby sealing rapidly. In sealing you must keep your eye on the ampul every second of the time you have the flame on the stem of the ampul, because if you do not you will blow a bulb on the point of the ampul, which will break if the flame is not removed as soon as the bulb begins to form. By following this method, you know the ampul is sealed, for the reason that the air inside of the ampul due to the heat used causes the expansion of the glass which, if not sealed, would escape and would not cause the formation of a bubble. We then wash and dry the ampuls and examine the point of each carefully for breakage. We are then ready for boxing. I find if we sterilize our solutions by the method I have spoken of, and our apparatus by the same method, it is not necessary to sterilize the ampuls after they are sealed.

I do not know how many ampuls I have put up, but I have never had a complaint and never a case of infection. Then why go to the extra trouble of sterilizing the ampuls after sealing? It all depends entirely on how well you look after the sterilization, the filtration and the handling of the ampuls. You might compare the process to an ordinary chain—the chain is no stronger than its weakest link—the value of the sterilization is in comparison to its weakest point. If you fall down on one point, the whole thing falls down just like a pile of bricks set on end; if one at the end falls, they all fall.

Of course, in doing this work I have a room set aside for that purpose, clean and free from currents of air. Sometimes, on a very hot day, it is rather uncomfortable to be closed up without fresh air, but you have your duty to perform and the best way to do it is with a smile; get down to it and do it as quickly as you can. Then go to the show.

SODIUM SALICYLATE.

Another ampul that is difficult to prepare is that of sodium salicylate. I have made sodium salicylate to get what I wanted and failed; I obtained the highest grade of pure salicylic acid from the Baker Chemical Company, washed all vessels with nitro-hydrochloric acid, then with tepid water and then with distilled water and double distilled water, and yet the finished sodium salicylate when dissolved in distilled water would show a brownish color, eventually turning black because the product contained traces of phenols. There is obtainable a brand of sodium salicylate that is absolutely pure, free from phenols and pharmacologically tested, and this is the only kind suitable for preparing ampuls of sodium salicylate.

Dr. H. A. B. Dunning, I think, was the first one to show me how to clean ampuls. Those we received at that time were in bad shape and had to be cleaned. The firm that furnished me ampuls now sends them clean-wrapped, free from foreign particles of glass or other foreign substance—carefully wrapped in tissue paper; but we examine them carefully and if not perfectly clean they must be washed. In washing, I use a separate arrangement that fits over an ordinary spigot to which a rubber tube and a hypodermic needle is attached. This flushes the ampul out thoroughly. To remove the water remaining in the ampul it is necessary to use another needle to which an ordinary atomizer bulb is attached, so that you can blow out the water.

The larger ampuls are more easily cleaned because the opening is larger and you can readily shake out the water. The average junior clerk can, in a short while, wash and clean many hundred.

I think I have mentioned about all that is necessary for a proper understanding of the methods used for making, filling and handling ampuls. I only want to mention one more thing.

ADEQUATE CHARGE MUST BE MADE.

The average pharmacist when he is called on for things out of the ordinary —such as work of this kind—thinks it is a lot of trouble; it takes much time and means a lot of unprofitable work, but with the training that we must have, all that is necessary is to have some simple apparatus and have everything in shape for quick use. The laborer is paid for his labor, why not the pharmacist? I charge accordingly. My time is worth several dollars an hour. For sterilization of anything, no matter how small, my charge is one dollar. Add to this the cost of materials, plus a fair and reasonable profit, make your selling price accordingly, and you can obtain a handsome profit with the expenditure of but little time, and have much interesting work to perform.

To illustrate, on an occasion recently, when two of my clerks were off for the afternoon and I had an order for a thousand ampuls for a physician that had to be delivered the following morning, I left my place of business at the usual time, drove six and a half miles to my home for dinner, and after dinner I said to Mrs. Hilton, "I am going to work to-night. You are a pretty good sport, I want you to accompany me and help me." I told her what I wanted, and within two and three-quarter hours after we reached my laboratory, we had filled and sealed 1178 ampuls.