(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2007 (08.02.2007)

PCT

(10) International Publication Number
WO 2007/016093 A3

(51) International Patent Classification:
A61K 47/26 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/US2006/028851

(22) International Filing Date: 25 July 2006 (25.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/702,546	26 July 2005 (26.07.2005)	US
11/492,153	24 July 2006 (24.07.2006)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

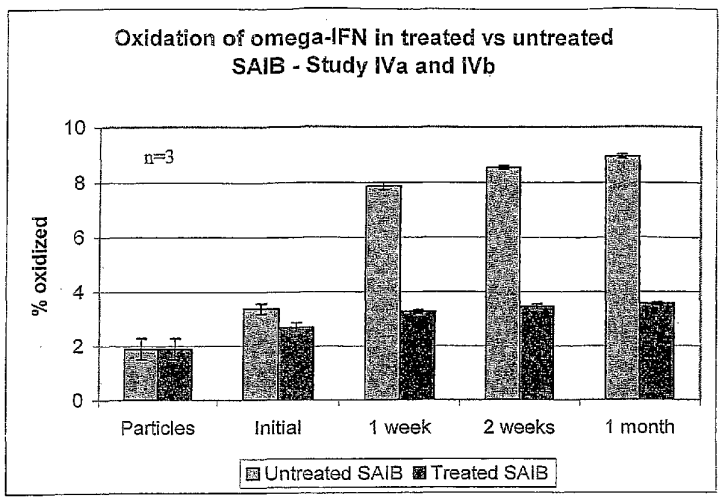
— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
2 August 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PEROXIDE REMOVAL FROM DRUG DELIVERY VEHICLE



Comparison of oxidation of omega-IFN in sodium metabisulfite treated and untreated SAIB

(57) Abstract: The present invention is related to methods for lowering peroxide levels in sucrose acetate isobutyrate formulations and to composition used in and formed by such methods.

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PEROXIDE REMOVAL FROM DRUG DELIVERY VEHICLE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application serial number 60/702,546, filed July 26, 2005, and U.S. application serial number _____, filed July 24, 2006, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for reducing peroxide levels in non-polymeric preparations and to compositions used in and prepared by such methods.

BACKGROUND OF THE INVENTION

[0003] Sucrose acetate isobutyrate ("SAIB") is a hydrophobic liquid with limited water solubility. It is soluble in a large number of biocompatible solvents. SAIB has an unusual property – it undergoes a dramatic change in viscosity with small additions of heat or with the

addition of solvents. It is a very viscous liquid, having a viscosity of approximately 3200 poise at 37° C. SAIB is produced by the controlled esterification of natural sugar (sucrose) with acetic and isobutyric anhydrides. SAIB metabolizes to sucrose, acetic acid and isobutyric acid.

[0004] SAIB is orally non-toxic and is currently used to stabilize emulsions in the food industry. In one example, SAIB is commonly found in the beverage industry, where it is used as a weighting agent to help stabilize the final beverage formula. Also, SAIB has been reported to be useful as a gelling system-type drug excipient that allows for sustained or controlled release of drugs. When in solution or in an emulsion, SAIB can be applied via injection or an aerosol spray. SAIB is compatible with cellulose esters and other polymers that can affect the rate of delivery of the substance. In one example, SAIB is the main ingredient for the SABER drug delivery system, which also consists of a pharmaceutically acceptable solvent.

[0005] Drug delivery systems, including SAIB delivery systems, are still confronted by various issues of drug instability, as such systems are considered for longer and longer drug delivery durations. Drug instability can occur via a number of factors, including denaturation, precipitation, oxidation, aggregation, and others. In particular, a number of excipients used to facilitate delivery and release of drugs have peroxides or are susceptible to the formation of peroxides, which may lead to oxidation of active ingredient in the formulation. In the example of SAIB, the presence of peroxides is deleterious to a drug incorporated in an SAIB drug formulation as the drug is likely to undergo oxidative degradation. Thus, in order to formulate any drug formulation based on SAIB that provides enough of a stable environment to facilitate the delivery of a drug, the peroxide levels must be reduced.

[0006] There is no known process for removal of peroxides from SAIB at present, despite availability of processes for the removal of peroxides from other materials such as

polymers. Therefore, there still remains a need for a drug formulation of SAIB having improved properties to reduce the degradation of the drug therein.

SUMMARY OF THE INVENTION

[0007] An aspect of the present invention comprises methods of treating sucrose acetate isobutyrate (SAIB) formulations to be used as drug delivery vehicles comprising adding to the formulations an amount of bisulfite salt effective to substantially remove peroxides, the bisulfite salt comprising sodium metabisulfite, potassium metabisulfite, sodium bisulfite, or potassium bisulfite, or a mixture thereof.

[0008] In another aspect of the present invention, provided are drug delivery vehicles adapted to provide prolonged stability of a drug that is to be delivered in vivo comprising sucrose acetate isobutyrate having substantially reduced levels of peroxide, the drug delivery vehicle being treated with an amount of bisulfite salt effective to substantially reduce levels of peroxide in said drug delivery vehicle, the bisulfite salt comprising sodium metabisulfite, potassium metabisulfite, sodium bisulfite, or potassium bisulfite, or a combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The invention is illustrated by way of example and is not intended to be limited by the accompanying figures.

[0010] Figure 1 illustrates a bar graph of the results of Study I - Stability of omega-interferon in untreated SAIB.

[0011] Figure 2 illustrates a bar graph of the results of Study IIa - Stability of omega-interferon in alumina treated SAIB.

[0012] Figure 3 illustrates a bar graph of the results of Study IIb - Stability of omega-interferon in alumina treated SAIB.

[0013] Figure 4 illustrates a bar graph of the results of Study III - Stability of omega-interferon in untreated SAIB.

[0014] Figure 5 illustrates a bar graph of the results of Study VIb - Stability of omega-interferon in untreated SAIB.

[0015] Figure 6 illustrates a bar graph of the results of Study VIa - Stability of omega-interferon in sodium metabisulfite treated SAIB.

[0016] Figure 7 illustrates a bar graph that provides comparisons of oxidation of omega-IFN in sodium metabisulfite treated and untreated SAIB.

