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DRY STRATIFORM PRODUCTS AND METHODS OF PRODUCING SAME

Charles W. Damaskus, 708 S. Madison St., La Grange, Ill., and James E. Alder, Grayslake, Ill., assignors, by mesne assignments, to said Charles W. Damaskus

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19 Claims. (Cl. 167—58)

This application is a continuation of our application Serial No. 491,768, filed March 2, 1955, now abandoned.

This invention relates to compositions of matter, and more particularly to stratiform products which may be obtained as a package containing a plurality of strata of dry matter in stacked relation.

An object of this invention is the provision of a dry product including layers of matter in stacked relation in which at least one of such layers includes a substance different from that contained in another of such layers. Another object is the provision of a package consisting of a container having received therein at least two strata of lyophilized matter in which at least one of such strata includes a substance different from that contained in another of such strata. An especial object is to provide a pharmaceutical package consisting of a container having received therein at least two strata of lyophilized matter in which each of such strata includes a physiological factor and in which the composition of at least one of such strata differs from that of another of such strata. Other objects, and the advantages of this invention, will become apparent as the specification proceeds.

One aspect of this invention pertains to a stratiform package consisting of a container having received therein at least two strata of dry matter in which at least one of such strata includes a substance different than that included in another of such strata. The substances included in these strata may differ qualitatively, e.g. chromatically, biologically, chemically, etc. The strata can be in stacked relation, and may be either a lyophilized plug or a pulverulent powder. When a transparent container is employed for this purpose the strata of lyophilized matter therein can differ visually, as by chromatic distinction, to produce a color contrast between layers of matter, resulting in a package especially suitable for retail sales display. However, the advantages of this invention may be achieved by employing any receptacle.

This stratiform package can be adapted to the packaging of chemical and pharmaceutical products. When a plurality of labile substances are to be combined as a unit, the susceptibility of such substances to degradation or decomposition through interaction, and the instability of such substances under common process conditions, must be guarded against. The packaging of a composition, including incompatible substances, may result in deterioration of such composition during processing and subsequent storage. We have devised a package in which a plurality of substances may be integrally combined and stored for a prolonged period of time without substantial deterioration. This package may consist of a container having received therein a plurality of strata of dry matter in which each of such strata includes a labile substance and in which at least one of such strata includes a substance different than that of another of such strata. When this package contains a plurality of physiological factors, i.e. substances having biological usefulness, an especially advantageous application of this invention is

achieved. For example, in the preparation of a pharmaceutical package, a plurality of medicinal agents may be formed into a therapeutic unit by including each of such agents in a stratum received into a container in lyophilized, stacked relation. For example, anti-anemia pharmaceutical package can be obtained by receiving into a container individual layers of vitamin B_{12}, an anti-anemia liver concentrate and folic acid in the lyophilized state. Thus, the three labile anti-anemia factors can be so arranged in a container as to prevent interaction thereof and deterioration during storage. Also, strata which include an adrenocorticotrophin substance and vitamin B_{12}, in the lyophilized state, may be received into a container to achieve a stable adrenocorticotrophin package product of enhanced therapeutic efficacy.

This stratiform product can be prepared by forming a plurality of layers of separately frozen matter in stacked relation. The frozen strata can be dehydrated to obtain the multi-layer composition in dry form. One method of obtaining a stratiform package involves filling a liquid composition into a receptacle, and freezing the liquid therein. Then, additional liquid matter can be filled into the receptacle and frozen to produce a second layer in the receptacle. Further layers of frozen matter can be obtained in a similar manner. The frozen strata in the receptacle may be dehydrated by sublimation. An especially desirable product results when the sublimation of these strata is obtained by lyophilization and evaporation. For example, an aqueous solution of vitamin B_{12} can be charged into a suitable container and frozen. The freezing of the liquid in the container can be obtained by storing such container in a freezer chest for a period of time sufficient to convert the liquid to the solid state. In the alternative, the container may be immersed in an alcohol or acetone dry ice bath to freeze the liquid as a layer. An aqueous solution of folic acid can then be filled into the receptacle, which already contains a frozen layer of vitamin B_{12}. This folic acid solution may then be frozen to form a layer superimposed upon the vitamin B_{12} stratum. Then, a solution of anti-anemia liver concentrate can be filled into the container in a similar manner, and frozen to produce a third layer therein. Thereafter, the receptacle can be subjected to lyophilization to dehydrate the layers of anti-anemia substances. The resulting package consists of three strata, each differing in color and composition, which color difference can be observed visually by employing a transparent container. Vitamin B_{12} has a natural pink color while folic has a yellow color, and that of the liver concentrate may be tan. Consequently the three layers of matter can be distinguished in the container as a tan stratum superimposed upon a yellow stratum with a subjacent pink stratum. Other substances can be combined with the aqueous solution of the physiological factor and included in the stratum contained in the receptacle. For example, gelatin may be included in such solution to add body to the strata or to enhance the therapeutic activity of the physiological factor contained therein. Also, artificial dyes, such as vegetable dyes, can be included in the strata of matter to produce a visual color difference in the receptacle. Further, the several strata in the container can be separated by strata of inert matter, and the inert matter may also be artificially colored to enhance the visual color contrast between such strata.

