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2,897,120

LOW VISCOSITY CMC PHARMACEUTICAL VEHICLE

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This invention relates to a pharmaceutical composition and more particularly relates to a vehicle intended primarily for improving the syringeability and suspendability characteristics of insoluble medicinal agents.

One of the most difficult problems faced by the pharmaceutical art has been the development of satisfactory vehicles for insoluble medicinal agents. This is especially true for injectables. Such injectable medicinal agents are generally sold in two forms: as a dry powder and as a liquid suspension. The dry powder is designed for the extemporaneous preparation of an aqueous fluid substantially immediately prior to use. A liquid suspension under modern practice is sold most frequently in small bottles from which the suspension is withdrawn into a syringe for immediate injection. Such suspensions are also sold in a disposable syringe ready for immediate use. The desirable physical characteristics of such a suspension can be fitted into two categories: suspendability and syringeability. Primarily, suspendability involves the problems of settling and re-suspendability, and syringeability involves drainage, needle clogging and freezing of the plunger in the barrel of the syringe. Settling is undesirable for several reasons: it causes uneven dosage, needle clogging and clumping. The ideal vehicle would not permit the insoluble medicinal to settle out at all, but some settling is bound to occur in the course of time. It is, therefore, desirable that the insoluble medicinal agent be re-suspendable with gentle shaking. Drainage is a matter of being able to remove all of the suspension from the container in which it is sold and, more important from the syringe from which it is ejected. The suspension should not cling to the walls of either type of container nor cloud it in such a way as to obscure the contents thereof or otherwise give the appearance of a contaminated product. Needle clogging is a serious problem for obvious reasons: it increases the difficulty of making an injection both from the standpoint of the patient and the person performing the injection; it also increases the difficulty of controlling the dosage of the medicinal agent administered.

It is an object of the present invention to provide an improved vehicle for suspending insoluble medicinal agents. Another object of the present invention is to provide aqueous suspensions of insoluble medicinal materials which remain suspended over prolonged periods of time. Another object is to provide such suspensions which are easily syringeable and therefore suitable for

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parenteral injection. Still another object of the present invention is to provide such suspensions which drain cleanly from the container from which they are dispensed, will not clog the needle of the hypodermic syringe, have little tendency to settle out after prolonged storage, and are easily resuspended with gentle shaking when settling does occur. Other objects will be apparent to one skilled in the art to which this invention pertains.

These objects are accomplished in the present invention by the use of a combination of hydrophilic polyvinyl compound, such as polyvinyl pyrrolidone, polyvinyl alcohol, or mixtures thereof, and a low viscosity alkaline salt of carboxymethylcellulose in an aqueous vehicle as the dispersion medium for insoluble medicinal materials. By means of this combination, suspensions of insoluble medicinal materials lacking the undesirable characteristics set forth above are obtained.

Although it is known that sodium carboxymethylcellulose is a useful suspending agent for procaine penicillin G, it is believed that the combination with hydrophilic polyvinyl compounds has never been used prior to the present invention or has there been any suggestion that the combination would possess unexpected advantages not attributable to either alone. For example, sodium carboxymethylcellulose when used with procaine penicillin is helpful in producing a suspension; but it does not drain well from a container, especially a hypodermic syringe. If used in great enough quantity to suspend procaine penicillin satisfactorily, the viscosity increases to an extent such that the drainage problem results. However the action of sodium carboxymethylcellulose as a suspending agent is unpredictable since it is entirely unsatisfactory when used to suspend such materials as cortisone acetate. Although such a suspension drains well from a bottle (contrary to the case of a procaine penicillin suspension) packing occurs and a uniform resuspension is unobtainable. When used with hydrocortisone a suspension was produced which was poorly dispersed and drained poorly. With hydrocortisone acetate the result was similar. When polyvinyl pyrrolidone is used alone as a suspending agent for procaine penicillin, packing and settling occurs although drainage is good. On the other hand when it is used in combination with cortisone acetate it not only sometimes causes hard packing, but the bottles drain poorly and a uniform resuspension is not obtainable at some temperatures. When used to suspend hydrocortisone, polyvinyl pyrrolidone tends to cause some packing; and the drainage is only fair. With hydrocortisone acetate polyvinyl pyrrolidone alone produces a hard cake which cannot be suspended. In view of these inconsistencies in the results obtained by the use of these suspending agents with different materials, it is truly remarkable that the combination of these materials produces consistently good results when used as a suspending medium for the materials mentioned as well as other insoluble medicinal agents.

