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[54] **SUSPENSION OF LOTEPRDNOL ETABONATE FOR EAR, EYE, OR NOSE TREATMENT**

[75] **Inventors:** Shimon Amselem, Rehovot; Doron Friedman, Carmei Yosef, both of Israel

[73] **Assignee:** Pharmos Corporation, Alachua, Fla.

[*] **Notice:** The term of this patent shall not extend beyond the expiration date of Pat. No. 5,540,930.

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Related U.S. Application Data

[63] **Continuation-in-part of Ser. No. 142,743, Oct. 25, 1993, Pat. No. 5,540,930.**

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[52] **U.S. Cl.** 424/427; 424/437; 424/434; 514/772.2; 514/772.3; 514/772.5; 514/778; 514/914; 514/937

[58] **Field of Search** 424/427, 437, 424/434, 489; 514/772.2-772.3, 772.5, 778, 914, 937

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Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Pennie & Edmonds

[57] ABSTRACT

The invention provides novel compositions of matter for delivering water-insoluble steroid drugs suitable for therapeutic use. The invention also provides stable aqueous suspensions of water-insoluble steroid drugs of particle sizes of $\leq 30 \mu\text{m}$ which remain in such a state so as to allow for immediate suspension, when desired, even after extended periods of settling.

30 Claims, No Drawings

**SUSPENSION OF LOTEPREDNOL
ETABONATE FOR EAR, EYE, OR NOSE
TREATMENT**

**CROSS-REFERENCE TO RELATED
APPLICATION**

This application is a continuation-in-part of application Ser. No. 08/142,743 filed Oct. 25, 1993, now U.S. Pat. No. 5,540,930.

FIELD OF INVENTION

The invention relates to aqueous suspensions for treatment of ophthalmic and otolaryngological inflammations.

BACKGROUND OF THE INVENTION

Numerous drugs are prepared in the form of suspensions for ophthalmic, oral, otic, nasal respiratory is topical, and parenteral applications. Formulation of pharmaceutical dosages of water-insoluble drugs as suspensions is frequently hampered by the subsequent formation of cakes resulting from aggregation of the suspended material. Polymeric compounds (e.g. polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), dextran) are commonly used to stabilize such suspensions. An alternative approach to the preparation of such drugs is to enhance the solubility of the drugs within the formulation by vehicles including emulsions, liposomes, and cyclodextrins. However, certain drugs, in their therapeutic concentrations, are not sufficiently stabilized or solubilized by these methods for the above-mentioned applications.

Topical steroids such as corticosteroids are commonly used for anti-inflammatory therapy of the eye, especially for treating inflammatory conditions of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe. Common therapeutic applications for steroids include allergic conjunctivitis, acne rosacea, superficial punctate keratitis and iritis cyclitis. Steroids also are used to ameliorate inflammation associated with corneal injury due to chemical or thermal burns, or penetration of foreign bodies. Such conditions may result from surgery, injury, allergy or infection to the eye and can cause severe discomfort.

Despite their therapeutic advantages, topical ocular use of corticosteroids is associated with a number of complications, including posterior subcapsular cataract formation, elevation of intraocular pressure, secondary ocular infection, retardation of corneal wound healing, uveitis, mydriasis, transient ocular discomfort and ptosis. Numerous systemic complications also may arise from the topical ocular application of corticosteroids. These complications include adrenal insufficiency, Cushing's syndrome, peptic ulceration, osteoporosis, hypertension, muscle weakness or atrophy, inhibition of growth, diabetes, activation of infection, mood changes and delayed wound healing.

Topical steroids for treating ocular inflammations can be based on soft drugs. Soft drugs, as is known in the art, are designed to provide maximal therapeutic effect and minimal side effects. By one approach, synthesis of a "soft drug" can be achieved by structurally modifying a known inactive metabolite of a known active drug to produce an active metabolite that undergoes a predictable one-step transformation in-vivo back to the parent, (see, U.S. Pat. Nos. 4,996,335 and 4,710,495 for soft steroids) inactive metabolite. "Soft drugs" therefore are biologically active chemical components characterized by predictable in vivo metabolism to non-toxic derivatives after they provide their therapeutic effect.

