United States Patent

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[54] MIXING VIAL

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[52] **U.S. Cl.** **128/272,** 128/218

[51] **Int. Cl.** **A61j 1/06**

[58] **Field of Search** ..... 128/272, 218 M; 215/6

[56] **References Cited**

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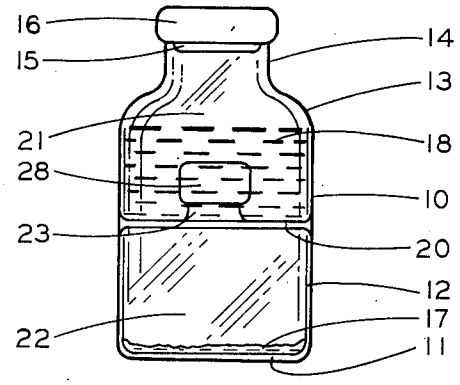
[57] **ABSTRACT**

A pharmaceutical mixing vial having a separate axial compartments for storing dissimilar component medicaments, at least one of which comprises water suitable as a vehicle for injection. A wall between the compartments includes a needle-pierceable static seal or plug. In use, the operator having a hypodermic syringe invades the vial and takes up liquid in one compartment, transfers it to a different compartment for mixing there with the separate component, and in turn aspirates the dispenses the resulting mixture.

6 Claims, 5 Drawing Figures



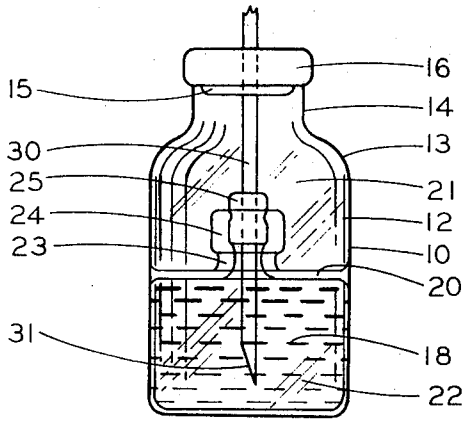


Fig. 1

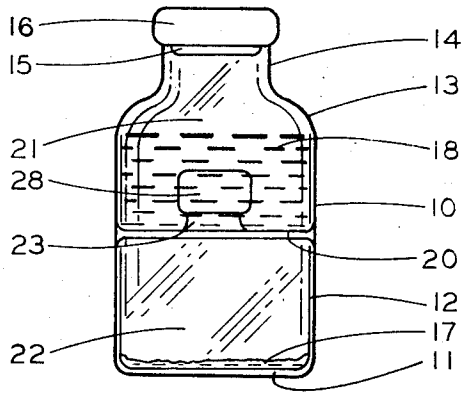


Fig. 2

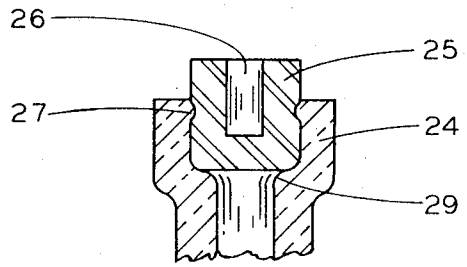


Fig. 1a

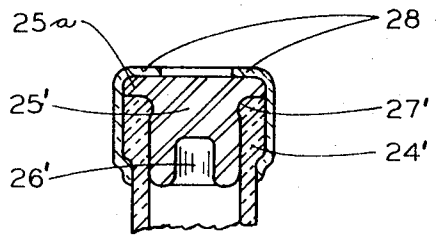


Fig. 2a

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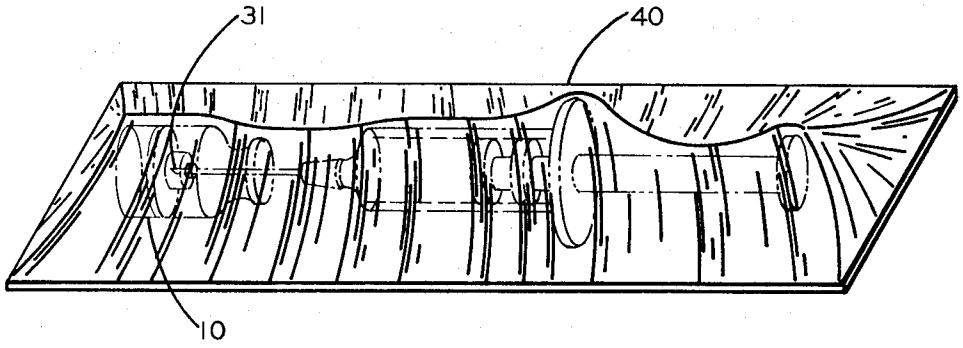

Fig. 3

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MIXING VIAL

SUMMARY AND DETAILED DESCRIPTION

This invention relates to pharmaceutical mixing vial means and more particularly to a compartmented vial of a novel type for storage of an aqueous component and a non-aqueous component which, to conserve pharmaceutical potency, are kept separate in the vial until just prior to dispensing and are then mixed in injectable form using a hypodermic syringe.