[0017] Figure 8 illustrates an osmotically pump-driven implantable device, Duros® being an example, that facilitates in vivo delivery of an active agent in an SAIB vehicle.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0018] In an aspect of the present invention, provided are methods of treating sucrose acetate isobutyrate formulations (SAIB) that are to be used as drug delivery vehicles comprising adding an amount of a bisulfite salt effective for substantially removing peroxide from the formulations, the bisulfite salt comprising sodium metabisulfite, potassium metabisulfite, sodium bisulfite, or potassium bisulfite, or a combination thereof. Preferably, the bisulfite salt is sodium metabisulfite. A ratio ranging from about 1:1 to about 1:4 (weight:volume) SAIB:aqueous solution of bisulfite salt ("aqueous bisulfite salt") can be used. Preferably, the bisulfite salt is a metabisulfite salt. In some embodiments, the bisulfite salt is preferably sodium metabisulfite. Preferably, the ratio of the aqueous bisulfite salt to SAIB is 1:1. In one example, to purify 1 kg of SAIB, a volume of sodium metabisulfite solution can be made up to 1 liter, and an approximate proportion of 1:1 of SAIB:aqueous sodium metabisulfite was used. The aqueous bisulfite salt in SAIB can be from about 0.1 % weight to volume of water (w/v) to about 50 %

w/v; preferably, from about 0.5 % w/v to about 30 % w/v. In some embodiments, the aqueous bisulfite salt is preferably from about 1 % w/v to about 15 % w/v. In some embodiments, the aqueous bisulfite salt is about 5 % w/v solution in water.

[0019] The method removes peroxide to a level that is at least less than 50 % of the levels before the method, or starting levels, and, preferably, less than 20 % of the starting levels. In some embodiments, peroxide is removed to less than 10 % of the starting levels. While in some embodiments, the method removes peroxide to a level that is less than 5 % of the starting levels. Furthermore, the method can remove peroxide so that the resulting SAIB formulation contains peroxide in amounts less than 20 ppm, and, preferably, less than 10 ppm. In some embodiments, the method removes peroxide to result in an SAIB formulation containing less than 5 ppm. In some embodiments, the resulting SAIB formulation from this method can serve as a drug delivery vehicle for use with a medical delivery device, including a drug eluting stent, a catheter, or other drug delivery implants. In one example, the SAIB formulation can be loaded into an osmotically pump-driven implantable device of the type disclosed in U.S. Patent No. 6,395,292, for example. Preferably, the osmotically pump-driven implantable device is a Duros® device (Alza Corporation, Mountain View, California). In other embodiments, the SAIB formulation can serve as a drug depot for drug delivery.

[0020] In some embodiments, the step of adding the bisulfite salt comprises mixing a solution of the bisulfite salt with the sucrose acetate isobutyrate formulation. The SAIB formulation can be further comprised of a cosolvent, which can be selected from a number of solvents including pharmaceutically acceptable solvents, *e.g.*, hexane, ethyl acetate, ethanol, benzyl benzoate, N-methyl pyrrolidone, and iso-propyl alcohol, among others. Preferably, the cosolvent is hexane or ethyl acetate. In some embodiments, the methods further comprise vacuum treating the formulation to remove the cosolvent. Also, some embodiments comprise

the additional step of removing bisulfite salt from the formulation. This removal step comprises washing the formulation with water to remove the bisulfite salt. In the embodiments that incorporate the washing step, a further step of drying the formulation over magnesium sulfate can be utilized to remove the water. Alternatively, calcium chloride anhydrous, calcium sulfate anhydrous, activated silica gel, phosphorous pentoxide, or drying under vacuum, or a combination thereof can be used to also remove the water. In alternative embodiments, glycerin can be used to wash the bisulfite-added formulation to remove the bisulfite salt. Afterwards, residual glycerin can be removed by washing with water and then drying to remove water.

[0021] In some aspects of the present invention, the methods of substantially removing peroxide from a sucrose acetate isobutyrate formulation (SAIB) comprising the steps of adding the aqueous bisulfite salt, washing the formulation, and drying the formulation are repeated at least once. The steps can be repeated to further reduce the levels of peroxide in the SAIB formulation.

[0022] In another aspect, the present invention includes a drug delivery vehicle comprising SAIB that provides for prolonged stability of a drug that is to be delivered by maintaining substantially reduced levels of peroxide, the drug delivery vehicle being treated with sodium metabisulfite. The prolonged stability comprises reduced oxidation, deamidation, or aggregation, *e.g.*, dimerization, of the drug over extended periods of time in which drug is within environment of delivery vehicle. Preferably the prolonged stability is reduced oxidation. The extended periods of time can be periods from about one week to a few months, and up to about a year. Preferably, the prolonged stability is evidenced by significant improvements in oxidation, deamidation, or aggregation levels of the drug when the delivery vehicle has been treated with a bisulfite salt versus untreated delivery vehicle. In some preferred embodiments, the prolonged stability is characterized as about 50 % less oxidation, about 33 % less deamidation, or about 75

% less dimerization as compared to untreated delivery vehicles. The drug can be selected from any known and desired biomolecular material that can act as therapeutics and other therapeutic active agents that are susceptible to oxidative degradation. As it is used herein, the term "biomolecular material" refers to peptides, polypeptides, proteins, nucleic acids, viruses, antibodies, small molecules susceptible to oxidation, and any other naturally derived, synthetically produced, or recombinantly produced active agent that includes nucleic or amino acid. In some embodiments, for example, drugs can be selected from among the following: a steroid, NSAIDS, peptides, proteins such as growth factors or hormones, anti-tumor agents, antibiotics, analgesics, local anesthetics, antiviral agents, antipsychotics, anticoagulants, oligonucleotides for gene therapy, active small molecules, and others.

[0023] As used herein, the term "removing" and all variations thereof, refer to decreasing by any measurable degree the level of peroxide present in a drug formulation. The term "substantially removing" is used herein to describe a dramatic decrease in the level of peroxide present in a drug formulation, such as SAIB formulation. The dramatic decrease is at least 50 % of original levels (levels before treatment) and in some instances is 10 % of original levels. In preferred aspects of the present invention, the "substantial removal" describes a decrease to less than 5 % of original levels.

[0024] As used herein, the term "drug delivery vehicle" or "delivery vehicle" refers to a formulation that is biocompatible and used to carry a drug without reacting with the same drug. Also, the vehicle does not alter or minimally alters the activity of the drug. Furthermore, the vehicle allows for the transport of the drug *in vivo* and eventual delivery of the drug to a biological site for therapeutic effect.

[0025] As used herein, the term "prolonged stability" is used to refer to the stabilizing effect of the drug delivery vehicles of the present invention on the carried drug. Prolonged

stability can be evidenced by significant improvements in oxidation, deamidation, or aggregation of the drug over extended periods of time.

Examples

[0026] Different approaches were investigated for removal of peroxides from SAIB, as indicated in Table 1.

Preparation of Suspension

[0027] Each of the experiments involved protein particles consisting of omega-interferon, which were suspended in SAIB at a particle loading of either 4 % or 10 % by weight. The suspensions were prepared in a dry box under nitrogen at 45°C. The suspension was mixed for 15 minutes while maintaining the temperature. Suspension mixing was performed by hand. Aliquots from the prepared suspensions were transferred to clear crimp-top glass vials and sealed under nitrogen. Each aliquot contained at least six milligrams of protein to allow for stability testing in triplicate. These samples were stored in an oven at 40° C. Samples were withdrawn at regular intervals (as indicated in Table 1) and analyzed for omega-interferon content and purity was assessed using reverse phase HPLC and size exclusion chromatography.