Pharmaceutical compositions of water-insoluble drugs such as corticosteroids in aqueous suspensions for ocular and other uses must satisfy constraints imposed by physiological compatibilities such as pH, osmolality, and particle size of the suspended steroids. Furthermore, these compositions must meet requirements for reservative efficiency and ease of suspension over extended periods of time.

Therapeutic suspensions of corticosteroids typically employ polymeric compounds such as polyvinyl pyrrolidone ("PVP") and polyvinyl alcohol ("PVA") as suspending agents in concentrations ranging from 0.1 to 10% (U.S. Pat. No. 2,861,920). Combinations of polymeric compounds such as PVP, PVA, sodium carboxymethylcellulose ("CMC"), and dextran, with surface-active agents such as Polysorbate 80, Polysorbate 20, and tyloxapol also have been used to stabilize corticosteroid suspensions intended for ophthalmic, nasal, and otic uses.

The amounts of polymeric compounds and surface active agents must be determined to provide stability to suspensions of corticosteroids. Excessive amounts of polymeric compounds may hamper the antimicrobial effects of preservatives added to the suspension. Also, pharmaceutical ocular and nasal dosages of these suspensions either must be buffered or have an appropriate pH with no buffering capacity. These suspensions also should be isotonic.

Loteprednol etabonate ("LE") is a known soft corticosteroid based on the known inactive metabolite prednisolone acetate of the active drug prednisolone. See U.S. Pat. Nos. 4,996,335 and 4,710,495.

LE is an analog of prednisolone that does not have a 20-keto group attached to the 17 β -position. Instead, the 17- β position is occupied with a metabolically-labile ester function. In biological systems, LE is hydrolysed to the inactive carboxylic acid metabolite (PJ-91) that does not bind to glucocorticoid receptors. LE also provides superior safety by reducing the risk of steroid induced cataracts and elevation of intra-ocular pressure. The lability of LE to enzymes located in the blood and/or liver also reduces the likelihood of systemic side effects. LE therefore provides therapeutic advantages over other corticosteroids by providing efficacy similar to its parent compound, namely, prednisolone acetate, with fewer deleterious systemic side effects. Soft steroids have the potential advantage of treating inflammation without inducing elevation of intraocular pressure. In addition, soft steroids can provide the added benefit of a lower tendency to induce cataracts which may result from interaction of corticosteroids with the ocular lens proteins.

Formulation of stable aqueous suspensions of LE for ocular applications and other uses, however, has been hampered by agglomeration of the steroid particles. Unexpectedly, common tonicity agents such as aqueous solutions containing 0.9% NaCl, 0.1% EDTA, or phosphate buffer, even in concentrations as low as 1 mM, can not be employed to provide stable aqueous suspensions of corticosteroids such as LE.

A need therefore exists for aqueous suspensions of corticosteroids such as LE which can be formulated without agglomeration. A further need exists for aqueous suspensions which have therapeutically effective amounts of corticosteroids such as LE but which avoid the problems associated with the steroid suspensions of the prior art.

SUMMARY OF THE INVENTION

The invention provides novel compositions of matter containing water-insoluble drugs suitable for therapeutic use. The invention provides stable aqueous suspensions of

water-insoluble drugs of mean particle sizes of $\leq 15 \mu\text{m}$ which remain in such a state so as to allow for immediate suspension, when desired, even after extended periods of settling.

More particularly, the invention is directed to aqueous suspensions of soft corticosteroids such as loteprednol etabonate suitable for therapeutic use in the eye, ear, or nose. The aqueous suspensions of LE are surprisingly stable and can remain in a state suitable for immediate suspension when desired, even after extended periods of settling. The suspensions of the invention, moreover, do not cause discomfort upon application.

Alternatively, the present invention is directed to aqueous formulations (e.g., suspensions or solutions) wherein the amount of corticosteroids is either minimized (e.g., suspensions) or altogether avoided (e.g., solutions) for the therapeutic use in the eye, ear, nose or throat for the topical treatment of inflammatory conditions therein.

The aqueous suspensions of the invention containing a steroid comprise component (A) of a therapeutic quantity of a "soft" steroid such as LE present as particles preferably having a mean diameter of less than about fifteen microns, component (B) of a suspending agent of a nonionic polymer in an aqueous medium, and component (C) of a nonionic surface active agent. Advantageous molar ratios of (A):(B):(C) can vary from about 1:0.01:0.05 to 1:20:1.

