Patented Mar. 6, 1951 2,544,272

UNITED STATES PATENT OFFICE

2,544,272

PENICILLIN SALT SUSPENSIONS

Henry C. Miller, Indianapolis, Ind., assignor to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

No Drawing. Application January 8, 1948, Serial No. 1,277

6 Claims. (Cl. 167—58)

1

This invention relates to penicillin salts and more particularly to improvements in oil suspensions of insoluble salts of penicillin.

It has recently been discovered that certain organic salts of penicillin having a substantial insolubility in water and oil are valuable in the treatment of infections for which penicillin itself is commonly used, and that these insoluble organic salts possess an advantage over aqueous solutions of the water-soluble metal salts of penicillin in that the duration of action of the penicillin is greatly enhanced. Thus, for example, only one or two parenteral administrations of the insoluble organic penicillin salts are required per diem in place of the six or more injections required when solutions of water-soluble penicillin salts are being administered.

The water-insoluble organic salts of penicillin which are capable of this unexpected prolongation are administered as suspensions in aqueous or oleaginous vehicles. When aqueous suspensions are used, the suspension must be freshly prepared because of the well known instability of penicillin in the presence of moisture. However, in the case of oil suspensions, the subject with which my invention is concerned, no substantial amount of moisture is present in the preparation and in such mixtures the penicillin salts are stable over a long period of time. Accordingly, it is most convenient to supply oil suspensions to the trade, and to furnish the preparations in bottles containing the insoluble penicillin salt in finely divided form already mixed with the oil vehicle. The insoluble salt of penicillin, which of course is finely divided to permit its free passage through the lumen of the hypodermic needle, does not remain in suspension, however, and before parenteral administration it is necessary for the technician or physician to resuspend the salt by agitating the preparation, as by shaking. It has been found that after standing for a period of a few days the finely divided salt which separates from the oil vehicle forms a stable mass of solid material which is resuspendable only by prolonged and violent agitation of the bottle containing the penicillin-oil mixture. The reason for the formation of this stable layer of solid material is not understood, but whatever its cause, it makes difficult the resuspension of the penicillin salt and the administration of the proper dosage.

Objects of the present invention are to provide preparations of insoluble penicillin salts in oleaginous vehicles in which the insoluble penicillin salts may readily be resuspended to form uniform suspensions of the salts. Other objects will become apparent from the following description.

2

In the accomplishment of the above and other objects I have discovered that readily resuspendable mixtures of finely divided insoluble organic salts of penicillin in oleaginous vehicles are obtained when there is added to the oleaginous mixture a small amount of one or more agents commonly classified as emulsifying agents. The small amount of emulsifying agent which is added is not sufficient to produce a stable suspension or even to cause any observable inhibition of the separation of the penicillin salt from the oil vehicle, but surprisingly, for some reason unknown to me, the small amount of agent does prevent the separated salt from forming the solid mass of salt which resists resuspension. Mixtures of insoluble organic penicillin salts and oleaginous vehicles prepared in accordance with this invention, unlike those which have hitherto been used, may be mixed by mere gentle shaking, to produce uniform and complete suspensions of the insoluble penicillin salts in the vehicles, even after the mixtures have stood for long periods of time.

In the provision of novel compositions according to my invention, care must be exercised in the selection of the emulsifying agents used to prevent the formation of the undesirable stable layer of insoluble penicillin salt, and especially so since the compositions are to be administered parenterally as medicaments. The agents chosen must be nontoxic, must be oil-soluble, must be substantially free from irritating properties, must not impart undesirable odor or color to the medicament and must have no untoward action upon the oil vehicle or the insoluble penicillin salt. I have found that emulsifying agents fully meeting the above medical and other requirements are compositions comprising a group consisting of the fatty acid partial esters of hexitol anhydrides, including such anhydrides as sorbitans, sorbides, mannitans and mannides, and the polyalkylene derivatives of the above anhydrides. Preferred compounds of the above described types of agents are those which contain fatty acid residues having from about 12 to about 18 carbon atoms, for example the residues of oleic, lauric and stearic acids. The preferred polyalkylene derivatives mentioned above are those prepared by reacting ethylene oxide or propylene oxide with the partial fatty acid esters of hexitol anhydrides, with the amount of ethylene oxide or propylene oxide introduced in the molecule

not exceeding a ratio of about 25 molecules of oxide to one of the anhydride.

