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(54) **PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

3,523,906	A		8/1970	Vrancken et al. 252/316
3,691,090	A		9/1972	Kitajima et al. 252/316
3,700,215	A	*	10/1972	Hardman et al. 259/98
3,737,337	A		6/1973	Schnoring et al. 117/100
3,773,919	A		11/1973	Boswell et al. 424/19
3,891,570	A		6/1975	Fukushima et al. 252/316
3,960,757	A		6/1976	Morishita et al. 252/316
4,221,862	A		9/1980	Naito et al. 430/536
4,384,975	A		5/1983	Fong 427/213.36
4,389,330	A		6/1983	Tice et al. 427/213.36
4,530,840	A		7/1985	Tice et al. 514/179
4,818,517	A		4/1989	Kwee et al. 424/488
4,940,588	A		7/1990	Sparks et al. 424/490
5,066,436	A		11/1991	Komen et al. 264/4.3
5,385,738	A		1/1995	Yamahira et al. 424/489
5,407,609	A		4/1995	Tice et al. 264/46
5,428,024	A		6/1995	Chu et al. 514/21
5,478,564	A		12/1995	Wantier et al. 424/426
5,541,172	A		7/1996	Labric et al. 514/169
5,612,346	A	*	3/1997	Mesens et al. 514/258
5,650,173	A		7/1997	Ramstack et al. 424/489
5,654,008	A		8/1997	Herbert et al. 424/489
5,654,010	A		8/1997	Johnson et al. 424/502
5,656,297	A		8/1997	Bernstein et al. 424/484
5,656,299	A	*	8/1997	Kino et al. 424/489
5,658,593	A		8/1997	Orly et al. 424/499
5,667,808	A		9/1997	Johnson et al. 424/501
5,688,801	A		11/1997	Mesens et al. 514/258
5,747,058	A		5/1998	Tipton et al. 424/423
5,770,231	A		6/1998	Mesens et al. 424/497
5,792,477	A		8/1998	Rickey et al. 424/501
5,871,778	A		2/1999	Kino et al. 424/489
5,916,598	A		6/1999	Rickey et al. 424/501
5,942,253	A		8/1999	Gombotz et al. 424/501
5,965,168	A		10/1999	Mesens et al. 424/497

FOREIGN PATENT DOCUMENTS

EP	0831773		12/1999
WO	WO 89/03678		5/1989
WO	WO 90/13361		11/1990
WO	0 486 959	A1	5/1992
WO	WO 94/10982		5/1994
WO	IB-WO 94/25460	A1	11/1994
WO	IB-WO 95/13799	A1	5/1995
WO	WO 95/13799		5/1995
WO	IB-WO 96/01652	A1	1/1996
WO	WO 96/40049		12/1996
WO	WO 97/41837		11/1997
WO	IB-WO 97/44039	A1	11/1997
WO	WO 99/12549		3/1999
WO	IB-WO 99/25354	A2	5/1999

OTHER PUBLICATIONS

M. J. Akers et al., "Formulation Design and Development to Parenteral Suspensions," Journal of Parenteral Science and Technology, vol. 41, No. 3, May–Jun. 1987, pp. 88–96.

Beck, L.R., et al., Biology of Reproduction, 28:186–195 (Feb. 1983).

Bodmeier, R., et al., International Journal of Pharmaceuticals, 43:179–186 (1988).

Stanislav Cajavec et al., "The primary chicken vaccination against Newcastle disease with antigenic virus subunits prepared in a water–in–oil–in–water emulsion," Periodicum Biologorum, vol. 99, No. 1, pp. 39–44, 1997.

Y. Cha and C.G. Pitt, "The Acceleration of Degradation–Controlled Drug Delivery from Polyester Microspheres," *Journal of Controlled Release,* 8(1989) 259–265.

Y. Cha and C.G. Pitt, "A One–Week Subdermal Delivery System for L–Methadone Based on Biodegradable Microparticles," *Journal of Controlled Release*, 7 (1988) 69–78.

"How to Avoid Clogging of Insulin Syringes," Diabetes Forecase, Nov.–Dec. 1976, pp. 27–29.

R. Jalil et al., Journal of Microencapsulation, vol. 7, No. 3, Jul.–Sep. 1990, pp. 297–319.

Wen–I Li et al., Journal of Controlled Release, 37:199–214 (Dec. 1995).

(List continued on next page.)

