Oct. 30, 1951 W. L. BENDER 2,573,637

TREATED STOPPER FOR AND METHOD OF INTRODUCING ANTIFOAM AGENT INTO A LIQUID MEDICAMENT OR THE LIKE

Filed May 22, 1950

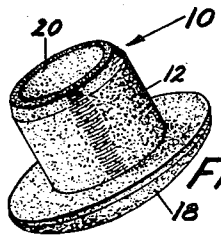


FIG. 1

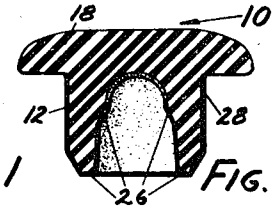


FIG. 5

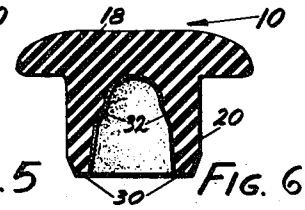


FIG. 6

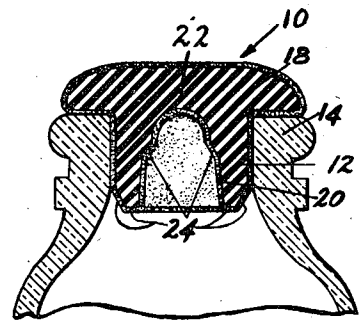


FIG. 2

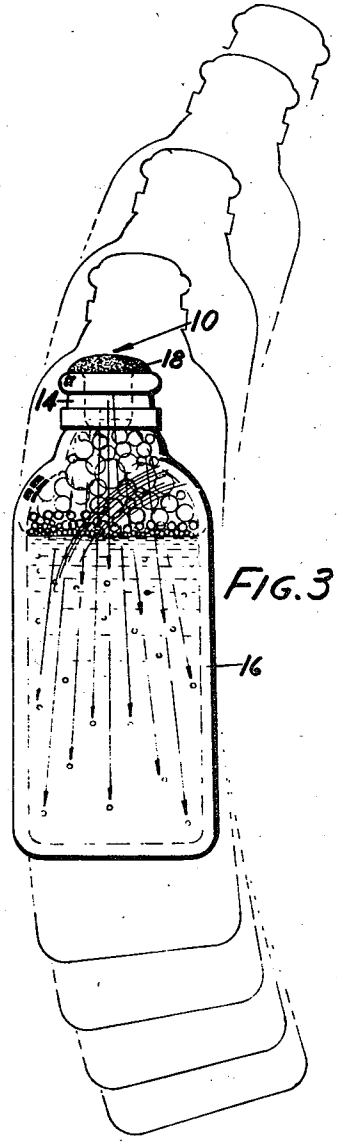


FIG. 3

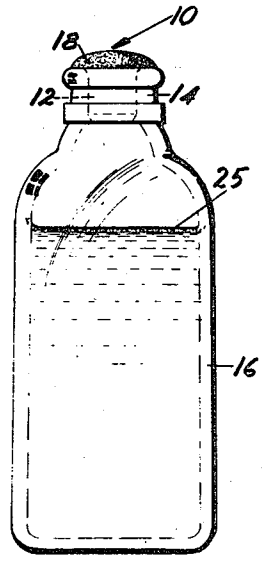


FIG. 4

INVENTOR.

BY WILLIAM L. BENDER

William Greenbaum

George A. Ordway.

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TREATED STOPPER FOR AND METHOD OF INTRODUCING ANTIFOAM AGENT INTO A LIQUID MEDICAMENT OR THE LIKE

William L. Bender, Plainfield, Ind., assignor to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

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10 Claims. (Cl. 128—272)

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This invention relates to closures for containers and more particularly to a stopper for medicament containers such as ampoules, vials or the like and to a method of introducing an anti-foam agent into a medicament. It has to do with introducing an anti-foam agent into a medicament, the maintainence of stoppers in proper, separated condition during and following sterilization operations, and facilitating the stoppering operations per se.