The amounts of the above emulsifying agents employed in compositions prepared in accordance with my invention are much less than the range of 2 to 5 percent commonly employed in preparing oil-water emulsions. In my invention, although concentrations of 2 or more percent by volume are effective, efficient results are obtained when the concentration of emulsifying agent employed in the penicillin salt-oil mixture does not exceed one percent, and surprisingly the effectiveness of the emulsifying agent in producing an easily redispersible penicillin salt mixture attains its optimal value when the concentration is about 0.125 percent. It is difficult to account for this surprising optimal concentration and I know of no suitable explanation of this phenomenon. I have found that a mixture of emulsifying agents of the above types may be employed and that the most effective results are obtained when the total concentration of the mixure of emulsifying agents is about 0.125 percent. Thus, preferred compositions prepared in accordance with my invention contain emulsifying agents in effective amounts up to about 1 percent, and most desirably they contain a concentration of about 0.125 percent by volume.

Illustrations of novel compositions and their preparation in accordance with my invention are set forth in the following specific examples.

Example 1

24 liters of sesame oil, 24 cc. of the polyethylene oxide derivative of sorbitan mono-oleate and 13.5 cc. of sorbitan mono-oleate are mixed with stirring and the mixture is sterilized by heating it to about 150° C. for 3 hours. The mixture is cooled to about 45° C., and under sterile conditions and with vigorous stirring 9 kg. (9 billion units) of the procaine salt of penicillin in finely divided condition (200 mesh screen) are added. The above composition has a total volume of about 30 liters and on a percentage basis contains about 0.125 percent of emulsifying agent. The sterile suspension thus obtained is then placed in small sterile bottles suitable for distribution to the trade, and sealed. During the filling of the bottles with the sterile suspension of procaine penicillin in oil, it is of course necessary to maintain an even distribution of the penicillin salt in the oil by agitation of the mixture.

A sample of the oil suspension of procaine penicillin prepared in accordance with the above procedure was allowed to stand for two weeks. At the end of the two weeks period the mixture was found to be readily resuspendable by gentle shaking for a few seconds. In comparison, a sample of procaine penicillin suspended in sesame oil without the addition of the emulsifying agent, and which was allowed to stand for two weeks, was found to be resuspendable only upon violent shaking of the sample for a period of about 20 minutes.

A sample of procaine penicillin oil suspension prepared in accordance with the above procedure and a sample of procaine penicillin in sesame oil which contained no emulsifying agent were centrifuged at 2500 R. P. M. for about 40 minutes to cause complete separation of the suspended procaine penicillin salt. The procaine penicillin salt in the mixture of oil and emulsifying agent was readily resuspendable upon gentle shaking for a few seconds, whereas the procaine penicillin salt in the plain oil vehicle was resuspendable only upon violent and prolonged shaking for many minutes.

Example 2

The procedure of Example 1 may be followed in preparing a composition comprising the following ingredients and proportions thereof:

Cottonseed oil	ml.	1200
Procaine penicillin	g.	450
Sorbitan mono-oleate	ml.	3.7

The above composition has a total volume of about 1500 ml. and contains about 0.25 percent of emulsifying agent.

Example 3

The following composition containing about 1 percent of emulsifying agent may be prepared according to the procedure of Example 1:

Peanut oil	ml.	1000
Profiavin penicillin	g.	250
Polyoxyalkylene derivative of sorbitan monopalmitate	ml.	9.25

Example 4

The following composition containing about 0.08 percent of emulsifying agent may be prepared according to the procedure of Example 1:

Sesame oil	ml.	2400
Procaine penicillin	g.	500
Gentian violet salt of penicillin	g.	400
Sorbitan mono-oleate	ml.	2.4

The above examples are illustrative only, and it will be apparent to those skilled in the art that variations in the concentration of the ingredients may be made and that equivalents of the ingredients may be employed.

