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MIXING VIAL CONSTRUCTION

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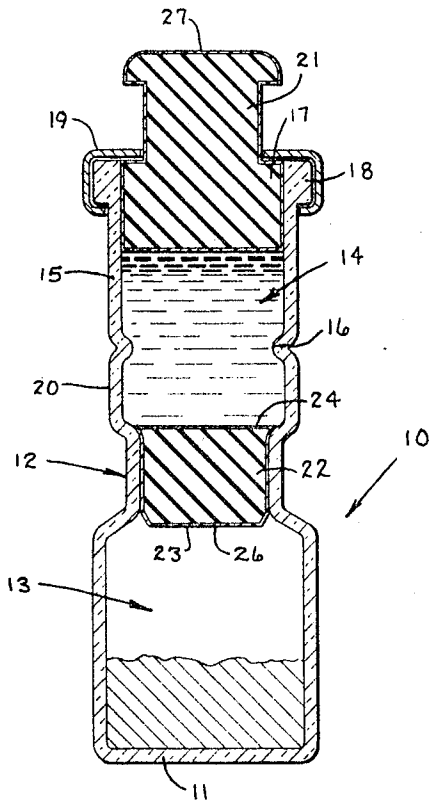

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MIXING VIAL CONSTRUCTION

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Int. Cl. A61j *1/00;* B65d *1/04, 79/00*

U.S. Cl. 128—272 1 Claim

ABSTRACT OF THE DISCLOSURE

A plural compartmented mixing vial is disclosed which has upper and lower chambers separated from one another by a center sealing plug of butyl rubber coated with silicone fluid. The upper chamber is liquid filled while the lower chamber contains a desiccated pharmaceutical product. A piston located at the top of the upper liquid containing chamber when compressed, hydraulically discharges the center plug into the lower chamber allowing mixing of the contents just prior to use. The sealing plug prevents moisture from passing into lower chamber since butyl rubber prevents moisture transmission therethrough. The silicone fluid aids as a lubricant in easy displacement of the butyl plug when the piston is actuated.

This application is a continuation-in-part of my application Ser. No. 752,907, filed Aug. 4, 1958, and now abandoned. The invention disclosed herein relates to an improvement in a plural compartment mixing vial construction and, more particularly, relates to an improved center seal plug which may be placed between the compartments for temporarily isolating same from each other.

It has been previously suggested to provide a two compartment mixing vial with a constriction between the compartments thereof defining a seat against which a natural or synthetic rubber plug was seated to thereby isolate the compartments from each other. One of the compartments is adapted to contain a solid material, such as a desiccated pharmaceutical product, while the other compartment is adapted to contain a liquid, such as an aqueous diluent or solvent for the solid material. A piston is snugly and slidably disposed at one end of the liquid-containing compartment and is arranged so that it can be manually forced into said compartment to pressurize the liquid therein and thereby exert sufficient hydraulic pressure on the plug to discharge it into the solids-containing compartment whereupon the liquid enters the compartment and is mixed with the solid material therein. Such vials are especially well adapted for use as packages for those pharmaceutical products which are used in solution form but are best stored in dry or solid form. In particular, such vials are useful for packaging parenteral formulations which are not stable for a prolonged period of time and, thus, must be formed immediately before use, usually by mixing the medicinal ingredients which are in a sterile powder form with a suitable sterile diluent which consists essentially of water. However, prior vial constructions of this type have not attained substantial commercial acceptance because an excessive amount of moisture is transmitted from the liquid contain-

the medicinal agents become unstable during prolonged storage, particularly when stored at elevated temperatures. Inasmuch as parenteral formulations are frequently stored by the purchaser thereof for an appreciable period of time before use, it is apparent that the quality of such a product could be, and was, deleteriously affected during long storage in the prior vial constructions and this prevented substantial commercial acceptance of this type of package.