As is well known, certain pharmaceuticals require shaking before use and this generally develops foam within their containers. Excessive foam often interferes with the withdrawal from the container into a syringe of the precise dose amount required. Patients having to self-administer injections are frequently reluctant to withdraw any medicament from the ampoule or other container until the foam subsides. Such subsidence, in the absence of an anti-foam agent in the medicament, is time consuming. It has been known to introduce a foam suppressing or anti-foam agent directly into a batch of liquid before filling the ultimate individual containers. This batch method of introducing the foam suppressor is not entirely satisfactory because it is difficult, if not impossible, to obtain and maintain complete and thorough dispersion of the anti-foam agent throughout the mass and, this non-homogeneous dispersion results in variations in the quantities of the agent dispensed into the individual containers. Introduction of the anti-foam agent agent directly into a dose container presents problems in that only a very minute quantity is necessary to accomplish the anti-foam action, and as a matter of fact, the necessary quantity is so minute as to make it extremely difficult to introduce such quantity in any manner which insures the desired degree of uniformity. On the other hand, if more anti-foam agent is introduced than is necessary, generally, because of the inherent characteristics of such agents, visible film areas, or globules of the agent, or both, form on the surface of the medicament and present an undesirable appearance from both a practical and an aesthetic aspect.

Certain types of ampoules employ as a sealing means, a rubber stopper formed with a depending shank adapted to fit securely within the neck of the ampoule and merging with a flanged top or cap adapted to seat flat on the upper rim of the ampoule neck. These stoppers are sterilized as by subjecting them to steam under pressure in an autoclave. Autoclaving frequently causes some of the stoppers to become tacky and

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to adhere one to another in groups or clusters. This clinging or clustering is undesirable, because efficient, expeditious and sterile mass production capping operations require that the stoppers be completely free from each other ready for unobstructed, individual removal from the sterilized batch and forthwith insertion into sealing position in the container. It is imperative that the stoppers be maintained sterile throughout the entire sealing operation.

The above referred to clustering as well as frictional resistance encountered in inserting an individual stopper into proper sealing relation within the neck of the ampoule reduces the speed and facility of the stoppering operations.

It is a general object of the present invention to provide a stopper for medicament containers which in large measure overcomes the aforesaid problems and difficulties.

It is an object of the invention to provide a stopper of the above character that serves as a depot where the anti-foam agent is conveniently, economically, and efficiently deposited in an accurate, minute quantity effective to produce the desired anti-foam action and is held ready for foam-suppressing dispersion into the medicament as the container is moved an extent sufficient to cause the medicament to contact the depot. Hence, the act of shaking which creates the foam is utilized to disperse the foam suppressing agent.

A further object is to provide such a stopper which during autoclaving or similar necessary sterilization treatment retains its separate, individual, status and will not adhere to another stopper during or following the subjection of a batch of stoppers to the high temperatures generally used in such sterilization processes.

A still further object is to provide a stopper which without undue friction slides smoothly and readily into effective sealing position within the neck of the container.

Other objects and advantages of the invention will be apparent as the description proceeds in conjunction with the accompanying drawings, and will be more particularly pointed out in the claims which follow.

In the drawings:

Fig. 1 is a perspective view of a stopper of the type in which this invention may be employed,

Fig. 2 is a side elevation of a medicament container, more specifically an ampoule, with the stopper inserted therein, the stopper and upper end of the ampoule being shown in highly magnified cross section,

Fig. 3 is a side elevation of a stoppered ampoule and illustrates in diagrammatic form how the anti-foam agent is dispersed from the depot into the medicament when the container is shaken,

Fig. 4 is a side elevation of a stoppered ampoule shown in rest position following the shaking operation and exaggeratedly indicates a film formed by the anti-foam agent over the surface of the medicament, and

Figs. 5 and 6 show modified forms of the invention.

Referring to Figs. 1 and 2 there is generally indicated at 10 a rubber stopper of the type in which my invention may be embodied, it being understood that the invention is not limited to any particular type of stopper nor to a stopper of any particular material or size. Stopper 10 includes a depending shank 12 adapted to fit securely within the neck 14 of the ampoule or other container 16. Shank 12 merges at its upper end into a flanged top or cap 18 which is adapted to seat flat against the upper face of neck 14. Generally, a stopper of the type illustrated is provided with a hollow bore 20 interiorly of its shank 12 so as to form a relatively thin walled portion 22 centrally of cap 18. This thin walled portion is easily punctured by a hypodermic needle (not shown) for withdrawing medicament from the ampoule into a syringe (not shown) associated with the needle.