Since very little is known about the mechanics of making suspensions suitable for therapeutic use, and since the action of the individual materials is wholly unpredictable, it is entirely unexpected that the combination of polyvinyl pyrrolidone or polyvinyl alcohol or a mixture

of the two or like hydrophilic polyvinyl compounds, with a low viscosity alkaline salt of carboxymethylcellulose would give markedly superior suspensions. The superior suspending properties of such combinations of hydrophilic polyvinyl compounds and a low viscosity alkaline salt of carboxymethylcellulose, coupled with other factors which complement or enhance the suspending action of the combination, such as the particle size of the insoluble materials utilized, the pH of the vehicle, the viscosity of the vehicle, the coatings on the insoluble medicinal agents involved, the amount of insoluble medicinal agent utilized, the coating on the bottles or containers from which the suspension is to be dispensed, and the preservative used where the suspension must be sterile for parenteral administration, provide suspensions suitable for therapeutic use which avoid difficulties heretofore encountered in the prior art.

The present invention, therefore, is directed broadly to the use of a combination of a hydrophilic polyvinyl compound, such as polyvinyl pyrrolidone, polyvinyl alcohol, and mixtures thereof, and a low viscosity alkaline salt of carboxymethylcellulose, such as the low viscosity sodium and other alkali metal salts of carboxymethylcellulose, as a suspending agent for an insoluble medicinal agent in an aqueous vehicle and more particularly to combinations embodying various of the other factors noted above as will be more particularly set forth hereinafter.

One of the more important factors which may be used to complement or enhance the combination suspending agent of the invention is the viscosity of the suspension. Thus it has been found advantageous in preparing suspensions according to the invention to maintain a viscosity of about fifteen to about eighty centipoises at room temperature and that optimum results are obtained ordinarily with a viscosity between about twenty and forty centipoises at room temperature. While several factors affect the viscosity of the suspensions, the amount of the hydrophilic polyvinyl compound, the amount of the low viscosity alkaline salt of carboxymethylcellulose, and the amount and character of the active material, that is, the insoluble medicinal agent which is to be suspended, and while the viscosity can sometimes be affected by the addition of surface-active agents and deflocculating agents, suitable viscosities are ordinarily obtained by the use of from about 0.1 to about three percent of polyvinyl pyrrolidone (percentages here weight by volume unless otherwise specified), and about 0.1 to about one percent of a low viscosity alkali salt of carboxymethylcellulose. The term "low viscosity alkaline salt of carboxymethylcellulose" is used herein to designate those alkali carboxymethylcelluloses, such as sodium carboxymethylcellulose, which have a viscosity in two percent aqueous solution of less than about 100 centipoises and advantageously between about 25 and fifty centipoises at 25 degrees centigrade using a Brookfield Viscometer Model LVF. Thus by combining between about 300,000 and about 600,000 units of procaine penicillin per milliliter of suspension, advantageously about 500,000 units per milliliter, with about 0.5 percent polyvinyl pyrrolidone and about 0.5 percent of low viscosity sodium carboxymethylcellulose, there are obtained suspensions which when prepared aseptically are particularly well suited for parenteral use and which can be injected through a hypodermic needle without the disadvantages heretofore encountered in this art.

It is most advantageous to use fifty percent of micronized procaine penicillin having a particle size ranging from two to ten microns together with fifty percent milled procaine penicillin with a particle size ranging from forty to sixty microns. The exact reason for the improved suspensions obtained by using particles of varying sizes is not known, but some observations regarding the properties of such suspensions have been made. For example, it has been observed that small particles apparently in-

crease the viscosity of the vehicle and tend to form aggregates or globules of the active ingredient. When all particles are of the same size, they seem to have a greater tendency to pack. When the suspension is prepared for injection through a syringe, the use of particles of the same size tends to create a sort of log jam when passing through the needle. There seems to be a lesser tendency to block a needle when the particles are of varying sizes. It has been observed that eighteen to 26 gauge needles can be used when the particles are of the varying sizes indicated. Of course, it is not absolutely essential to the present invention to have varying particle sizes of between about two to sixty microns of the active medicinal agent to be suspended, but more consistent results will be obtained if varying particle sizes are used.

Further improvement is obtained by coating the insoluble material to be suspended with a phospholipid, such as lecithin, cephalin and the like. This is the subject matter of copending application Serial Number 108,419, filed August 3, 1949, now Patent Number 2,694,665, issued November 16, 1954. Thus lecithin coating has been successfully utilized on procaine penicillin. Although the role of the phospholipid as a coating for the insoluble medicinal agent in the compositions of the present invention is more fully explained in the copending application indicated, it should be noted that such coated materials contribute much to the success of suspensions such as dealt with in the present invention. Besides contributing to the overall qualities of the suspension, a phospholipid coating seems to act as a sort of dispersing agent for the insoluble medicinal agent. Without such a coating procaine penicillin particles, for example, do not wet properly. However, any such observation as to the contribution of lecithin to the preparation of a successful suspension will not withstand critical scrutiny. It is only important to note that lecithin does contribute to the overall success of the suspension, both as an individual ingredient and in combination with the other materials indicated.