The problem of providing a structure for temporarily isolating a compartment containing a solid pharmaceutical product from a compartment containing an aqueous solution to prevent water transference therebetween has long been recognized by workers in the art and great amounts of time, effort and expense have been expended to solve same but without commercially acceptable results, insofar as I am aware, prior to the present invention. It was believed that the water passed through the microscopic cracks and crevices in the mating walls of the vial and the plug which are inherently present as a result of the manufacturing operation thereof. Accordingly, the art has attempted to solve this problem by using a more deformable rubber plug and applying an increased pressure thereon when seating same against the internal wall of the vial so that the plug will deform to more completely fill such cracks and crevices. The art has also increased the length of the plug and the seat portion of the vial in order to provide a longer surface of contact between the seat and the plug to minimize such moisture transmission. Neither of these expedients has successfully solved the afore-mentioned problem.

A further problem involved in prior vial construction of the aforementioned type arose from the fact that the plug is of substantially cylindrical shape and therefore has relatively little size tolerance. In many instances a natural rubber plug will, on storage of a given vial and particularly where the plug is in continuous contact with an aqueous solution, tend to change in size and thereby materially change the pressure required to move the plug into the solids-containing compartment. In some instances, natural rubber plugs have been known to shrink sufficiently upon prolonged storage of the vial and upon being in contact with an aqueous solution such that the seal between the compartments is substantially impaired. To cure this, the prior art has attempted to use rubber plugs of maximum resiliency in order to accept a high degree of compression. This leads to the use of an oversize plug and, since the plug is cylindrical rather than tapering, thus renders the insertion of the plug very difficult.

A still further problem of prior vial constructions of the afore-mentioned type arose from the fact that plugs of rubber tend to vary in regard to their frictional characteristics with respect to the vial wall and the tolerances between the internal wall of the vial and the external wall of the plug vary from batch to batch depending upon the composition and the manner in which the plugs are compounded and molded. This, in turn, causes very great difficulty in effecting, and perhaps even renders impossible, the proper insertion of the plugs in the vials and also causes variations in the amount of pressure which the user must exert on the piston to displace the plug into the solids-containing compartment. While such variation is ordinarily of little or no consequence in the use of the

result thereof that the product packaged therein is of inferior workmanship and this, of course, will detrimentally affect the commercial acceptance of the product. Moreover, where the plug is so dimensioned with respect to vial so as to have optimum qualities as far as preventing moisture transference is concerned, the plug may actually seize upon or so tightly engage the seat of the vial that it cannot be displaced therefrom by operation of the piston. Although considerable effort has been made to solve the problem of obtaining a plug which can be displaced from the seat of such a vial in a uniform manner, it has not been possible heretofore to provide a plug capable of operation in such a uniform manner which will also satisfactorily prevent the transmission of water from the liquid-containing to the solids-containing compartment.

A plug suitable for temporarily isolating the compartments of a two compartment mixing vial must have additional characteristics which have further complicated the problem of providing a suitable plug structure. Rubbery compositions are often reactive with the medicinal ingredients and, thus, may cause contamination thereof. Further, during continuous contact of the plug with an aqueous solution, as is required for the purposes of the present invention, various ingredients of the plug may be leached or attacked and may enter into solution therewith and, thus, may render the liquid unfit for use as a diluent in a parenteral formulation.

Accordingly, the objects of the invention include the following:

(1) To provide an improved plug for use in a plural compartment mixing vial to temporarily isolate the compartments from each other;

(2) To provide an improved plug, as aforesaid, which will virtually eliminate transference of moisture from one compartment to the other;

(3) To provide an improved plug, as aforesaid, which will sealingly engage the internal wall of the vial between the compartments with a substantiallly uniform pressure so that it may be displaced from such sealing engagement by application of a suitable pressure, which pressure will be substantially uniform for vials of similar construction;

(4) To provide an improved plug, as aforesaid, which will not deleteriously affect the contents of either of the compartments;

(5) To provide an improved plug, as aforesaid, which may be continuously exposed to a liquid diluent consisting essentially of water without either permitting transference of moisture or effecting any contamination of the water or the solid materials; and

(6) To provide an improved plug, as aforesaid, which is well adapted to be loaded by unskilled operators using automatic or semi-automatic filling machinery.

