

United States Patent

[11] 3,608,593

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[21] Appl. No. 15,269
[22] Filed Feb. 27, 1970
[45] Patented Sept. 28, 1971
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Indianapolis, Ind.
Continuation-in-part of application Ser. No.
858,541, Sept. 16, 1969, now abandoned.

[54] **METHOD OF FILLING POWDERS INTO
CONTAINERS**
6 Claims, No Drawings

[52] U.S. Cl. 141/11,
302/66
[51] Int. Cl. B65b 1/04,
B65b 3/04

[50] Field of Search..... 141/1, 4-7,
11, 69, 82, 70; 55/75; 302/14, 66

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ABSTRACT: Powders are filled into bottles, ampoules, vials, syringes, and other containers by suspending the powder in an inert, volatile, liquid diluent, filling the suspension into the container, and evaporating the inert, liquid diluent, leaving the dry powder in the container.

METHOD OF FILLING POWDERS INTO CONTAINERS

CROSS-REFERENCE

This application is a continuation-in-part of our copending application Ser. No. 858,541, filed Sept. 16, 1969, now abandoned.

BACKGROUND OF THE INVENTION

Heretofore, the filling of powders into containers has been beset with several problems inherent in the operation. The accuracy of fill was always in question, especially on small, critical-fill volumes. Containers much larger than desired with oversized fill openings were necessary due to the near impossibility of getting the powder into a container with a small opening. The operation was usually very dusty, particularly with low-density powders, necessitating cleanup of the containers and the work area and resulting in losses of the powder.

SUMMARY

We have now found that these problems inherent in filling powders into containers can be overcome by a filling process which comprises suspending the powder in an inert, liquid diluent having a boiling point below about 100° C., adding the suspension to the container, and evaporating the inert liquid diluent, leaving the powder in the container. By means of this process powders can be filled in containers having very small openings using conventional liquid filling equipment. Accurate measurement of the powder introduced into the container can be realized, and the presence of the liquid prevents the dusting usually accompanying powder-fill operations.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Our process can be used for the filling of any powder for which a suitable inert, liquid diluent can be found. We expect that the process will find its greatest utility in the filling of pharmaceutical powders into vials, ampoules, and syringes. These types of containers normally have very small openings which make them difficult to fill with powders. Typical of the powders which might be filled by our process are cephalothin, cephaloridine, potassium penicillin G, streptomycin sulfate, phenobarbital sodium, amobarbital sodium, and secobarbital sodium. This list is merely illustrative of the types of the powders that can be filled by our process and is by no means all-inclusive or limiting. The particular powder being filled is unimportant since our invention lies in the method of filling, regardless of the powder being filled.

The inert, volatile, liquid diluent in which the powder is suspended is one having a boiling point below about 100° C., preferably below about 50° C., and still more preferably below about 30° C. The lower limit for the boiling point of the diluent is controlled only by the necessity of operating under superatmospheric pressure or reduced temperatures to prevent volatilization of diluents boiling below room temperature at atmospheric pressure. This inert, liquid diluent is preferably one in which the powder is essentially insoluble. If a solution of the powder is used rather than a suspension of the powder, there is a greater likelihood of caking occurring when the liquid is evaporated. Volatile diluents are preferred to facilitate diluent removal after the suspension has been added to the container. It will be understood that the diluent must be one that can be removed at a temperature at which the powder is stable. Vigorous removal of the diluent is preferably avoided since this might result in spattering with loss of powder or unsightly splotches of powder on the sides of the container.

If the diluent employed is one boiling below about 30° C. it will be easily removed by a stream of air or slight vacuum. However, the volatility of such diluents does present other problems. A diluent boiling at about 50° C. is more easily handled but is more difficult to evaporate. Diluents boiling at temperatures up to about 100° C. may require special evaporation procedures, especially if the powder is thermally unstable.

One such special procedure will be described in some detail below.

Typical examples of suitable inert, liquid diluents include alkanes such as cyclobutane, n-pentane, isopentane and neopentane; alkenes such as 2-butene, 1-pentene, 2-pentene, 3-methylbutene-1, and 2-methylbutene-2; alkynes such as 1-butyne, 2-butyne, and 1-pentyne; dienes such as 1,2-butadiene; halogenated hydrocarbons such as methyl chloride, methyl bromide, methylene chloride, ethyl chloride, ethyl bromide, isopropyl chloride, fluorotrichloromethane, and fluorodichloromethane; ethers and epoxides such as diethyl ether, methyl ethyl ether, ethylene oxide and propylene oxide; alcohols such as methanol, ethanol and isopropanol; esters such as methyl formate; and inorganic diluents such as sulfur dioxide. It is to be understood that mixtures of these diluents may also be used.

The choice of diluent to be used will depend upon the properties of the powder being filled. For example, what constitutes an inert diluent will depend upon the types of reactive chemical groups present in the powder. The choice of inert diluent will also be affected by the solubility characteristics and thermal stability of the powder. A skilled chemist or chemical engineer will have no difficulty in selecting a suitable diluent for any given powder.

The concentration of powder in the suspension will determine the size container necessary to hold a given amount of powder. In general, in the case of medicinal powders the powders are removed from the container by dissolving in a suitable solvent such as water. In such cases the dry powder usually occupies only a part of the volume of the container. Therefore, suspensions containing on the order of 25 to 30 percent of the powder can be used in the filling operation. In those cases where less free space is needed in the finished container more concentrated suspensions of 50 percent or higher may be used. The only upper limit on the concentration is a practical one controlled by the fluidity and ease of handling of the suspension.

The suspension of the powder in the liquid diluent is fluid so that conventional liquid-filling equipment with slight modification may be used to introduce the suspension into the container. In some instances it may be necessary to modify the liquid-filling equipment by providing some means of agitation in the suspension storage tank to prevent settling.