Depending upon the nature of the insoluble medicinal agent to be suspended, it may prove desirable to utilize a buffer to control the pH of the suspension within a desired range. For example, it is desirable to use sodium citrate where procaine penicillin, cortisone acetate, hydrocortisone, hydrocortisone acetate and similar materials are to be suspended. For procaine penicillin it is desirable to use sufficient buffer to keep the suspension close to but below a pH of about 7, that is between about 5 and about 7. It should also be noted that the pH may change upon storage depending upon the temperature. For example, if the pH starts out at about 6.3 to 6.5, it will probably go down to about 5.5 to 5.8 upon storage at room temperature for any considerable length of time.

Further improvement for the suspensions of the present invention can be obtained by the use of silicone coated bottles as containers therefor. These tend to impart proper wetting characteristics to the surface of glass from which such suspensions are dispensed. From this standpoint it should be noted that the vehicle of the present invention works in a very satisfactory manner, in silicone coated bottles, while vehicles containing such surface active materials as Tween 80 (a polyoxyethylene ether of a partial higher fatty acid ester of sorbitan) so affect the silicone coating as to give undesirable results. For example, a silicone coated bottle containing such a surface active agent causes a haze in the bottle and clouds it in such a way as to obscure its contents, tends to indicate poor drainage, or give the impression of a contaminated product.

When the suspensions of the present invention are utilized for sterile purposes, such as for parenteral injection, it is desirable to utilize a preservative such as methyl, propyl, or butyl parabens. Although such preservatives do not contribute anything to the suspension of insoluble

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medicinal agents, they are also not adversely affected by the vehicle utilized in the present invention.

The phrase "procaine penicillin" is used in the present specification in a generic sense and is intended to include the various forms of penicillin, such as G, O, K and the like, as well as other derivatives of procaine, such as 2-chloroprocaine, which are capable of forming insoluble salts with penicillin. Likewise other insoluble penicillin salts such as N,N-dibenzylethylenediamine penicillin, are successfully suspended by the vehicle of the present invention.

It will be apparent from the foregoing that a considerable number of variables can and are involved in preparing successful suspensions such as contemplated by the present invention. Numerous experiments have been conducted in an attempt to adjust the variables to prepare the most successful product. While there is little doubt that the basic combination of a hydrophilic polyvinyl compound and a low viscosity alkaline salt of carboxymethylcellulose is the most important or fundamental factor in the present invention, the other factors indicated are definite improvements thereof.

Among the numerous experiments conducted with the vehicle of the present invention are the following, presented in summarized form:

Materials used	Results obtained
Comparison of sodium carboxymethylcellulose (CMC) of different viscosities, high, medium, low, with the addition of polyvinyl pyrrolidone (PVP) at one percent concentration.	Vehicles of various concentrations plus procaine penicillin G were evaluated on the basis of suspending quality and drainage in silicone treated bottles; and the results indicated that suspensions with sodium carboxymethylcellulose alone did not drain as well as suspensions with sodium carboxymethylcellulose (CMC) and polyvinyl pyrrolidone (PVP) only low viscosity CMC was suitable
Comparison of various combinations of procaine penicillin G 300,000 units/cc. and PVP vehicles (1%).	Resuspending qualities of suspensions made with vehicle containing PVP without CMC were generally poorer (packing, settling, and resuspendability) than those suspensions made with CMC and PVP. Resultant suspension would not readily resuspend.
Aqueous suspension of 2-chloroprocaine penicillin O 300,000 units/cc. and PVP vehicle (1%).	This suspension would not readily resuspend after three weeks storage at room temperature (25° C.).
Aqueous suspension of procaine penicillin G 300,000 units/cc. in PVP vehicle (1%).	This suspension remained stable physically at room temperature for five months. At five and one-half months it had settled enough to give poor syringeability results.
Aqueous suspension of procaine penicillin G 500,000 units/cc. in PVP vehicle (1%).	This suspension remained stable at room temperature for eight months and is easily ejected. The samples of this suspension stored in the refrigerator for eight months are easily syringed and have not packed or settled out.
Aqueous suspension of procaine penicillin G 300,000 units/cc. in PVP (1%)-LV* CMC (0.2%) vehicle.	The powder, when constituted, gives a suspension of excellent drainage, good resuspendability and good syringeability.
1,000,000 unit vial of procaine penicillin G (800,000 units) and sodium penicillin G (200,000 units) with 0.5% LV CMC and 0.5% PVP.	Viscosity of this suspension was low and the material settled out and packed.
Aqueous suspension of procaine penicillin G 300,000 units/cc. in 1% PVP vehicle.	This suspension had a low viscosity and good drainage and resuspendability.
Aqueous suspension of procaine penicillin G 300,000 units/cc. in PVP (1%) and LV CMC (0.5%).	Viscosity of this suspension was high (128 cps.) and gave poor drainage.
Aqueous suspension of procaine penicillin G 300,000 units/cc. in LV CMC (0.5%) vehicle.	Various suspensions in vials have been shipped from Kalamazoo, Michigan to Los Angeles, Minneapolis and Atlanta by train, plane, and truck. Evaluation of samples on return shows that the PVP-LV CMC vehicle gives a product with good drainage, good resuspendability, and good syringeability while neither PVP alone nor CMC alone does.
Various suspensions using PVP alone, LV CMC alone, and PVP + LV CMC.	