As previously stated it is desirable to suppress the foaming of certain medicaments such as are packaged in containers or ampoules of the class just described. The present invention provides a convenient, accurate and efficient means for and method of introducing the anti-foam agent into the medicament or into any liquid which foams. This is accomplished by dipping a batch of stoppers such as 10 in a dispersion of anti-foam agent of the silicone type. The particular silicone compound preferably used is commercially available under the trade name "D. C. Antifoam A." This compound is colorless and translucent. It has a slight but unobjectionable odor, is non-toxic and heat stable. It is lighter than water and is insoluble therein. It is dispersible in solvents such as cyclohexane, ethyl ether, methylene chloride, trichloroethylene and the like. Preferably, the anti-foam agent is dispersed into the solvent in a quantity on the order of five percent of the volume of the solvent. The concentration of the dispersion to be employed may be varied in accordance with

(*a*) The foaming propensities of the particular medicament to be packaged,

(*b*) The quantity of medicament to be contained within an individual container, and

(*c*) The surface area of the particular stopper which is used to close the container.

Having established the proper concentration in accordance with the above variables, a batch of the stoppers is treated simply by dipping the batch momentarily into the solvent dispersion. Upon withdrawal, the solvent is permitted to evaporate leaving an extremely thin film of the anti-foam agent completely over and upon all of the surfaces of the treated stopper. If desired the evaporation of solvent may be expedited as by subjecting the treated stoppers to vacuum or placing them in a heated air current or the like. Referring to Fig. 2, the film coating is shown in greatly magnified form and it will be understood that the thickness shown is exaggerated many, many times for the purpose of illustration only, the fact being that the only difference in appearance of the stoppers is that of a glacé or sheen cast which contrasts somewhat with the flat or matte finish of untreated stoppers. By momentarily immersing the stoppers in the manner above described a very minute quantity of the solvent dispersion is thoroughly, completely, economically and efficiently distributed over the entire surface area of the stopper. The quantity of coating applied to each stopper by this dipping procedure is minute and remarkably uniform. That portion of the film which coats the lower end of shank 12 and extends upwardly and interiorly of bore 20 provides a depot 24 from which the anti-foam agent is dispersed into the medicament. Such dispersion is brought about by such movement of the container as will cause the medicament to contact the depot 24.

Mass production machines such as are presently used for handling containers of the type described are generally provided with endless belts which transport the ampoules from a capping station where operators insert the caps by means of sterilized tweezers into the ampoules, to a station where an airtight sealing rim of gelatin (not shown) is applied around the neck of the ampoule over the junction between the upper surface of neck 14 and the lower face of the cap 18. If desired, the stoppers may be further sealed in stoppering position in the ampoule by applying a metallic cap or banding ring (not shown) over the stopper and under the peripheral ledge of the neck 14 of the ampoule. On such machines, in presenting the ampoule to the gelatin applying mechanism, the ampoule is rocked from a vertical into a horizontal position. This movement is sufficient to cause the medicament to come into contact with depot 24 of stopper 10. In this manner the anti-foam agent is at least partially removed from depot 24 and dispersed into the medicament forthwith following the capping operation and before any shaking is imparted to the container. Such removed quantity may be effective to impart sufficient anti-foam qualities to the medicament to effect the desired anti-foam action. However, if such horizontal positioning of the container should not be employed, or if sufficient quantity of the anti-foam agent is not dispersed from depot 24 by such movement of the container, the anti-foam agent positively will be dispersed in sufficient quantity from the depot into the medicament upon the shaking of the container in the manner illustrated in Fig. 3.

Upon the medicament coming to rest as illustrated in Fig. 4, the particles of the anti-foam agent which were dispersed therein incident to the shaking operation, being lighter than and insoluble in the medicament, rise to the surface thereof, assert their foam suppressing action upon the bubbles creating the foam, thereby breaking the foam, and finally coalesce to form a film indicated at 25 over the upper surface of the medicament. It is to be noted that the film 25 shown in Fig. 4 is for the purpose of illustration only; as a matter of fact the film is not more than a few molecules in thickness and is completely invisible. It will be understood that upon a reshaking of the ampoule 16 this film of silicone anti-foam agent will be redispersed into the medicament as illustrated in Fig. 3, and that the subsidence of the foam created by such shaking shall be much more rapid than it would be without the presence of the anti-foam agent. As the particles again ascend to the surface, the foam is destroyed and the particles again merge to form the film 25 as shown in Fig. 4.