(7) To provide an improved plug, as aforesaid, which can be inserted into the vial with greater ease and with less pressure, and which once positioned in the vial will remain in such position with no tendency to slide into the upper or the lower compartment until it is forced to do so by the user of the vial.

Other objects and advantages of the invention will become apparent to those acquainted with devices of this type upon reading the following description and inspecting the accompanying drawing which is a central sectional view through a vial structure embodying the invention.

In all of the foregoing discussion, as well as in the specific description hereinafter following, it has been and will continue to be assumed for illustrative purposes that the lower portion of the vial contains a soluble solid material and the discussion will proceed on this assumption. It will, however, be recognized that said compartment may within the scope of the invention contain a dilutable liquid instead of or in addition to a soluble solid, providing only that the upper compart-

and all of the discussion herein will be understood accordingly.

I have discovered, unexpectedly in view of the prior art, that the abovementioned problems are satisfactorily solved where the center seal plug for temporarily isolating the compartments from each other is formed of butyl rubber and the center seal plug is coated with a thin film of a silicone. The term "butyl rubber" as used in the description and the annexed claims shall include both substantially pure butyl rubber and blends of butyl rubber with other rubbery materials so long as such blends have substantially the same physical and chemical characteristics as butyl rubber. The term "silicone" refers to organo-polysiloxanes. Contrary to the opinion of the other workers in the art, I have discovered that a primary cause of moisture transmission through natural rubber center seal plugs is the permeability of the plugs themselves to passage of moisture. That is, a substantial amount of the water which moves from the water-containing to the solids-containing compartment passes through the natural rubber plug rather than between the plug and the wall of the vial and, thus, no matter how tight a seal is provided between the plug and the vial, a substantial amount of moisture will be transferred, which amount has, in the past, been sufficient to deleteriously affect the solid contents of the other compartment, particularly where such contents are solid pharmaceutical ingredients sensitive to moisture.

A further and unexpected advantage of the butyl rubber plugs of the invention lies in its relatively high resistance to shrinkage. The natural rubber center seal plugs, heretofore used, have a marked tendency to shrink upon aging either in air or in contact with water. Such shrinkage seriously impairs the seal between the compartments of the vial and permits still further moisture transference. A butyl rubber plug has a much higher degree of stability as regards shrinkage, either in air or in contact with an aqueous liquid, and hence maintains a much more reliable seal between the compartments. This is of particular advantage where both compartments contain aqueous solutions. In such a case, transfer of water vapor between the compartments is of little consequence since the only effect thereof would be to change the relative concentrations of the solutions in the respective compartments and this can ordinarily be accommodated. On the other hand, if the plug should shrink sufficiently to permit seepage of a solution from one compartment into the other, the solute in such solution would be mixed with the solute in the other compartment prematurely and thus, a primary purpose of the vial, i.e., to isolate the solutes in the compartments from each other would be defeated. Therefore, it is apparent that substantial advantages are attained by the butyl rubber center seal plug of the invention since its resistance to shrinkage effectively eliminates the possibility of the solutions in the respective compartments passing into the other and, thus, the aforesaid primary purpose of the vial is effectively accomplished.

I have further discovered that when a butyl rubber plug is coated with a thin film of silicone, the insertion of the plug into the vial can be effected more easily and with less pressure than is the case with an uncoated plug which is otherwise identical and which is so dimensioned with respect to the vial as to have optimum properties as far as preventing moisture transference between the compartments is concerned. Further, the pressure required to displace the silicone-coated, butyl rubber plug into the lower compartment will be much more uniform for a series of vials of the same size. Silicone-coated, butyl rubber plugs will not stick to one another and they will slide easily along the parts of the stoppering machine and, hence, they can be placed in the vial with a minimum of difficulty. Insofar as I am aware, it has not been suggested

ever, that a butyl rubber plug coated with a thin silicone film effectively solves the problem of preventing moisture transference between the compartments of a mixing vial and at the same time it provides substantially uniform operation.