*Low viscosity material which at 2% concentration in aqueous solution has a viscosity of 25 to 50 centipoises at 25° C.

PVP is, of course, an abbreviation for polyvinyl pyrrolidone, while CMC is an abbreviation for sodium car-

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boxymethylcellulose. Similar results are obtained by using polyvinyl alcohol and other alkaline salts of carboxymethylcellulose.

The polyvinyl hydrophilic compounds of the invention are of pharmaceutical grade, non-toxic, inert and capable of being sterilized without change in composition. On the addition of water to a dry composition containing a steroid and the selected hydrophilic polyvinyl compound, followed by mixing, a stable steroid suspension is readily obtained.

The polyvinyl pyrrolidone used in the compositions described herein is sold by the General Aniline and Film Company under the trademark "Plasdone" and is characterized by a viscosity coefficient, i.e., K value, of 26 to 36 and a molecular weight of about 40,000. However, it is to be understood that the invention is not to be limited to the use of this specific polyvinyl pyrrolidone since other equivalent polyvinyl pyrrolidones of pharmaceutical grade are likewise suitable. While a polyvinyl pyrrolidone of pharmaceutical grade possessing a molecular weight between twenty and eighty thousand is preferred, satisfactory results are also obtained by the use of a polyvinyl pyrrolidone outside of this molecular weight range.

The polyvinyl alcohol utilized in the compositions described herein is sold by the Du Pont Company under the trademark "Elvanol" 51-05 and is characterized by a viscosity of four to six centipoises (four percent aqueous solution at twenty degrees centigrade), a pH of six to eight and a 86 to 89 percent hydrolysis from polyvinyl acetate. It is to be understood, however, that the invention is not limited to the use of this specific polyvinyl alcohol since any other equivalent polyvinyl alcohol of pharmaceutical grade can likewise be used to achieve similar results.

Similar experiments and similar results have been obtained with the basic combination of a hydrophilic polyvinyl compound with a low viscosity alkaline salt of carboxymethylcellulose in an aqueous vehicle for other insoluble medicinal agents. For example, the following tables demonstrate the use of the aforesaid vehicle for various steroids such as cortisone acetate, hydrocortisone, and hydrocortisone acetate. The vehicles are rated in the tables by an arbitrary scale ranging from "0" to "4+." The preparations were graded for such characteristics as appearance, resuspendability, syringeability, drainage and changes in particle size. A preparation with an "0" rating is entirely unacceptable and indicates physical instability on short term storage at various temperatures. A "4+" preparation has the best physical characteristics of the materials listed in the tables. Values of 1+ to 3+ were assigned to preparations falling in between these two extremes. Suspensions rated 1+ or 2+ are not regarded as satisfactory for commercial purposes. A composite evaluation of samples stored at forty degrees centigrade, 25 degrees centigrade, and four degrees centigrade was made, and the rating assigned to the whole group. Pertinent remarks are included under the heading "comments." It will be noted that various amounts of polyvinyl pyrrolidone and low viscosity sodium carboxymethylcellulose were used.

Other materials (e.g., buffers, preservatives, surface active agents, and the like) were also included to determine their effect upon the suspension. Where type of particle is not stated it is to be understood that a precipitated or crystalline product was used. The term "sodium CMC L.V." refers to sodium carboxymethylcellulose having a viscosity in 2% aqueous solution of 25 to 50 centipoises at 25 degrees centigrade. The term "sodium CMC H.V." refers to sodium carboxymethylcellulose having a viscosity in 1% aqueous solution of 1300 to 2200 centipoises at 25 degrees centigrade. In Table I except where otherwise indicated, the suspension contained 0.57 percent sodium citrate and 0.26 percent methylparaben. All amounts are indicated in percentages.