The steroid of component (A) preferably is loteprednol etabonate and is added to obtain a final concentration in the suspension of 0 to about 2% by weight, more preferably about 0.01–1% by weight and most preferably about 0.05–0.5% by weight. The suspending agent may be any nonionic polymer which is soluble in an aqueous medium, and can be present in an amount of about 0.2 to 2% by weight, preferably about 0.3 to 1.75% by weight, more preferably about 0.4–1.5% by weight. The molar ratio of component (A) to component (B) typically is in the range of about 1:0.01 to about 1:20, preferably about 1:0.05 to about 1:10 and more preferably about 1:0.1 to 1:3.

The nonionic surfactant of component (C) of the composition may be any one of a wide variety of nonionic alkylene oxide condensates of an organic compounds which contain one or more hydroxyl groups. This component (C) is advantageously present in an amount of between about 0.05 and 1% by weight of the composition. The molar ratio of component (A) to component (C) typically is in the range of about 1:0.05 to about 1:1.

The compositions generally include component (D) of a nonionic tonicity agent for producing isotonicity, and, if necessary, component (E) of one or more preservatives.

It is essential that these components (A)–(D) be nonionic insofar as possible since it has now been discovered that the presence of ions is the major cause of caking. Thus, the preferred tonicity agents would be nonionic diols such as glycerol or mannitol rather than the commonly used sodium chloride. The nonionic tonicity agent is preferably present in an amount of about 0.5 to 10% by weight, more preferably about 1 to 7%, and most preferably about 1.5 to 4%.

Accepted preservatives such as benzalkonium chloride and disodium edetate (EDTA) may be included in the suspensions of the invention in concentrations sufficient for effective antibacterial action, preferably about 0.0001 to 0.025%, based on the weight of the suspension.

Having briefly summarized the invention, the invention will now be described in detail by reference to the following specification and non-limiting examples. Unless otherwise specified, all percentages are by weight.

DETAILED DESCRIPTION OF THE INVENTION

Therapeutic suspensions of LE for ophthalmic or otolaryngological uses are made by aseptic preparation. Purity levels of all materials employed in the suspensions of the invention exceed 98%. The suspensions of the invention are prepared by thoroughly mixing the drug (component (A)), suspending agent (component (B)), and surface active agent (component (C)). Optionally, tonicity agents (component (D)) and preservatives (component (E)) may be included.

Drugs of component (A), when used, are preferably soft steroids and most preferably LE. Also, other steroids such as beclomethasone, betamethasone, fluocinolone, fluorometholone, exednisolone, may be employed. The suspensions of component (A) of the invention have a particle size of about 0.1–30 μm , preferably about 1–20 μm , most preferably about 2–10 μm in mean diameter. LE in this size range is commercially available from suppliers such as the Sipsy Co. (Avrillé, France).

The nonionic polymer of component (B) can be any nonionic water-soluble polymer. Typical compounds such as PVP, PVA, dextran or cyclodextrin can be used in a concentration of about 0.2–2% by weight, and preferably about 0.3–1.75% by weight.

Component (C) is a surface-active agent that is acceptable for ophthalmic or otolaryngological uses. Preferably, this surfactant is non-ionic. Generally, the nonionic surfactant is a nonionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups. For example, ethoxylated and/or propoxylated alcohol or ester compounds or mixtures thereof are commonly available and are well known to those skilled in the art. Useful surface active agents include but are not limited to POLYSORBATE 80, tyloxapol, TWEEN 80 (e.g., polyoxyethylene sorbitan mono-oleate ester; ICI America Inc., Wilmington, Del.), PLURONIC F-68 (from BASF, Ludwigshafen, Germany) and the POLOXAMER (e.g., poly(oxypropylene)-poly(oxyethylene) copolymer) surfactants can also be used. See, Remington's Pharmaceutical Sciences, 16th Edition, Arthur osol, Editor, Mack Publishing Company, Easton, Pa. (1980). See also, The United States Pharmacopeia, 21st Revision, The National Formulary, 16th Edition, United States Pharmacopeial Convention, Inc., Rockville, Md., (Jan. 1, 1985). The tyloxapol and TWEEN surfactants are preferred because they are FDA approved for human use. The concentration in which the surface active agent may be used is only limited by neutralization of the bacteriocidal effects on the accompanying preservatives, or by concentrations which may cause irritation. Advantageously, the concentration of component (C) is about 0.05 to 1% based on the weight of the suspension (or solution), and preferably about 0.1 to 0.6%.

