United States Patent [19]

Romberg et al.

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[45] **Date of Patent: * Nov. 27, 1990**

[54] **PHARMACEUTICAL ELASTOMERIC COATING**

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[73] Assignee: **The West Company Incorporated**, Phoenixville, Pa.

[*] Notice: The portion of the term of this patent subsequent to Feb. 28, 2006 has been disclaimed.

[21] Appl. No.: **267,828**

[22] Filed: **Nov. 7, 1988**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 37,959, Apr. 13, 1987, Pat. No. 4,808,453.

[51] **Int. Cl.**[5] **B65D 81/24**

[52] **U.S. Cl.** **428/36.8;** 428/494; 428/495; 428/519; 428/521; 215/364; 220/DIG. 19; 528/396

[58] **Field of Search** ..... 215/364; 220/19, DIG. 19; 428/36.8, 494, 495, 519, 521; 528/396

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,288,728	11/1966	Gorham et al.	528/125
3,300.332	1/1967	Gorham et al.	428/403
3,342,754	9/1967	Gorham et al.	428/195
3,927,695	12/1975	Crockwell	138/137
4,082,862	4/1978	Esemplare et al.	428/494
4,808,453	2/1989	Romberg et al.	428/36.8

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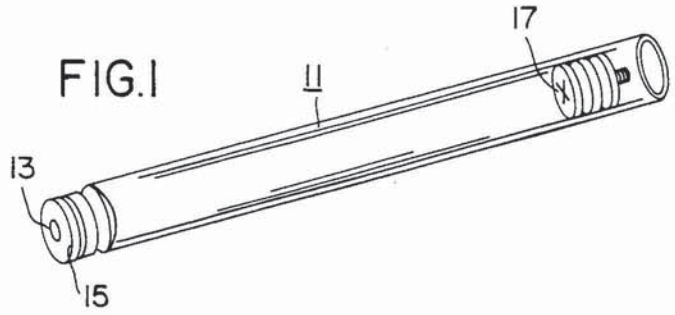
[57] **ABSTRACT**

An elastomeric member for use with a container and in contact with pharmaceutically pure contents therein. The elastomeric member has an elastomeric base and a continuous polyparaxylylene coating on the base. The coating ranges from about 0.5 microns to about 2.0 microns in thickness. The closure member has a coefficient of friction of less than 1.0 and is capable of substantially preventing metal extraction from said elastomers.