Suspensions prepared from different lots of cortisone acetate

The different lots of cortisone acetate are representative of different preparations having different particle types and crystal structures. The data given in Table I shows therefore that the combination suspending agent or dispersion medium of the invention can be used to prepare acceptable suspensions of a wide variety of different forms of cortisone acetate.

Suspensions of hydrocortisone acetate

Percentage composition						Evaluation of suspensions			Comments
Hydrocortisone acetate	PVP	Sodium CMC LV	Sodium citrate	Sodium chloride	Preservative	1 mo.	3 mos.	6 mos.	
2.5	0.5	0.5	-----	0.9	0.01 thimerosal	++	++	---	Agglomerated particles. Suspend O.K. 1.0% Propylene glycol.
2.5	0.1	0.5	-----	0.9	0.1 thimerosal	+++	+++	---	Particles not entirely wetted by vehicle. 0.1% Tween 80.
2.5	0.1	-----	-----	0.9	0.26 methylparaben	0	-----	---	Viscosity too great. Unable to resuspend. 0.5% sodium CMC H.V., 0.2% Pluronic F68.
2.5	0.75	0.75	0.57	-----	do	+++	++	---	Caking. Difficulty in resuspension.
5.0	0.1	0.75	-----	0.9	do	0	-----	---	Caking—unable to resuspend. 0.2% Pluronic F68.
5.0	0.5	0.5	-----	0.9	do	++++	+++	---	Slight caking. Resuspends O.K.
5.0	0.5	0.5	0.57	-----	do	++++	---	---	Good, all temperatures.
5.0	0.5	-----	0.57	-----	do	0	-----	---	Hard cake. Unable to suspend.
5.0	-----	0.5	0.57	-----	do	+	-----	---	Agglomerated, poor drainage—poor dispersion of solids.
5.0	0.75	0.75	0.57	-----	do	++++	++++	---	Good.
5.0	0.75	0.75	-----	0.9	0.2 methylparaben	++++	+	---	Slight shaking. Resuspend O.K.
5.0	0.75	0.75	0.5	0.7	do	++++	+	---	
5.0	0.5	0.75	0.5	0.7	do	++++	+	---	
5.0	0.1	0.75	0.5	0.7	do	++++	+	---	
5.0	0.5	0.5	0.5	0.7	do	++++	+	---	
5.0	0.1	0.5	0.5	0.7	do	++++	+	---	
5.0	0.1	0.5	0.5	0.9	0.1 thimerosal	+++	+++	---	Slight tendency to cake. Resuspends easily.
5.0	0.1	0.5	-----	0.9	do	+++	+++	---	Particle not entirely wetted by vehicle.
5.0	0.1	0.3	-----	0.9	0.1 methylparaben and 0.02 propylparaben.	+++	---	---	Caking, clumping, foam. 0.1% Pluronic F68.
5.0	0.2	0.3	-----	0.9	0.18 methyl and 0.02 propylparaben.	+++	---	---	Slight haze in vehicle.
5.0	0.3	0.3	-----	0.9	do	+++	---	---	Slight film of solids on walls of glass.
5.0	0.1	0.4	-----	0.9	do	+++	---	---	Do.
5.0	0.2	0.4	-----	0.9	do	+++	---	---	Do.

