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PROPANEDIOL SOLUTION OF DIGITALIS

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The present invention relates to a stable solution of a glycoside or a glycoside bearing drug. More particularly, it relates to a stable solution of a drug of the digitalis group which is capable of parenteral administration.

The physiologic glycosides, such as digitoxin, digitalin Kiliani, scillaren, strophanthin and gitalin are subject to hydrolysis when employed in an aqueous solution with the result that the pharmaceutical potency of a solution of an extract of such glycoside changes continuously after formation and upon standing. Such products have been known to lose as much as sixty (60%) per cent of their strength during a period of sixty days following manufacture and thereafter deteriorate at a slower rate, averaging twenty to thirty (20%—30%) per cent loss in pharmaceutical potency in the course of a year. This undesirably large variation has restricted the shelf life of such glycoside solutions to such an extent as to render them incapable of general usage for parenteral administration.

In an effort to enhance the stability of such glycosides solutions the tendency has been to increase the concentration of the non-aqueous solvent in which they are dissolved. The preferred non-aqueous solvent has been ethyl alcohol and this solvent has been employed in solutions up to seventy (70%) per cent alcohol in an effort to increase the stability of the glycosides. The stability apparently increases directly with the concentration of the non-aqueous solvent.

Although such high content alcoholic solutions of glycosides have to a large extent solved the problem of pharmaceutical stability so far as glycoside solutions for oral administration are concerned, this practice has not been even a partial solution to the problem of increasing the stability of solutions for parenteral administration because the high alcoholic content renders them too painful for parenteral administration. Also, the introduction of such a large quantity of alcohol into the blood stream would create a danger of vascular damage.

Intravenous solutions, from a physiochemical standpoint, are preferably made by the use of a sterile aqueous solvent because of the fact that the water forming the solvent has no appreciable effect on the blood stream and is readily eliminated from the blood stream through natural processes. The lack of stability of such a solution, however, has militated against this use because unless made up fresh substantially immediately prior to each application, or assayed

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prior thereto, it has been impossible to insure the administration of an accurate therapeutic dose. In view of the precautions invariably surrounding the administration of a substance having cardio-tonic properties, the result has been a tendency to administer a weakened or a deficient dose in order to avoid the danger of overdosage. This inability to maintain stocks of parenteral solutions of extracts of glycosides has detracted from their value as an intravenous agent, because such substances are frequently required to be administered under emergency conditions where the time factor prevents their being made up or assayed immediately prior to administration.

The present invention has overcome the foregoing shortcoming of intravenous solutions of extracts of glucosides, and is based preponderantly on our finding that the propanediols can be employed as solvents for glycoside extracts to form solutions of such extracts which are stable both in regard to pharmaceutical potency and freedom from the formation of precipitants for a long period of time, and that such solutions can be administered parenterally without any discomfort to the patient and without any undesirable results caused by the introduction of the propanediol into the blood stream.

The present invention has for an object the provision of a stable solution of a cardio-tonic glycoside or glycoside bearing drug which is capable of use for parenteral administration.

It is another object of the present invention to provide a stable solution of a drug of the digitalis group which can be administered by parenteral injection without objectionable pain to the patient and without the inducement of harmful effects such as thrombosis or danger of vascular or lymphatic damage.

It is a further object of the present invention to provide a stable solution of a glycoside or aglycone which is not deteriorated by sterilization by heat incidental to ensealment in ampules or other preservation instrumentalities.

Other objects and advantages, if not specifically pointed out, will be apparent to those skilled in the art from the following detailed description of what is now considered to be the preferred embodiment of the invention.

The invention in general comprises a solution of a drug of the digitalis group which does not vary appreciably in therapeutic potency or undergo precipitation upon storage for periods of time, even in excess of a year, and comprises a drug of this group dissolved in an aqueous solu-

tion of propanediol, preferably 1,2-propanediol.

The invention accordingly comprises a product possessing the features and the components which will be exemplified in the product hereinafter described and the scope of the invention will be indicated in the claims.

A solution forming the product of the present invention is prepared by dissolving a drug of the digitalis group, preferably but not necessarily concentrated in accordance with the invention described in application Serial No. 494,675, filed concurrently herewith, in an aqueous solution of propanediol.

The drugs of the digitalis group are to be understood as comprising digitalis, squills, convallaria, adonis, strophanthus, apocynum and thevetia.

The preferred solvent is 1,2-propanediol, but 1,3-propanediol may also be used if desired. The solvent may contain from thirty-five to one hundred (35%-100%) per cent propanediol by weight; a preferred solution is one containing fifty (50%) per cent propanediol and fifty (50%) per cent water. Such a solvent can be used to form a solution of cardio-tonic glycoside which will be stable as previously described for an indefinite period.

The solution is preferably formed by diluting the propanediol with distilled water until the proper concentration of the propanediol is reached, and the powdered extract of the cardio-tonic glycoside is dissolved in the propanediol solution with vigorous stirring until complete solution of the powdered extract is obtained. The solution so formed is thereafter filtered, introduced into ampules which are thereafter sterilized preferably by heat in accordance with well known procedure which within itself forms no part of the present invention.

The product of the present invention is well adapted for use for oral administration as well as parenteral administration in that the therapeutic stability renders accurate oral dosage possible even after the product has been manufactured for a considerable length of time.

The high degree of sterility desired for parenteral substances is accomplished in the case of glycosides for the first time by the product of the present invention. This high degree of sterility is obtained by boiling the ampules for any desired time after they are sealed. All attempts to so sterilize solutions of cardio-tonic glycosides heretofore have failed because boiling has caused precipitation of the less soluble ingredients as well as deterioration of the pharmaceutical potency of the solution. The precipitation rendered the product unsuitable for intravenous injection because the solid particles caused stoppages in the injection apparatus and also created a hazard to the welfare of the recipient because

of the danger inherent in the introduction of any solid particles into the blood stream. The product of the present invention is free from precipitants both immediately following sterilization and after standing for many months. This factor, in addition to the assurance of the administration of a proper therapeutic dosage in each instance, has opened the field of cardio-tonic glucoside therapy to intravenous injection technique, which field has been unavailable heretofore because of the defects in the glycoside solutions.

Since certain changes may be made in the above article and different embodiments of the invention could be made without departing from the scope thereof, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

The invention having been described, what is claimed is:

1. A heat sterilized therapeutic composition free of precipitation, stabilized as to pharmaceutical potency and capable of parenteral administration comprising an extract of digitalis in a solvent consisting of a mixture of water and propanediol in which the concentration of the propanediol is at least thirty-five (35%) per cent by weight.

2. A heat sterilized therapeutic composition free of precipitation, stabilized as to pharmaceutical potency and capable of parenteral administration comprising digitalis dissolved in a solvent consisting of a mixture of fifty (50%) per cent water and fifty (50%) percent propanediol by weight.

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