Size Exclusion Chromatography

[0028] Size exclusion chromatography (SEC) was used to monitor the omega-interferon content and purity in the formulations. The percentages of monomer and dimer in the formulation were quantified using SEC. The stability of omega-interferon was judged by using a stability indicating chromatographic technique based on reverse phase HPLC (rp-HPLC). This technique was used to monitor the oxidation, deamidation and formation of an unknown species of omega-interferon in the formulations. The peroxide content of the vehicle was determined

using EP 2002, 2.5.5 (Method A with auto titration). See Extra Pharmacopoeia, 2002 Ed. Content and purity assay of omega-interferon by size exclusion chromatography (SEC).

Reverse Phase High Performance Liquid Chromatography

[0029] Purity assay and identity of omega-interferon recombinant in suspension systems by reverse phase high performance liquid chromatography (rp-HPLC).

[0030] The stability of omega-interferon was monitored in two different lots of untreated SAIB (as received) and in treated SAIB (removal of peroxides), when treatment was applied.

[0031] The studies are outlined below:

- Study I: Stability in untreated SAIB (lot #TD1030507) for 2 weeks
- Study IIa: Treatment of SAIB (lot #TD1030507) with neutral alumina by heating and stability in this treated SAIB for 4 weeks
- Study IIb: Treatment of SAIB (lot #TD1030507) with neutral alumina in presence of ethanol and stability in this treated SAIB for 4 weeks
- Study III: Stability in untreated SAIB (lot #TD2032663) for 2 weeks
- Study IV: Treatment of SAIB (lot #TD2032663) with basic alumina by heating
- Study V: Treatment of SAIB (lot #TD2032663) with 10 % aqueous methionine solution by heating
- Study VIa: Treatment of SAIB (lot #TD2032663) with 5 % aqueous solution of sodium metabisulfite and stability in treated SAIB for 8 weeks
- Study VIb: Stability in untreated SAIB (lot #TD2032663) for 8 weeks

Table 1. Details about stability studies of omega-interferon in SAIB

Study #	SAIB (Lot #)	Treatment	Particle loading	Time points	Tests
I	TD1030507	Untreated	4%	0, 4, 7, 14 days	SEC, RP-HPLC
IIa	TD1030507	Treated with neutral alumina by heating	10%	0, 2, 4 weeks	SEC, RP-HPLC
IIb	TD1030507	Treated with neutral alumina using ethanol	10%	0, 2, 4 weeks	SEC, RP-HPLC
III	TD2032663	Untreated	10%	0, 1, 2 weeks	SEC, RP-HPLC
IV	TD2032663	Treated with basic alumina by heating	NA	NA	NA
V	TD2032663	Treated with 10 % aqueous solution of methionine	NA	NA	NA
VIa	TD2032663	Treated with hexane and sodium metabisulfite	10%	0, 1, 2, 4, 8 weeks	SEC, RP-HPLC
VIb	TD2032663	Untreated	10%	0, 1, 2, 4, 8 weeks	SEC, RP-HPLC

Materials and Equipment

[0032] The following tables, Table 2 and Table 3, provide a list of materials and equipment that can be utilized to perform the experiments described, below.

Table 2. List of materials

Materials
Spray dried omega-interferon particles
SAIB, Eastman Chemical Company
Aluminum oxide (Powder)
Ethanol, absolute, 200 proof, AAPER
Aluminum oxide, basic, standard activity I, 50 –200 μm, Sorbent Technologies

Aluminum oxide, basic, Super I, 50 –200 μm, Sorbent Technologies
Methionine, USP, Ph Eur, JP

Table 3. List of equipment

Equipment
Branson Ultrasonic Cleaner Model 2510
VAC Dry Box
Mettler AT261 Delta Range Balance
Mettler PJ3000 Balance
Sartorius Genius Electronic Analytical Balance
Hot plate
Oven (40°C)
Millipore filter, white hydrophilic, Durapore Disc, SLVP, 25 mm, 5 μm
PTFE membrane filter, 0.2 μm, Titan filtration systems

Example 1
Study I: Stability in untreated SAIB (lot #TD1030507) for 2 weeks

Table 4. Stability of omega-interferon in untreated SAIB (lot #: 1030507) – Study I

	Analysis by RP-HPLC (n=3)**			
	Initial (t=0) (AR 48452) (protein particles)***	4 days AR48424	7 days AR48562	14 days AR48450
Assay (%)	NA	0.59* (0.02)	0.72 (0.00)	0.68 (0.00)
% omega-IFN Purity	93.37 (0.40)	89.06 (0.46)	87.65 (0.06)	87.67 (0.26)
%Oxidized	2.8 (0.71)	7.21 (0.88)	7.79 (1.09)	8.31 (0.10)
% Deamidated	0.8 (0.02)	1.21 (0.00)	1.28 (0.01)	1.63 (0.03)
% Unknown	3.03 (0.62)	2.25 (0.66)	3.27 (0.79)	2.39 (0.38)

*sampled by scraping container walls, so values might not be representative of the bulk

	Analysis by SEC (n=3)**			
	Initial (AR 48452) (protein particles)***	4 days AR48424	7 days AR48562	14 days AR48450
% Monomer	100.00 (0.00)	99.96 (0.01)	99.60 (0.02)	99.40 (0.00)
% Dimer	ND	0.04 (0.00)	0.38 (0.01)	0.58 (0.02)
Unknown	ND	ND	0.01 (0.00)	0.01 (0.01)

ND = Not detected,
standard deviation in parenthesis; * protein particles – t =0 for suspension

[0033] The preliminary stability study of omega interferon in untreated SAIB (lot # TD1030507, peroxide value – 71.4 ppm) was over 2 weeks. The results indicated that up to 8.31% of omega-interferon was oxidized in two weeks, which corresponds to an increase of 5.51% with respect to particles (2.8% oxidation at t=0). See Table 4, Figure 1. Furthermore, a small increase occurred in the percentage of deamidated form (+ 0.83%) of omega-interferon and the dimer (+ 0.58%). The high level of oxidation can be attributed to the high peroxide content of SAIB.

Example 2
Study IIa and IIb: Stability of SAIB (lot #TD1030507) treated with neutral alumina with heating or neutral alumina in presence of ethanol for 4 weeks

Treatment of SAIB with neutral alumina with heating

[0034] SAIB was heated to 75° C. Alumina (15 % w/w) was added to the heated SAIB. The mixture was stirred for 40 minutes and filtered though a 5.0 μm filter at 75° C. The treated SAIB was then collected, sampled for peroxide testing, and used for preparation of suspension for stability testing.