Heretofore, conventional articles of the kind in question have included separate compartments, one "wet" and one "dry," isolated by a slideable plug temporarily seated in an intercommunicating passageway. A common problem has been the uncontrolled leakage of moisture around or through the plug. Means to overcome this have included more readily deformable rubber plugs, longer axial contact between the plug and the plug seat, greater seating pressure, etc. Another approach has been to coat the plug with a thin film of silicone. The result has been less than completely satisfactory, however, since failures are inevitable whenever the plug is prematurely displaced, for example, when the vial undergoes excessive temperature change while in storage causing the aqueous fill to expand and dislodge the plug. Aside from leakage, a further limitation is that the prior articles are operated by depressing a plunger piston upon the aqueous compartment and, thus, require a substantially complete liquid fill so that the same is free of voids and can readily transmit the compressive force.

It is therefore an object of the present invention to provide a multicompartmented vial unaffected, as regards leakage, by changes in temperature and pressure.

It is also an object of the invention to provide unitary compartmented vial means for separately storing the components of a composite medication required to be combined, mixed, and dispensed only at the site of ultimate use.

Another object is to provide a wet-dry mixing vial adapted for vacuum or inert gas loading.

Still another object is to provide a wet-dry mixing vial wherein the wet compartment can be located either above or below the dry compartment, as desired.

Yet another object is to provide a wet-dry mixing vial which operates independent of piston-actuated barrier means.

These and other objects, advantages, and purposes will be seen in the following description of the invention and in the accompanying drawing in which:

FIG. **1** is an elevational view of a preferred embodiment of a vial according to the invention;

FIG. **1***a* is an axial section of a portion of the barrier means separating the compartments of the vial of FIG. **1**;

FIG. **2** is a view in elevation of another preferred mixing vial according to the invention;

FIG. **2***a* is an axial section of part of the barrier means between the compartments of the vial of FIG. **2**; and

FIG. **3** illustrates a package for a mixing vial and syringe supplied as an integral unit on a backing card.

Referring to FIGS. **1** and **2**, the invention in a preferred form contemplates a transparent glass bottle or vial **10** which is an upright cylinder with a round base **11**, tubular walls **12**, and shoulder **13** converging in a neck **14**. The latter terminates in a flanged opening sealed by a vial stopper **15** which in turn is secured by a retaining cap or collar **16** having an open zone (not shown) over the center of the top of the stopper for piercing with a cannula **30** as illustrated in FIG. **1**. The vial is divided by wall **20** into an outer compartment **21** and an inner compartment **22**. The latter contains a predetermined quantity of medicament **17** (FIG. **2**); the outer compartment **21** contains liquid vehicle **18**.

The circular disc-like wall **20** illustrated is uniform in thickness and has a central round opening which communicates directly with the compartments **21** and **22**. The wall merges at its circumference with the sidewalls **12**. Surrounding the opening of wall **20** is neck **23** which terminates in flange **24**. To seal the opening, a plug **25** is provided. In the embodiment shown in FIG. **1***a*, the plug **25** is tubular, slightly

larger than the opening of flange **24**, and having a central recess **26** to accommodate free entry of a cannula end **31**. The flange **24** flares inwardly in a construction **29** which serves as a stop, preventing further entry of the plug into the opening. The flange also has an inward lip **27** which clamps the plug in place and keeps it permanently in place. In FIG. **2***a*, which is another preferred embodiment, the plug **25'** includes a peripheral extension **25***a* which seats directly upon the top of flange **24'** and serves as a rigid restraint limiting further entry of the plug **25'** into the opening. The plug has a central recess **26'** and is secured onto the flange by a collar **28**. As indicated, the collar has an open zone at the center which exposes the top of plug **25'** for puncture with a needle point.

