PATENT SPECIFICATION

760,087

Date of Application and filing Complete Specification: Oct. 5, 1954. No. 28698/54.

Application made in Denmark on Oct. 13, 1953.

(Patent of Addition to No. 737,242 dated Sept. 16, 1953.)

Complete Specification Published: Oct. 31, 1956.

Index at acceptance:—**Class 81(1)**, A, B4.

COMPLETE SPECIFICATION

The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act, 1949, are KARL PETERSEN, of 176, Bellahøjvej, Copenhagen, Denmark, and HANS JACOBSEN, of 25, Herluf Trollesgade, Copenhagen, Denmark, both Danish Subjects.

Process of Increasing the Physical Stability of Aqueous Suspensions of Penicillin Compounds

We, NOVO TERAPEUTISK LABORATORIUM A/S, a Danish Limited Liability Company, of 115, Fuglebakkevej, Copenhagen N, Denmark, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Specification No. 25652/53 (Serial No. 737,242) relates to a process of increasing the physical stability of aqueous suspensions of penicillin compounds such as procaine penicillin, wherein atmospheric oxygen is removed from the unfilled space in the containers in which the suspensions are stored, before, during or after the suspensions are filled into these containers. The said removal may be achieved by replacing the atmospheric oxygen by an inert gas, for instance, nitrogen, or a mixture of inert gases, for instance, nitrogen and hydrogen.

In the above specification it is mentioned that the process in question is applied to aqueous suspensions of penicillin compounds preferably in ampoules, and that these ampoules may have the form of small bottles with a tight cover or lid of rubber. Such ampoules are commonly known, and the tight rubber closing device consists either of a tight rubber cap or of a rubber disc or a rubber stopper which is fixed by means of a ring of metal or plastic with a downwardly extending flange closely surrounding the neck of the bottle.

The present invention relates to an improvement in or modification of that feature of the invention of the above mentioned specification, according to which the aqueous suspensions of the penicillin compounds are kept in ampoules or vials with a tight rubber closure member, and the characteristic feature of the present invention consists in that butyl rubber is used for the closure member instead of the previously used rubber material.

It has been found that this results in a considerably better physical stability of the suspensions when stored than when other rubber materials are used.

The process according to the invention can be carried out by filling the sterile suspensions in the usual way into sterile ampoules or vials having the form of bottles and then closing the ampoules, also in the usual way, but by means of the tight butyl rubber closure member. The atmospheric air in the ampoule is then replaced by an inert gas, preferably nitrogen, by piercing a thin hollow needle, for instance, a cannula, through the rubber closure member and then successively applying vacuum and supplying an inert gas to the ampoule through the needle until the atmospheric air is entirely or substantially replaced by the inert gas. Tests which have been performed have shown that the perforation of the rubber closure member when performed with the usual syringe needles has no detrimental influence on the physical stability of the suspensions.

In order to illustrate the effect obtainable according to the invention two series of tests are described below which tests have been performed during the industrial manufacture of aqueous procaine penicillin suspensions filled into glass ampoules having the form of bottles sealed with a rubber disc kept in position by a metal ring with a downwardly extending flange closely surrounding the neck of the bottle. The volume of the ampoules is about 8 millilitres and each ampoule contains about 5 millilitres of the procaine penicillin suspension containing 300.000 units of penicillin per millilitre. In each series 25 ampoules are used, and the ampoules are stored at 37° or 25°C. as stated. At intervals samples of the stored ampoules are taken out for examination in order to determine the period after which the suspensions have lost their stability

[*Price* 3/-]

(physical stability) i.e., are unable to form a uniform and injectable suspension on shaking up.

In both series of tests the atmospheric air of the ampoules is replaced in the above mentioned way by nitrogen which does not contain detectable amounts of oxygen, by piercing a 0.9 mm cannula through the rubber closure member and evacuating and supplying nitrogen in turn three times in all.

In the first series of tests rubber discs of natural rubber are used, and in the second series of tests rubber discs of butyl rubber are used. The results of the tests are given in the table below:

TABLE:

Storing Temperature:	*Natural Rubber*:	*Butyl Rubber*:
37°C.	about 70 days	about 100 days
25°C.	about 7 months	about 12 months

Thus, it is seen that an increase of the stability of about 43% at 37°C. and about 70% at 25°C. is obtained by using butyl rubber instead of natural rubber.