Treatment of SAIB with neutral alumina in presence of ethanol

[0035] SAIB was mixed with 15% absolute ethanol to reduce the viscosity. Basic alumina (15 % w/w) was added to the SAIB containing ethanol. The resulting mixture was stirred for 1 hour and filtered though a 0.2 μm filter. The filtered SAIB was placed overnight under vacuum at 60° C to remove the ethanol. This treated SAIB was then collected, sampled for peroxide testing, and used for preparation of suspension for stability testing.

Table 5. Stability of omega-interferon in alumina treated SAIB ((lot #: 1030507) – Studies IIa and IIb

SAIB treated with neutral alumina by heating - Study IIa

	Analysis by RP-HPLC (n=3)**			
	Initial (t=0) (protein particles)	Initial (t = 0) AR 48570	2 weeks AR 48572	1 month AR 48565
Assay (%)	NA	1.68 (0.01)	1.70 (0.00)	1.72 (0.01)
% omega-IFN Purity	89.08 (0.56)	87.56 (0.47)	83.90 (0.15)	82.97 (0.50)
%Oxidized	1.72 (0.12)	3.45 (0.06)	6.85 (0.14)	7.39 (0.21)
% Deamidated	1.49 (0.01)	1.46 (0.03)	1.84 (0.03)	2.42 (0.05)
% Unknown	7.70 (0.45)	7.52 (0.45)	7.41 (0.01)	7.22 (0.46)

	Analysis by SEC (n=3)**			
	Initial (t=0) (protein particles)	Initial (t=0) AR 48570	2 weeks AR 48572	1 month AR 48565
% Monomer	100.00 (0.00)	100.00 (0.00)	99.89 (0.01)	99.50 (0.02)
% Dimer	trace	0.00	0.11 (0.01)	0.50 (0.02)
Unknown	0.00	0.00	0.00	0.00

SAIB treated with neutral alumina using ethanol - Study IIb

	Analysis by RP-HPLC (n=3)**			
	Initial (t=0) (protein particles)	Initial (t=0) AR 48570	2 weeks AR 48572	1 month AR 48565
Assay (%)	NA	1.66 (0.02)	1.70 (0.01)	1.70 (0.00)
% omega-IFN Purity	89.08 (0.56)	88.12 (0.49)	83.76 (0.09)	82.65 (0.19)
%Oxidized	1.72 (0.12)	3.08 (0.07)	6.98 (0.12)	7.42 (0.10)
% Deamidated	1.49 (0.01)	1.47 (0.01)	1.88 (0.02)	2.45 (0.09)
% Unknown	7.70 (0.45)	7.32 (0.48)	7.38 (0.02)	7.48 (0.05)

	Analysis by SEC (n=3)**			
	Initial (t=0) (protein particles)	Initial (t=0) AR 48570	2 weeks AR 48572	1 month AR 48565
% Monomer	100.00 (0.00)	100.00 (0.00)	99.87 (0.01)	99.43 (0.02)
% Dimer	trace	0.00	0.13 (0.01)	0.57 (0.02)
Unknown	0.00	0.00	0.00	0.00

**standard deviation in parenthesis

[0036] The stability of omega-interferon in alumina treated SAIB was tested. After one month in the neutral alumina treated SAIB (Study IIa and IIb), oxidation of omega-interferon increased by about 5.7% for both IIa and IIb. This indicates that alumina treatment of SAIB did not improve the stability of omega-interferon in SAIB. See Table 5. In addition, this analysis is also reflected in the high peroxide content of alumina treated SAIB (66.3 and 62.9 ppm, respectively). Treatment with neutral alumina was not effective in decreasing peroxide content.

Example 3

Study III: Stability in untreated SAIB (lot #TD2032663) for 2 weeks

Table 6. Stability of omega-interferon in untreated SAIB ((lot #: 2032663) – Study III

	Analysis by RP-HPLC (n=3)**			
	Initial (t=0) (AR 48217) (protein particles)	Initial (t=0) AR 49640	1 week AR 49644	2 weeks AR 49647
Assay (%)	NA	1.69 (0.01)	1.70 (0.00)	1.68 (0.01)
% omega-IFN Purity	88.98 (0.09)	88.21 (0.03)	84.95 (0.58)	83.71 (0.48)

%Oxidized	1.63 (0.04)	3.20 (0.03)	6.39 (0.05)	7.21 (0.10)
% Deamidated	1.45 (0.01)	1.66 (0.01)	1.45 (0.40)	1.84 (0.03)
% Unknown	7.94 (0.12)	6.93 (0.04)	7.22 (0.45)	7.24 (0.45)

	Analysis by SEC (n=3)**			
	Initial (t=0) (AR 48217) (protein particles)	Initial (t=0)* AR 49640	1 week AR 49644	2 weeks AR 49647
% Monomer	99.93 (0.01)	99.83 (0.02)	99.75 (0.01)	99.51 (0.01)
% Dimer	0.07 (0.01)	0.17 (0.02)	0.25 (0.01)	0.49 (0.01)
Unknown	ND	ND	ND	ND

ND = Not detected
*n = 6
**standard deviation in parenthesis

[0037] Stability of omega-interferon in untreated SAIB was again tested. The results of a two week stability study (Study III) of omega-interferon in SAIB (lot # TD 2032663) are comparable to studies I and II. See Table 6, Figure 4. The amount of oxidation was found to have increased by 5.58%, while deamidation increased by 0.39% and dimerization increased by 0.42%.

Example 4

Study IV and V: Treatment of SAIB (lot #TD2032663) with basic alumina with heating or with 10 % aqueous methionine solution

Treatment of SAIB with basic alumina with heating

[0038] SAIB was heated to 90° C. Basic alumina (15 % w/w) was added to the heated SAIB. Two different grades of alumina were used – Basic Super I and Basic Standard Activity I. The resulting mixture was stirred for 40 minutes. The mixture was then centrifuged at 4000 rpm while temperature was maintained at 75° C. After centrifugation, the supernatant was collected and sampled for peroxide analysis.

Treatment of SAIB with 10% aqueous solution of methionine

[0039] One part of SAIB was vigorously agitated with 4 parts of 10 % aqueous solution of methionine at 80° C for 45 minutes using a magnetic stirrer. (Evaporated water was replenished as necessary) Afterwards, the methionine solution was decanted. SAIB was then washed with 4 parts of water by agitating for 15 minutes at 70° – 80° C. This washing step was carried out three times. SAIB was placed overnight in vacuum oven at 70° C to remove residual water, and, afterwards, was sampled for peroxide analysis.

[0040] The peroxide content of SAIB treated with basic alumina or with aqueous methionine solution was determined to be 109.3 and 95.7 respectively (Study IV and V), indicating that these approaches were not successful in the removal of peroxides. See Figure 7.