As heretofore mentioned, such stoppers are, before use, sterilized as by autoclaving. During such sterilization process the stoppers are deposited as a batch in random fashion, i. e., with different surface portions of different stoppers contacting one another, into an autoclave. Efficiency and economy militate against individual handling of the stoppers in the sterilization process and while the batch autoclaving method is highly satisfactory from this standpoint it has a serious drawback in that under the high temperatures employed, the surfaces of the stoppers become tacky resulting in certain of the stoppers of the batch sticking to one another along those surface portions which contact each other.

In one method of capping the ampoules, an operator grasps a stopper with sterile tweezers (not shown), places a forefinger on the upper surface of cap 18 and by means of the tweezers directs the leading edge of shank 12 into the neck 14. When all portions of the leading edge of the shank have been tucked within the confines of the neck, the pressure by the forefinger on the cap 18 forces the shank downwardly into the neck until the under surface of cap 18 seats against the upper surface of neck 14 as clearly shown in Fig. 2. In certain instances it may be necessary to impart a slight twisting motion to cap 18 at the same time that the downward pressure is exerted thereupon to overcome the friction normally present between the outer surface of shank 12 and the inner surface of the neck 14.

Bearing in mind the technique employed in inserting the caps into the necks of the ampoules, it will be realized that when an operator encounters a cluster of stoppers, the smooth routine of the capping procedure is disrupted because the operator must pull all of the stoppers forming the cluster, except the one grasped by the tweezers, from the latter. This act involves the risk of contamination to the removed cluster of stoppers and hence the remaining cluster must be discarded, to be later separated, reautoclaved and again presented to the capping station where the procedure outlined above is again carried on, i. e., individual stoppers are inserted in the ampoules and the clusters encountered are discarded for later separation and reautoclaving and so on.

The glacé sheath of film coating of a silicone anti-foam agent covering entirely all of the surfaces of the stopper completely eliminates this clustering problem. Such film is stable under the temperatures used in autoclaving, gives a slight but effective lubricating action and thereby prevents the surfaces of the stoppers from becoming tacky and sticking together or clustering. Batches of stoppers coated with the silicone type anti-foam agent may be sterilized by mass production autoclave methods and will retain such separate, individual status as they would if a prohibitively costly method of having each stopper handled separately, i. e., sterilized in an individual compartment, were to be employed. Hence, the improved stopper completely overcomes the problem of clustering and the difficulties attendant thereto in capping operations. This results in marked savings in time and cost in mass production capping operations.

In addition to the foregoing, the slight lubricating quality of the film of the anti-foam agent on the external surface of shank 12 facilitates the easy insertion of the shank within the neck of the bottle, and overcomes any undue friction caused by engagement of the external surface of the shank with the internal surface of neck

14. This enables the stopper to be seated smoothly and readily into effective sealing position within the neck of the ampoule and thereby expedites the stoppering operations.

It will be understood that the application of the silicone agent to the stopper may be accomplished in any suitable manner and not only by dipping the stoppers within a dispersion of the anti-foam agent. Such coating can be applied as by flow or roller coating the dispersed anti-foam agent upon the stoppers or by brushing or spraying it thereon, or by impregnating the closures or the material from which they are made with the anti-foam agent. However, it is noted that the dipping method heretofore described is a convenient and efficient method of applying a thin film of the dispersion to the stoppers and is highly desirable for obtaining deposition of uniformly accurate and minute quantities in a simple and economical manner.

Referring now to Fig. 5, it will be seen that, if desired, a stopper 10 may be treated with the agent so that only certain portions of its surface area receive the coating of the silicone anti-foam agent. In Fig. 5 the film is shown as applied to all exposed surfaces of the stopper except the under and upper surfaces of the cap 18. This can be accomplished as by using a brush or spray method of application, provision being made to mask those surfaces upon which there is to be no coating applied. A stopper coated as illustrated in Fig. 5 has the advantage of providing a convenient depot 26, similar to the depot 24 for the anti-foam agent and also has the film 28 around the external surface of shank 12 which, by virtue of its lubrication qualities, facilitates the insertion of the stopper within the neck 14. Such a stopper might not be as satisfactory as the stopper disclosed in Figs. 1 and 2 except perhaps for some special purpose because the uncoated upper and lower surfaces of cap 18 would invite the possibilities of the sticking together of these portions in the batch autoclave sterilization method.

