PATENT SPECIFICATION

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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.

COMPLETE SPECIFICATION

Improvements in and relating to Closures for Containers for Therapeutic Substances which are Sensitive to Moisture

We, NOVO TERAPEUTISK LABORATORIUM A/S, of 115, Fuglebakkevej, Copenhagen, Denmark, a limited liability company, duly organised under the laws of 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:—

This invention relates to improvements in closures for containers for therapeutic substances which are sensitive to moisture.

A series of therapeutic substances which are sensitive to moisture and are adapted for treatment of wounds or for administration par os or by injection after incorporation into a suitable quantity of a sterile liquid, are marketed in the form of tablets, pills or a loose powder in containers provided with a closing member entirely or partly consisting of a rubber composition. Examples of such therapeutic substances are antibiotics, for instance penicillin and streptomycin compounds, blood plasma, serums, vaccines, hormones and enzymes.

With the rubber materials hitherto employed it has, however, not been possible to obtain impermeability to water vapour. During storage in humid air, water vapour will diffuse through the rubber material, and this diffusion will increase with increasing temperature. The moisture will be absorbed by the said substances which may cause such an agglomeration of a loose powder that it will not dissolve or suspend in the quantity of liquid destined for this purpose and moreover the absorption of the moisture, as regards some substances for instance penicillin salts, may also involve a decomposition resulting in a change of the therapeutic activity whether loose powder, tablets or pills are concerned. These drawbacks will be particularly apparent upon storage for a considerable time, especially in tropical or sub-tropical countries.

The said drawbacks can be avoided by storing the therapeutic substances in metal containers of similar constructions to cans, but these containers are unsuitable for direct sales to the consumers and especially in the case of storage of small quantities, such as a prescribed number of tablets or pills or a few grams or less of a loose powder intended for injection purposes directly from the container. In such cases it has been proposed to use glass containers provided with a screw lid having a washer of impregnated or laminated paper or provided with a rubber stopper enclosed in a sealed glass stem, but the former containers do not offer satisfactory protection against the humidity of the air, and the latter are relatively expensive which limits their applicability.

There has been no lack of experiments to find rubber compositions which will show a sufficient impermeability to moisture. Thus, a long series of investigations of different compositions based on natural rubber has been made, and attempts have also been made to substitute the natural rubber by the synthetic rubber "neoprene," vide e.g. E. W. Flosdorff: "Freeze-Drying," New York, 1949, pages 150—164. However, these investigations showed that neither based on natural rubber nor with the tested compositions based on synthetic rubber was it possible to provide a closure which was sufficiently moisture-tight, unless precautions were taken that the rubber material had no possibility at all of coming

[*Price 3s. 0d.*]

into contact with the surrounding atmosphere.

The problem has been particularly important in connection with the various antibiotics, especially penicillin, which are marketed in the form of tablets in bottles with screw lids or in the form of a loose powder in small bottle-like glass containers (vials) the opening of which is closed by means of a rubber disc or a rubber stopper kept in position by a metal ring with a downwardly extending flange closely surrounding the neck of the bottle. In order to prevent the rubber coming into contact with the surrounding atmosphere, the metal ring has been provided with a central tear off top which covers the rubber, or alternatively use has been made of a removable metal cap placed on the said closure. However, these closing devices are not sufficiently effective.

The purpose of the present invention is to solve the sealing problem without being obliged to use auxiliary means which complicates the closure and makes it more expensive, and which requires removal of one or more parts of the closure before the therapeutic substance in the container becomes available for administration.

The invention is based on the observation that stoppers and discs of butyl rubber mixed with the filling substances ordinarily used in the rubber industry, and vulcanized in the usual way, show a high impermeability to water vapour.

It is known that vulcanized butyl rubber compositions in a similar manner to other artificial rubber compositions, for instance neoprene compositions, show a high impermeability to air. However, in the experiments referred to above, neoprene has shown the same easy permeability to moisture as natural rubber. Consequently, from impermeability to air no conclusions can be drawn regarding impermeability to moisture. Hence, it could not be forseen that butyl rubber would show such an impermeability to moisture that substantial advantages would result from the use of butyl rubber instead of another synthetic rubber (neoprene) or natural rubber.

In conformity with the observation referred to above, the present invention relates to 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 butyl rubber.