Example 5

Study VIa and VIb: Stability of SAIB (lot #TD2032663) treated with 5 % aqueous solution of sodium metabisulfite or untreated for 8 weeks

Treatment of SAIB with 5 % aqueous solution of sodium metabisulfite in presence of hexane

[0041] SAIB was dissolved in two parts of hexane. The resulting solution was treated with a 5 % aqueous solution of sodium metabisulfite by vigorous shaking. The aqueous layer was removed and the SAIB layer was washed with water. The SAIB layer was dried with $MgSO_4$. Hexane was removed from SAIB by evaporation under vacuum at 50° C. The treated SAIB was sampled for peroxide analysis and used for preparation of suspension for stability testing.

Table 7. Stability of omega-interferon in untreated SAIB and treated SAIB – Study VIa and VIb
Stability of omega-IFN in **Untreated SAIB** (Lot: TD 2032663)

	Analysis by RP-HPLC (n=3)**					
	Initial (t=0) Protein particles	Initial (t=0)	1 week	2 weeks	4 weeks	8 weeks
	AR 48219	AR 48445	AR48441	AR 48440	AR 50132	AR 50161
Assay (%)	11.45 (0.24)	1.00 (0.01)	1.00 (0.01)	1.00 (0.01)	0.94 (0.01)	0.94 (0.03)

% omega-IFN	88.91 (0.39)	87.29 (0.25)	83.10 (0.08)	81.62	80.17	79.35
%Oxidized	1.90 (0.39)	3.38 (0.19)	7.86 (0.14)	8.54 (0.07)	8.94 (0.08)	8.86 (0.06)
% Deamidated	2.02 (0.01)	2.15 (0.03)	2.24 (0.09)	2.59 (0.15)	3.33 (0.04)	4.46 (0.07)
% Unknown	7.17 (0.44)	7.18 (0.47)	6.80 (0.02)	7.25 (0.36)	7.55 (0.05)	7.33 (0.47)

	Analysis by SEC (n=3)**					
	Initial (t=0) Protein particles	Initial (t=0)	1 week	2 weeks	4 weeks	8 weeks
	AR 48219	AR 48445	AR48441	AR 48440	AR 50132	AR 50161
% Monomer	99.67 (0.01)	99.57 (0.02)	99.16 (0.01)	98.93	99.15	97.18
% Dimer	0.25 (0.01)	0.31 (0.02)	0.72 (0.01)	1.01 (0.04)	0.47 (0.05)	2.53 (0.13)
Unknown	0.08 (0.00)	0.12 (0.01)	0.12 (0.00)	0.06 (0.00)	0.38 (0.02)	0.30 (0.05)

Note: The omega content in the suspension was 1.00 % and not 1.66% because the particles contained 11.45% omega and the loading of particles in suspension was at 10%

Stability of omega-IFN in **Treated SAIB** (Lot: TD 2032663)

	Analysis by RP-HPLC (n=3)**					
	Initial (t=0) Protein particles	Initial (t=0)	1 week	2 weeks	4 weeks	8 weeks
	AR 48219	AR 48445	AR48441	AR 48440	AR 50132	AR 50161
Assay (%)	11.45 (0.24)	1.17 (0.01)	1.15 (0.00)	1.16 (0.00)	1.15 (0.00)	1.14 (0.01)
% omega-IFN	88.91 (0.39)	88.11 (0.35)	86.25 (0.41)	85.83	85.41	84.52
%Oxidized	1.90 (0.39)	2.69 (0.17)	3.26 (0.07)	3.46 (0.09)	3.56 (0.05)	4.16 (0.11)
% Deamidated	2.02 (0.01)	2.26 (0.04)	2.81 (0.01)	2.94 (0.04)	3.21 (0.06)	3.64 (0.06)
% Unknown	7.17 (0.44)	6.97 (0.39)	7.68 (0.37)	7.77 (0.38)	7.81 (0.45)	7.77 (0.55)

	Analysis by SEC (n=3)**					
	Initial (t=0) Protein particles	Initial (t=0)	1 week	2 weeks	4 weeks	8 weeks
	AR 48219	AR 48445	AR48441	AR 48440	AR 50132	AR 50161
% Monomer	99.67 (0.01)	99.59 (0.02)	99.34 (0.02)	99.41	99.42	99.00
% Dimer	0.25 (0.01)	0.35 (0.02)	0.53 (0.02)	0.54 (0.02)	0.29 (0.01)	0.94 (0.06)
Unknown	0.08 (0.00)	0.05 (0.00)	0.13 (0.01)	0.05 (0.01)	0.29 (0.01)	0.06 (0.01)

Note: The omega content in the suspension was 1.17 % and not 1.66% because the particles contained 11.45% omega and the loading of particles in suspension was at 10%.
**standard deviation in parenthesis

[0042] The stability study (Study VIa and VIb, Table 7, Figures 5 - 7) conducted in treated (5 % aqueous solution of sodium metabisulfite) and untreated SAIB shows that oxidation levels are reduced at 8 weeks, along with the reduction of peroxide levels - 4.16 % in treated SAIB versus 8.86 % in untreated SAIB equivalent to a change of 2.26 % and 6.96 %, respectively, from t=0 values of the protein particles. (For all relative changes reported herein,

the changes are based on differences between the percentage values, *e.g.*, percent oxidation, at t_n and t =0 of the particles as opposed to relative percent change from value at t=0). Deamidation increased by 2.44 % and 1.62 % in untreated and treated SAIB, respectively. Dimerization increased by 2.28 % and 0.59 % in untreated and treated SAIB%, respectively. The quantities of unknown did not change significantly over time, which indicates that the extent of oxidation, deamidation and dimerization in treated SAIB (low peroxide value of 2.6 ppm) was lower than in untreated material. This treatment decreased the peroxide content substantially.

Table 8. Peroxide content of SAIB

Study #	SAIB (Lot #)	Treatment	Peroxide value (ppm)*	AR numbers
I	TD1030507	Untreated	71.4	48557
IIa	TD1030507	Treated with neutral alumina by heating	66.3	48568
IIb	TD1030507	Treated with neutral alumina using ethanol	62.9	48568
III	TD2032663	Untreated	115.9	48581
IV	TD2032663	Treated with basic alumina by heating	109.3	48581
V	TD2032663	Treated with 10% aqueous solution of methionine	95.7	48446
VIa	TD2032663	Treated with hexane and sodium metabisulfite	2.6	49648
VIb	TD2032663	Untreated	115.9**	48581

*oxidative activity equivalent to hydrogen peroxide (n =1)

**peroxide content determined during Study III

[0043] As shown in Figure 7, along with data provided in Table 8, treatment with an aqueous solution of sodium metabisulfite was effective in significantly reducing peroxide levels from 115.9 ppm to 2.6 ppm – almost 45 times, or 45 fold decrease. In comparison, treatment with neutral alumina, either with heat or with ethanol, resulting in only a nominal change in peroxide levels - a 7 % or 12 % decrease, respectively. In addition, treatment with basic alumina with heat or 10% aqueous methionine only resulted in nominal change in peroxide levels – a 6 % or 18 % decrease, respectively.