As regards the results obtained it should be remarked that sealed ampoules containing distilled water in the same amount as the procaine penicillin suspension, and in which the atmospheric air has been replaced by nitrogen in the same way as in the above mentioned series of tests, upon analysis were found to contain on the average about 5% of the original amount of oxygen in the ampoules, which means that not all the oxygen can have been removed from the ampoules containing the procaine penicillin suspension. If the process is performed in such a way that all the oxygen is removed from the ampoules, still better results can be obtained.

The process according to the invention can also be carried out in such a way that the atmospheric air is replaced by an inert gas after the suspension has been filled into the ampoules, but before the ampoules are closed, the filling and closing process being performed in a closed chamber in the following manner:

The ampoule is entirely or partly introduced into a chamber whereupon the atmosphere in the chamber, after the latter has been sealed, is replaced by an inert gas, the filling of the suspension into the ampoule is performed and the ampoule is sealed, whereupon the sealed ampoule is taken out of the chamber. Replacing of the atmosphere of the chamber may be carried out by evacuating the chamber and subsequently introducing the inert gas into the chamber. It is preferable to undertake the evacuation of the chamber and the introduction of the inert gas successively several times.

It is also possible to carry out the process according to the invention by first producing sterile suspensions substantially free from atmospheric oxygen, by subsequent evacuation of the suspensions and introduction of the inert gas which introduction may take place by letting the inert gas bubble through the suspension until the atmospheric air is entirely or substantially replaced by the inert gas, and then effecting the filling of the suspension and the sealing of the ampoules in an inert atmosphere.

When the suspensions are produced substantially free from atmospheric oxygen it is also possible to accomplish the filling operation after the sealing operation. In such case the atmospheric air is removed from the empty sterile ampoules, which are then sealed with a butyl rubber closing or sealing device whereupon the sealed ampoules are filled by piercing a small hollow needle, for instance, a cannula, through the butyl rubber closure member, supplying the suspension through the needle and removing the needle. If the atmospheric air in the empty ampoule has been removed by replacing the air by an inert gas so that there is no reduction of pressure in the sealed ampoule, the suspension should be supplied under pressure through the needle.

The butyl rubber discs or the butyl rubber stoppers, used according to the invention, may be produced in a manner known *per se*, use being made of an addition of the fillers usually employed in the rubber industry, such as carbon black and kaolin, in order to provide for strength and elasticity, and of a method of vulcanization using the vulcanizers, vulcanization accelerators, such as thiuram sulphides, and activators which are known to be used in connection with butyl rubber.

Though the present invention may be employed with aqueous suspensions of penicillin compounds in general, it aims specially at an increase of the stability of aqueous suspensions of penicillin salts which are slightly soluble in water, preferably procaine penicillin.

In our Specification No. 745,790, we claim a container suitable for containing a moisture-sensitive therapeutic substance in solid form and provided with closing or sealing means entirely or partly consisting of a butyl rubber composition. We also claim a disc, washer or stopper of a butyl rubber composition for use in a closure for a container, and a sealing cap of a butyl rubber composition for a container, said container in each case being especially a bottle-shaped ampoule or vial, suitable for containing a moisture-sensitive therapeutic substance.

What we claim is:—

1. A method of storage of aqueous suspensions of penicillin compounds whereby the physical stability thereof is prolonged, in which method such a suspension is filled into ampoules each having a tight butyl rubber closure member, atmospheric oxygen be-

(physical stability) i.e., are unable to form a uniform and injectable suspension on shaking up.

In both series of tests the atmospheric air of the ampoules is replaced in the above mentioned way by nitrogen which does not contain detectable amounts of oxygen, by piercing a 0.9 mm cannula through the rubber closure member and evacuating and supplying nitrogen in turn three times in all.

In the first series of tests rubber discs of natural rubber are used, and in the second series of tests rubber discs of butyl rubber are used. The results of the tests are given in the table below:

TABLE:

Storing Temperature:	*Natural Rubber*:	*Butyl Rubber*:
37°C.	about 70 days	about 100 days
25°C.	about 7 months	about 12 months

Thus, it is seen that an increase of the stability of about 43% at 37°C. and about 70% at 25°C. is obtained by using butyl rubber instead of natural rubber.

As regards the results obtained it should be remarked that sealed ampoules containing distilled water in the same amount as the procaine penicillin suspension, and in which the atmospheric air has been replaced by nitrogen in the same way as in the above mentioned series of tests, upon analysis were found to contain on the average about 5% of the original amount of oxygen in the ampoules, which means that not all the oxygen can have been removed from the ampoules containing the procaine penicillin suspension. If the process is performed in such a way that all the oxygen is removed from the ampoules, still better results can be obtained.

