Sample No.	Source of sample and remarks.	Percent total ash.	Percent ash insoluble in 5% HCl.
25.	Commercial, Peeled Italian Licorice, bought 1921, apparently prepared from *Glycyrrhiza glabra*, powdered in this laboratory...	4.02	0.67

DEPARTMENT OF PHARMACOGNOSY,
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THE MANUFACTURE OF EFFERVESCENT SALTS.*

BY ROBERT C. WHITE.

A very interesting class of the less important pharmaceutical preparations are those known as "Effervescent Salts." An Effervescent Salt, as we all know, is really a medicated ingredient in combination with an effervescent base designed to present the medicated agent in a palatable effervescing drink. The textbooks contain a good deal of information regarding salts of this character, but are deficient in certain interesting facts concerning the manufacture of these products on the larger scale.

GENERAL NOTES.

Effervescent Salts have been very well known for the past thirty-five years. It might be said that they attained the peak of their popularity about fifteen years ago. The novelty, however, of watching the bubbles has suffered a very serious decline in the last few years, as may be noted by the fact that there are only five Effervescent Salts officially recognized in the present Pharmacopoeia. A very much larger number, however, are offered by manufacturers, and there is still considerable demand for these products. The base of this class of products is composed of practically the same ingredients, no matter what the medicinal agent, although the proportions may vary widely on account of the differences in the physical properties of the active agents used. In all cases the ingredients must be reduced to a moderately fine powder, and these are thoroughly mixed before any attempt is made at granulating. For years sugar was used in the base, not only on account of its ofttimes rendering the taste more pleasant but because sugar, when moistened or heated, makes an excellent binder for holding granules in even-size particles. It was long ago discovered, however, that sugar could not be introduced into a salt without greatly lessening its keeping qualities. There will also develop a discoloration, tapering from a pale cream color to a dark chocolate brown, even though the package remains unopened and according to the length of time the product is kept on hand. For years effervescent salts were made by the simple method of triturating the ingredients into a fine powder, mixing them, and then moistening the entire mass with alcohol. It will be noted here that strong alcohol only could be successfully employed, as the presence of water produced a very sticky mass, permitting a very generous reaction between the acid and alkali in the base, and thus rendering the ultimate product much more inert so far as effervescence was concerned, and much more slowly soluble. The moistened mass was forced through a well-tinned screen of proper mesh to produce

* Read before Pennsylvania Pharmaceutical Association, Philadelphia meeting, 1921.

granules of the size desired. The drying of these moistened granules was then carried on as expeditiously as possible in order to prevent any loss of effervescent properties. The temperature employed usually was not over 130° F., in order to prevent the decomposition of sodium bicarbonate. These salts, as we all know, should be preserved in well-stoppered bottles, and even then should be stored in a dry place. It has been found practical in a good many cases to use bottles of blue glass, when the salts are to be kept for a time, as they discolor more readily in flint containers.

PHARMACOPOEIAL DIRECTIONS.

The U. S. Pharmacopoeia, at the present time, directs that for the preparation of an Effervescent Salt the mixed powders be placed on a sheet of glass or in a suitable dish, and then put into an oven heated to between 93° and 140° C. (199° to 219° F.); when the mass, after careful manipulation with a wooden spatula, has acquired a moistened condition it is to be rubbed through a number six well-tinned iron sieve. This is then to be dried at a temperature not exceeding 54° C. (129° F.). The formulas of the Pharmacopoeia, however, are defective, as too little citric acid is employed, and a good granule cannot be produced; no allowance is made for loss through the escape of moisture and carbon dioxide, which is bound to take place during manufacture; as this loss is due to climatic conditions, which are subject to change, it is readily seen that the percentage content of the medicinal ingredient may vary from 8 to 14 percent. In all cases the citric acid should be the last ingredient added, as otherwise, if made during humid weather, the mass will moisten unevenly, producing translucent particles which will be very slowly soluble when brought in contact with water.

NATIONAL FORMULARY DIRECTIONS.

The general formula given in the National Formulary is also faulty in some respects. The mixing of the ingredients in a mortar, as directed, will produce an undesirable gummy mass, probably on account of the pressure exerted by trituration. The stirring of the mass in an evaporating dish over a water-bath, kept at a temperature of from 60° to 70° C. (140° to 160° F.) until dry, will produce a great deal of fine powder and irregular sized granules and, for reasons heretofore stated, sugar should not be employed.

MANUFACTURE IN LARGE QUANTITIES.

Now regarding manufacture in larger quantities (that is, where salts are manufactured in five hundred, one thousand and two thousand pound lots).—The manufacturer's definition of an Effervescent Salt would probably be—"A medicinal ingredient in combination with an acid and alkali which form in the presence of moisture an effervescing compound."