[0044] Figure 8 illustrates an osmotically pump-driven implantable device for delivering an SAIB formulation acting as a drug delivery vehicle, active agent within. Depicted in Fig. 8 is an osmotically pump-driven implantable device 10 shown comprising an impermeable reservoir 12. The reservoir 12 is divided into two chambers by a piston 16. The first chamber 18 is adapted to contain an SAIB formulation 19 containing an active agent 20 and the second chamber 21 is adapted to contain a fluid-imbibing agent. A back-diffusion regulating outlet 22 is inserted into the open end of the first chamber 18 and a semipermeable membrane 24 encloses the open end of the second chamber 21. The piston 16 is driven towards the open end of the first chamber 18 by the osmotic pressure generated by the fluid-imbibing agent in the second chamber 21. The pressure created by the piston 16 can force the contents of the first chamber 18 out the opening, *i.e.*, the SAIB formulation 19 comprising active agents 20. The release rate of the active agent can be governed by the osmotic pumping rate.

[0045] It is to be appreciated that certain features of the invention which are, for clarity, described above in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any

subcombination. Further, reference to values stated in ranges includes each and every value within that range, unless clearly expressed otherwise.

[0046] The entire disclosure of each patent, patent application, and publication cited or described in this document is incorporated herein by reference.

We Claim:

1. A method of treating a sucrose acetate isobutyrate formulation to be used as a drug delivery vehicle comprising adding to the formulation an amount of bisulfite salt effective to substantially remove peroxides, the bisulfite salt comprising sodium metabisulfite, potassium metabisulfite, sodium bisulfite, or potassium bisulfite, or a mixture thereof.

2. The method of claim 1, wherein the bisulfite salt is sodium metabisulfite.

3. The method of claim 1, wherein the method removes peroxide to a level that is 10 % or less than the level present I the formulation before addition of the bisulfite salt.

4. The method of claim 1, wherein the method removes peroxide to result in a formulation having less than 5 ppm of peroxide.

5. The method of claim 1, wherein the formulation serves as a drug delivery vehicle for use with an osmotically pump-driven implantable device.

6. The method of claim 1, wherein the adding step comprises mixing a solution of bisulfite salt with the sucrose acetate isobutyrate formulation.

7. The method of claim 1, wherein the formulation further comprises a cosolvent comprising hexane, ethyl acetate, ethanol, benzyl benzoate, N-methyl pyrrolidone, or iso-propyl alcohol, or a combination thereof.

8. The method of claim 7, wherein the cosolvent is hexane or ethyl acetate.

9. The method of claim 7, further comprising vacuum treating the formulation to remove the cosolvent.

10. The method of claim 1, further comprising washing the formulation with water to remove the bisulfite salt.

11. The method of claim 1, further comprising washing the formulation with glycerin to remove the bisulfite salt.

12. The method of claim 10, further comprising drying the formulation using magnesium sulfate, calcium chloride anhydrous, calcium sulfate anhydrous, activated silica gel, phosphorous pentoxide, or vacuum, or combinations thereof.

13. The method of claim 10, further comprising drying the formulation using magnesium sulfate.

14. The method of claim 10, wherein the steps of adding a bisulfite salt, washing the formulation, and drying the formulation are repeated at least once.

15. A drug delivery vehicle for a drug that is to be delivered in vivo comprising sucrose acetate isobutyrate having substantially reduced levels of peroxide, the drug delivery vehicle being treated with an amount of bisulfite salt effective to substantially reduce levels of peroxide in said drug delivery vehicle, the bisulfite salt comprising sodium metabisulfite, potassium metabisulfite, sodium bisulfite, or potassium bisulfite, or a combination thereof.

16. The drug delivery vehicle of claim 15, wherein the bisulfite salt is sodium metabisulfite.

17. The drug delivery vehicle of claim 15, wherein the prolonged stability comprises reduced oxidation, reduced deamidation, or reduced aggregation of the drug.

18. The drug delivery vehicle of claim 15, wherein the prolonged stability is reduced oxidation of the drug.

19. The drug delivery vehicle of claim 15, wherein the substantially reduced levels of peroxide are levels at or below 20 ppm in the drug delivery vehicle.

20. The drug delivery vehicle of claim 15, wherein the substantially reduced levels of peroxide are levels at or below 10 ppm in the drug delivery vehicle.

21. The drug delivery vehicle of claim 15, wherein the substantially reduced levels of peroxide are levels at or below 5 ppm in the drug delivery vehicle.

22. The drug delivery vehicle of claim 15, wherein the treatment with the bisulfite salt comprises removal of the bisulfite salt from the drug delivery vehicle.

23. The drug delivery vehicle of claim 15, wherein the vehicle is adapted to serve as a drug depot.

24. The drug delivery vehicle of claim 15, wherein the vehicle is adapted for delivery from an implantable device.

25. The drug delivery vehicle of claim 24, wherein the implantable device is an osmotically pump-driven implantable device.

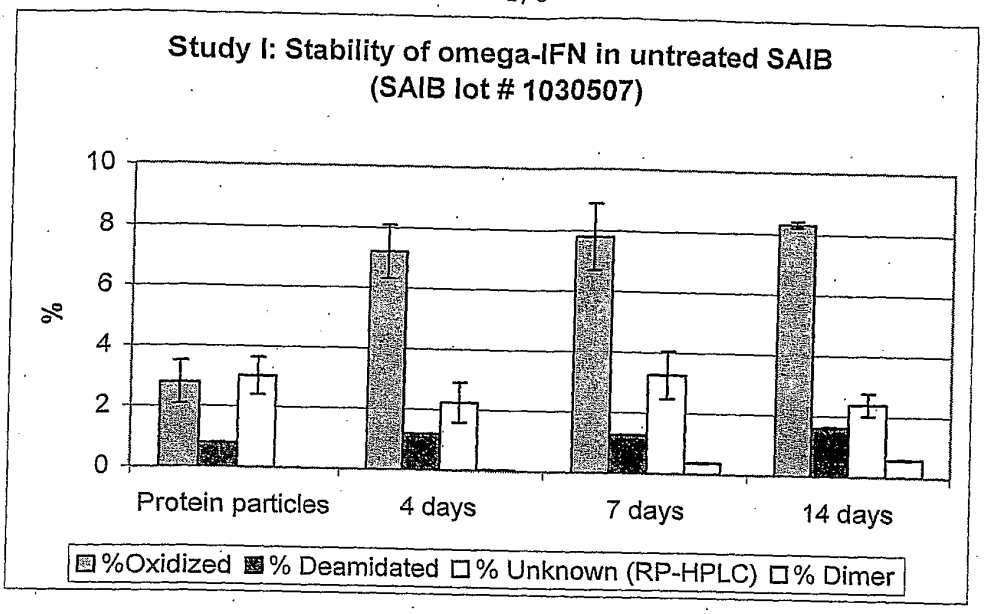

Figure 1. Stability of omega-interferon in untreated SAIB – Study I (n=3)

