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(54) **Abrasion resistant stopper to prevent generation of particles by piercing**

Verschleissfester Stöpsel zur Vermeidung des Erzeugungs von Teilchen beim Durchbohren

Bouchon résistant à l'abrasion pour éviter la formation de particules lors de la perforation

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## Description

This invention relates to a stopper for a container and, more particularly, to an improved stopper for a container of parenteral solutions which is suitable for infusion spike penetration without producing unacceptable amounts of particulate matter.

Stopper systems for vials, bottles and the like are made of materials that are resistant to chemicals and pharmaceuticals such as corrosive materials, reagents, parenteral solutions and solid formulations reconstitutable with a solvent prior to use. The most commonly used stopper system for such products has been glass or plastic bottles and vials equipped with rubber stoppers made of elastomeric materials. The system appears to provide for good hermetical seal, safe storage and easy access to the content through the elastomeric stopper via the use of an infusion spike when withdrawal of the content is desired. The elastomeric stopper used comprises an elastomeric base, such as natural or synthetic rubber and an inert coating covering at least some portions of the stopper. The coating used heretofore includes chlorobutyl rubber, polymeric fluorocarbon resins such as polytetrafluoroethylene (TEFLON) and various thermoplastic films. The coating is intended to insulate the elastomeric stopper base from the content of the container in order to prevent contact and possible chemical reactions therebetween.

One of the major concerns in all products, and especially pharmaceutical parenteral products, is the generation of particulate foreign matter which may contaminate such products. In order to eliminate macroscopic and microscopic particulates, elaborate measures have been taken to remove them, such as filtration of the product and special washing and drying of the stopper system components. These steps help assure that the products meet the requirements and guidelines of the pharmaceutical industry, such as compendia guidelines, when the products reach the point of use. However, at the point of use, such as in the case of a parenteral product, new particulate matter is frequently generated by the practitioner when the stopper is penetrated by a spike of an infusion set or an infusion spike. During such penetration a combination of elastic and plastic deformation of the stopper target area increases the stopper contact surface with the infusion spike as it is pressed into the stopper. Typically, untreated elastomeric stoppers offer a high degree of resistance against the exterior surface of the spike as the spike is being pushed into the penetration area. Most frequently, when stopper fragments are generated, they are the result of the elastomeric portion of the stopper being abraded off the upper surface of the stopper as it conforms to the shape of the penetrating spike. The fragments are then transported into the interior wall of the vial as the spike rolls and drags the fragments during penetration.

In addition to the problem of particulate matter produced and carried into the vial during the spiking procedure, there are two other, although less frequently occurring, anomalies: stopper push-through into the vial and spike blow-out caused by residual elastic tension of the stopper against the spike which urges the spike outward.

The most common solution to these problems has been the application of silicone lubricant to the stopper and/or the spike to reduce the frictional drag between the stopper and the spike. It is thus known to provide an abrasion resistant stopper for a medical vial containing a fluid therein, the stopper being adapted to be pierced by an infusion spike and comprising a stopper body of an elastomeric material having a head portion and a fluid contacting leg portion, said leg portion being adapted to be inserted into said medical vial to hermetically seal said fluid therein, said head portion having a bottom, fluid-contacting surface and a top having a central pierceable portion, said central portion having a spike-receiving surface. Silicone lubricant applied to the top of the stopper body head portion provides abrasion resistance. However, while silicone does reduce particle generation from the spiking procedure it also increases the risk of product contamination from its own composition.

Another approach proposed in the prior art to reduce the tendency of the stopper to generate particulate matter during manufacturing and storage is to coat the elastomeric core of the stopper with a thermoplastic film on the fluid-contacting side thereof. We have found, however, that the use of such construction is less than satisfactory to solve the problem.

The present invention addresses the need to eliminate or at least greatly reduce the particle generation from surface erosion of the stopper during spike penetration. In addition, the invention reduces the risk of the push-through and blow-out tendency by minimizing frictional drag and residual elastic tension during spike penetration. These advantages are achieved without the use of a lubricant, such as silicone oil, which could contaminate the product contained in the vial or bottle.

We have found surprisingly that if a non-reactive, inert, coating which is highly resistant to abrasion is applied to the upper surface of an elastomeric stopper where spike penetration will take place, particle generation during spiking is all but eliminated and the tendency of push-through as well as blow-out of the spike is greatly reduced.