TABLE III
Suspension of hydrocortisone

Percentage composition						Evaluation of suspensions			Comments
Hydrocortisone	PVP	Sodium CMC LV	Sodium citrate	Sodium chloride	Preservative	1 mo.	3 mo.	6 mo.	
5.0----	0.1	0.75	-----	0.9	0.26 methylparaben	++++	++++	---	Slight caking at 40°, 3 mos. Resuspends O.K. 0.2% Pluronic F68.
5.0----	0.5	-----	0.57	-----	do.	++	-----	---	Packing at 25 and 4°. Drainage only fair.
5.0----	-----	0.5	0.57	-----	do.	+	-----	---	Agglomerated-poor dispersion of solids. Drainage poor.
5.0----	0.5	0.5	0.57	-----	do.	++++	-----	---	Slight caking on stopper.
5.0----	0.5	0.5	0.57	-----	do.	++++	++++	---	Some agglomeration.
5.0----	0.75	0.75	0.57	-----	do.	++++	++++	---	40°, 3 mos. gummy mass. Unable to resuspend.
5.0----	0.75	0.75	0.57	-----	do.	++++	++++	---	Drainage fair.
5.0----	0.75	0.75	0.57	-----	do.	++++	++++	---	Drainage fair, 4° best.
10.0----	0.5	0.5	0.57	-----	do.	+	-----	---	Do.
5.0----	0.1	0.5	0.5	0.7	0.2 methylparaben	++++	-----	---	Slight film of solids sticks to walls. Some agglomeration.
5.0----	0.75	0.75	0.5	0.9	do.	++++	++++	---	Do.
5.0----	0.75	0.75	0.5	0.7	do.	++++	++++	---	Drainage fair, 4° best.
5.0----	0.5	0.75	0.5	0.7	do.	+	-----	---	Slight caking tendency after 3 mos.
5.0----	0.1	0.75	0.5	0.7	do.	++++	++++	---	Some agglomeration.
5.0----	0.5	0.5	-----	0.9	do.	++++	++++	---	Drainage fair.
5.0----	0.5	0.5	0.5	0.7	do.	++++	++++	---	Some agglomeration.
5.0----	0.1	0.5	-----	0.9	0.01 thimerosal	++++	++++	---	Slight film of solids sticks to walls. 0.1% Pluronic F68.
5.0----	0.1	0.3	-----	0.9	0.18 methyl and 0.02 propylparaben	++++	++++	---	Slight film of solids sticks to walls.
5.0----	0.2	0.3	-----	0.9	do.	++++	-----	---	Do.
5.0----	0.3	0.3	-----	0.9	do.	++++	-----	---	Do.
5.0----	0.1	0.4	-----	0.9	do.	++++	-----	---	Do.
5.0----	0.2	0.4	-----	0.9	do.	++++	-----	---	Do.

The following examples are illustrative of the compositions and process of the present invention but are not to be construed as limiting.

EXAMPLE 1

A sterile suspension containing 300,000 units of procaine penicillin G in each cubic centimeter is prepared as follows:

Each cc. of the vehicle contains—

Sodium citrate, granular, U.S.P.	Mg. 5.7
Sodium carboxymethylcellulose, viscosity 25 to 50 centipoises at 25° C. and 2% conc	5.0
Plasdone (polyvinyl pyrrolidone)	5.0
Sterile methylparaben, U.S.P.	2.63
Water of injection, sufficient to make up 1.0 cc.	

The sodium citrate, sodium carboxymethylcellulose and the Plasdone are mixed in sufficient water for injection and sterilized by heating to 120 degrees centigrade for thirty minutes. When the vehicle has cooled, the sterile methylparaben is added. The methylparaben is ethylene oxide or formaldehyde sterilized.

The final suspension is prepared as follows:

Each cc. of the suspension contains—

157,500 units sterile bulk procaine penicillin G milled (4% lecithin ¹ coated)	
157,500 units sterile bulk procaine penicillin G micronized (1.25% lecithin ¹)	
Q.s. sterile vehicle (as prepared above)	

The sterile bulk procaine penicillin G, milled (4% lecithin coated) and the sterile bulk procaine penicillin G, micronized (1.25% lecithin coated) are sterilized by treatment with ethylene oxide. This is done before the lecithin coating is applied. After the penicillin is ethylene oxide sterilized, it is handled aseptically. The sterile milled and micronized penicillins are added under aseptic conditions, and the sterile suspension is passed through a colloid mill and filled aseptically into sterile containers.

It should be noted that "micronizing" produces particle sizes of about two to ten microns, and "milling"

produces particle sizes ranging from forty to sixty microns.

EXAMPLE 2

35 A sterile suspension containing 300,000 units of procaine penicillin G in each cubic centimeter is prepared as follows:

Each cc. of the vehicle contains—

40 Sodium citrate, granular, U.S.P.	Mg. 5.7
Sodium carboxymethylcellulose, viscosity 25 to 50 centipoises at 25° C. and 2% conc	7.5
Plasdone (polyvinyl pyrrolidone)	7.5
Sterile methylparaben, U.S.P.	1.5
Sterile propylparaben, U.S.P.	0.2
45 Water for injection, sufficient to make up 1.0 cc.	

The sodium citrate, sodium carboxymethylcellulose and the Plasdone are mixed in sufficient water for injection and sterilized by heating to 120 degrees centigrade for thirty minutes. When the vehicle has cooled, the sterile methylparaben and the sterile propylparaben are added.

The final suspension is prepared as follows:

Each cc. of the suspension contains—

55 157,500 units sterile bulk procaine penicillin G milled (4% lecithin coated)	
157,500 units sterile bulk procaine penicillin G micronized (1.25% lecithin)	
Q.s. sterile vehicle (as prepared above)	

60 The sterile milled and micronized penicillins are added to sufficient sterile vehicle in a sterile container and mixed well. The sterile suspension is passed through a colloid mill.