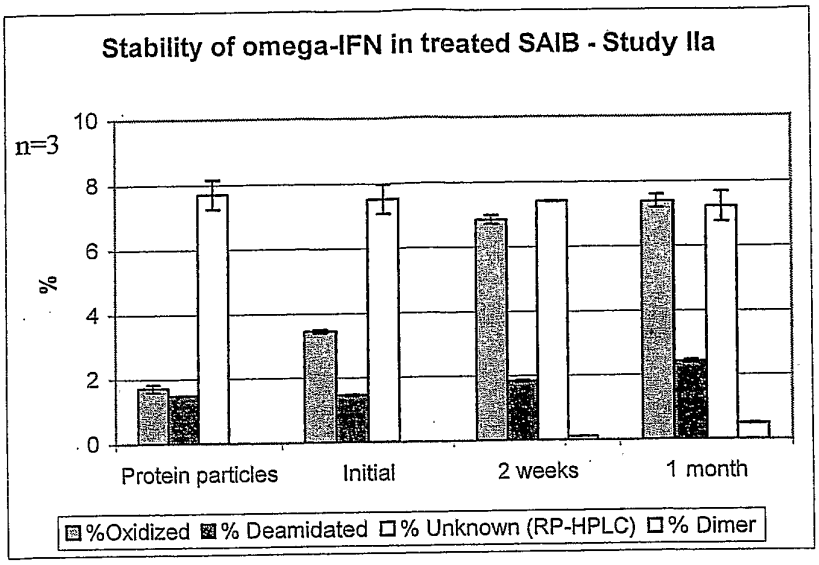

Figure 2. Stability of omega-interferon in alumina treated SAIB Study IIa

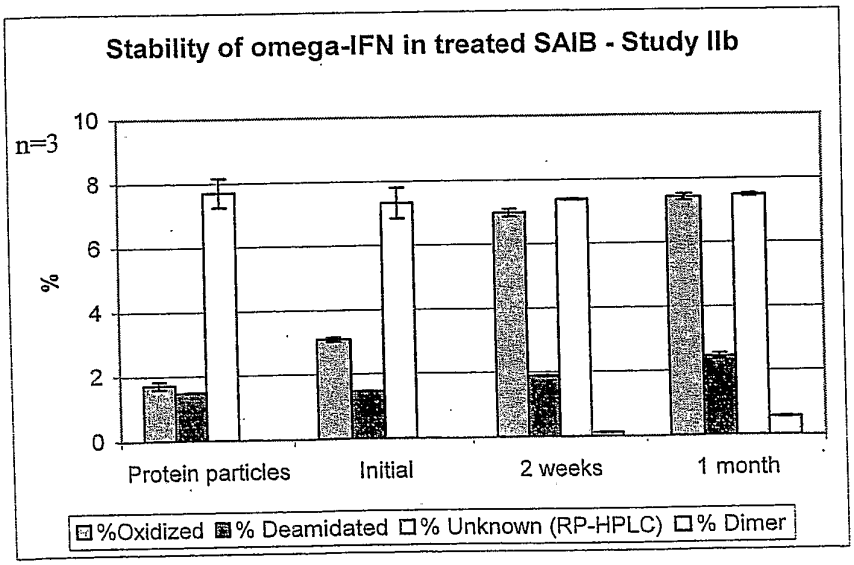

Figure 3. Stability of omega-interferon in alumina treated SAIB Study IIb

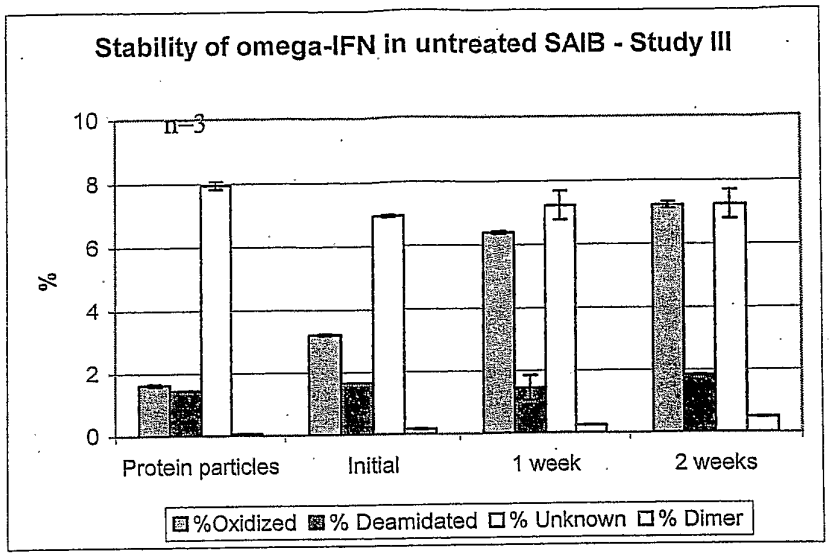

Figure 4. Stability of omega-interferon in untreated SAIB Study III

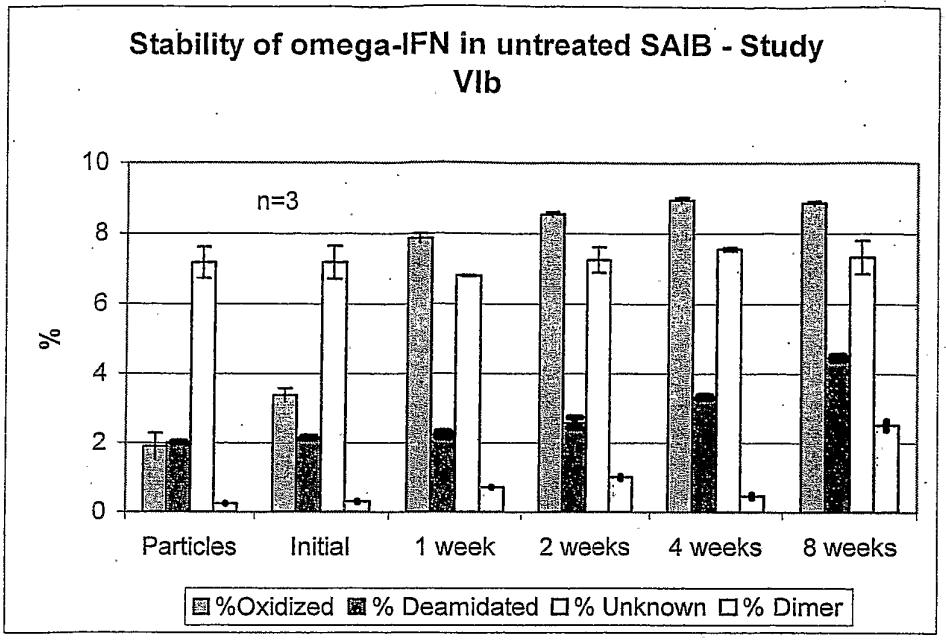