It is known from EP-A-0 294 127 to provide a fluorine resin film on the top of an elastomeric stopper, and from US-A-4 499 148 to provide a polyolefin film on the top of an elastomeric stopper. In both cases, the film is intended to reduce the occurrence of elastomeric particles due to a coring process when a hypodermic needle pierces the elastomer, resulting in the cutting out of a cylindrical elastomeric portion which may then undergo fragmentation into smaller pieces. The documents are not concerned with the problem of abrasion between the outer surface of an infusion spike and the surface of a hole which it creates.

Viewed from one aspect, the present invention is characterised in that said spike-receiving surface is coated with an abrasion resistant film, said film being adapted to conform to the edges of a hole created by an infusion spike upon said spike piercing the stopper and providing a barrier between the spike and the elastomeric material, thereby preventing mechanical contact between the spike and the elastomeric material and the consequent generation of elastomeric particles by abrasion, said abrasion-resistant film being selected from the group consisting of polystyrene, polyvinyl acetate, polyvinyl chloride, polyvinylidene chloride, copolymer of polyvinyl chloride and polyvinylidine chloride, polymethylene oxide, polyphenylene oxide, polyphenylene sulfone, polyethylene terephthalate, polycarbonate, copolyesters and polycaprolactam.

Preferably the top of the head portion has a region surrounding the coated central portion which is not coated.

In use, the coating on the top surface of the stopper conforms to the deformation of the stopper caused by the spike penetration procedure. It appears that, upon piercing, the spike is not in contact with the elastomeric stopper body but only with the abrasion-resistant coating thereby circumventing abrasion and eliminating the formation of elastomeric particulate materials.

Viewed from another aspect, therefore, the present invention provides a method of preventing the generation of elastomeric particles by abrasion between an infusion spike and an abrasion resistant stopper as defined above, wherein during piercing of the stopper by the infusion spike the abrasion resistant film of the stopper provides a barrier between the infusion spike and the elastomeric material of the stopper thereby preventing mechanical contact between the infusion spike and the elastomeric material and the consequent generation of elastomeric particles by abrasion.

Certain preferred embodiments of the invention will now be described by way of example and with reference to the following drawings in which

FIG. 1 is a perspective view of one embodiment of the stopper of the present invention;
FIG. 2 is a plan view of the stopper shown in FIG. 1;
FIG. 3 is a cross-sectional view of the stopper shown in FIG. 2 taken along the line a-a;
FIG. 4 is a perspective view of another embodiment of the stopper of the present invention;
FIG. 5 is a plan view of the stopper shown in FIG.4;
FIG. 6 is a cross-sectional view of the stopper shown in FIG. 2 taken-along the line b-b; and
FIG. 7 is a cross-section of a vial containing an injectable liquid closed with the stopper of the present invention.

Referring to FIGS. 1, 2 and 3, numeral 10 shows one embodiment of the stopper of the present invention comprising: a head portion 20 and a leg portion 30. Head portion 20 comprises a flange 22 which is adapted to cover a corresponding planar, circular mouth portion of a medical vial, while leg portion 30 is adapted for insertion into the neck of the vial to tightly seal the content therein. Numeral 40 shows an abrasion-resistant film mounted on the centre part of the head portion 20 which serves as the piercing area for insertion and withdrawal of a spike.

Referring to FIGS. 4, 5 and 6, numeral 10 shows another embodiment of the stopper of the present invention comprising: a head portion 20 and a leg portion 30. Head portion 20 comprises a flange 22 which is adapted to cover a corresponding planar, circular mouth portion of a medical vial, while leg portion 30 is adapted for insertion into the neck of the vial to tightly seal the content therein. Numeral 40 shows an abrasion-resistant film mounted on the top part of the head portion 20. In this embodiment recess 32 extends toward the top surface of the head portion 20 forming a thin portion 34 in head portion 20 for facilitating piercing of the stopper by a spike.

FIG. 7 illustrates a stopper 10 having an abrasion-resistant film 40 covering vial 1. Vial 1, containing an injectable fluid 5, is sealed by a stopper (which could be the stopper of FIGS. 1-3 or that of FIGS. 4-6) by inserting leg portion 30 of the stopper into the neck 7 of the vial 1. Flange portion 22 of head portion 20 tightly seals the mouth 8 of vial 1. A thin metal foil 9 is crimped over head portion 20 and flange portion 22 of the stopper to tightly seal and securely hold the stopper in vial 1.