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(57) **ABSTRACT**

Injectable compositions having improved injectability. The injectable compositions include microparticles suspended in an aqueous injection vehicle having a viscosity of at least 20 cp at 20° C. The increased viscosity of the injection vehicle that constitutes the fluid phase of the suspension significantly reduces in vivo injectability failures. The injectable compositions can be made by mixing dry microparticles with an aqueous injection vehicle to form a suspension, and then mixing the suspension with a viscosity enhancing agent to increase the viscosity of the fluid phase of the suspension to the desired level for improved injectability.

53 Claims, No Drawings

OTHER PUBLICATIONS

H. V. Maulding et al., "Biodegradable Microcapsules: Acceleration of Polymeric Excipient Hydrolytic Rate by Incorporation of a Basic Medicament," Journal of Controlled Release, 3:103–117 (Mar. 1986).

Pharmaceutical Dosage Forms Disperse Systems, edited by Herbert A. Lieberman, Martin M. Rieger, Gilbert I. Bank, Second edition, Chapter 7, "Injectable Emulsions and Suspensions," 1:261–318.

Pharmaceutical Dosage Forms Disperse Systems, edited by Herbert A. Lieberman, Martin M. Rieger, Gilbert I. Bank, Second edition (1996), Chapter 7, "Viscosity–Impairing Agents in Disperse Systems," 2:287–313.

Hongkee Sah et al., Pharmaceutical Research, 13:360–367 (Mar. 1996).

Toyomi Sato et al., Pharmaceutical Research, 5:21–30 (1988).

J. R. Zingerman et al., "Automatic injector apparatus for studying the injectability of pareteral formulations for animal health," International Journal of Pharmaceuticals, 36 (1987) 141–145

* cited by examiner

PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to preparation of injectable compositions. More particularly, the present invention relates to injectable suspensions having improved injectability, and to methods for the preparation of such injectable suspensions.

2. Related Art

Injectable suspensions are heterogeneous systems that typically consist of a solid phase dispersed in a liquid phase, the liquid phase being aqueous or nonaqueous. To be effective and pharmaceutically acceptable, injectable suspensions should preferably be: sterile; stable; resuspendable; syringeable; injectable; isotonic; and nonirritating. The foregoing characteristics result in manufacturing, storage, and usage requirements that make injectable suspensions one of the most difficult dosage forms to develop.

Injectable suspensions are parenteral compositions in that they are introduced into an organism or host by means other than through the gastrointestinal tract. Particularly, injectable suspensions are introduced into a host by subcutaneous (SC) or intramuscular (IM) injection. Injectable suspensions may be formulated as a ready-to-use injection or require a reconstitution step prior to use. Injectable suspensions typically contain between 0.5% and 5.0% solids, with a particle size of less than 5 μm for IM or SC administration. Parenteral suspensions are frequently administered through needles about one-half to two inches long, 19 to 22 gauge, with an internal diameter in the range of 700 to 400 microns, respectively.

To develop an effective and pharmaceutically acceptable injectable suspension, a number of characteristics must be evaluated. These characteristics include syringeability, injectability, clogging, resuspendability, and viscosity. As will be readily apparent to one skilled in the art, other characteristics and factors should be considered in developing an injectable suspension (see, for example, Floyd, A. G. and Jain, S., Injectable Emulsions and Suspensions, Chapter 7 in *Pharmaceutical Dosage Forms: Disperse Systems Vol.* 2, Edited by Lieberman, H. A., Rieger, M. M., and Banker, G. S., Marcel Dekker, New York (1996), the entirety of which is incorporated herein by reference and referred to herein as "the Floyd et al. Chapter").

Syringeability describes the ability of an injectable suspension to pass easily through a hypodermic needle on transfer from a vial prior to injection. It includes characteristics such as ease of withdrawal, clogging and foaming tendencies, and accuracy of dose measurements. As described in the Floyd et al. Chapter, increase in the viscosity, density, particle size, and concentration of solids in suspension hinders the syringeability of suspensions.

Injectability refers to the performance of the suspension during injection. Injectability includes factors such as pressure or force required for injection, evenness of flow, aspiration qualities, and freedom from clogging.

Clogging refers to the blockage of syringe needles while administering a suspension. It may occur because of a single large particle, or an aggregate that blocks the lumen of the needle due to a bridging effect of the particles. Clogging at or near the needle end may be caused by restrictions to flow

from the suspension. This may involve a number of factors, such as the injection vehicle, wetting of particles, particle size and distribution, particle shape, viscosity, and flow characteristics of the suspension.

Resuspendability describes the ability of the suspension to uniformly disperse with minimal shaking after it has stood for some time. Resuspendability can be a problem for suspensions that undergo "caking" upon standing due to settling of the deflocculated particles. "Caking" refers to a process by which the particles undergo growth and fusion to form a nondispersible mass of material.