Classification.—The manufacturer being a busy man and ofttimes surrounded by helpers whose knowledge of pharmaceutical terms and procedures is limited, frequently resorts to the simplest and most practical way of classifying his products: The Headache Class, the Diuretic Group, and the Laxative Group. This separation seems crude perhaps, but, after all, is a very simple subdivision for manufacturing designations. The first named—the "headache group"—combines those having sedative and analgesic properties, their use being entirely confined,

by the layman at least, to his treatment of headaches; they chiefly embrace the salts containing acetanilid and phenacetin and their compounds. The "diuretic group" includes those products which increase renal secretions, etc., such well-known products as lithium carbonate and citrate, also such alkaline salts as potassium acetate, etc. The third and last group is the greatest of all, namely, the "laxative group;" the term covers them broadly, and includes the well-known Effervescent Salts of sodium phosphate, magnesium sulphate, sodium sulphates, etc.

Working Methods.—After a definite formula has been determined upon all ingredients should be reduced to a sufficiently fine powder and screened, bearing in mind that all screens must be well tinned, in order to prevent contamination.

Mixing.—These ingredients should then be placed in a well-enameled mixer, the powdered citric acid is added last, and in all cases prepared from uneffloresced crystals. When these powders are mixed thoroughly which, in the case of 100 lb. working batches, should not be for less than fifteen minutes, the powders are placed in shallow enameled pans, or in plates of glass, or in shallow well-enameled steam jacketed pans. The question of the proper amount of heat to use at this stage is one which requires careful determination.

Heating.—Such salts as those containing citrated caffeine, acetylsalicylic acid, or such like acting products, should not be exposed to too high a temperature. These three methods of heating demand some explanation. When the simple pan method is employed it is necessary to have the salts only of sufficient depth that the heat may readily penetrate all portions thereof. These pans when placed in a heated closet are very cool, or moderately cool, which means that the exposed upper surface of the salt mass coming in contact with the heated atmosphere will soften, or at a high temperature almost melt before that section protected by the pan has arrived at the plastic state. The same applies to the glass plate method, although in this case the glass plates are usually allowed to remain in the heated chamber, which is a better method. However, it means that we have the reverse conditions of the pan method, namely, the surface lying directly against the heated sheet of glass will melt first, whereas the surface coming in contact with the atmosphere is more slowly affected by the heating; therefore, the need for manipulation. The simplest plan after all is the one where the salts are placed either in shallow jacketed steam pans, or on an enameled surface steam table and considerably manipulated, so as to bring all parts into equal contact with the heated surface according to the amount of water of crystallization present in the ingredients. While the manufacturer may know the technical reasons for the difference in this mixed mass at various stages, he cannot be independent of the operator himself who determines the condition of the mass by taking a handful and squeezing it to discover its degree of plasticity, or, as the operator would say, "the feel of it." This is after all the most difficult stage in the making of effervescent salts, regardless of what may be written.

Weather Conditions.—The manufacturer is not independent in the majority of cases of weather conditions; on a very humid day some of these masses will melt down very rapidly, while in very dry weather after the usual length of exposure to heat the mass will not become quite plastic enough, and would result in a powdery preparation. A very few of the manufacturers in this country

have made efforts to overcome this condition, as for years it was impossible along the Atlantic seaboard to make effervescent salts during July and August.

Air Drying.—The writer's experience has been that the only way to become independent of this condition is to have in reserve a trough which can be filled with calcium chloride. This may be made of heavy lumber 12 feet in length, 12 inches square and tilted so sharply that when calcium chloride is placed in the upper opening it will slide downward and thus keep packing itself. A suction blower is then arranged to draw the air through and over the calcium chloride into the room where this work is done. The advantage of this tilting of the calcium chloride tube is that the chemical itself may be deposited at the upper end, while from the lower end the saturated solution, from the moisture in the air, continually drains off, thus allowing the calcium chloride to drop downward, and leave space for more to be added at the upper end. This method, while crude, is effective, and is much superior to that of heating the atmosphere of the room to such a degree that the operator cannot work. Even this method, however, is not sufficiently dependable to permit the use of a set formula. The adjustment has to be continually made between the tartaric and citric acids in the base as the tartaric acid contains practically no water, and the citric acid in crystal form does.

Acids.—It might be well to state, at this stage, that citric acid makes a finer salt than tartatic acid, but a combination of the two is preferable, as it permits of the adjustment of the water of crystallization in the base without materially changing the taste of the finished salt. Tartaric acid does not possess the pleasant taste of citric acid, it has a salty taste and lacks the fruity element combined with the sourness of citric acid. The physical disadvantage of using tartaric acid in the place of citric acid is that the resultant granules are soft and chalky, and these granules break down with handling and in shipping. The writer has found that a combination of one-third tartaric acid and two-thirds citric for the acid content will give a mass of pleasant taste, and uniform granules. Unless for good and sufficient reason, the manufacturer should not change these acids, as it is quite possible when the medicated salt contains water of crystallization to make this adjustment without changing the balance of the base.