The tonicity agents of component (D) can be nonionic diols including mannitol and preferably glycerol, in sufficient amounts to achieve isotonicity. The nonionic tonicity agent is advantageously present in an amount of about 1 to 7% by weight, and preferably about 1.5 to 4%.

The nonionic polymeric compounds of component (B), and the surface active agents of component (C) have good solubility in water, have sufficient number of hydroxyl groups to interact with the steroid, and have mild effects on the viscosity of the suspension. Final viscosity should not exceed 80-centipoise.

In a preferred aspect, stable aqueous suspensions of LE are provided by preparing aqueous suspensions of LE in concentrations of about 0.05–0.2% with about 0.3–1.5% PVP, about 2–3% glycerol, and about 0.05–1% tyloxapol.

The suspensions of the invention also may include additional therapeutic drugs such as drugs for treating glaucoma, anti-inflammatory drugs, antibiotic drugs, anti-cancer drugs, anti-fungal drugs and anti-viral drugs. Examples of anti-glaucoma drugs include but are not limited to timolol-base, betaxolol, atenolol, levobunolol, epinephrin, dipivalyl, oxonolol, acetazolamide-base and methazolamide. Examples of anti-inflammatory drugs include but are not limited to non-steroids such as piroxicam, indomethacin, naproxen, phenylbutazone, ibuprofen and diclofenac. Additional therapeutic materials which may be employed include but are not limited to tobramycin, gentamycin or other antibiotics.

Health regulations in various countries generally require that ophthalmic preparations shall include a preservative. Many well known preservatives that have been used in ophthalmic preparations of the prior art, however, cannot be used in the preparations of the invention, since those preservatives may no longer be considered safe for ocular use, or may interact with the surfactant employed in the suspension to form a complex that reduces the bacteriocidal activity of the preservative.

The preservatives of component (E) employed in the suspensions of the invention therefore are chosen to not interact with the surface active agent to an extent that the preservatives are prevented from protecting the suspension from microbiological contamination. In a preferred embodiment benzalkonium chloride may be employed as a safe preservative, most preferably benzalkonium chloride with EDTA. Disodium edetate has also been found to be effective in reducing microbial growth in the present formulations. Other possible preservatives include but are not limited to benzyl alcohol, methyl parabens, propyl parabens, thimerosal, chlorbutanol and benzethonium chlorides. Preferably, a preservative (or combination of preservatives) that will impart standard antimicrobial activity to the suspension and protect against oxidation of components (A)-(D) is employed. These preservatives are generally used in an amount of about 0.0001 to 0.025% by weight and preferably 0.001 to 0.015%.

Stable aqueous suspensions of the invention can be produced over a broad range of pH values. A pH of about 4.5-7.4 especially is useful for preparing the stable LE suspensions of the invention.

It has been surprisingly discovered that the carriers (i.e., components (B), (C), (D) and, optionally, (E)) for component (A) have anti-inflammatory properties of their own. Thus, a solution of components (B), (C), (D) and, optionally, (E), at least partially relieves inflammation when applied to inflamed ophthalmic or otolaryngological tissue. Thus, for example, when applied to the eye, in the absence of a

corticosteroid, a solution of components (B), (C) and (D) surprisingly produces at least a partial reduction of the inflammation of the eye. The addition of component (E) does not detract from this result.

Formulations in the form of a solution, when component (A) is absent, are prepared according to the procedures outlined for Examples 1-37, *infra*, with the exception that the concentration of component (B) is changed to preferably between about 0.3-1.75% by weight and more preferably between about 0.4-1.5% by weight. Components (C), (D) and (E) can be used in the same amounts as stated above.

For formulations in the form of a suspension, the aforementioned concentration(s) of component (B) (see preceding paragraph) can be used in combination with the concentration of component (A) as indicated below. The concentration of component (A) is typically between about 0.01-2% by weight, preferably between about 0.03-1% by weight, more preferably between about 0.05-0.5% by weight and most preferably between about 0.05-0.2% by weight. Such suspensions are prepared according to the procedures outlined for Examples 1-37, *infra*, with the exception that the concentration of components (A) and (B) is changed as indicated herein. Components (C), (D) and (E) can be used in the same amounts as stated above.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments therefore are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. In the following examples, all parts and percentages are by weight unless otherwise indicated.