Viscosity describes the resistance that a liquid system offers to flow when it is subjected to an applied shear stress. A more viscous system requires greater force or stress to make it flow at the same rate as a less viscous system. A liquid system will exhibit either Newtonian or non-Newtonian flow based on a linear or a non-linear increase, respectively, in the rate of shear with the shearing stress. Structured vehicles used in suspensions exhibit non-Newtonian flow and are typically plastic, pseudoplastic, or shear-thinning with some thixotropy (exhibiting a decrease in viscosity with an increase in the rate of shear).

In design of injection vehicles, viscosity enhancers are added in order to retard settling of the particles in the vial and syringe. However, viscosity is typically kept low, in order to facilitate mixing, resuspension of the particles with the vehicle, and to make the suspension easier to inject (i.e., low force on the syringe plunger). For example, Lupron Depot from TAP Pharmaceuticals (mean particle size of approximately 8 μm) utilizes an injection vehicle with a viscosity of approximately 5.4 cp. The fluid phase of a suspension of Decapeptyl from DebioPharm (mean particle size of approximately 40 μm), when prepared as directed, has a viscosity of approximately 19.7 cp. Conventional parenteral suspensions are dilute, with limitations for viscosity because of syringeability and injectability constraints. See, for example, the Floyd, et al. Chapter noted above.

Injectable compositions containing microparticle preparations are particularly susceptible to injectability problems. Microparticle suspensions may contain 10–15% solids, as compared with 0.5–5% solids in other types of injectable suspensions. Microparticles, particularly controlled release microparticles containing an active agent or other type of substance to be released, range in size up to about 250 μm, as compared with a particle size of less than 5 μm recommended for IM or SC administration. The higher concentration of solids, as well as the larger solid particle size, make it more difficult to successfully inject microparticle suspensions. This is particularly true since it is also desired to inject the microparticle suspensions using as small a needle as possible to minimize patient discomfort.

Thus, there is a need in the art for an injectable composition with improved injectability. There is a particular need in the art for an injectable composition that solves the injectability problems associated with microparticle suspensions. The present invention, the description of which is fully set forth below, solves the need in the art for such injectable compositions.

SUMMARY OF THE INVENTION

The present invention relates to injectable compositions having improved injectability, and to methods for the preparation of such injectable compositions. In one aspect of the invention, a composition suitable for injection through a needle into a host is provided. The composition comprises microparticles having a polymeric binder, with a mass

median diameter of at least about 10 μm. The composition also includes an aqueous injection vehicle (the injection vehicle not being the aqueous injection vehicle that consists of 3% by volume sodium carboxymethyl cellulose, 1% by volume polysorbate 20, 0.9% by volume sodium chloride, and a remaining percentage by volume of water). The microparticles are suspended in the injection vehicle at a concentration of greater than about 30 mg/ml to form a suspension, the fluid phase of the suspension having a viscosity of at least 20 cp at 20° C. In other embodiments, the fluid phase of the suspension has a viscosity at 20° C. of at least about 30 cp, 40 cp, 50 cp, and 60 cp. The composition may also comprise a viscosity enhancing agent, a density enhancing agent, a tonicity enhancing agent, and/or a wetting agent. The composition can be administered to a host by injection.

In another aspect of the present invention, a method of making a composition suitable for injection through a needle into a host is provided. The method comprises:

(a) providing microparticles comprising a polymeric binder, said microparticles having a mass median diameter of at least about 10 μm;

(b) providing an aqueous injection vehicle having a viscosity of at least 20 cp at 20° C., wherein said injection vehicle is not the aqueous vehicle consisting of 3% by volume sodium carboxymethyl cellulose, 1% by volume polysorbate 20, 0.9% by volume sodium chloride, and a remaining percentage by volume of water; and

(c) suspending the microparticles in the aqueous injection vehicle at a concentration of greater than about 30 mg/ml to form a suspension.

In a further aspect of the present invention, another method for preparing a composition suitable for injection through a needle into a host is provided. In such a method, dry microparticles are mixed with an aqueous injection vehicle to form a first suspension. The first suspension is mixed with a viscosity enhancing agent to form a second suspension. The viscosity enhancing agent increases the viscosity of the fluid phase of the second suspension. The first suspension may be withdrawn into a first syringe, prior to mixing with the viscosity enhancing agent. The first suspension may be mixed with the viscosity enhancing agent by coupling the first syringe containing the first suspension to a second syringe that contains the viscosity enhancing agent. The first suspension and the viscosity enhancing agent are then repeatedly passed between the first and second syringes.