Adjustment of Base.—For instance, in a formula for Sodium Phosphate, Effervescent it is best to make the moisture adjustment between the proportions of dried and powdered sodium phosphate, and a small proportion of crystals of sodium phosphate which is retained in the product, and contains between fifty and sixty percent of water of crystallization.

Sifting.—When the plastic mass has been sufficiently heated it is then placed in a mechanical sifter and forced through a screen of the proper size, usually a number 6 or 8 mesh, and the soft granulation is then ready for drying. These moist granules must not be placed in too thick a layer, as their own weight would cause them to cling together again.

Drying.—We now reach the drying stage. There are various forms of dryers. For years the old-fashioned trays the bottom of which was composed of netting, canton flannel, canvas, or some such coarse fabric were used in what was known as the ordinary air dryer, a set of which looks like a small row of bathhouses. These closets are equipped with steam coils at the bottom, an opening

being provided at the bottom and one at the top permitting the incoming air to be heated, ascend and escape at the top, drying the ingredients which were placed upon these trays. This method, in recent years, has come into disuse with the majority of manufacturers as the wooden frames and fabric bottoms of these trays were liable to contamination and stains, which also made for unsightliness and disorder. Sheets of glass, aluminum trays, and block tin trays are steadily coming into use. The old air dryer has given way to such improved apparatus as was described in a previous publication by the writer on "Tablet Manufacture."[1]

Belt Dryer.—Very large manufacturers have experimented, and some successfully, with belt dryers, the principle of these being that at one end at the top of a large drying chamber the moist salts are automatically fed to a belt which slowly carries them 30 or 40 feet through the heated atmosphere, and drops them on a belt below, traveling the other way, which returns them to the end at which they had been injected, and so back and forth until the salts drop off the lowest belt perfectly dry. The speed of these belts is regulated to carry the salts out only in the time necessary, and the temperature of the dryer is capable of accurate control. In fact, this method has been long in use by the manufacturer of one of our best known trade name effervescent salts. This method is chiefly applicable to a plant manufacturing one salt continuously, but shows great disadvantages.

Vacuum Drying.—Probably the best form of drying salts in large or small quantities of different kinds is in the vacuum dryer which has been quite extensively used for the last ten years. This vacuum dryer consists of a large cast iron chamber containing hollow shelves which are filled with steam or hot water as the case may require; the salts in shallow aluminum trays spread about one inch deep are placed on these heated shelves, the door tightly bolted, and the vacuum pump turned on. A very speedy cessation of reaction takes place under these conditions, and as the moisture is drawn off the reaction gradually ceases, and a higher vacuum is obtainable. These vacuum dryers can be operated with a working vacuum of from 26 to 28 inches, which is unquestionably a very fine working vacuum. Other advantages of the vacuum system are that the salts can be dried more rapidly, there can be no contamination from outside sources, and if the new working batch is just about completed when the quitting hour arrives the pumps may be shut down, the vacuum chamber sealed, and if the apparatus be in perfect working condition the vacuum chamber may be left unopened with perfect safety until the next working day. This is a vital matter so far as the manufacturer is concerned in these days of workmen who are demanding thirty-six hour weeks, with eighty hour pay, and double pay for overtime. As this dryer can be equipped so that the heated shelves may be filled with steam or hot water it will be readily seen that there is a very great flexibility of control of temperature. Some salts will stand a temperature of 160° F.; those containing caffeine will show sublimation of the caffeine on the walls and sight glass of the chamber at even 110° F.

Removal.—The salts when properly dried are removed from the dryer, and rapidly screened in order to break up the granules which have clung together, thus resulting in a uniformity of granules. Great care is exercised in the selection

[1] Jour. A. Ph. A., 9, 788, 1920.

of mesh for this purpose as all manufacturers desire a finished salt having uniform granules, and as little dust powder as possible. Some manufacturers endeavor to rework the dust which they may screen from the finished product. This, however, should not be done, as it will be found that the proportion of ingredients present will differ considerably in different lots, and a partially insoluble salt will result. These dry granules are then either filled immediately, or stored in air-tight containers. The writer has found it advantageous to store these salts for a period of three days in order to become assured that the product is perfectly dry, and that all reaction has ceased. A simple method, but one which he has not seen used elsewhere, is to place these in 50-pound air-tight containers having a small pet-cock which is kept closed. When the salts are ready for filling, a small rubber tube is adjusted over this pet-cock, the end placed in lime water, and the pet-cock opened. If any further reaction has taken place the carbon dioxide coming through the tube will produce the usual milky reaction which indicates that the salts should be re-dried immediately.