EXAMPLE 3

65 A sterile suspension containing 500,000 units of procaine penicillin G in each cubic centimeter is prepared as follows:

Each cc. of the vehicle contains—

70 Sodium citrate, granular, U.S.P.	Mg. 5.7
Sodium carboxymethylcellulose, low viscosity	2.0
Plasdone (polyvinyl pyrrolidone)	10.0
Sterile methylparaben, U.S.P.	1.5
Sterile propylparaben, U.S.P.	0.2
75 Water for injection, sufficient to make up 1.0 cc.	

¹ The lecithin coating is carried out as disclosed in U.S. application Serial Number 108,419, filed August 3, 1949.

The sodium citrate, sodium carboxymethylcellulose and the Plasdone are mixed in sufficient water for injection and sterilized by heating to 120 degrees centigrade for thirty minutes. When the vehicle has cooled, the sterile methylparaben and sterile propylparaben are added.

The final suspension is prepared as follows:

Each cc. of the suspension contains—

382,500 units sterile bulk procaine penicillin G, milled (1.25% lecithin)

127,500 units sterile bulk procaine penicillin G micronized (1.25% lecithin)

Q.s. sterile vehicle (as prepared above)

The sterile milled and micronized penicillins are added to sufficient sterile vehicle in a sterile container and mixed well. The sterile suspension is passed through a colloid mill.

EXAMPLE 4

Following the procedure of Example 3, a suspension containing polyvinyl alcohol is prepared by substituting an equal amount of polyvinyl alcohol for polyvinyl pyrrolidone to prepare a suspension having excellent physical stability and syringeability characteristics.

EXAMPLE 5

Following the procedure of Example 3, a suspension of cortisone acetate is prepared by substituting 25 milligrams per cubic centimeter of cortisone acetate (precipitated or micronized) for the procaine penicillin to produce a suspension possessing excellent physical stability and good syringeability characteristics.

Good suspensions of cortisone acetate can also be formed by omitting the lecithin coating.

EXAMPLE 6

Following the procedure of Example 3, a suspension of hydrocortisone is prepared by substituting fifteen milligrams per cubic centimeter of hydrocortisone (milled or precipitated) for the procaine penicillin to produce a suspension possessing excellent physical stability and good syringeability characteristics.

Good suspensions of hydrocortisone can also be obtained by omitting the lecithin coating.

EXAMPLE 7

Following the procedure of Example 3, a suspension of hydrocortisone acetate is prepared by substituting fifteen milligrams per cubic centimeter of hydrocortisone acetate (milled or precipitated) for the procaine penicillin to produce a suspension possessing excellent physical stability and good syringeability characteristics.

Good suspensions of hydrocortisone acetate can also be obtained by omitting the lecithin coating.

EXAMPLE 8

A sterile powder containing 800,000 units of procaine penicillin G and 200,000 units of sodium penicillin G can be prepared as follows:

Each vial contains—

675,000 units sterile bulk procaine penicillin G (4% lecithin coated)

225,000 units sterile micronized crystalline procaine penicillin G

300,000 units sterile crystalline penicillin G, sodium milled

7 mg. sterile sodium citrate, granular, U.S.P.

5.6 mg. sterile sodium carboxymethylcellulose, low viscosity

5.6 mg. sterile Plasdone (polyvinyl pyrrolidone)

The powders are sterilized separately by treatment with ethylene oxide and then blended in a suitable sterile blender and packaged in a sterile bottle. On addition of one cubic centimeter of sterile water a satisfactory suspension for parenteral use is obtained on shaking.

Numerous other compositions embodying the vehicle

of the present invention can be prepared. Many of these are illustrated in the various tables and general descriptive matter in the present specification. Most of the specific examples are directed to parenterals. The necessity for good suspensions in that field is very acute. However, good suspensions are also important in other pharmaceutical preparations, such as liquid oral preparations ophthalmic preparations, sprays, lotions, and the like. These can be prepared in the vehicle of the present invention by using conventional pharmaceutical techniques.

Likewise the specific insoluble medicinal agents included in the specific examples are illustrative only, since the vehicle of the present invention is equally effective with many other such medicinals, for example, progesterone, testosterone propionate, estradiol monobenzoate, sulfamerazine, sulfadiazine, sulfamethazine, aluminum salts of p-aminobenzenesulfonamides, complex aluminum salts of penicillin and p-aminobenzenesulfonamides, riboflavin, barbiturates (e.g., phenobarbital), salicylamide, and the like.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. An aqueous vehicle for insoluble medicinal agents comprising about 0.1 to about one percent of a low viscosity alkaline salt of carboxymethylcellulose and about 0.1 to about three percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol.

2. An aqueous vehicle for insoluble medicinal agents comprising from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose and about 0.1 to about three percent of polyvinyl pyrrolidone.