An example of this method for preparing a pharmaceutical package involved filling into a sterilized 1 cc. pharmaceutical vial, 0.3 cc. of a sterile solution consisting of 20 mcg. of vitamin B_{12} in aqueous gelatin. The filled

vial was held in a freezer chest at a temperature of minus 60° C. until the liquid had become frozen. 0.3 cc. of a parenteral liver concentrate in a dilute aqueous gelatin solution, including 6 mcg. of vitamin B_{12} potency, was filled into the vial containing the frozen layer of vitamin B_{12}. The concentration of liver concentrate contained in this gelatin solution was 6 mgs. The filled vial was again placed in the freezer chest at a temperature of minus 60° C. until the contents had frozen. Then 0.3 cc. of a dilute gelatin solution, containing 7.5 mgs. of folic acid, was filled into the vial containing frozen vitamin B_{12} and liver concentrate strata. Again the filled vial was placed in the freezer chest at a temperature of minus 60° C. until the contents thereof had frozen. The vial, containing the frozen matter, was introduced into a lyophilizer apparatus and dried for a period of time such that the moisture content thereof was reduced to less than 5%. The resulting vial, containing the dry plug, showed good demarcation between the individual strata of vitamin B_{12}, liver concentrate, and folic acid. This demarcation could be ascertained by the color contrast between strata.

When the volume of liquid introduced into the container is increased, the depth of plug produced upon dehydration will also be increased. The filling and lyophilizing operations may be accomplished under asceptic conditions to produce a sterile pharmaceutical package suitable for parenteral administration. The lyophilized product obtained in this process can be reconstituted with a liquid vehicle to produce a composition suitable for medical purposes.

While in the foregoing specification, this invention has been exemplified by various embodiments and specific details thereof have been set forth for the purpose of illustration, it will be apparent to those skilled in the art that the invention is susceptible to other embodiments and that details can be varied widely without departing from the basic concept and spirit of the invention.

The invention is hereby claimed as follows:

1. In a process for obtaining a package containing at least two strata of dry matter incompatible with each other in the presence of moisture, the steps of charging a liquid composition into a container, freezing said composition to form a stratum thereof, superimposing on said stratum a liquid composition consisting essentially of a substance different from that included in said stratum, then freezing said liquid composition to form another stratum in said container and simultaneously dehydrating the frozen strata.

2. In a process for obtaining a pharmaceutical package containing at least two strata of dry matter incompatible with each other in the presence of moisture, the steps of charging into a container a liquid composition consisting essentially of at least one physiological factor, freezing said liquid composition to form a stratum thereof, charging into said container a liquid composition consisting essentially of a physiological factor different from that included in said stratum, then freezing said liquid composition to form another stratum in said container, and simultaneously dehydrating the resulting strata.

3. A package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation incompatible with each other in the presence of moisture, wherein each of said strata is a substantially coherent mass and wherein said strata are equally lyophilized and at least one of said strata consists essentially of a substance different from that of another of said strata.

4. A package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass, and wherein said strata are equally lyophilized and at least one of said strata consists essentially of a substance incompatible with that of another of said strata.

5. A pharmaceutical package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass, wherein said strata are equally lyophilized and at least two of said strata consist essentially of a physiological factor, and wherein the physiological factor of at least one of said strata is incompatible with that of another of said strata.

6. An anti-anemia pharmaceutical package, comprising a container having received therein at least three strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass, wherein said strata are equally lyophilized and one of said strata consists essentially of vitamin B_{12}, wherein another of said strata consists essentially of folic acid, and wherein still another of said strata consists essentially of anti-anemia liver concentrate.

7. An anti-anemia pharmaceutical package, comprising a container having received therein at least three strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass, wherein said strata are equally lyophilized and one of said strata consists essentially of a mixture of vitamin B_{12} and gelatin, wherein another of said strata consists essentially of a mixture of folic acid and gelatin, and wherein still another of said strata consists essentially of a mixture of anti-anemia liver concentrate and gelatin.

8. An adrenocorticotrophin pharmaceutical package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass, wherein said strata are equally lyophilized and at least one of said strata consists essentially of adrenocorticotrophin, and wherein another of said strata consists essentially of vitamin B_{12}.

9. A package, comprising a transparent container having received therein at least two lyophilized plugs in stacked relation and which are incompatible with each other in the presence of moisture, wherein said plugs are equally lyophilized and at least two of said plugs consist essentially of a physiological factor, wherein the physiological factor of at least one of said plugs differs from that of another of said plugs, and wherein at least one of said plugs differs chromotographically from another of said plugs.

10. The package of claim **9** in which at least one of said plugs contains a body adding substance.

11. The process of producing a storage-stable solid, freeze-dried composition containing a plurality of components which are incompatible with each other in the presence of moisture, which comprises freezing a layer of solution, capable of being freeze-dried, and containing one of said incompatible components, adding at least a second layer of solution, capable of being freeze-dried, and containing another of said incompatible components, freezing said second layer, and freeze-drying the frozen layers.

12. The process as defined in claim **11**, wherein at least one of said layers includes a body adding agent.

13. The process as defined in claim **11**, wherein at least one of said layers includes gelatin as a body adding agent.

14. The process as defined in claim **11**, wherein said components comprise vitamin B_{12}, folic acid, and anti-anemia liver.

15. The process as defined in claim **11**, wherein said components comprise vitamin B_{12}, folic acid, and anti-anemia liver and a body adding agent.

16. The process as defined in claim **11**, wherein said components comprise vitamin B_{12}, folic acid and anti-anemia liver and gelatin as a body adding agent.

17. A package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass and wherein said strata are equally ly-

ophilized and at least one of said strata consists essentially of a labile substance different from that of another of said strata.

18. A package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass and wherein said strata are equally lyophilized and at least one of said strata consists essentially of a substance physiologically different from that of another of said strata.

19. A package, comprising a container having received therein at least two strata of lyophilized matter in stacked relation, wherein each of said strata is a substantially coherent mass and wherein said strata are equally lyophilized and at least one of said strata consists essentially of a substance chromatically different from that of another of said strata.

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JULIAN S. LEVITT, *Primary Examiner.*

S. ROSEN, *Assistant Examiner.*