8 Claims, 2 Drawing Sheets

FIG.1



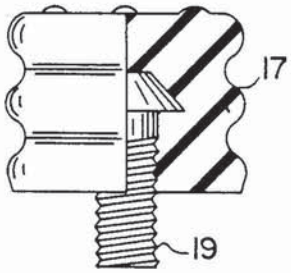


FIG.2

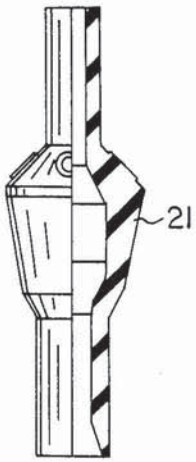


FIG.3

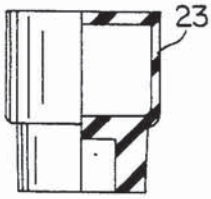


FIG.4

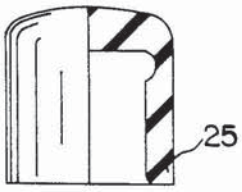


FIG.5

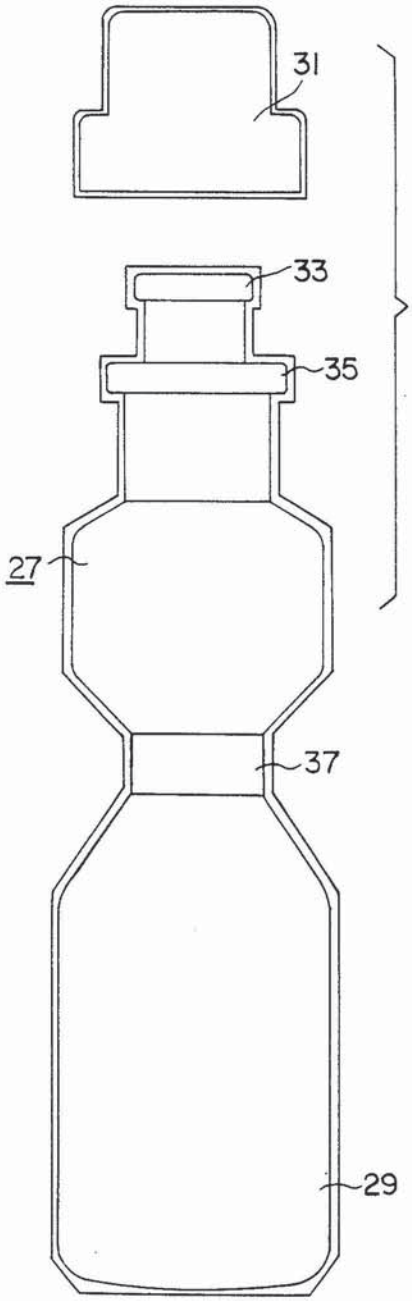


FIG.6

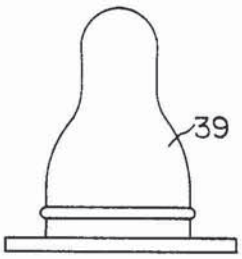


FIG.7

PHARMACEUTICAL ELASTOMERIC COATING

FIELD OF THE INVENTION

This invention relates to pharmaceutical products which includes a container having pharmaceutically pure contents and an elastomeric member which is also in contact with the contents. The elastomeric member has an elastomeric base and a continuous poly (p-xylylene) coating of from about 0.5 microns to 2 microns in thickness.

BACKGROUND OF THE INvENTION

For many years, the most successful closure system for pharmaceutical products has been the use of elastomeric members in glass or plastic vials. The glass and rubber combination has been useful for a wide variety of pharmaceutical ingredients combining both safe storage of the medicine and easy access through the rubber stopper. Particularly, when liquids are contained in the vial, a needle can easily penetrate the rubber to withdraw the desired amount of ingredient without otherwise interfering with the integrity of the closure. Even when powders are stored in such containers, the elastomeric member can be penetrated with a needle to activate the powder by adding liquid such as pure water. The activated medicine remains in a safe, protected environment.

Because of the success of these types of pharmaceutical devices, and as more and more systems have been using rubber in combination with glass containers, the rate at which these devices can be manufactured contributes greatly to the economic efficiencies of this otherwise desirable component design. For example, conventional pharmaceutical devices which are useful for filling vials rely on a mechanical implantation of the rubber stopper into the neck of the vial or other shaped container. Just prior to the mechanical insertion, the rubber stoppers are transported from a hopper to the stoppering equipment, usually by centrifugal, vibrating or gravity feed. It is essential that the rubber components not hang up on each other or on the transfer equipment. It is essential that they flow smoothly into the capping or closure-forming device. The equipment, particularly that for transferring components, is normally made from stainless steel or other materials which can be kept extremely clean for pharmaceutical purposes. The ability of the rubber component to slide smoothly on the surface is directly dependent upon its coefficient of friction, with the lower values for coefficient of friction being far more desirable. Also, it is important that the elastomeric components do not stick to one another during travel through this transfer equipment.

In the prior art, the high coefficient of friction of rubber stoppers and other rubber materials which are being fed to closure devices and other pharmaceutical devices has been the limiting factor in the speed of the machine. Whether gravity of centrifugal force or vibration feeding devices are used, they require that the rubber stoppers or other elastomeric components move smoothly over the surface of the feeding unit as rapidly as possible. Typically, rubber devices of the type used in pharmaceutical closures have coefficients of friction of at least 1.2. This clearly acts as an impediment to rapid movement and, therefore, efficient and low cost production.

