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(54) Title: A BIOMOLECULE-CONTAINING FORMULATION OF INCREASED STABILITY

(57) Abstract: A suspension formulation for therapeutic use includes a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics, a dry particle formulation comprising a biomolecule dispersed in the vehicle, and a surfactant incorporated in at least one of the vehicle and dry particle formulation. A dry particle formulation includes an interferon, a buffer, a surfactant, and one or more stabilizers selected from the group consisting of a carbohydrate, an antioxidant, and an amino acid.

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FORMULATIONS STABLE DURING TRANSITION FROM HYDROPHOBIC VEHICLE TO HYDROPHILIC MEDIUM

BACKGROUND OF THE INVENTION

[0001] The invention relates generally to formulations deliverable via sustained release systems, such as implantable drug delivery devices and depot injections.

[0002] Interferons are a group of glycoprotein cytokines produced by cells in response to various stimuli, such as exposure to virus, bacterium, parasite, or other antigen. Interferons have antiviral, immunomodulatory, and antiproliferative activities. Interferons are classified as Type I or Type II. Interferons classified as Type I bind to a common receptor called the Interferon Type I or α-β receptor and are produced by leukocytes, fibroblasts, or lymphoblasts in response to virus or interferon inducers. Interferon Type I includes interferon alpha (IFN-α), interferon beta (IFN-β), and interferon omega (IFN-ω), but IFN-ω has limited homology to human IFN-α (about 60%) and human IFN-β (about 29%). Interferons classified as Type II are produced by T-lymphocytes. Interferon Type II includes interferon gamma (IFN-γ). Interferons are used for treatment of viral hepatitis, multiple sclerosis, and certain cancers. IFN-ω in particular has been indicated for treatment of Hepatitis B & C populations. The injectable form of IFN-ω is currently in Phase II clinical studies. This injectable form is solution-based and is not formulated for sustained delivery.

[0003] There is interest in delivering interferons to patients in a controlled manner over a prolonged period without intervention. For instance, sustained delivery of IFN-ω can improve the therapeutic effect of IFN-ω by reduction or elimination of peak plasma-level related effects of multiple bolus injections, thereby potentially minimizing systemic side effects such as fatigue and flu-like symptoms. Sustained delivery of a beneficial agent without intervention can be provided by implantable drug delivery devices, e.g., osmotic, mechanical, or electromechanical pump implants, and depot injections. Implantable drug delivery devices are attractive for a number of reasons. For example, implantable drug delivery devices can be designed to provide therapeutic doses of the drug over periods of weeks, months, or even a year. Depot injections typically provide therapeutic doses over periods of weeks. Implantable drug delivery devices once inserted

therapeutic doses over periods of weeks. Implantable drug delivery devices once inserted in the patient are not easily tampered with by the patient. Thus, patient compliance is generally assured.

[0004] Sustained delivery of an interferon requires the interferon to be contained within a formulation that is substantially stable at elevated temperature, e.g., 37°C or higher, over the operational life of the implantable delivery drug device. Interferon is a biomolecule, specifically a protein. Generally speaking, protein formulations that are stable at elevated temperature for a long duration, e.g., weeks, months, or a year, are difficult to design. Proteins are naturally active in aqueous environments. Therefore, it would be convenient to formulate proteins as aqueous solutions. Unfortunately, proteins are typically only marginally stable in aqueous formulations for a long duration. One reason for this is that proteins can degrade via a number of mechanisms, such as deamidation (usually by hydrolysis), oxidation, disulfide interchange, and racemization, and water is a reactant in many of these degradation pathways. Water also acts as a plasticizer and facilitates denaturation and/or aggregation of protein molecules.

[0005] Aqueous protein formulations can be reduced to dry particle protein formulations using drying techniques such as freeze-drying (or lyophilization), spray-drying, and dessication. Such dry particle protein formulations can exhibit significantly increased stability over time at ambient and even elevated temperature. However, it is difficult to controllably deliver dry particle formulations from an implantable drug delivery device at a desired flow rate. It has been suggested to suspend the dry particle protein formulation in a non-aqueous, flowable vehicle. Preferably, the suspension vehicle has a high viscosity, e.g., 1 kP or more, so that the particles are substantially uniformly dispersed in the suspension for a desired duration. Further, the suspension formulation should be stable at storage and delivery conditions for the desired duration and maintain its flowability for the operational life of the implantable drug delivery device.

[0006] Non-aqueous suspension vehicles for delivering beneficial agents via implantable drug delivery devices have been described in literature. For example, U.S. Patent No. 5,904,935 (Eckenhoff et al.) teaches non-aqueous suspension vehicles that include waxes having a softening temperature at or less than body temperature,

hydrogenated vegetable oils, silicon oil, medium chain fatty acid monoglycerides, and polyols. The viscosity of these suspension vehicles can be increased to a desired level using thickening agents such as hydrogels, such as cellulose ethers, e.g., hydroxypropyl cellulose and povidone. U.S. Patent No. 6,264,990 (Knepp et al.) discloses non-aqueous, anhydrous, aprotic, hydrophobic, non-polar suspension vehicles with low reactivity. Examples of such vehicles include perfluorodecalin, methoxyflurane, and perfluorotributylamine. Polymeric materials, such as polyvinylpyrrolidone (PVP), may also be used as suspension vehicles.

[0007] U.S. Patent Publication No. US-2004-0224903-A1, discloses suspension vehicles made of single-phase, viscous, flowable compositions that are substantially formed of hydrophobic, non-polymeric materials. Non-polymeric materials used in forming these suspension vehicles include, but are not limited to, hydrophobic saccharide materials, organogels, or lipid materials that behave as single-phase vehicles. According to the publication, exemplary saccharide materials that may be used in formulating a suspension vehicle include, but are not limited to, substituted sucrose esters that exist as fluids at ambient or physiological temperatures, such as sucrose acetate isobutyrate (SAIB). These non-polymeric materials allow the formulation of protein suspensions that are not only stable at ambient and physiological temperatures but are also capable of maintaining substantially uniform dispersion of protein particles.