The invention particularly relates to such containers having the form of a bottle-shaped ampoule (vial) the opening of which is sealed by a sealing butyl rubber cap or by a butyl rubber disc, washer or stopper intended to be kept in position by a ring of metal or plastic material with a downwardly extending flange closely surrounding the neck of the bottle. The invention, however, can also be used with great success in connection with containers, preferably of glass, provided with a lid, preferably a screw lid, with a sealing washer or disc of butyl rubber.

The effect obtainable by means of the invention may be illustrated as follows:

If 120 mgs of crystalline sodium penicillin are stored in bottle-shaped glass vials or ampoules provided with a closure as described above, the containers being kept in air saturated with water vapour for a time at 37° C., for a time at 25° C., and for a time at 37° C., during every other period of 24 hours, and at 4° C., during every alternate period of 24 hours, an increase of weight of each vial will be found averaging about 1.5 mgs after the course of 50 days and nights and averaging about 1.8 mgs after the course of 100 days and nights, provided butyl rubber is used as closure material. If the butyl rubber is replaced by natural rubber there will be obtained an increase of weight averaging about 6 mgs after the course of 50 days and nights, and averaging about 8 mgs after the course of 100 days and night. Thus when using butyl rubber the increase in weight is about one fourth of that when using natural rubber. When for comparison with butyl rubber neoprene is used instead of natural rubber, the difference is still more pronounced.

However, in a blank experiment the empty sealed vials will also increase in weight under the above mentioned storage conditions. When a closure of natural rubber is used, an increase of weight of about 3 mgs will be obtained in the course of 50 days and nights. With butyl rubber the increase of weight will amount to about 1.5 mgs.

Hence, it must be assumed that the moisture absorption of the sodium penicillin is materially less than appears from the increase of weight of the containers. After correction for the increase of weight of the empty vials, the absorption of water of the sodium penicillin stored in vials with a closure of natural rubber will be about 3 mgs while the absorption of water if butyl rubber is employed will be less than the experimental error.

After storage at 25° C. and at 37° C. during 100 days and nights the pulverulent crystalline sodium penicillin will have lost its pulverulent consistency when natural rubber has been used in the closure. An agglomeration of the powder has taken place, and the sodium penicillin has assumed a yellowish colour as a consequence of the decomposition caused by the absorption of water and has lost so much of its biological activity that it is no longer practically utilizable. If, however, butyl rubber has been employed for the closure, no physical or biological change of the crystalline sodium penicillin under the same conditions will have taken place.

For use for the purpose of the invention the butyl rubber is mixed with the fillers ordinarily employed in the rubber industry, such as carbon black and kaolin, in order to

obtain strength and elasticity, whereas use is made of a vulcanization method using the vulcanizers, vulcanization accelerators such as thiuram sulphides, and activators, commonly used in connection with butyl rubber.

The present invention is of importance in all cases where solid therapeutic substances which are sensitive to humidity are to be stored for a considerable time before use. The invention is of especial importance in connection with such substances as are destined for injection and are stored in vials, and where it is decisive that no deterioration of the therapeutical properties of the substance must take place. In the case of therapeutic substances which are sensitive to humidity it generally applies that they are more hygroscopic in amorphous form than in crystalline form. Consequently, the effect obtained according to the invention is comparatively greatest in connection with products which have been brought into amorphous form by means of dehydration, for instance by freeze-drying, atomizing or precipitation.

Among the therapeutic substances which are particularly sensitive to humidity there should be particularly mentioned the various antibiotics, such as penicillin and streptomycin in crystalline or amorphous form and also enzymes such as trypsin, particularly in freeze-dried form.

Finally, it may be mentioned that the invention also comprises discs, washers or stoppers of butyl rubber for use in closures for the containers referred to, particularly vials or ampoules, and also sealing caps for such containers.

What we claim is:—

1. 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.

2. A container as claimed in Claim 1, in the form of a bottle-shaped ampoule or vial, the opening of which is sealed by a butyl rubber cap or by a butyl rubber disc, washer or stopper intended to be kept in position by a ring of metal or plastic material with a downwardly extending flange closely surrounding the neck of the bottle.

3. A container as claimed in Claim 1, provided with a lid, preferably a screw lid, with a sealing washer or disc of butyl rubber.

4. A disc, washer or stopper of a butyl rubber composition, for use in a closure for a container especially a bottle-shaped ampoule or vial, suitable for containing a moisture-sensitive therapeutic substance.

5. A sealing cap of a butyl rubber composition for a container, especially a bottle-shaped ampoule or vial, suitable for containing a moisture-sensitive therapeutic substance.

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