The elastomeric material of the stopper body must be a fluid-impervious, resilient and inert material without leachable additives therein in order to prevent any alteration of the product contained in the vial. It may be of a single component or a blend of components.

The elastomeric material may be made into the desired stopper configuration by known methods. Such methods conventionally include the use of a curing agent, a stabilizer and a filler and comprise a primary and secondary curing step at elevated temperatures.

The abrasion-resistant coating for covering the top portion of the stopper, but at least the centre, pierceable portion thereof, may be: polystyrene, polyvinyl acetate (PVA), polyvinyl chloride (PVC), polyvinylidene chloride (PVDC), a copolymer of PVC and PVDC, polymethylene oxide, polyphenylene oxide, polyphenylene sulphone, polyethylene terephthalate (PET), polycarbonate, copolyesters and polycaprolactam (Nylon 6).

The coating thickness will be in the range of about 0.002 to 1.0 mm, and preferably about 0.02 to 0.5 mm. The coating may be applied or bonded to the stopper body in any suitable manner known in the art, such as, but not limited to, by the use of adhesives, solvents, spray applications, radio waves, infrared, microwaves, ultrasonics and heat or a combination thereof.

The present invention has been described in connection with the preferred embodiments shown in the drawings but is in no way limited thereto. It is to be noted that various changes and modifications of the invention

as claimed are apparent to those skilled in the art.

## Claims

1. An abrasion resistant stopper (10) for a medical vial (1) containing a fluid therein, the stopper being adapted to be pierced by an infusion spike and comprising a stopper body of an elastomeric material having a head portion (20) and a fluid contacting leg portion (30), said leg portion being adapted to be inserted into said medical vial to hermetically seal said fluid therein, said head portion having a bottom, fluid-contacting surface and a top having a central pierceable portion, said central portion having a spike-receiving surface, characterised in that said spike-receiving surface is coated with an abrasion resistant film (40), said film being adapted to conform to the edges of a hole created by an infusion spike upon said spike piercing the stopper and providing a barrier between the spike and the elastomeric material, thereby preventing mechanical contact between the spike and the elastomeric material and the consequent generation of elastomeric particles by abrasion, said abrasion-resistant film being selected from the group consisting of polystyrene, polyvinyl acetate, polyvinyl chloride, polyvinylidene chloride, copolymer of polyvinyl chloride and polyvinylidine chloride, polymethylene oxide, polyphenylene oxide, polyphenylene sulfone, polyethylene terephthalate, polycarbonate, copolyesters and polycaprolactam.

2. An abrasion resistant stopper as claimed in claim 1, wherein the top of the head portion (20) has a region surrounding the coated central portion which is not coated.

3. A method of preventing the generation of elastomeric particles by abrasion between an infusion spike and an abrasion resistant stopper (10) as claimed in claim 1 or 2, wherein during piercing of the stopper by the infusion spike the abrasion resistant film (40) of the stopper provides a barrier between the infusion spike and the elastomeric material of the stopper thereby preventing mechanical contact between the infusion spike and the elastomeric material and the consequent generation of elastomeric particles by abrasion.

## Patentansprüche

1. Abriebfester Stopfen (10) für eine medizinische Phiole (1), die ein Fluid enthält, wobei der Stopfen von einer Infusionsnadel durchstochen wird und einen Stopfenkörper aus Elastomermaterial mit einem Kopfabschnitt (20) und einem mit Fluid in Kontakt kommenden Fußabschnitt (30) umfaßt, wobei der Fußabschnitt in die medizinische Phiole eingeführt wird, um das Fluid darin hermetisch abzudichten, wobei der Kopfabschnitt eine untere, mit Fluid in Kontakt kommende Fläche und eine Oberseite mit einem zu durchstechenden Mittelabschnitt aufweist, wobei der Mittelabschnitt eine Nadelaufnahmefläche hat, **dadurch gekennzeichnet,** daß die Nadelaufnahmefläche mit einem abriebfesten Film (40) beschichtet ist, wobei sich der Film an die Ränder eines Lochs anpaßt, das von einer Infusionsnadel erzeugt wird, wenn die Nadel den Stopfen durchsticht, und eine Sperrschicht zwischen den Nadel und dem Elastomermaterial bildet, um so mechanischen Kontakt zwischen der Nadel und dem Elastomermaterial und die dadurch bewirkte Erzeugung von Elastomerteilchen durch Abrieb zu verhindern, wobei der abriebfeste Film aus der Gruppe ausgewählt wird, die aus Polystyrol, Polyvinylacetat, Polyvinylchlorid, Polyvinylidenchlorid, Copolymer aus Polyvinylchlorid und Polyvinylidinchlorid, Polymethylenoxid, Polyphenylenoxid, Polyphenylensulfon, Polyethylenterephthalat, Polycarbonat, Copolyester und Polycaprolactam besteht.