Once the measured amount of suspension has been added to the container the only remaining step is the evaporation of the liquid diluent. This may be done at any pressure under which the liquid diluent can be removed while maintaining the temperature at a level at which the powder is stable. This evaporation may be conducted by passing the filled containers through a heated chamber, either at atmospheric or reduced pressure. Evaporation at atmospheric pressure is preferred. It is also possible to effect the evaporation by blowing warm air over the open mouth of the container. Various methods of evaporating the diluent are well known to those skilled in the art, and any of these methods may be used. The particular method employed is not important to our invention.

A particularly useful procedure for evaporating higher boiling diluents at temperatures below their boiling points utilizes an intermittent buildup and release of air pressure in what amounts to a "pumping" effect. This is accomplished by placing the filled containers in a closed evaporation vessel, introducing warm air (at a temperature below the boiling point of the diluent) under a positive pressure, and periodically venting the evaporation vessel. The warm air may be at a pressure below about 15 p.s.i., such as 5 to 10 p.s.i. The venting may be automatically accomplished by having the evaporation vessel equipped with a pressure relief valve to automatically vent at some preset pressure such as 3 to 5 p.s.i. By means of such a procedure a high-boiling diluent may be evaporated at a temperature well below its boiling point more rapidly than by the use of a steady stream of air at the same temperature.

The use of such a procedure allows the use of higher boiling diluents with thermally sensitive powders. For example,

isopropanol can be used as a diluent for cephalothin. It is also possible to use a mixture of isopropanol and some other diluent such as ethylene oxide.

Our process will be further illustrated by the following examples.

EXAMPLE 1

A suspension of powdered cephalothin in a 2:1 mixture of methyl chloride and ethylene oxide was prepared in which one gram of cephalothin was added for each 2.5 cc. of mixed diluent. This suspension was taken up in a 20 cc. syringe with an open-barrel needle which had been previously chilled in a dry ice/acetone bath. The suspension was then injected from the syringe into glass ampoules No. 5888 having a 13-millimeter inside-diameter mouth. An amount of suspension containing 1 g. of cephalothin was introduced into each ampoule. The filled ampoules were dried at 20° C. in a hood under turbulent airflow conditions at atmospheric pressure. The drying required about 15 minutes and left 1 gram of cephalothin in the ampoule.

EXAMPLE 2

A suspension of cephalothin was prepared as in example 1 except that the diluent was only methyl chloride. The suspension was taken up in a chilled 20 cc. syringe with an open-barrel needle and was filled into glass ampoules No. 5807 having an 8 mm. inside diameter opening such that the suspension in each ampoule contained 1 gram of cephalothin. The methyl chloride was removed at 25° C. with a warm-air blower in a glove box with a nitrogen purge at atmospheric pressure. Drying under these conditions required about 10 minutes.

EXAMPLE 3

A suspension of 1 gram of cephaloridine in 3 cc. of a 9:1 mixture of methyl chloride and ethylene oxide was prepared. Using a chilled 20 cc. syringe with an open-barrel needle, the suspension was filled into glass ampoules No. 5807 at a temperature of 5° C. The methyl chloride/ethylene oxide mixture was evaporated at 20° C. in a glove box with a nitrogen purge at atmospheric pressure. The drying operation required about 10 minutes left 1 gram of cephaloridine in the ampoule.

EXAMPLE 4

A suspension containing 1 gram of cephalothin per 3 cc. of isopropanol was filled into No. 5807 glass ampoules using an automatic hand pipette such that each ampoule contained 1 gram of cephalothin. The ampoules were placed in a closed vessel equipped with an air feed line and a pressure relief valve set to open at 3 p.s.i. Air at 70° C. was fed to the vessel at a rate of 15 cubic feet per hour under a pressure of 10 p.s.i. The relief valve opened about once each second to expel air having a temperature of about 60° C. In this manner the isopropanol was evaporated in 30 minutes to leave 1 gram of dry cephalothin in the ampoule.

In all the examples the powder remaining in the ampoules after evaporation of the diluent was unchanged chemically or physically from that used to prepare the suspensions. Also, the reconstitution (resolution) characteristics of the powders were unchanged. There was no problem of dusting in the operation and no need to clean the ampoules after filling. Because the amount of powder in the suspension was known, the correct amount of suspension could be accurately measured into the ampoule to leave one gram of powder after evaporation of the diluent.

We claim:

1. A method for filling powders into containers which comprises suspending the powder in an inert, liquid diluent having a boiling point below about 100° C., filling the suspension into the container and evaporating the inert, liquid diluent, leaving the powder in the container.

2. A method as in claim 1 wherein the inert, liquid diluent has a boiling point below about 50° C.

3. A method as in claim 2 wherein the powder is cephaloridine.

4. A method as in claim 2 wherein the powder is cephalothin.

5. A method as in claim 1 wherein the inert, liquid diluent is evaporated by placing the filled container in a closed evaporation vessel, introducing warm air into the vessel under a positive pressure, and periodically venting the vessel.

6. A method as in claim 5 wherein the powder is cephalothin and the inert, liquid diluent is isopropanol.

Disclaimer

3,608,593.—*Samuel L. McCormick, Jr.* and *John J. Burke*, Indianapolis, and *Arthur R. Morstadt*, Speedway, Ind. METHOD OF FILLING POWDERS INTO CONTAINERS. Patent dated Sept. 28, 1971. Disclaimer filed Oct. 6, 1976, by the assignee, *Eli Lilly and Company*.

Hereby enters this disclaimer to all claims of said patent.

[*Official Gazette January 11, 1977.*]