Figure 5. Stability of omega-interferon in untreated SAIB Study VIb

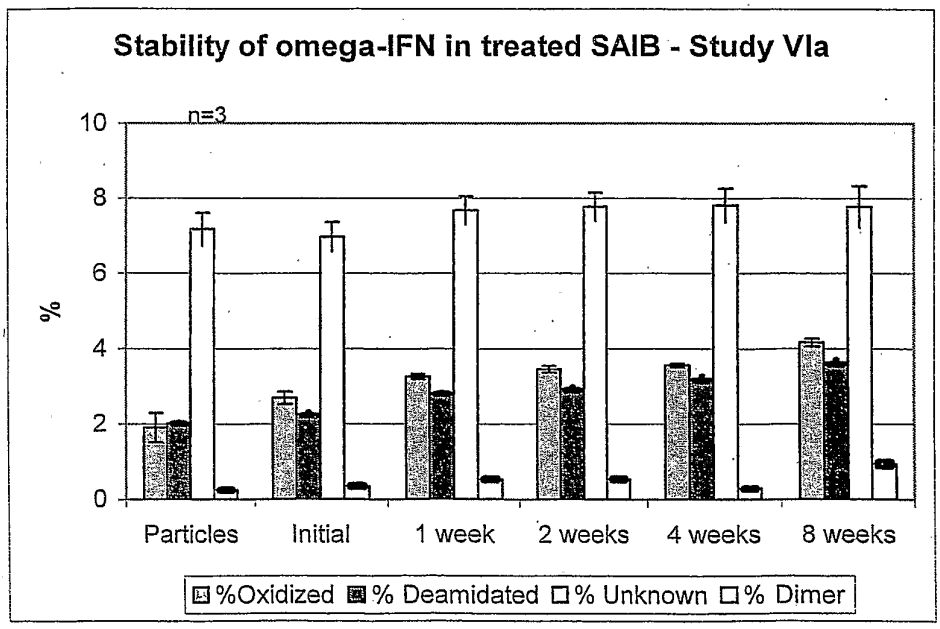

Figure 6. Stability of omega-interferon in sodium metabisulfite treated SAIB Study VIa

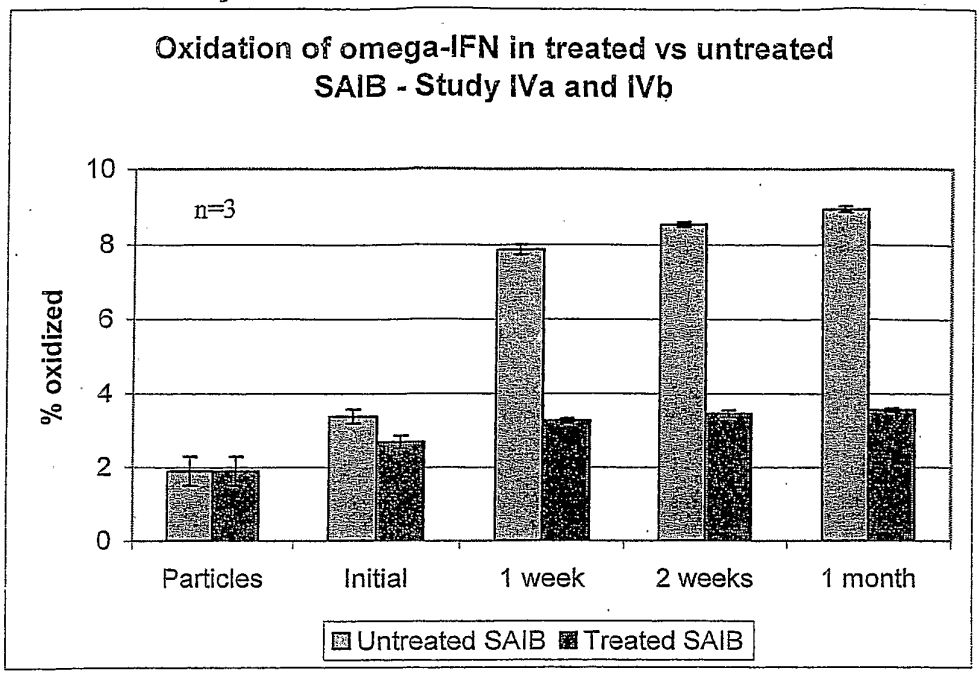

Figure 7. Comparison of oxidation of omega-IFN in sodium metabisulfite treated and untreated SAIB

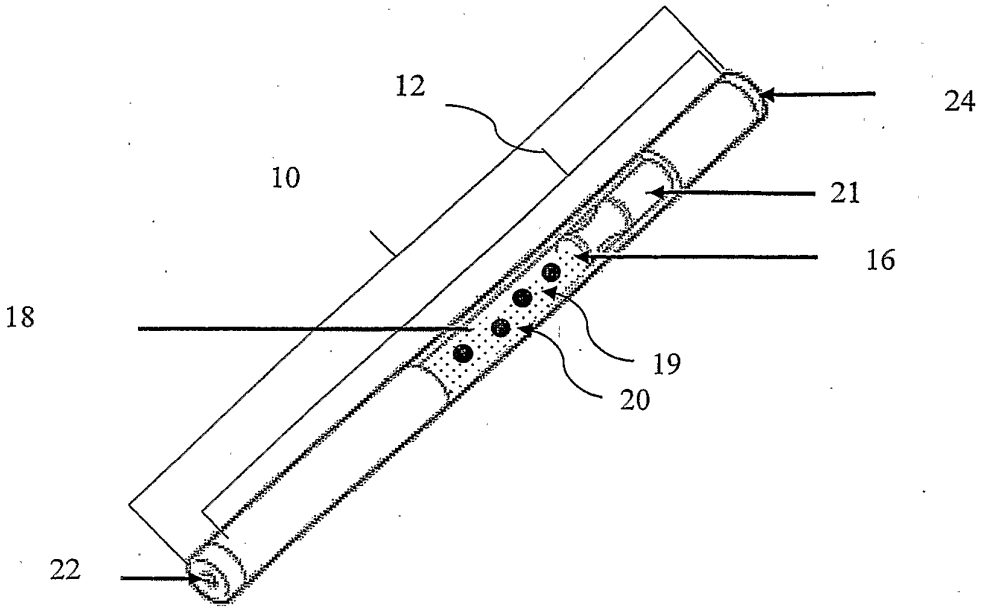

FIGURE 8