

Nov. 19, 1957

G. C. COLOVOS
PACKAGE AND PROCESS
Filed March 21, 1955

2,813,623

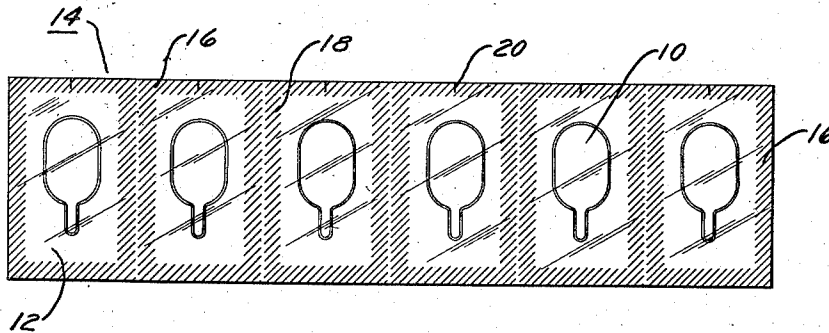


fig. 1

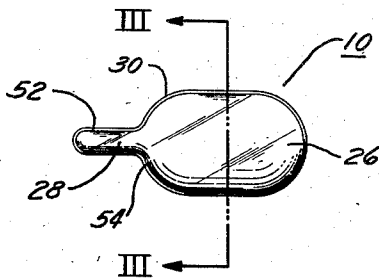


fig. 2

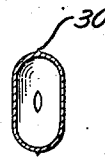


fig. 3

INVENTOR
GEORGE C. COLOVOS

BY *Garland W. Hunsicker*
ATTORNEY

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PACKAGE AND PROCESS

George C. Colovos, Kalamazoo Township, Kalamazoo County, Mich., assignor to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

Application March 21, 1955, Serial No. 495,567

15 Claims. (Cl. 206—46)

This invention relates to a novel package and to a process for making the same and is particularly directed to a sterile, single-dose, multiple-unit applicator-package of medicament, and to a method for making the same.

It has been customary heretofore to dispense medicinal preparations, such as those used for ophthalmic purposes in multiple-dosage units, such as metal tubes and dropper bottles. This method of dispensing has the disadvantage that the tip of the tube and the tip of the dropper were not sterile and even if they had been, could not be maintained in a sterile condition once opened. Application of medicaments in this wise, therefore, tended to promote collateral infection. It is also known to dispense medicinal preparations in unit-dosage containers but none of the known expedients of this kind have been adapted to or useful in the dispensing of medicinal preparations, such as ophthalmic medicaments, where both the contents and the package are required to be in a sterile condition. Nor has it been heretofore possible effectively to sterilize unit-dosage packages, especially if the packaging material and/or the medicament were sensitive to the usual methods of sterilization.

It is an object of this invention to provide ways and means whereby medicinal preparations which must be kept sterile can be effectively dispensed in unit-dosage applicator-packages. It is a further object of the invention to provide novel, sterile, single-dose, multiple-unit packages of medicament and to provide a novel method for making them. It is a further object of the invention to provide a process and applicator-package in which both the contents and the package material inside and out are obtained and maintained in a sterile and attractive condition. It is a further object to provide a process and package in which sterilizing can be effected with ionizing radiation without adverse effect on any of the components thereof. Still further objects will become apparent as the description proceeds.

It is customary in the art to dispense medicinal preparations in soft elastic capsules of such size as to contain a single dose. These capsules are commonly made of gelatin which has been softened by a suitable plasticizer. Glycerol is commonly used as the plasticizer.

It has been found, according to this invention, that when glycerol-plasticized gelatin capsules are irradiated with ionizing rays, such as cathode rays or gamma rays, the glycerol, notwithstanding that the temperature elevation due to the irradiation rarely exceeds about four or five degrees centigrade, is vaporized to such an extent that if the capsules are confined in a transparent envelope, fogging of the envelope sometimes occurs due to the condensation of glycerol thereon.

It has been found further, according to this invention, that the fogging of the transparent envelopes containing glycerol-plasticized, soft elastic capsules which results after exposure to ionizing radiation, can be avoided by interposing a film of moisture-impervious material between the inner surface of the envelope and the outer surface of the capsules. Thus if the inner surface of the transparent envelope or the outer surface of the capsule (or both) is provided with a moisture-impervious coating or film, fogging of the transparent envelope by

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glycerol as a result of exposure to ionizing radiation is minimized and/or completely avoided.

It is known that anti-water-fogging properties can be imparted to transparent films by coating them with wetting agents. (See for example U. S. Patents 2,489,026 and 2,561,010.) Unfortunately, these same anti-water fogging coatings have been found to be relatively ineffective in preventing glycerol-fogging due to exposure to ionizing radiation of transparent envelopes containing glycerol-plasticized, soft elastic, gelatin capsules. The finding of this invention that water-impervious coatings on the inside surface of such envelopes or on the outside surface of the capsules act to prevent glycerol-fogging, was, therefore, unexpected.

