United States Patent Office 3,035,984 Patented May 22, 1962

3,035,984
DIHYDROCODEINONE RESIN COMPLEX SUSPENSIONS

Richard D. Mierswa, Fairport, N.Y., assignor to Wallace & Tiernan Inc., a corporation of Delaware

No Drawing. Filed Aug. 26, 1958, Ser. No. 757,204
2 Claims. (Cl. 167—82)

The present invention relates to pharmaceutical suspensions, and more especially, to pharmaceutical compositions wherein water-insoluble solids are suspended in such pharmaceutical suspensions for administration either orally or by injection.

Suspensions of relatively water-insoluble drugs in aqueous systems present many problems. Since such preparations are administered orally, or by intramuscular injection, they should be homogeneous to provide a uniform dispersion of medicament for oral administration, and relatively fluent so as to be readily drawn into a syringe and easily injected. However, the usual suspensions of medicinals in aqueous systems either are too viscous or gradually settle, forming a hard sediment very difficult to dislodge and uniformly resuspend. Frequently, moreover, excessive pain and the formation of lumps follow injection of such suspensions even when the active medicinals are in finely-divided form, apparently due to the clumping of the particles on sedimentation; hence the importance of the physician's effecting a thorough and uniform resuspension just prior to administration.

It is the object of this invention to provide improved suspensions of relatively water-insoluble drugs in aqueous suspensions in which settling is eliminated for at least one year.

In preparing the suspensions of the present invention, it has been found that a centrifugal mixing device, particularly a centrifugal mixing device which applies forces upon the fluid being mixed in two spaced areas, may be advantageously used. More specifically, the device is a double-ended mechanism which provides a suction effect at both ends. In the normal course of operation of this mixing device it is held in vertical position so that its lower end provides a flow effect upon the fluid at the bottom of the mixing vessel, and the upper end provides a flow effect upon the fluid at the top of the mixing vessel, bringing the phases together under mechanical and hydraulic shearing action. Consequently, if the fluid has two components, one of which is relatively heavy and the other of which is relatively light, the lower end of the mixing device will apply a suction force to the heavier component which normally tends to settle to the bottom of the mixing vessel, and the upper end of the mixing device applies a suction force to the lighter component which normally tends to rise to the top of the mixing vessel, thus providing two-way flow in addition to tangential shear.

The centrifugal mixing device which is used in the present invention in provided with its own mixing chamber at each end, the two mixing chambers being in communication with each other through passageways which link them. It is by this means that the fluid drawn into the upper end of the mixing device is itself thoroughly mixed, and then both mixtures are brought together and intimately intermingled. The device may be used in several forms. In some of these forms the passageways between the two mixing chambers are fixed dimensionally, and in one form they are adjustable so as to control the flow between the mixing chambers. Suitable dispersator devices for this purpose are described in U.S. Patent No. 2,635,860.

In preparing the pharmaceutical preparations of this invention in this manner, air bubbles are uniformly distributed throughout the suspension, while at the same time a colloidal suspending agent, which is a potassium salt of the sulphuric ester of a high molecular weight polysaccharide obtained by water extraction from the seaweed *Furcellaria fastigiata*, and water are intimately mixed so as to establish a balance between the colloidal material and the water so as to obtain a true, uniform, initially thixotropic suspension.

The mechanism of the improvement obtained by this invention is not known with certainty, but apparently is not emulsification, since the formation of an emulsion would adversely affect the rate of flow of the product. It would seem that as the colloid is added to the water, the action of the mixing device exposes a large surface of the colloid to rapid hydration by the water, thus quickly forming the thixotropic gel of the present invention. It is not intended, however, that the invention shall be limited by this explanatory hypothesis.

The following example is illustrative of the invention:

Example I

Methyl paraben	gms.	810
Propyl paraben	gms.	162
F.D.C. yellow #5	gms.	43.2
Sodium sucaryl	gms.	660
T.F. peach	cc.	357
T.F. pineapple	cc.	357
Propylene glycol	cc.	960
Glycerine	cc.	637.5
Ethyl alcohol	cc.	3205.5
TIC Colloid 600	gms.	2970
70% sorbitol solution	liters.	144

Deionized water, g.s. 540 liters.