The modification shown in Fig. 6 is substantially identical with that shown in Fig. 5 except that the film 28 on the external surface of shank 12 is omitted. That is, the only film coating on the stopper shown in Fig. 6 is that which is applied to the bottom surfaces 30 of shank 12 and to the internal surface 32 of bore 20. A stopper treated in this manner would have the anti-foam advantage provided by the film on the portions 30—32. The same difficulties would be encountered in autoclaving as described in conjunction with the stopper shown in Fig. 5, and greater friction would be encountered in inserting the shank 12 within the neck 14 of the ampoule 16, due to the absence of the lubricating film of anti-foam agent on the external surface of shank 12; however, under certain circumstances such a partially coated stopper might well satisfy the requirements of a specific packaging problem.

From the foregoing it is seen that my invention provides a closure or stopper for a container of medicament or other liquid, which closure or stopper accurately, conveniently, and economically provides a depot for an anti-foam agent and that my invention simultaneously provides stoppers that will retain their free, independent, disconnected character during and after subjection to high temperature sterilizing operations, and slide smoothly into stoppering position without undue friction within the container. It will

also be apparent that the method of introducing the anti-foam agent provides a simple, inexpensive, convenient and efficient procedure for obtaining the anti-foam action and one which utilizes the very act which creates the foam, i. e., the shaking or disturbance of the liquid, to disperse the foam suppressing agent thereinto.

I claim.

1. A closure for a container of liquid which foams upon being shaken, said closure being treated with an anti-foam agent of the silicone type over at least a portion thereof which will be contacted by said liquid in said container upon sufficient movement being imparted to the container to bring the liquid into contact with said portion.

2. A stopper for a container for liquid medicament or the like; said stopper having a thin, invisible, glacé film coating of a silicone anti-foam agent thereover, said film being adapted to be dispersed into the liquid contents of said container upon said liquid contacting said film, serving to prevent sticking of the stoppers during heat sterilization, and imparting lubrication to facilitate application of the stoppers into sealed relation with said container.

3. A stopper for use in a container for liquid medicaments or the like that foam upon being shaken, said stopper being treated with a silicone anti-foam at at least a portion thereof communicating with the interior of the container, said treated interiorly communicating portion providing a depot for receiving a minute quantity of said agent and dispersing said agent into said liquid upon contact of said liquid with said depot.

4. A stopper for use with a container for liquid medicaments or the like, said stopper being treated with an anti-foam agent of the silicone type in such manner as to provide a thin, invisible glacé film thereover effective to prevent said treated stoppers for sticking one to another during sterilization in an autoclave.

5. A stopper for use with a container for liquid medicaments or the like, said stopper being treated with an anti-foam agent of the silicone type in such manner as to provide a thin, invisible glacé film thereover effective to facilitate placement of said stoppers into sealing relation with their respective containers.

6. A stopper for use with a container for liquid medicaments or the like, said stopper being treated with an anti-foam agent of the silicone type in such manner as to provide a thin, invisible glacé film thereover effective to disperse said anti-foam agent from a portion thereof contacted by said liquid into the liquid upon the latter being shaken within the container.

7. The method of introducing an anti-foam agent into a liquid within a container having a closure therefor, comprising the steps of treating the closure for such container with said anti-foam agent, applying said closure to said container, and imparting sufficient movement thereto to bring the liquid contained therein into contact with said treated closure for dispersion of said agent into the liquid.

8. The method of introducing a silicone anti-foam agent into a liquid medicament or the like within a container having a closure therefor, comprising the steps of applying a thin, invisible, glacé film coating of said anti-foam agent to said closure, applying said coated closure to said liquid container and imparting movement to said container sufficient to cause said liquid to contact a portion of said film coating and disperse said film in particulate form throughout the liquid contained in said container.

9. The method of introducing an anti-foam agent into a liquid medicament or the like which requires shaking before use and is packaged within a container having a closure therefor, including the steps of treating at least that portion of the container closure communicating with the interior of the container with an anti-foam agent of the silicone type, applying said closure to a container containing said liquid, and utilizing the required act of shaking which creates the foam to cause the liquid to contact said treated portion and disperse the anti-foam agent thereinto.

10. The method of introducing an anti-foam agent into a liquid medicament or the like packaged within a container having a closure therefor, comprising the steps of momentarily dipping the closure in a dispersion of an anti-foam agent of the silicone type in a solvent, evaporating the solvent from the dipped closure, applying the closure into closing relation with the container in which the liquid is contained, and imparting movement to the closed container sufficient to cause the liquid to contact the treated closure and thereby disperse the anti-foam agent into the liquid.

WILLIAM L. BENDER.

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