In discovering that a butyl rubber plug coated with a silicone film satisfactorily solves the afore-mentioned problems I have disregarded the prior art teaching that the rubber plug should be as compressible and elastic as possible in order to effect a tight seal and that such a plug should be substantially compressed so that it will be in tight sealing engagement with the internal wall of the vial. Butyl rubber is substantially less elastic and compressible than other rubbery materials, and, in fact, is rather dead since it will not bounce to any appreciable extent. Thus, it would appear following the prior art teachings that a butyl rubber plug would be less satisfactory than is a natural rubber plug for providing a seal between the compartments. However, I have discovered that such is not the case since a butyl rubber plug coated with a silicone film will provide an effective seal between the compartments, which seal is of such effectiveness that moisture transmission therebetween is virtually eliminated. The effectiveness of the seal is enhanced by the fact that a butyl rubber plug coated with a silicone film readily remains in the shape to which it is deformed or distorted when it is compressed into sealing engagement with the vial seat and has a higher degree of dimensional stability. Thus, when the butyl rubber plug coated with a silicone film is in sealing engagement with the vial seat, it will remain in such position, whereas plugs of more resilient rubbery materials will tend to work out of such position and, thus, will allow moisture transmission to occur.

Insofar as I am aware, the present invention represents the first instance wherein a butyl rubber plug of generally cylindrical shape has been coated with a silicon film and has been used as a sealing device under conditions where the plug occupies a narrow passageway connecting a pair of compartments and is constantly in contact with a liquid diluent consisting essentially of water for a parenteral pharmaceutical formulation. Water, together with a suitable preservative, such as methylparaben, propylparaben or chlorobutanol, and if needed, a solubilizing agent, such as dimethylacetamide, is used as a liquid diluent. It has not been previously considered by workers in the art that a butyl rubber plug coated with a silicone film could be used as a seal under conditions where it had to be in continuous contact with such an aqueous solution and would provide a satisfactory seal to prevent moisture transmission therethrough into a solids-containing compartment. Since many types of rubbery compositions are frequently reactive with either the solid medicinal agents or with the diluent or, in some instances, the diluent attacks the plug so that certain ingredients thereof are placed in solution, it is apparent that the selection of a suitable material for a center seal plug is necessarily a difficult and time consuming task. Further, reports of workers in the art on the suitability of various compositions of plugs for various uses are confusing and conflicting and do not lead to a correct selection of a suitable composition of a plug for a particular use and, in particular, do not lead to the selection of an acceptable composition for a plug capable of preventing moisture transmission between a compartment filled with an aqueous solution and a compartment containing a solid sensitive to moisture.

While butyl rubber is known to be somewhat difficult to adhere with other materials, I have discovered that a butyl rubber plug will accept sufficient silicone coating which can be baked thereon to form a plug suitable for use as a center seal plug in a two compartment mixing vial.

Referring now to the drawing, there is shown a vial illustrative purposes only since the center seal plug to which the invention relates can be used with any two compartment vial having a seat between compartments. The vial **10** has a closed bottom wall **11** and has a constriction or neck portion **12** of reduced diameter intermediate the ends thereof which divides the vial into a lower, solids-containing compartment **13** and an upper, diluent-containing compartment **14**. An inwardly extending ridge **16** is provided on the inner surface of the side wall of the upper compartment **14** and divides same into an upper section **15** and a lower section **20**. A piston **17** is snugly but slidably disposed within the upper section **15** and is movable between the upper end thereof and a position substantially abutting against the ridge **16**. The upper end of the vial **10** has an enlarged flange **18** extending around the periphery thereof. An annular retainer cap **19** is sleeved over the reduced portion **21** of the plunger **17** and the peripheral portion thereof is turned downwardly and then inwardly to embrace the flange **18** and thereby prevent removal of the plunger **17** from the vial.