2. Abriebfester Stopfen nach Anspruch 1, wobei die Oberseite des Kopfabschnitts (20) einen den beschichteten Mittelabschnitt umgebenden Bereich aufweist, der nicht beschichtet ist.

3. Verfahren, mit dem die Erzeugung von Elastomerteilchen durch Abrieb zwischen einer Infusionsnadel und einem abriebfesten Stopfen (10), wie er in Anspruch 1 oder Anspruch 2 definiert ist, verhindert wird, wobei beim Durchstechen des Stopfens mit der Infusionsnadel der abriebfeste Film (40) des Stopfens eine Sperrschicht zwischen der Infusionsnadel und dem Elastomermaterial des Stopfens bildet und so mechanischen Kontakt zwischen der Infusionsnadel und dem Elastomermaterial und die dadurch bewirkte Erzeugung von Elastomerteilchen durch Abrieb verhindert.

## Revendications

1. Bouchon (10) résistant à l'abrasion pour un flacon médical (1) contenant un fluide intérieurement, le bouchon étant adapté pour être transpercé par une aiguille de perfusion et comprenant un corps de bouchon en matière élastomère ayant une partie tête (20) et une partie branche (30) qui entre en contact avec le fluide, ladite partie branche étant adaptée pour être enfoncée dans le flacon médical pour y enfermer hermétiquement ledit fluide, ladite partie tête possédant une surface inférieure, de contact avec le fluide, et une partie supérieure centrale transperçable, ladite partie centrale ayant une surface de réception de l'aiguille, caractérisé en ce que la surface de réception de l'aiguille est revêtue d'un film résistant à l'abrasion (40), ledit film étant adapté pour se conformer aux bords d'un trou créé

par une aiguille de perfusion au moment où ladite aiguille transperce le bouchon, et interposant un écran entre l'aiguille et la matière élastomère, pour éviter de cette façon le contact mécanique entre l'aiguille et la matière élastomère, et la production consécutive de particules d'élastomère par abrasion, ledit film résistant à l'abrasion étant choisi dans le groupe comprenant : polystyrène, acétate de polyvinyle, chlorure de polyvinyle, chlorure de polyvinylidène, copolymère de chlorure de polyvinyle et de chlorure de polyvinylidène, oxyde de polyméthylène, oxyde de polyphénylène, polyphénylène sulfone, téréphtalate de polyéthylène, polycarbonate, copolyesters et polycaprolactame.

2. Bouchon résistant à l'abrasion selon la revendication 1, dans lequel la face supérieure de la partie tête (20) possède une région non revêtue qui entoure la partie centrale revêtue.

3. Procédé pour prévenir la production de particules d'élastomère par abrasion entre une aiguille de perfusion et un bouchon résistant à l'abrasion (10) selon la revendication 1 ou 2, dans lequel, pendant le transpercement du bouchon par l'aiguille de perfusion, le film résistant à l'abrasion (40) du bouchon interpose un écran entre l'aiguille de perfusion et la matière élastomère du bouchon, en prévenant ainsi le contact mécanique entre l'aiguille de perfusion et la matière élastomère, et la production consécutive de particules d'élastomère par abrasion.