3. An aqueous vehicle for insoluble medicinal agents comprising about 0.5 percent of low viscosity sodium carboxymethylcellulose and about 0.5 percent of polyvinyl pyrrolidone.

4. A composition of matter comprising an insoluble medicinal agent and from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose and about 0.1 to about three percent of polyvinyl pyrrolidone.

5. A composition of matter comprising procaine penicillin and from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose and about 0.1 to about three percent of polyvinyl pyrrolidone.

6. A composition of matter comprising an insoluble steroid and from about 0.1 to one percent of low viscosity sodium carboxymethylcellulose and about 0.1 to three percent of polyvinyl pyrrolidone.

7. Product of claim 6 wherein the insoluble steroid is cortisone acetate.

8. Product of claim 6 wherein the insoluble steroid is hydrocortisone.

9. Product of claim 6 wherein the insoluble steroid is hydrocortisone acetate.

10. An aqueous dispersion medium for insoluble medicinal agents comprising minor proportions of low viscosity sodium carboxymethylcellulose and polyvinyl pyrrolidone in such amounts as to maintain a viscosity between about fifteen and eighty centipoises at 25 degrees centigrade.

11. An aqueous dispersion medium for insoluble medicinal agents comprising minor proportions of low viscosity sodium carboxymethylcellulose and polyvinyl pyrrolidone in such amounts as to maintain a viscosity between about twenty and forty centipoises at 25 degrees centigrade.

12. A therapeutic composition in an injectable aqueous vehicle having a viscosity between about fifteen and eighty centipoises comprising low viscosity sodium carboxymethylcellulose, polyvinyl pyrrolidone, a buffer,

and procaine penicillin coated at least in part with lecithin.

13. A therapeutic composition in an injectable aqueous vehicle comprising about 0.1 to one percent of low viscosity sodium carboxymethylcellulose, about 0.1 to three percent polyvinyl pyrrolidone, and procaine penicillin of particle sizes ranging from about two to sixty microns and coated at least in part with lecithin.

14. A therapeutic composition in an injectable aqueous vehicle to be dispensed from a silicone coated glass container, having a pH between about 5 and 7 and a viscosity between about fifteen and eighty centipoises, which composition comprises a preservative, a buffer, a member selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol, a low viscosity alkaline salt of carboxymethylcellulose, and from about 300,000 to 600,000 units per cubic centimeter of procaine penicillin in varying particle sizes ranging from about two to sixty microns and coated at least in part with lecithin.

15. A therapeutic composition in an injectable aqueous vehicle to be dispensed from a silicone coated glass container having a pH between about 6.5 and 6.8 and a viscosity between about twenty and forty centipoises, which composition comprises a member selected from the group consisting of methyl, propyl and butyl parabens, sodium citrate, from about 0.1 to about three percent of polyvinyl pyrrolidone, between about 0.1 and about one percent of low viscosity sodium carboxymethylcellulose, and from about 300,000 to 600,000 units per cubic centimeter of procaine penicillin in varying sizes ranging from about two to sixty microns and coated at least in part with lecithin.

16. A dry composition for the extemporaneous preparation of an aqueous fluid which composition comprises a low viscosity alkaline salt of carboxymethylcellulose and a member selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol, in the proportions of about 0.1 to 1 to about 0.1 to 3, and an insoluble medicinal agent.

17. A dry composition for the extemporaneous preparation of an aqueous fluid which composition comprises from about 0.1 to about one part of a low viscosity alkaline salt of carboxymethylcellulose, from about 0.1 to about three parts of a member selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol, and an insoluble medicinal agent, characterized in that on shaking with about 100 parts of water an aqueous suspension having a viscosity between about fifteen and eighty centipoises at 25 degrees centigrade is produced.

18. A composition of matter comprising a water-insoluble medicinal agent having approximately equivalent

portions of particles from about two to about ten microns and particles from about forty to about sixty microns, at least a partial lecithin coating on said particles, from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose, and from about 0.1 to about three percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol.

19. An injectable aqueous suspension having a viscosity between about fifteen and eighty centipoises at 25 degrees centigrade and comprising a water-insoluble medicinal agent having approximately equivalent portions of particles from about two to about ten microns and particles from about forty to about sixty microns, at least a partial lecithin coating on said particles, low viscosity sodium carboxymethylcellulose and a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol.

20. An injectable aqueous suspension having a viscosity of between about twenty and about forty centipoises at 25 degrees centigrade and comprising a water-insoluble medicinal agent having approximately equivalent portions of particles from about two to about ten microns and particles from about forty to about sixty microns, at least a partial lecithin coating on said particles, from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose, and from about 0.1 to about three percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol.

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