375 l. of D.I. water are measured into a batch tank and the temperature raised to 75° C. While the water is heating, the methyl paraben and sucaryl sodium are added and slowly agitated. When the temperature reaches 75° C. the propyl paraben is added, agitation is continued and the temperature held at 75° C. until solution is complete. The contents of the tank are pumped into a second tank and allowed to cool to 50° C. While the preserved water is cooling, the F.D.C. yellow #5 is dissolved in 750 ml. of D.I. water. The following are mixed in a suitable container: T.F. peach, T.F. pineapple, propylene glycol, glycerine, and alcohol.

To the solution in the second tank at 50° C., with the dispersator running, is *slowly* added the TIC Colloid 600 over a 30 minute period, at an even rate. The dispersator is run for 30 minutes after the last of the colloid has been added. The dispersator is stopped; the flavor mixture described above is then added by pouring in a thin stream on the surface of the tank to break the foam. When the foam-breaking effect is complete, the dispersator is turned on for 1 minute. The 70% sorbitol solution is added, with the dispersator running, and after this addition the dispersating is continued for up to 55 minutes. At the end of this period the color is added, and recirculation is begun and continued for 60 minutes with 1 minute of dispersating every 15 minutes. The recirculation is then stopped, the lines drained and the draining returned to the tank, and the batch is covered and allowed to stand overnight. The following morning the dispersator is turned on, together with recirculation, until the liquid is free-flowing. Dihydrocodeinone resinate is added to complete the final product.

The dihydrocodeinone resinate is prepared by dissolving 5.00 grams of dihydrocodeinone bitartrate in about 400 mls. of distilled water and adding the mixture to a resin slurry prepared by suspending 8.00 grams of IR–120 in the hydrogen cycle in about 100 mls. of distilled water and stirring for about one hour. The entire mixture is

then stirred for about 3 hours. The compound contains 26.22% by weight of dihydrocodeinone. IR–120 is a cation exchange resin having a polyvinyl styrene nucleus.

The products of this invention are obtained initially in the form of thixotropic gels, which, after shaking or stirring, flow as liquids but set as gels upon standing. The thixotropic character of the suspensions of the present invention may be maintained for a long period of time, but may be destroyed if the thixotropic gels are shaken, or stirred, for a prolonged period. While such shaking or stirring may destroy the thixotropic character of the suspensions, the suspensions remain uniform and do not settle on standing.

As used in Example I, the trademark TIC Colloid 600 refers to a potassium salt of the sulphuric ester of a high molecular weight polysaccharide obtained by water extraction of the seaweed *Furcellaria fastigiata*.

A large number of therapeutic agents may be suspended in the suspensions or gels of the present invention. The following have been found to make up highly desirable therapeutic preparations by adding the therapeutic agents to the gel as described in the above example: antibiotics, such as procaine penicillin, chloromycetin, erythromycin stearate; gastro-intestinal medicinal agents such as aluminum hydroxide gel, aluminum phosphate gel, magnesium trisilicate, polyamine methylene resins, kaolin and bismuth subcarbonate; diuretics and cardiovascular agents such as theophylline; vasodilators such as quinidine; steroids such as progesterone and testosterone; and particularly sulfa drugs, such as sulfamethazine, sulfadiazine, sulfaethylthiadiazole, sulfaguanidine, sulfamerazine, etc.

The invention may be variously otherwise embodied, within the scope of the appended claims.

It is claimed:

1. A pharmaceutical composition comprising a thixotropic aqueous suspension of a potassium salt of a sulphuric ester of a high molecular weight polysaccharide obtained by water extraction of the seaweed *Furcellaria fastigiata*, and a dihydrocodeinone resin complex.

2. A pharmaceutical composition comprising a thixotropic aqueous suspension of a potassium salt of a sulphuric ester of a high molecular weight polysaccharide obtained by water extraction of the seaweed *Furcellaria fastigiata*, and a dihydrocodeinone resin complex, and air.

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