The invention now may be more fully understood by referring to the accompanying drawing in which:

Figure 1 is a plan view of a sterile, single-dose, multiple-unit package according to the invention;

Figure 2 is a plan view of a single-dose unit according to the invention; and

Figure 3 is a sectional view taken along line III—III of Figure 2.

Referring now to the drawing, there is shown in Figure 1 a plurality of single-dose, glycerol-plasticized, soft elastic, gelatin capsules 10, each contained in a separate hermetically sealed compartment 12 of a multiple-compartment envelope 14. The envelope 14 is advantageously made from two sheets of transparent, heat-sealable material as will be more particularly described hereinafter, heat-sealed along the sides as shown at 16 and crosswise at spaced intervals, as shown at 18, to provide a separate compartment for each of the single-dose units. If desired, the edges 16 can be cut or scored, as shown at 20 so that the individual compartments can be torn open readily.

Referring now to Figures 2 and 3, there will be found enlarged detailed views of a single-dose capsule, according to the invention. The single-dose capsule consists of a body portion 26 which is approximately twice as long as it is wide, having an elongated tip 28 projecting from one end along the major axis. The unit is formed of two sheets of glycerol-plasticized gelatin, united entirely around the circumference, as shown at 30, to form an ovate tubular capsule. The glycerol-plasticized gelatin sheets are cut, filled, and united according to any of the well known methods for forming soft elastic capsules.

The single-dose capsules thus prepared make it possible easily and effectively to administer a single dose of sterile medicament. All that is necessary is to clip the end from the elongated tip 28 and squeeze the body portion 26 between the thumb and forefinger. In this way, a fine stream of medicament is exuded from the clipped tip onto or into the affected part, such as the eye or eyes. The amount of material and the size of the unit are such as to provide only so much material as is needed for a single application. Once the application is made, the whole unit can be disposed of, thus insuring against contamination and collateral infection.

In order to provide effective discharge of so small a quantity of medicament, the unit is designed with its body portion having a length which will fit comfortably in the normal area of contact between the thumb and forefinger of an individual, say, between about one-half and one and one-half centimeters. The width of the body is between about two and three-fourths the length of the body and the cross section is ovate, advantageously with a thickness which is approximately one-half the width. With a unit of proper shape, as described, the body portion can be held comfortably between the thumb and forefinger and rolled back and forth as necessary effectively to squeeze out the medicament.

The elongated tip 28 is advantageously circular or ovate

in cross section and of substantially smaller diameter than the minimum diameter of the body portion. The tip 28 may, if desired, be tapered so that it is wider near the body portion 26 than at the end so that the opening can be made larger by clipping the tip nearer the body 26. Suitably the angle of taper may be ten degrees or less. A taper of about four degrees has been found satisfactory.

The side edges 52 of the tip merge gradually into the bottom portion 26 forming between the body and the tip a truncated surface 54 unitary with both the body 26 and tip 52, the elements of which truncated surface have an ogee curvature as shown at 54.

The capsules 10 are formed from glycerol-plasticized gelatin sheets in capsulating machines having suitably shaped dies. The procedure used and design of such machines are well known to those skilled in the art and need not be described herein. Similarly the composition and preparation of glycerol-plasticized gelatin sheets for this purpose are also well known in the art and need not be described. It may be given by way of example, however, that a suitable formulation of glycerol-plasticized gelatin for use in accordance with the present invention, contains 38 percent gelatin, 29 percent glycerol, 33 percent deionized water, and traces of preservatives such as methylparaben, and coloring matter. Parts and percentages given herein are by weight unless otherwise specified.

The capsules can be filled with any medicament which is stable to ionizing radiation and which does not dissolve or otherwise adversely affect the gelatin. A suitable medicament especially useful for ophthalmic purposes has the following formulation:

Hydrocortisone acetate, fine powdered.....	mg..	15
Neomycin sulfate, powdered.....	mg..	6
Liquid Petrolatum U. S. P. (viscosity 180-200 seconds Saybolt).....	percent..	25
Wool fat U. S. P.....	do.....	20
White petrolatum U. S. P.....	q. s. to 1 gm.	

According to one embodiment of the invention, the transparent envelope 14 is made of Saran, a transparent plastic sheet made of vinyl chloride-vinylidene chloride copolymer and the capsules are coated with a water-imperious material, such as varnish, lacquer, shellac, and the like.