A substantially cylindrical plug **22** is provided for sealingly contacting the neck portion **12** of the vial. The plug has a frusto-conical end portion **23** at the lower end thereof whereby the plug may be more easily centered in the neck portion **12**. The plug is normally of somewhat larger external diameter than the internal diameter of the neck portion **12**, and, thus, when the plug is inserted into the neck portion, it is deformed somewhat and an upwardly flaring enlargement **24** is formed at the upper end thereof, which flaring enlargement sealingly contacts the upper end of the neck portion **12**. The plug **22** when compressed and seated in the neck portion **12** provides a fluid tight seal between the lower compartment **13** and the upper compartment **14**.

The plug **22** is coated over its entire surface with a thin silicone film **26**. While not in all cases essential, the piston **17** also is coated over its entire surface with a thin silicone film **27** and this will promote the ease of displacing the plug **22** and will provide even greater uniformity in the pressure required to do so.

When the plunger **17** is moved downwardly within the upper compartment **14**, a hydraulic pressure will be imposed upon the plug **22** by the liquid within the upper compartment and it will displace the plug from within the neck portion **12** into the lower compartment **13**. When such occurs, the diluent within the upper compartment will be admitted into the lower compartment and the solids in such lower compartment may be placed in solution or suspension therewith.

It is essential for the purposes of the invention that the plug **22** be formed of butyl rubber since it has been found that a butyl rubber plug is substantially less permeable to transfer of vapor or moisture than other rubbery materials. Further, since butyl rubber is a rather dead material, that is, it is not as elastic as other rubbery materials, the plug will not work out of the neck portion of the vial as sometimes occurs with other rubbery materials but must be deliberately displaced therefrom by moving the plunger within the upper compartment **13**. The lesser elasticity of the butyl rubber plug is also advantageous since it provides for a more uniform operation of the plunger of the piston when the plug is to be displaced into the lower compartment. Further, it has been found that the use of a butyl rubber plug makes it possible to satisfactorily accommodate greater variation in the tolerances of the plug and the vial than is possible with natural rubber plugs because butyl rubber plugs readily remain in a deformed condition. The plug 22 is coated with a silicone fluid, say as Dow Corning DC 35 Mold Release Emulsion, to enhance the ease of displacing the plug into the lower compartment. I have found that the hardness of the butyl rubber plug should lie within a range of from 30 to 60 as measured by a Shore hardness test.

The silicone films 26 and 27 are provided on the plug 22 and the piston 17 by applying a silicone carried in a vaporizable liquid carrier to said plug and said piston, such as by placing plugs and pistons in an aqueous silicone emulsion. The excess emulsion is drained and then the plugs and pistons are heated in closed container to bake the silicone coating thereon. Thereafter, the carrier is evaporated leaving a thin, transparent silicone coating on the plugs and pistons.

The silicones used are dimethylpolysiloxanes of various molecular weights and viscosities. They must be non-irritating, non-toxic and non-volatile at the temperatures used for baking the silicone coating on the butyl rubber parts. I prefer to use a silicone fluid having a viscosity of about 350 centistokes at 25° C., but silicone fluids of somewhat lower or higher viscosity can be used. Of the presently commercially available silicone fluids, those having viscosities of 5 centistokes or lower at 25° C. are not suitable because they are too volatile. Silicone fluids of higher viscosity (up to 60,000 centistokes at 25° C., or more) are usable but offer no advantage over the lower viscosity silicone fluids.

The preferred silicon fluid is DC 35 emulsion (Dow Corning) that is, an equeous emulsion having the following formula (percentages by weight):

35% dimethylpolysiloxanes
1.75% oleic acid
0.55% ethanol-diisopropanol amine
Water q.s.

The above-described silicone fluid is diluted with water before it is applied to the butyl ruber parts. The preferred concentration of the silicone fluid is 4% by weight of the total weight of the solution but a somewhat lower concentration, such as about 3% by weight can be used. Moreover, higher concentrations can be used with slightly improved results although the 4% concentration is adequate for commercial purposes.

