

UNITED STATES PATENT OFFICE

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LONG-ACTING MORPHINE INJECTION

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This invention relates in general to therapeutic compounds, and pertains to a compound for injection into the body tissues whose beneficial effects are more prolonged than those compounds usually used for this purpose, and in which objectionable side effects are absent.

Specifically, this invention relates to the preparation of sedative drugs in suspension in a mixture of edible oils or oils suitable for injection into the body tissues, so that after parenteral administration of the compound the drug is slowly absorbed in the body tissues to produce all the beneficial effects, without the side effects which are now produced by water solutions of the drug.

It has been found that a certain degree of shock occurs after the administration of water soluble morphine solutions due to a sudden depression of the nervous system. Nausea and vomiting are also caused by these solutions, presumably because of the relative rapidity with which water solutions are carried in the circulation of the body fluids.

Furthermore, it has been found that when morphine sulfate is placed in a semi-solid mixture of hydrogenated oil and other oils the drug is slowly absorbed, so that a longer time may elapse between administrations of the drug, resulting in use of lesser amounts of the drug and consequently less hazard of drug addiction.

To achieve the prolongation of the effects of a drug in an oil suspension by this invention it has been found that it is desirable to saponify the fatty acids which are naturally present in certain oils such as cottonseed oil and sesame oil. The presence of the soap formed apparently helps to retard the rate of dispersion of the drug in the body tissues.

This therapeutic compound is prepared by using a mixture of any edible oil, or one suitable for injection into the body tissues, preferably sesame oil. With this is mixed a low melting point hydrogenated oil, preferably cottonseed oil. The most desirable proportions of the oil in this mixture is that one which results in the mixture of oils having a melting point near that of the body, or 98.6 degrees F. This also aids in causing the drug to remain at the site of the injection, instead of diffusing into the body tissues as do the water solutions. The mixed oils are then reacted with a base, such as alcoholic so-

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dium hydroxide, for the purpose of standardizing the mixture at a pH value of 6.5, or slightly below, and at the same time to form a soap of the fatty acids naturally occurring in the mixed oils. In general, the pH of the mixture may be in the range of 6-7. To the above treated oils is added the desired amount of the sedative. As an example, there may be added between 1 and 2 grams of morphine sulfate to 100 cc. of the mixed oils, forming a homogeneous dispersion of the sedative in the oils. Depending upon the drug to be used, the amounts may vary. In the case of morphine sulfate a concentration of less than 10 milligrams per cc. of the mixed oils is ineffective, while a concentration of more than 20 milligrams per cc. of the mixed oils would be toxic.

A compound of this type may be prepared in this manner. A mixture of 600 cc. of hydrogenated oil, such as hydrogenated cottonseed oil, 380 cc. of sesame oil, 20 cc. of benzyl alcohol, and a minute quantity, such as for example 2 cc. of alcoholic sodium hydroxide, is placed in a glass volumetric flask and warmed to about 60° C. The solution is then filtered through paper until free from lint, and autoclaved for 20 minutes at 15 lbs. pressure. After this, 18 grams of morphine sulfate is placed in a sterile mixing container and thoroughly mixed with the filtered solution above.

At this point an analytical check is made by transferring 5 cc. of the suspension to an accurately weighed fritted glass crucible. The suspension in this crucible is washed with anhydrous ether until free from oil. The crucible and contents are dried to a constant weight, after repeated washing with ether. The weight should then be not less than 85 mg., nor more than 95 mg.

The suspension is then filled into 1 cc. straight neck ampuls. This filling may be done by an automatic pipette set to deliver 1.2 cc. at each operation. The suspension should be under constant agitation while being filled into the ampuls, and the ampuls should be sealed the same day they are filled.

This invention has shown that the iso-electric point of precipitation of morphine sulfate in water is about pH 6.5. As stated above, it is desired to prepare the mixed oils used in this com-

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pound so that they have a pH value of about 6.5, or slightly below. The result is that when the compound is injected into the body tissues the morphine sulfate is partially precipitated by the body fluids at the site of the injection, and thereafter slowly absorbed, while some of the morphine sulfate is changed to morphine alkaloid, which is even more insoluble than the sulfate.

It has thus been found that with the use of this compound there is no stipulation of the vomiting center of the brain, no shock, no nausea, and no side effects, all due to the slow absorption from the site of the injection. With the use of this compound it is necessary to give injections in post-operative cases only once in ten hours, instead of every three hours in the case of morphine in water solution. In some cases there are records which show that this new compound gave full relief from pain with injections given every twenty hours.

The invention claimed is:

1. A therapeutic composition for parenteral administration having a suspension of a water-soluble, sedative morphine salt in a semi-solid mixture of sesame oil and low-melting hydrogenated cottonseed oil, in which mixture free fatty acids therein are combined in the form of soap, the said mixture of said oils saponified to

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a pH of 6 to 7 and melting at a temperature equivalent to human body temperature.

2. A therapeutic composition, as claimed in claim 1, in which the said semi-solid mixture of sesame oil and low-melting hydrogenated cottonseed oil contains benzyl alcohol.

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