OPERATION

For purposes of illustration, the following description will set forth a typical procedure for first filling a medicament vial according to the invention and then opening the same for dispensing the contents. Starting with an empty open vial of the type illustrated and using aseptic procedures, a predetermined quantity of an aqueous biological material of known titer is filled into the inner compartment **22** and subjected to freeze-drying, which process removes all moisture from the vial and leaves the dry medicament residue **17**. The plug **25** is then introduced through the open neck **14** and seated within the opening in neck **23**. When using a vial plug of the type shown in FIG. **2***a*, a heat-shrinkable plastic collar is also inserted, placed around the flange **24'** and subjected to elevated temperature to cause the collar to shrink firmly down into a secure fit to hold the extension **25***a* compliantly onto the flange. Although the use of such a collar is preferred, the registry of the plug **25** and **25'** with the respective flange **24** and **24'** will ordinarily be quite secure, according to the invention, so that fluid leakage will not occur, especially since the flange lip **27** and stop means **29** (FIG. **1***a*) and flange lip **27'** and stop means **25***a* (FIG. **2***a*) keep the plug static and prevent it from moving slideably towards or away from the lower chamber **22**. In other words, the invention contemplates that the seal or plug means between the compartments will remain completely static as regards relative movement of the contacting surfaces of the flange **24** and plug **25**. A quantity of physiological saline or water for injection is next introduced into the upper chamber (FIG. **2**) and the vial is finally stoppered and sealed by means of a suitable vial cap **16**. Where appropriate the procedure can include a sterilization step. In a preferred embodiment of the invention one or both of the plug means **15** and **25** are self-resealing as described below so that the compartments can be fluid-filled, vacuum filled, or freeze-dry processed, by needle means, after the first sealing step.

The vial thus finished can be kept in storage for long periods, it has been discovered, under widely varying conditions without failures due to malfunction in the barrier means between the compartments. The vial in this respect is completely satisfactory and remains unaffected by pressure changes, ambient temperatures, shaking, etc.

For dispensing using a hypodermic syringe, the cannula point **31** is inserted on or near the central axis through the outer stopper **15** into compartment **21** and with the vial inverted the liquid contents are aspirated into the syringe barrel. The cannula is then further inserted on the axial line through plug **25** into compartment **22**. The syringe contents are injected into the compartment (in the manner and with the result shown in FIG. **1**) and mixed with the medicament **17** (suitably with the syringe needle still in place) to provide a syringeable solution or suspension. The mixture is then aspirated from the vial held in inverted position and dispensed, injected, or otherwise used in conventional manner. The empty vial is discarded.

The described arrangement with the dry-fill in the inner chamber and wet-fill in the outer chamber is particularly well suited to situations where there might be a question of accuracy of dry-fill, that is, where the unit dose is relatively small, as

with substances like ACTH, oxytocin, etc. Where larger amounts of medicament are suitable per unit dose, so that the accuracy of a dry-fill is not in question, the vehicle conveniently can be filled in the inner chamber and the active component, either wet or dry, can be loaded into the outer chamber. The latter technique is particularly suitable for those instances where medicament is to be administered as a suspension. Here, it is well-known that most medication is stable in dry, solid form. Use of this technique ensures that there will be no problem of settling or caking of a pre-mixed suspension and that there is absolutely no opportunity for change of particle form or size. The invention contemplates having not only a wet-dry filling, as described, but also a wet-wet filling in which one compartment contains aqueous fill and the other compartment non-aqueous liquid.

The vials of the invention can be supplied separately for use with conventional syringe equipment. Each vial can also be supplied with its own syringe and cannula in a suitable sterile envelope, preferably with the component parts pre-assembled and having the cannula fully injected into the vial but short of the position shown in FIG. **1**, such that the cannula point **31** is completely engaged by plug **25** with the cannula lumen blocked off so that in such packaged form there is no open communication between the chambers or between the interior of the vial and the syringe. By this means, the plugs **15** and **25** cooperate with the vial to provide not only compartmented chambers but also a pre-set sterile cannula cover which by a single controlled shifting motion or manipulation, according to the invention, is removed and the cannula simultaneously placed in contact with the contents, all without affecting the sterile environment. In a preferred construction shown in FIG. **3**, the syringe and cannula are supplied as an integral unit with the cannula completely engaged as described, the outer chamber of the vial being filled dry or with a compatible liquid and the assembly being held in fixed position by a protective transparent packaging film heat shrunk around a backing card **40** to provide overall dimensional rigidity (for example, see U.S. Pat. No. 3,392,726). The film serves to maintain sterility of the contents and also to stabilize the component parts against relative movement or shifting so that the desired complete blockage of the cannula lumen is assured until the time of its intended use.