As is known to the art, a wide variety of oleaginous media may be employed in the preparation of penicillin salt suspensions suitable for therapeutic purposes. Suitable oleaginous dispersion media comprising oils and liquid oil-wax mixtures which may be referred to as physiologically compatible oils, and with which my invention is operative, include both parenterally and topically useful oils. Oils suitable for parenteral administration include the non-drying vegetable oils, such as rapeseed, cottonseed, poppy seed oil and the like, as well as the lower aliphatic esters of the fatty acids, for example ethyl oleate and ethyl stearate. An illustrative example of an oil suitable for topical application is liquid petrolatum. Examples of physiologically compatible waxes are beeswax and spermaceti.

As is known, for therapeutic purposes, compositions containing the insoluble penicillin salt in finely divided form are desirable. This fine division is especially desirable in compositions intended for injection purposes to avoid the tendency of the particles of the penicillin salt mechanically to "pack" in the lumen of the hypodermic needle. Thus it is the practice to provide penicillin salt-oil suspensions in which the penicillin has been ground or powdered until it will pass through a 200-mesh screen. However, the size of the penicillin salt particles is not critical for the purposes of my invention, and my invention is operative with penicillin salt particles even of such size as will pass through a 40-mesh or coarser screen. In general, it may be said that the more finely divided the penicillin salt, the more tenaciously the particles of salt adhere to each other and the more difficultly the solid mass which settles out is redispersible. Hence, my in-

vention is of greater importance in connection with penicillin salt-oil suspensions in which the penicillin salt is in a finely divided state, a condition which is presently preferred for therapeutic compositions.

I claim:

1. A readily redispersible substantially water-free therapeutic composition comprising a major proportion of an oleaginous vehicle, a minor proportion of a finely divided water-insoluble, and oil-insoluble organic penicillin salt and an amount effective to cause redispersion and less than about one percent by volume of at least one emulsifying agent of the group consisting of the fatty acid partial esters of hexitol anhydrides and their polyalkylene oxide derivatives.

2. An injectable readily redispersible therapeutic composition being substantially water-free, comprising a non-drying vegetable oil, a finely divided water-insoluble, and oil-insoluble organic penicillin salt and in total amount about 0.125 percent by volume of at least one member of the group consisting of the fatty acid partial esters of hexitol anhydrides and their polyakylene oxide derivatives.

3. A readily redispersible substantially water-free therapeutic composition comprising a non-drying vegetable oil, finely divided procaine penicillin and an amount effective to cause redispersion and less than about one percent by volume of at least one member of the group consisting of the fatty acid partial esters of hexitol anhydrides and their polyalkylene oxide derivatives.

4. A readily redispersible substantially water-

free therapeutic composition comprising sesame oil, finely divided procaine penicillin and an amount effective to cause redispersion and less than about one percent by volume of at least one member of the group consisting of the fatty acid partial esters of hexitol anhydrides and their polyalkylene oxide derivatives.

5. A readily redispersible substantially water-free therapeutic composition comprising sesame oil, finely divided procaine penicillin and an amount effective to cause redispersion and less than about one percent by volume of a mixture of sorbitan mono-oleate and the polyethylene oxide derivative of sorbitan mono-oleate.

6. A composition according to claim 5 in which the mixture of sorbitan mono-oleate and the polyethylene oxide derivative of sorbitan mono-oleate is present in a concentration of about one eighth of one percent by volume.

HENRY C. MILLER.

REFERENCES CITED

The following references are of record in the file of this patent:

OTHER REFERENCES

Public Health Reports, Jan. 3, 1947, vol. 62, No. 1, pages 1 to 9, 10 to 19.

Proc. Staff Meetings Mayo Clinic, Dec. 10, 1947, page 567.

Drug & Cosmetic Industry, Nov. 1947, page 595.

"Spans & Tweens," Atlas Powder Co., Nov. 1942, pages 7 and 8.