In accordance with another embodiment of the invention, the transparent envelope 14 can be made of heat-sealable, moisture-proof cellophane. Any of the wide variety of commercially available heat-sealable, moisture-proof cellophane sheets can be utilized for this purpose. A suitable product is cellophane 300 MSAT made by E. I. du Pont de Nemours and Company which is made up of a regenerated cellulose sheet having a nitrocellulose moisture-proof coating topped with a wax coating. Other suitable grades of du Pont cellophane are 300 MST-57, 300 MSC and 300 MSRC. Other suitable heat-sealing, moisture-proof, transparent films can be prepared according to U. S. Patents 2,236,546, 2,321,764, 2,430,726, and 2,354,060.

The following table illustrates the effect of water-imperious coatings applied according to the invention on glycerol-fogging in radiation-sterilized packages. Each package was irradiated with 2×10^6 volt electrons for a 2×10^6 R. E. P.'s exposure.

Type of Envelope	Coating on Escap	Results
Saran.....	None.....	Fogged.
Cellophane MSAT 300.....	do.....	Clear.
Saran.....	Regular Pharmaceutical Glaze No. 3—Shellac, 3 lbs./gal. Pharm. Glaze No. 2 (Wax Free)—Shellac 2 lbs./gal.	Do.
Do.....	White shellac.....	Do.
Do.....	Varnish (Spar).....	Do.
Do.....	Lacquer (nitro-cellulose).....	Do.
Do.....	Bakelite Varnish (phenol-formaldehyde resin).....	Do.

It will be understood that the formulation given above is by way of illustration only and that any formulation which can be packaged in soft elastic, gelatin capsules and which can be safely sterilized by ionizing radiation are within the purview of the invention. If it is desired to use water-containing formulations, polyoxyalkylene ethers of aliphatic polyols may be incorporated in the formulation in accordance with U. S. Patent 2,667,268.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

I claim:

1. A radiation-sterilized package comprising a glycerol-plasticized, soft elastic, gelatin capsule loosely enclosed in an hermetically-sealed envelope of transparent material, characterized by a film of moisture-imperious material between the inner surface of the envelope and the outer surface of the capsule which completely surrounds the capsule.

2. A radiation-sterilized package comprising a glycerol-plasticized, soft elastic, gelatin capsule loosely enclosed in an hermetically-sealed transparent envelope, characterized in that the entire inner surface of the envelope is coated with a water-imperious film.

3. A radiation-sterilized package comprising a glycerol-plasticized, soft elastic, gelatin capsule loosely enclosed in an hermetically-sealed transparent envelope, characterized in that the entire outer surface of the capsule is coated with a water-imperious film.

4. The package of claim 2 in which the transparent envelope is formed of heat-sealable, moisture-proof cellophane.

5. The package of claim 3 in which the coating on the capsule is phenol-formaldehyde resin varnish.

6. In a process for preparing sterile packages in which a glycerol-plasticized, soft elastic, gelatin capsule is hermetically sealed loosely in a transparent envelope and the resulting package sterilized by radiation, the method of preventing fogging of the transparent envelope as a result of the radiation sterilization which comprises hermetically sealing the glycerol-plasticized, soft elastic, gelatin capsule loosely in a transparent envelope with a continuous film of moisture-imperious material interposed between the inner surface of the envelope and the outer surface of the capsule and then subjecting the resulting package to radiation sterilization.

7. The process of claim 6 characterized in that the moisture-imperious film is a coating on the entire inner surface of the envelope.

8. The process of claim 6 characterized in that the moisture-imperious film is a coating on the entire outer surface of the capsule.

9. The process of claim 8 in which the coating on the capsule is phenol-formaldehyde resin varnish.

10. In a process for preparing sterile packages in which a glycerol-plasticized, soft elastic, gelatin capsule is hermetically sealed in a transparent envelope and then sterilized by radiation, the method of preventing fogging of the transparent envelope as a result of the radiation sterilization which comprises hermetically sealing the glycerol-plasticized, soft elastic, gelatin capsule loosely in a transparent envelope formed of heat-sealable, moisture-proof cellophane whereby a continuous film of moisture-proof material is interposed between the inner surface of the envelope and the outer surface of the capsule and then subjecting the resulting package to radiation sterilization.

11. A package formed by hermetically sealing a glycerol-plasticized, soft elastic, gelatin capsule loosely in a transparent envelope with a continuous film of moisture-imperious material interposed between said capsule and said transparent material and subjecting the package to

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radiation sterilization, said radiation-sterilized package being free of glycerol fogging.

12. The package of claim 11 in which the moisture-impervious film is a coating on the entire inner surface of the envelope.

13. The package of claim 11 in which the moisture-impervious film is a coating on the entire outer surface of the capsule.

14. The process of claim 13 in which the coating on the capsule is phenol-formaldehyde resin varnish.

15. A package formed by hermetically sealing a glycerol-plasticized, soft elastic, gelatin capsule loosely in a transparent envelope formed of heat-sealable, moisture-proof cellophane whereby a continuous film of moisture-

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impervious material is interposed between said capsule and said transparent material and subjecting the package to radiation sterilization, said radiation-sterilized package being free of glycerol fogging.

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