The preferred procedure for applying the silicone coating consists in washing uncoated butyl rubber parts in a detergent (Dreft) solution in a laundry type washing machine having a rotating tub (Norwood Washer). The parts then are rinsed thoroughly in the washer with pyrogen free water. The parts then are rinsed in the washer with a 4% by weight solution of DC 35 emulsion, said solution being 1.40% by weight dimethylpolysiloxanes. The excess emulsion is drained from the parts by tumbling in the washer. Thereafter the parts are placed in glass containers, covered and heated in an autoclave at 121° C. for 30 minutes which bakes on the silicone coating and also sterilizes the parts. The parts are then dried in a hot air oven at 96–100° C.

The procedure for applying the silicone coating can be varied considerably. For example, the silicone can be

It is to be noted that inner surfaces of the glass vial **10** and particularly the neck portion **12** thereof are free from any coating so that the plug **22** contacts an uncoated glass surface. It has been found that to provide a coating, such as silicone coating, on the inner surface of the vial does not either by itself or in combination with a silicone coated butyl rubber plug, effectively solve the problems involved. In particular, the use of a silicone-coated vial and a silicone-coated butyl rubber plug is unsatisfactory because the plug can slide too easily and, thus, does not provide a reliable seal betwen the vial compartments.

EXAMPLE

A series of tests were run to determine the respective amounts of moisture transmisison with a natural rubber center plug and a butyl rubber center plug coated with a silicone film as above described. In each instance, the vials were of the construction illustrated in the drawing in this application and each thereof contained identical solids in the lower compartment and identical liquids in the upper compartment. The percentage of moisture in the powder was determined for vials stored at different temperatures, the tests being made at the time intervals indicated in the following list.

Percent of moisture in powder						
	Storage temperature					
	40° C		25° C.		4° C.	
Center seal composition	Natural rubber	Butyl rubber	Natural rubber	Butyl rubber	Natural rubber	Butyl rubber
Storage period:						
Initial	0.35	0.35	0.35	0.35	0.35	0.35
	0.14	0.14	0.14	0.14	0.14	0.14
	0.28	0.28	0.28	0.28	0.28	0.28
1 month	1.54	None				
	1.12					
2 months	2.86	0.42				
	2.48	0.42				
3 months	2.48	0.49	1.49	0.49		
	3.28	0.70	0.97	0.14		
6 months	5.86	0.79	3.39		1.06	0.70
	5.89	0.56	3.52		0.98	0.42
9 months	7.35	1.27	3.96	0.41	1.10	0.35
	6.54	1.37	3.38	0.62	1.11	0.35
12 months	8.35	1.12	4.65	1.14	0.35	1.10
	7.71	0.84		0.77	0.70	0.77

Further, tests indicated that at least some types of natural rubber plugs shrink appreciably upon aging, both in contact with aqueous material and dry, and thereby materially impair the seal otherwise existing between two compartments. This impairment of such seal was cured by the use of plugs of butyl rubber coated with a silicone film.

From the above, it will be apparent that the use of a butyl rubber plug coated with a silicone film virtually eliminates any significant moisture transmission between the compartments.

While a particular preferred embodiment of the invention has been disclosed hereinabove, this invention contemplates such modifications or changes therein as lie within the scope of the appended claim.

What is claimed is:

1. A packaged pharmaceutical product comprising in combination:

a substantially tubular glass body being closed at one end thereof and open at the other end thereof and having a cylindrical portion of reduced cross-sectional area spaced from both ends of the body, said body having a first chamber and a second chamber on opposite sides of said cylindrical portion, said second chamber being adjacent said one end of said body, said cylindrical portion being of constant diameter between the ends thereof and providing a passageway connecting said chambers and defining a seat therebetween, the internal wall of said seat being free of any coating;

a one-piece, solid and cylindrical plug of butyl rubber

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