FIG.1

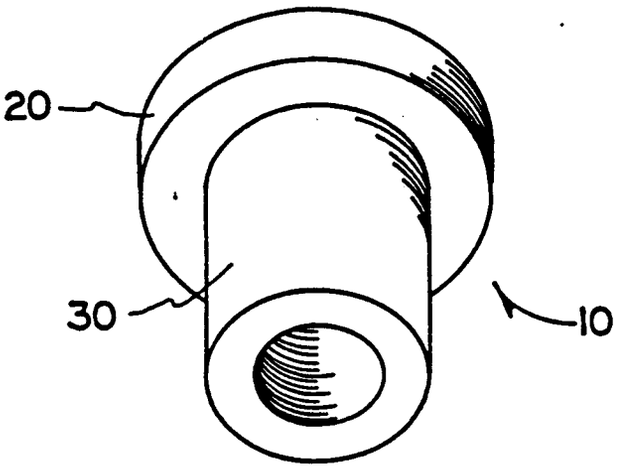


FIG. 2

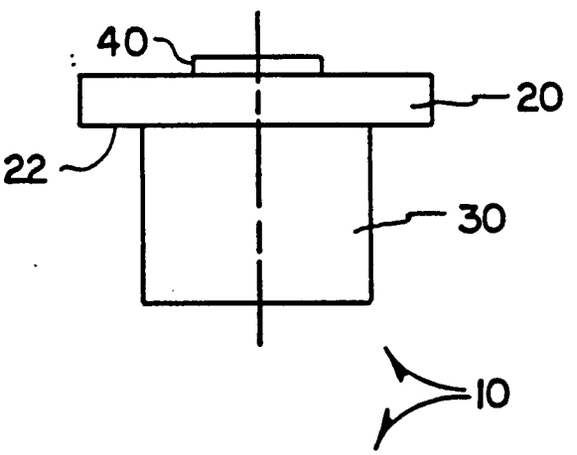


FIG.3

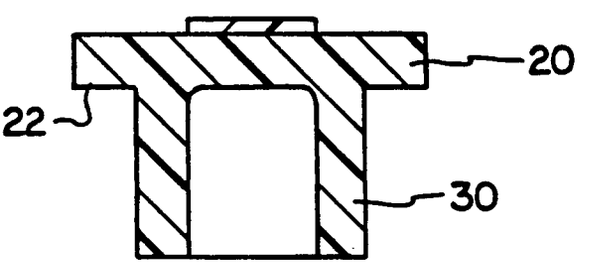

FIG.4

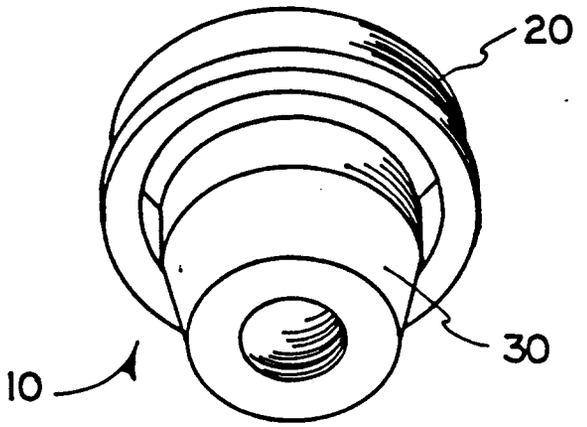


FIG. 5

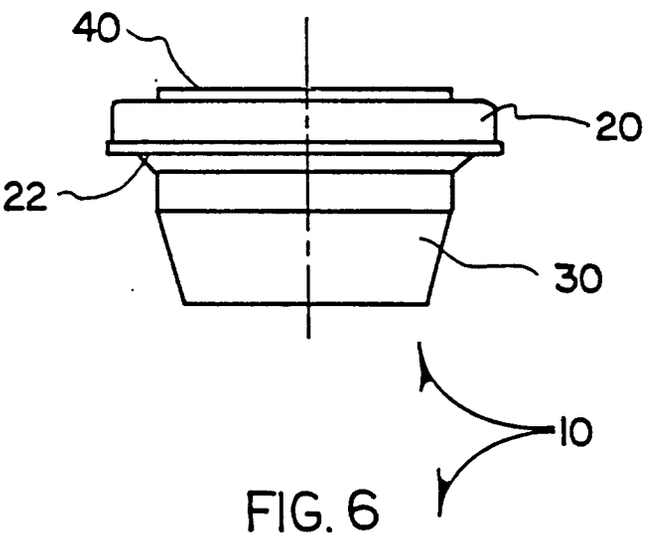


FIG. 6

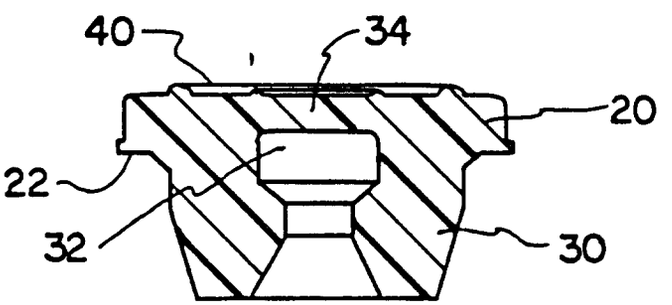

FIG. 7