In yet a further aspect of the present invention, a method for administering a composition to a host is provided. The method comprises:

(a) mixing dry microparticles with an aqueous injection vehicle to form a first suspension;

(b) mixing the first suspension with a viscosity enhancing agent to form a second suspension, wherein the viscosity enhancing agent increases the viscosity of the fluid phase of the second suspension; and

(c) injecting the second suspension into the host.

In still a further aspect of the present invention, another method for administering a composition to a host is provided. The method comprises:

(a) mixing dry microparticles with an aqueous injection vehicle to form a suspension, wherein the aqueous injection vehicle has a viscosity at 20° C. of less than about 60 cp;

(b) changing the viscosity of the fluid phase of the suspension;

(c) withdrawing the suspension into a syringe; and

(d) injecting the suspension from the syringe into the host.

In a further aspect of the invention, step (b) is carried out by changing the temperature of the fluid phase of the suspension. In another aspect, step (c) is performed prior to step (b). Step (b) may be carried out by adding a viscosity enhancing agent to the suspension in the syringe to thereby increase the viscosity of the fluid phase of the suspension.

In still a further aspect of the invention, a method for preparing a composition suitable for injection through a needle into a host is provided. The method comprises:

(a) mixing dry microparticles with an aqueous injection vehicle that comprises a viscosity enhancing agent to form a suspension;

(b) removing water from the suspension; and

(c) reconstituting the suspension with a quantity of sterile water for injection to form an injectable suspension, wherein the quantity of sterile water for injection is sufficient to achieve a viscosity of a fluid phase of the injectable suspension that provides injectability of the composition through a needle ranging in diameter from 18–22 gauge.

Features and Advantages

A feature of the present invention is that the injectable compositions can be used to inject varying types of microparticles, and varying types of active agents or other substances, into a host.

A further feature of the present invention is that it allows microparticles to be wetted to achieve a homogeneous suspension, while improving injectability into a host and reducing in vivo injectability failures.

The present invention advantageously provides medically acceptable injectability rates for high concentration suspensions, and for suspensions having large particle size.

The present invention also advantageously provides an efficient method of improving in vivo injectability without introducing microbial contamination or compromising aseptic conditions.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Overview

The present invention relates to injectable compositions having improved injectability, and to methods for the preparation of such injectable compositions. The injectable compositions of the present invention overcome injectability problems, particularly injectability failures that occur upon injection into muscle or subcutaneous tissue. Such injectability failures will be referred to herein as "in vivo injectability failures." In vivo injectability failures often manifest themselves in the form of a plug at the tip of the needle, and occur immediately or shortly after injection has been initiated. In vivo injectability failures are typically not predicted by laboratory or other in vitro testing.

The inventors have unexpectedly discovered that injectability is improved, and in vivo injectability failures significantly and unexpectedly reduced, by increasing the viscosity of the fluid phase of an injectable suspension. This is in contrast to conventional teachings that an increase in the viscosity hinders injectability and syringeability.

Viscous vehicles, however, are not optimal for preparing homogeneous suspensions of microparticles because of the relative inability of viscous vehicles to penetrate and wet out

a mass of dry particles. Suspensions prepared with viscous vehicles are prone to clump irreversibly. Consequently, such suspensions are not injectable via needles of medically acceptable size. A further disadvantage of viscous suspensions is the lack of ease of transferring such suspensions from the vial or container used to prepare the suspension to the syringe used for injection.

The present invention also solves the additional problems that arise from use of a viscous injection vehicle. In accordance with the present invention, microparticles are suspended in an injection vehicle having suitable wetting characteristics. The viscosity of the fluid phase of the injectable suspension is increased prior to injecting the suspension in order to improve injectability, and to reduce in vivo injectability failures.

To ensure clarity of the description that follows, the following definitions are provided. By "microparticles" or "microspheres" is meant particles that contain an active agent or other substance dispersed or dissolved within a polymer that serves as a matrix or binder of the particle. The polymer is preferably biodegradable and biocompatible. By "biodegradable" is meant a material that should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body. By "biocompatible" is meant not toxic to the body, is pharmaceutically acceptable, is not carcinogenic, and does not significantly induce inflammation in body tissues. As used herein, "body" preferably refers to the human body, but it should be understood that body can also refer to a non-human animal body. By "weight %" or "% by weight" is meant parts by weight per hundred parts total weight of microparticle. For example, 10 wt. % active agent would mean 10 parts active agent by weight and 90 parts polymer by weight. Unless otherwise indicated to the contrary, percentages (%) reported herein are by volume. By "controlled release microparticle" or "sustained release microparticle" is meant a microparticle from which an active agent or other type of substance is released as a function of time. By "mass median diameter" is meant the diameter at which half of the distribution (volume percent) has a larger diameter and half has a smaller diameter.