The materials for fabrication of the vial according to the invention are commercially available, and the general methods required for manufacture are well-known in the bottle-making art. The vial envelope including the walls **12** and **20**, neck portions **14** and **23**, and flanges **24**, is conveniently made of glass of a single fusible type suitable for contact with pharmaceuticals. The glass may be a hard glass such as borosilicate glass, although for economic considerations a soft glass is preferred. The manufacturing operation is conveniently accomplished by ring-sealing to incorporate the upper portion of a standard vial around the neck and shoulders of a pre-formed lower vial. The stopper **15** and plug **25** suitably can be made of resilient rubber or elastomer meeting pharmaceutical standards for safety and compatibility and being impermeable to water in any form whether liquid or vapor. One preferred stopper is butyl rubber coated with silicone oil as described in U.S. Pat. No. 2,652,182. Another preferred material for the plug **25** is a silicone elastomer (for example, the elastomer known as Silastic) meeting government requirements, such as specified in 21 CFR 121.2562. One such preferred plug is supplied by the Kontes Glass Co. as item K-774200 designed to fit a pyrex glass socket identified as item K-672800. The invention contemplates the use of plugs and stoppers that are readily pierceable by a hypodermic needle, are self-resealing after withdrawal of the needle, and are resistant to coring or blocking of the cannula opening. For this purpose chromatographic grade plugs are preferred, particularly those having a long "injection life." The property of resealing makes possible the filling of the vial compartments with the intended medicament components and in a subsequent step evacuating air in the compartments or replacing the air with an inert gas such as nitrogen, carbon dioxide, etc., by needle means. The collar stop means for securing the plug **25** can, for purposes of the invention, be a structure such as the construction **29** (FIG. **1***a*) cooperating with lip **27** or the combination of the lip **27** and extension **25***a* alone (FIG. **2***a*) or operating together with the heat-shrinkable plastic collar **28**, or an equivalent structure. A preferred plastic collar film is an inert polyolefin film of the type commonly used for shielding electric wiring and available as an extended tubing in any desired length. The term "medicament" is used herein in its broad sense and is intended to include not only pharmacological substances, but also other components such as water, isotonic solutions, physiological saline, buffering agents, emulsifiers, etc.

While the invention in the mixing vial has been described in detail in the foregoing specification, it will be realized by those skilled in the art that considerable variation can be made in such detail without departing from the spirit of the invention.

I claim:

1. In a pharmaceutical glass vial having segregated outer and inner compartments for storing dissimilar materials prior to dispensing the same as a syringeable mixture and having barrier means between the compartments isolating the same,

the improvement wherein the barrier means comprises rigid glass wall means integral with the compartments including a neck defining an axial opening common to the compartments, and a cooperating water-impermeable elastomeric plug in static immovable engagement in the opening thereby sealing the same, the plug being relatively small such that it can be inserted axially through the outer compartment while the latter is open and can be advanced into said engagement in the opening, in combination with collar stop means permanently retaining the plug in said static sealing relation within the opening, the plug being needle-pierceable whereby with the plug still in the original static sealing relation contents in the compartments can, by syringe means, be taken up, mixed, withdrawn, and dispensed in an aqueous vehicle.

2. A mixing vial according to claim **1** wherein the outer compartment contains a dry fill.

3. A mixing vial according to claim **1** wherein the plug is self-resealing.

4. A mixing vial according to claim **3** wherein at least one of the compartments contains a medicament and an injected gaseous atmosphere inert to the medicament.

5. A cylindrical glass mixing vial in combination with a syringe and open-ended cannula, the vial comprising outer and inner cylindrical compartments and having coaxial needle-pierceable elastomeric plug means for sealing openings in the compartments including a first plug for sealing an external opening of the outer compartment and a second plug being substantially smaller than said external opening such that said second plug is insertable axially through the open outer compartment for engagement in an inner opening located in common wall means between the compartments, such engagement constituting a static immovable contact between the second plug and wall means thereby providing a permanent fluid-tight barrier between the compartments, the cannula being slideably located partly within the vial along the central axis thereof piercing the first and second plugs, the tip of the cannula being located within the second plug whereby communication between the compartments and the interior of the cannula is blocked off.

6. The combination of claim **5** in sterile form contained in a removable protective transparent packaging film heat shrunk around a backing card, providing overall dimensional rigidity preventing premature axial dislocation of the cannula tip with respect to the second plug.

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