One solution which has been proposed to improve the general processibility of rubber closures and which has at least kept the individual rubber stoppers from binding to one another during autoclaving and other treating steps, is the use of silicone oil as a coating on the outside of the stoppers. Silicone oil has improved the lubricity of the rubber closures but has also added additional problems. The use of silicone oil increases the particle count found during the inspection of various drug solutions. The Food and Drug Administration evaluates processes by counting the number of particles present, without concern for the source or nature of the particles. Silicone oil in small amounts, is normally not an undesirable contaminant in medicine but its use still adds to the count of particles and, therefore, detracts from the overall acceptance of its use in processing equipment. While the amount of silicone oil is minimal, being only that amount necessary to prevent the individual stoppers from sticking to one another, silicone oil is not able to adequately lower the coefficient of friction of rubber stoppers for use in high speed capping equipment so as to give uniform faster movement, particularly with centrifugal feeding systems. Finally, the rubber stoppers which have been treated by the use of silicone oil are not any more effective in surviving chemical tests concerning the compatibility with and contamination of material contained in the vials. Similarly, in plunger tips for syringes, the need for silicone lubricant to reduce break loose and extrusion forces required for operation is another area of significant silicone contamination which has been necessary to this time.

The elastomeric materials which are used in the pharmaceutical industry are carefully selected and formulated to be as inert as possible when in contact with pharmaceutical products such as medicines and the like. Formulations and products are checked constantly to determine that they are not being contaminated. Of particular importance in addition to the above-mentioned particle count produced by silicone oil are particles which come off of the elastomeric closure itself. Additionally, certain trace metals are employed in the manufacture of elastomeric compounds in many instances, and it is essential that these materials not be extracted to any significant extent by the medicines or other pharmaceutical fluids which are in contact with the elastomeric products. Of particular concern are metals such as calcium, aluminum and heavy metals such as zinc and lead. Accelerated and ultra-vigorous tests are used to determine the amount of these undesirable materials which potentially may be extracted from elastomeric materials. If the quantity of extractable metals produced when products are subjected to vigorous testing is not beyond the level produced under normal conditions, the medicine would be free from likely contamination.

At the present time, pharmaceutical products have not been manufactured using a container having pharmaceutically pure contents therein and an elastomeric closure member closing said container, wherein the elastomeric closure member has an elastomeric base and a coating over the elastomeric base which substantially improves the coefficient of friction and significantly reduces the amount of extractable metal ions which are potentially extractable from the elastomeric closure member. A variety of materials have been proposed as coating materials for a variety of other purposes generally. However, coating the entire surface of elastomeric

closure members such as rubber stoppers for use with containers having pharmaceutically pure contents therein has not become an accepted practice in the pharmaceutical industry wherein the objects would be satisfied. It is particularly undesirable to coat a pharmaceutical product with a material which alters the physical characteristics of the elastomer, such as by increasing stiffness on "feel".

One material which has been found to be extremely useful as a coating material generally are the polymers of the various paraxylylenes. Gorham U.S. Pat. No. 3,288,728 discloses a basic method of preparing linear copolymers from paraxylylenes using temperature conditions between 450° C. and 700° C. This patent suggests that small articles can be protected or encapsulated with these polymers to obtain the insulative and protective properties of the polyparaxylylenes. The reference generally suggests that there are enumerable possible applications for the polymer as a coating material.

Gorham U.S. Pat. No. 3,342,754 describes the broad method of preparing linear polymers of paraxylylene and particularly in preparing coatings using that material. The patent is replete with a variety of examples of variations and suggests that these polymers are desirable for use as a film, fiber, surface coating, or electrical insulation. Both this patent and the previous Gorham patent, offers the general suggestion that almost any material may be coated with the paraxylylene polymers, although neither has a specific example relating to the pharmaceutical industry.

Tittman et al U.S. Pat. No. 3,379,803 describes particular apparatus and methods useful for polymerizing paraxylylene. General disclosures using this material indicating that a continuous film may be prepared on a wide variety of substrates. Tittman et al's related U.S. Pat. No. 3,472,795 describes an additional method for increasing the coating thickness.