The process according to the invention can also be carried out in such a way that the atmospheric air is replaced by an inert gas after the suspension has been filled into the ampoules, but before the ampoules are closed, the filling and closing process being performed in a closed chamber in the following manner:

The ampoule is entirely or partly introduced into a chamber whereupon the atmosphere in the chamber, after the latter has been sealed, is replaced by an inert gas, the filling of the suspension into the ampoule is performed and the ampoule is sealed, whereupon the sealed ampoule is taken out of the chamber. Replacing of the atmosphere of the chamber may be carried out by evacuating the chamber and subsequently introducing the inert gas into the chamber. It is preferable to undertake the evacuation of the chamber and the introduction of the inert gas successively several times.

It is also possible to carry out the process according to the invention by first producing sterile suspensions substantially free from atmospheric oxygen, by subsequent evacuation of the suspensions and introduction of the inert gas which introduction may take place by letting the inert gas bubble through the suspension until the atmospheric air is entirely or substantially replaced by the inert gas, and then effecting the filling of the suspension and the sealing of the ampoules in an inert atmosphere.

When the suspensions are produced substantially free from atmospheric oxygen it is also possible to accomplish the filling operation after the sealing operation. In such case the atmospheric air is removed from the empty sterile ampoules, which are then sealed with a butyl rubber closing or sealing device whereupon the sealed ampoules are filled by piercing a small hollow needle, for instance, a cannula, through the butyl rubber closure member, supplying the suspension through the needle and removing the needle. If the atmospheric air in the empty ampoule has been removed by replacing the air by an inert gas so that there is no reduction of pressure in the sealed ampoule, the suspension should be supplied under pressure through the needle.

The butyl rubber discs or the butyl rubber stoppers, used according to the invention, may be produced in a manner known *per se*, use being made of an addition of the fillers usually employed in the rubber industry, such as carbon black and kaolin, in order to provide for strength and elasticity, and of a method of vulcanization using the vulcanizers, vulcanization accelerators, such as thiuram sulphides, and activators which are known to be used in connection with butyl rubber.

Though the present invention may be employed with aqueous suspensions of penicillin compounds in general, it aims specially at an increase of the stability of aqueous suspensions of penicillin salts which are slightly soluble in water, preferably procaine penicillin.

In our Specification No. 745,790, we claim a container suitable for containing a moisture-sensitive therapeutic substance in solid form and provided with closing or sealing means entirely or partly consisting of a butyl rubber composition. We also claim a disc, washer or stopper of a butyl rubber composition for use in a closure for a container, and a sealing cap of a butyl rubber composition for a container, said container in each case being especially a bottle-shaped ampoule or vial, suitable for containing a moisture-sensitive therapeutic substance.

What we claim is:—

1. A method of storage of aqueous suspensions of penicillin compounds whereby the physical stability thereof is prolonged, in which method such a suspension is filled into ampoules each having a tight butyl rubber closure member, atmospheric oxygen be-

* C L M S *

ing removed from the unfilled space in the ampoules, before, during or after the suspension is filled into the same.

2. A method as claimed in Claim 1, wherein the atmospheric air in an ampoule is replaced by an inert gas, preferably nitrogen, after filling and sealing the ampoule, by piercing a thin hollow needle, for instance, a cannula, through the butyl rubber closure member whereupon successively vacuum is applied and the inert gas is supplied through the needle to the ampoule until the atmospheric air is entirely or substantially replaced by the inert gas.

3. A method as claimed in Claim 2, wherein evacuation and supply of inert gas to the ampoule are repeated several times.

4. A method as claimed in Claim 1, wherein the atmospheric air in a sterile suspension is replaced by an inert gas, whereupon the suspension is filled into sealed sterile ampoules which have been freed from their contents of atmospheric air, by piercing a small hollow needle through the butyl rubber closure member, supplying the suspension through the needle and removing the needle.

5. A method of storage of aqueous suspensions of penicillin compounds whereby the physical stability thereof is prolonged, conducted substantially as described herein.

ABEL & IMRAY,
Agents for the Applicants,
Quality House,
Quality Court, Chancery Lane,
London, W.C.2.

Printed for Her Majesty's Stationery Office by Wickes & Andrews, Ltd., E.C.4. 684/2.—1956.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