METHOD AND EXAMPLES

The following examples are provided to explain the invention, and to describe the materials and methods used in carrying out the invention. The examples are not intended to limit the invention in any manner.

Example 1—In vitro Sieve Test Study

To evaluate in vivo injectability failures, an in vitro sieve test study was conducted to assess and predict in vivo injectability, and to determine the key factors affecting injectability. The following factors were investigated during the in vitro sieve test study: injection vehicle formulation; microparticle morphology; needle diameter; suspension concentration; and particle size as exhibited by sieve screen size used to screen the microparticles during the manufacturing process.

Three batches of risperidone microparticles were manufactured at a 125 gm scale using a process substantially the same as that disclosed in U.S. Pat. No. 5,792,477, the entirety of which is incorporated herein by reference (see, for example, Example 1 in U.S. Pat. No. 5,792,477). Three batches of risperidone microparticles were manufactured at a 1 Kg scale using the process described below in Example 7. All batches had similar particle sizes (ranging from a Mass Median Diameter of 91 μm to 121 μm) based on Hyac-Royco analysis of representative bulk material sieved through a 180 μm sieve screen. A 160 mg or 320 mg quantity of the microparticles (equivalent to a 50 or 100 mg dose of the risperidone active agent) was transferred, using a manual Perry powder filler with a 5/16 inch ID barrel, into a 5 cc glass vial, and capped with a Teflon lined septum.

Two injection vehicles were used in the in vitro sieve test study. The first injection vehicle ("Formula 1") was an aqueous vehicle consisting of 1.5% by volume carboxymethyl cellulose (CMC), 30% by volume sorbitol, and 0.2% by volume Tween 20 (polysorbate 20). The viscosity of the first injection vehicle was approximately 27 cp at 20° C. The second injection vehicle ("Formula 2") was an aqueous vehicle consisting of 0.75% by volume CMC, 15% by volume sorbitol, and 0.2% by volume Tween 20 (polysorbate 20). The viscosity of the second injection vehicle was approximately 7 cp at 20° C.

The microparticle suspension was prepared as follows. The injection vehicle was aspirated into a 5 cc syringe through a needle. The vehicle was then injected into the glass vial containing the microparticles, and the needle was removed. The glass vial was then rolled between the palms until the microparticles were completely suspended, approximately one minute. The needle was reinserted into the vial so that the bevel of the needle was just through the septum with the opening facing toward the vial bottom. The vial was inverted and the suspension was withdrawn. The syringe was rotated 180° around its axis, and the remaining suspension was aspirated into the syringe.

Sieve screens with mesh opening sizes of 180, 212, 250, 300, 355, and 425 μm were used. The bevel of the syringe needle was placed on the mesh of the sieve screen so that the bevel was in full contact with the mesh. The needle was oriented so the opening of the needle was flush against the mesh of the screen. This prevented the mesh from entering the bevel, while maintaining the required restrictive area. The suspension was tried on the smallest sieve mesh first (highest screen resistance). If the suspension fouled the needle on this sieve mesh, the needle was unclogged by retracting the plunger of the syringe, depressing the plunger while the syringe was in the upward position, and passing an aliquot of suspension through the needle. The injection process was tried again using the next greater mesh size, and repeated until the suspension was successfully injected. All preparations were done in triplicate.

A three-factor Box-Behnken statistical designed experiment was constructed to evaluate the following independent variables: manufacturing bulk sieve size (125, 150, and 180 μm); needle ID (19 TW, 20 RW, and 22 RW gauge—ID of 19 TW (thin wall) equivalent to 18 RW (regular wall)); and suspension concentration (0.074, 0.096, and 0.138 w/w—responds to approximately 300 mg microparticle dose diluted with 4, 3, and 2 cc, respectively, of injection vehicle). The following scoring system was used:

Score	Result
0	Needle Block
1	Passes through a 425 μm screen
2	Passes through a 355 μm screen
3	Passes through a 300 μm screen
4	Passes through a 250 μm screen
5	Passes through a 212 μm screen

Table 1 below shows the score obtained for screen resistance tests using this scoring system for the 1 Kg and the 125 gm batches for each of the injection vehicles tested.

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