Parent U.S. Pat. No. 4,225,647 discloses a process for coating an extremely broad list of materials with polymers of paraxylylene. The coating of articles may range from less than 50 Angstroms to as thick as 5 mils or more. The Parent patent suggests that a first layer of substituted silicon compounds be employed prior to the polyparaxylylene coating.

Finally, Gorham et al U.S. Pat. No. 3,300,332 describes a coating process wherein the object is to coat with an insoluble coating. The thickness of the coating is not described in detail but Gorham suggests that the thickness of the polymeric coating is not narrowly critical but is dictated by the end use of the product. He describes a coating of 0.1 mil as being very thin and useful when desiring resistance to solvent or reactive attack. In one Example, six rubber stoppers are coated to protect them from swelling from solvents such as heptane. The amount of coating added ranges from 0.22 to 0.28 grams, indicating a thickness of at least 1 mil. There is, of course, no indication that the coefficient of friction or the resistance to extraction by various means of metals could be accomplished so as to provide a superior product for use with pharmaceuticals. Tests have been run which clearly demonstrate that stoppers of the Gorham et al patent are totally non-functional as stoppers, for example. In one test, 4 out of 10 stoppers were unable to seal at all. Needle penetration increased by over 80%, based upon an uncoated stopper.

In most cases, pharmaceutical elastomers must be selected with extreme care to prevent metals and organics from being extracted. Turbidity is also a problem which requires special procedures and material selection for elastomers.

When elastomers are selected for baby bottle nipples, a particular concern arises in that infant feeding is extremely sensitive to texture and softness of the product. Therefore, any coating such as that of Gorham et al which materially alters the physical nature of the bottle nipple is totally undesirable. In this particular health care product, efforts to improve the product texture and softness have caused an increase in the quantity of elastomers being used, as softness and strength are conflicting attributes.

SUMMARY OF THE INVENTION

Accordingly, it has now been discovered that an improved pharmaceutical product may be prepared for use in the following manner. The product comprises a container with a pharmaceutically pure contents therein and an elastomeric member closing said container. The elastomeric member has an elastomeric base and a continuous polyparaxylylene coating of from about 0.5 microns to about 2 microns on the elastomeric closure. The coating is sufficient to reduce the coefficient of friction of the closure member to less than 1.0 and preferably less than about 0.5. The coating is also sufficient to substantially prevent metal ion extraction from the elastomer. Particularly, the coating acts to prevent metal ion extraction so that from 50 to 1000 fold less metal ions are extracted in one hour when autoclaving in 1 molar hydrochloric acid. Also, substantial reduction or elimination of organic extractables is achieved by the use of the present invention. In the baby bottle nipple, the tensile strength of an uncoated base increased without increasing the hardness of the elastomer.

It has been found that the narrow range of about 0.5 microns to about 2.0 microns is particularly suited for preparation of coatings on elastomeric members. The coating substantially improves the economics of manufacturing pharmaceutical products because of the significant improvement in coefficient of friction, thereby allowing the production of finished products at much higher rates. At the same time, the amount of coating employed is significantly less than what one would expect in accomplishing the barrier properties which are necessary for this process, thereby significantly reducing the cost contribution of the polyparaxylylene which is employed.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other objects of the present invention and the various features and details of the operation and construction thereof are hereinafter more fully set forth with reference to the accompanying drawings, where:

FIG. **1** shows a perspective view of a syringe cartridge and plunger;

FIG. **2** shows an enlarged view of the plunger shown in FIG. **1**;

FIG. **3** is a perspective view of a flashback bulb;

FIG. **4** is a perspective view of a sleeve stopper;

FIG. **5** is a perspective view of an elastomeric cap;

FIG. **6** is a perspective view of a combination two-compartment vial package with an elastomer top plunger and an elastomer center seal; and

FIG. **7** is a perspective view of a baby bottle nipple.

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