EXAMPLES 1-37

Each of Examples 1-37 are prepared by dissolving the suspending agent (Component B) in water by gentle mechanical mixing. Subsequently, the surfactant (Component C), the tonicity agent(s) and the preservatives (Components (D) and (E), respectively) are added in that order. The solution is then sterilized by filtration or autoclaving. LE, presterilized by irradiation, is added aseptically to the solution, and the dispersion is then mixed at 12,000 rpm for one minute. The amounts of these components are shown in Table 1.

SIZE DETERMINATION

The size distributions of the LE particles in the samples of Table 1 are measured with a Coulter[®] LS 130 instrument. An acceptable average particle size for ophthalmic suspensions is $\leq 15 \mu\text{m}$. The results appear in Table 2.

TABLE 1

Example	SAMPLE COMPOSITION (% w/w)											
	Number	LE	Tween 80	Tyloxapol	Poloxamer-188	HPMC ¹	PVA	PVP	dextran	Osmolarity Agent	EDTA ⁴	BKA ⁵
1	0.5	—	—	0.2	—	—	0.6	—	—	—	—	—
2	0.5	0.2	—	—	—	—	—	0.2	—	10 mM PBS ²	—	—
3	0.5	—	—	0.4	—	0.2	—	0.4	—	—	—	—
4	0.5	—	—	0.2	—	—	0.2	—	—	10 mM PBS	—	—
5	0.5	0.6	—	—	—	0.4	—	—	—	100 mM PBS	—	—
6	0.5	0.4	—	—	—	—	1.4	—	—	5 mM PBS	—	0.001
7	1	—	—	0.2	—	—	—	1	—	—	—	—
8	1	—	—	0.6	—	—	—	1.4	—	—	—	—
9	1	0.6	—	—	—	—	—	1.4	—	—	—	—

TABLE 1-continued

Example	SAMPLE COMPOSITION (% w/w)											
	Number	LE	Tween 80	Tyloxapol	Poloxamer-188	HPMC ¹	PVA	PVP	dextran	Osmolarity Agent	EDTA ⁴	BKA ⁵
10	0.5	—	—	0.4	—	—	1	—	—	0.9% saline ³	—	0.001
11	0.5	0.4	—	—	—	—	1	—	—	0.9% saline	—	0.001
12	0.5	0.6	—	—	—	—	—	2	—	2.4% glycerol	0.01	0.01
13	0.5	—	—	0.3	—	—	—	1.5	—	2.4% glycerol	0.01	0.01
14	0.5	—	—	0.3	—	—	—	0.6	0.5	2.4% glycerol	0.01	0.015
15	0.5	0.4	—	—	—	—	1.4	—	—	2.4% glycerol	—	0.001
16	1	—	—	0.2	—	—	—	1	—	2.4% glycerol	—	0.01
17	0.5	—	—	0.6	—	—	—	1.4	—	2.4% glycerol	—	0.01
18	0.5	—	—	—	0.6	—	—	2	—	2.4% glycerol	0.01	0.004
19	0.5	0.4	—	—	—	—	—	—	1.6	2.4% glycerol	0.01	0.004
20	0.5	—	—	0.4	—	—	—	—	2.4	2.4% glycerol	0.01	0.01
21	0.5	—	—	0.3	—	—	—	1	—	2.4% glycerol	0.01	0.01
22	0.5	0.6	—	—	—	—	1.4	—	—	2.4% glycerol	—	—
23	0.5	0.6	—	—	—	—	1.4	—	—	2.4% glycerol	—	0.004
24	0.5	0.6	—	—	—	—	—	—	2	2.4% glycerol	0.01	0.01
25	0.5	—	—	0.3	—	—	—	0.6	—	2.4% glycerol	0.01	0.01
26	0.5	—	—	0.3	—	—	—	0.6	0.5	2.4% glycerol	0.01	0.01
27	1	—	—	0.3	—	—	—	0.6	0.5	2.4% glycerol	0.01	0.015
28	1	—	—	0.3	—	—	—	0.6	—	2.4% glycerol	0.01	0.015
29	1	—	—	0.1	—	—	—	0.4	—	2.4% glycerol	0.01	0.01
30	0.5	—	—	0.2	—	—	—	0.6	—	2.4% glycerol	0.01	0.01
31	1	—	—	0.2	—	—	—	0.6	—	2.4% glycerol	0.01	0.01
32	1	—	—	0.2	—	—	—	0.8	—	2.4% glycerol	0.01	0.015
33	0.5	—	—	0.3	—	—	—	1.5	—	2.4% glycerol	0.01	0.015
34	1	—	—	0.4	—	—	—	0.4	—	2.4% glycerol	0.01	0.01
35	0.5	—	—	0.3	—	—	—	0.6	0.3	2.4% glycerol	0.01	0.01
36	0.5	—	—	0.1	—	—	—	0.4	0.3	2.4% glycerol	0.01	0.01
37	0.5	—	—	0.3	—	—	—	0.6	—	2.4% glycerol	0.01	0.015