Filling.—The salts should be opened quickly in a room containing dried air, corked and filled immediately, the bottles before filling being withdrawn from a heated chamber, and the salts filled from a heated hopper. Under these heated conditions there is less possibility of the salts absorbing moisture. It must be remembered that the effervescence of the finished salt may be largely controlled, for by changing the proportions in the base we can develop a salt which may go to the bottom of a glass and then effervesce, or which will entirely effervesce on the surface of the water, or even effervesce when half way down in the water, and then completely dissolve before touching the bottom. The manufacturers of some salts demand greater effervescence than others, if they think that a rapidly soluble and live effervescence is more pleasing to the customer. These, of course, are matters of personal taste, as is evidenced by the following story. The granulation for effervescent tablets such as Lithia Tablets is manufactured in exactly the same way as effervescent salts. In fact an effervescent tablet is frequently nothing more than a compressed tablet of an effervescent salt. The writer, while serving his time as an effervescent salts maker, discovered that after having kept a year's record of humidity and temperature taken every hour of the day he could, knowing the temperature and humidity, determine speedily what amount of water of crystallization should be used in any salt manufactured on that specific day. From this series of determinations it was but a step to find how to make salts effervesce more readily and abundantly, how to make salts effervesce on top of the water, under the water, or from the bottom of the water; and then being filled with great pride in his accomplishment, he determined to make a very live Lithium Citrate Tablet. The best record, taken from competitors' tablets, was one which dissolved in forty seconds in ice water. Please do not forget that ice water is the hardest test for quick effervescence of a salt. He then developed a tablet which would completely dissolve in twenty seconds, and proudly showed his product to certain members of the firm. At this stage the wet blanket was applied, and he was told that the person who had to use Lithia Tablets was usually inclined to be gouty, or full of uric acid from too high living, and that he was one whose condition proved he loved to linger at the table and who consequently liked to see the tablet flop up and down and effervesce in a dignified manner. 'So there you are.

You may juggle the acid and alkali in the base, you may either use high or low steam pressure in making the mass, and thus take your choice of whether you want a lively effervescent salt, or one more dignified in reaction. A peculiar thing is that while we have been accustomed to effervescent salts for years, the majority of users seem to think it necessary to swallow the salt at its highest point of effervescence, thus filling the mouth and nose with carbon dioxide, and in some cases producing discomfort. An effervescent drink of this kind should be taken just when effervescence subsides, as then the drink is fully charged, without an overabundance of effervescence.

Concluding Remarks.—Now for exact and intimate information regarding details which are not published in our textbooks. The temperature of the room in which effervescent salts are made usually runs from 110° to 120° F. The operator should, therefore, equip himself with a two-piece garment, ordinarily known as shirt and overalls. The floor being hot it is necessary for him to wear shoes. His elimination will be perfect, as with his very active work in this temperature he will perspire profusely. A pair of leather-faced gloves are always held in reserve as it is impossible to handle these hot trays and dryers unless the hands are protected. After two or three years' training under these conditions a man is not only down to his best weight, but he has demonstrated that he is capable of standing considerable hardship, and the writer has noted that no actual effervescent salts maker who indulges in the work himself ever finds it necessary to take any of the bath treatments which are strongly recommended by many of our sanatoriums, and as many of the products he makes are similar to the analyses of well-known springs it has been noted that he never goes to any until he leaves this work and advances to a position of higher responsibility. Under these circumstances, do not envy the effervescent salts operator. His lot is not an easy one, and a last problem:—after all precautions in drying thoroughly the air in a room which is maintained at a temperature of 120° F., how can you keep the operators from generating considerable moisture in the form of profuse perspiration?

I rarely look at an operator when in full working condition that I do not think of the scriptural injunction—"In the sweat of thy face shalt thou eat bread."

SHALL WE REQUIRE FOUR YEARS OF HIGH SCHOOL STUDY?*

BY AUGUSTUS S. DOWNING.[1]

The suggestion to amend the New York State pharmacy practice act so as to

* This important communication is reprinted from the August *Druggists' Circular*, p. 285, and is based on an inquiry addressed to Dr. Downing by the *Druggists' Circular* when it became known that he had expressed his opposition to any change in the New York State Pharmacy Law, which would make the completion of four years of high school study a prerequisite to pharmaceutical registration after July 1923. *The readers will understand that the personal references are made to the publication from which the communication is reprinted.*

Data relative to prerequisite legislation will be found on p. 500 *et seq.* (June issue JOURNAL A. PH. A.) in an article by Joseph W. England. Copies of Dr. Downing's communication have been sent to college deans; quite a number of replies are expected which the *Druggists' Circular* hopes to print as a symposium. The JOURNAL A. PH. A. has asked for replies from allied bodies of the American Pharmaceutical Association.—The Editor.

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