¹hydroxypropylmethyl cellulose
²phosphate buffered physiological saline
³sodium chloride
⁴ethylene diamine tetraacetic acid
⁵benzalkonium chloride

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TABLE 2

Example	Particle Size(s) (µm) and Fraction of Total Population				
	Number	Population A	A%	Population B	B%
1	3.906+-2.677	86.62	53.67+-13.13	13.38	—
2	112.7+-13.27	100	—	—	—
3	3.526+-1.706	100	—	—	—
4	111.4+-18.59	100	—	—	—
5	23.52+-20.58	100	—	—	—
6	32.83+-2.563	48.74	94.06+-40.57	51.26	45
7	4.596+-2.698	92.43	57.91+-18.14	7.57	—
8	3.805+-2.417	93.14	62.38+-20.38	6.86	—
9	6.591+-3.566	100	—	—	—
10	3.828+-2.693	17.52	96.28+-38.13	82.48	—
11	3.888+-2.69	14.02	110.1+-58.02	85.98	—
12	3.559+-1.469	5.62	82.84+-13.08	94.38	50
13	2.932+-2.32	3.52	100.1+-24.56	96.48	—
14	88.52+-30.19	100	—	—	—
15	3.652+-2.692	100	—	—	—
16	3.851+-2.401	100	—	—	—
17	3.969+-2.572	100	—	—	—
18	4.926+-2.955	92.29	41.59+-7.125	7.71	55
19	4.429+-2.732	100	—	—	—
20	3.980+-2.566	100	—	—	—
21	3.633+-2.457	100	—	—	—
22	4.716+-2.762	100	—	—	—
23	4.789+-2.823	100	—	—	—
24	4.528+-2.552	100	—	—	—
25	5.261+-2.990	100	—	—	—
26	5.262+-3.013	100	—	—	—
27	5.204+-2.985	100	—	—	—
28	4.918+-2.832	100	—	—	—
29	4.126+-2.390	100	—	—	—
30	12.45+-10.91	100	—	—	—
31	3.976+-2.245	100	—	—	—

TABLE 2-continued

Example	Particle Size(s) (µm) and Fraction of Total Population				
	Number	Population A	A%	Population B	B%
32	3.789+-1.609	100	—	—	—
33	3.821+-2.181	46.77	107.3+-14.74	53.23	—
34	3.813+-2.305	100	—	—	—
35	3.385+-1.506	78.44	25.16+-1.421	21.56	—
36	3.737+-2.044	100	—	—	—
37	3.965+-2.229	100	—	—	—

1. In the Coulter particle size analysis two distinct populations of particles were sometimes discerned. In these cases the two populations are denoted as populations A and B. If only a single population was detected it is denoted population A.

EVALUATION OF SUSPENDABILITY OVER TIME

Samples containing particles with desirable size distributions (average of 2-10 µm) are tested for stability using accelerated stability tests as well as "real time" studies.

Accelerated stability studies are performed by subjecting the samples to a centrifugal force of 5000×G for two minutes. The suspendability of the settled material is tested by measuring the number of seconds of wrist shaking required to eliminate visible residue attached to the container. Since existing marketed products require as much as sixty seconds of wrist shaking to suspend the entire amount of settled residue, ten seconds is determined to be an acceptable amount of time to suspend the residue. The results are shown in Table 3.

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