[0008] Hydrophobic vehicles, such as SAIB, particularly when used without added excipients, can behave like a depot in the presence of a hydrophilic medium. This means that the protein suspended in the vehicle would not be instantaneously released from the vehicle in the presence of the hydrophilic medium. For depot injection applications, the depot effect of the suspension vehicle is typically desirable. For implanted delivery devices, when the suspension vehicle behaves like a depot in the release medium, control of release by the suspension vehicle is cumulative to the control of release by the delivery device. This additional control of release by the suspension vehicle may or may not be desirable depending upon the application. Anyhow, non-instantaneous release of the protein from the suspension vehicle would only be acceptable if the protein is stable in the vehicle in the presence of the release medium and during transition from the suspension vehicle into the release medium.

[0009] From the foregoing, there continues to be a desire for improved stable formulations of biomolecules, particularly proteins, more particularly interferons, that are deliverable via a sustained delivery system, such as an implantable drug delivery device or depot injection.

SUMMARY OF THE INVENTION

[0010] In one aspect, the invention relates to a suspension formulation for therapeutic use which comprises a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics, a dry particle formulation comprising a biomolecule dispersed in the vehicle, and a surfactant incorporated in at least one of the hydrophobic vehicle and dry particle formulation.

[0011] In another aspect, the invention relates to a dry particle formulation comprising an interferon, a buffer, a surfactant, and one or more stabilizers selected from the group consisting of a carbohydrate, an antioxidant, and an amino acid.

[0011a] In another aspect, the invention relates to a suspension formulation that is deliverable via an implantable delivery device comprising: a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics; and a dry particle formulation comprising a biomolecule dispersed in the vehicle; characterized in that a first surfactant is incorporated in the vehicle and a second surfactant is incorporated in the dry particle formulation.

[0012] In yet another aspect the invention relations to an implantable delivery device comprising: a suspension formulation comprising a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics and a dry particle formulation comprising an interferon dispersed in the vehicle, characterized in that a first surfactant is incorporated in the vehicle and a second surfactant is incorporated in the dry particle formulation; and a reservoir containing the suspension formulation in an amount sufficient to provide continuous delivery of the interferon in a therapeutically effective dose in an environment of use over at least one month.

[0012a] In yet another aspect the invention relates to a method of enhancing release of interferon omega in a hydrophilic release rate medium, comprising: suspending a dry particle formulation of interferon omega in a non-aqueous, non-polymeric, hydrophobic vehicle; and incorporating a first surfactant in the dry particle formulation and a second surfactant in the hydrophobic vehicle.

[0013] In another aspect, the invention relates to a method of enhancing release of interferon omega in a hydrophilic release rate medium which comprises suspending a dry particle

formulation of interferon omega in a non-polymeric, hydrophobic vehicle and incorporating a surfactant in at least one of the dry particle formulation and the hydrophobic vehicle.

[0014] Other features and advantages of the invention will be apparent from the following description.

BRIEF DESCRIPTION OF DRAWINGS

[0015] FIG. 1 shows a scanning electron microscope (SEM) image of spray dried IFN-ω particles according to one embodiment of the invention.

[0016] FIG. 2 shows SEM image of IFN-ω particles spray dried with Pluronic F68.

[0017] FIG. 3 shows fraction of IFN-ω recovered from aqueous phase over time at 37°C.

[0018] FIG. 4 shows total IFN-ω recovered from aqueous and solid phases over time at 37°C.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The invention will now be described in detail with reference to a few preferred embodiments, as illustrated in accompanying drawings. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be apparent to one skilled in the art that the invention may be practiced without some or all of these specific details. In other instances, well-known features and/or process steps have not been described in detail in order to not unnecessarily obscure the invention. The features and advantages of the invention may be better understood with reference to the drawings and discussions that follow.

[0020] The invention provides formulations including biomolecules that are deliverable via sustained delivery systems, in particular implantable drug delivery devices and possibly depot injections. Biomolecules considered herein are those that may provide a therapeutic benefit to an animal or human subject and exhibit increased stability when formulated in a non-aqueous suspension. Biomolecules considered herein are generally degradable in water but generally stable as dry particles at ambient and physiological temperatures. Examples of biomolecules include, but are not limited to, peptides, polypeptides, proteins, amino acids, nucleotides, polymers of amino acid residues or nucleotide residues, hormones, viruses, antibodies that are naturally derived, synthetically produced, or recombinantly produced, conjugated proteins, such as lipoproteins and post

translationally modified forms, e.g., glycosylated proteins, and proteins having D-amino acids, modified, derivatized or non-naturally occurring amino acids in the D- or L-configuration and/or peptomimetic units as part of their structure.

[0021] Specific examples of biomolecules that may provide a therapeutic effect include, but are not limited to, baclofen, GDNF, neurotrophic factors, conatonkin G, Ziconotide, clonidine, axokine, anitsense oligonucleotides, adrenocorticotropic hormone, angiotensin I and II, atrial natriuretic peptide, bombesin, bradykinin, calcitonin, cerebellin, dynorphin N, alpha and beta endorphin, endothelin, enkephalin, epidermal growth factor, fertirelin, follicular gonadotropin releasing peptide, galanin, glucagon, gonadorelin, gonadotropin, goserelin, growth hormone releasing peptide, histrelin, insulin, interferons, leuprolide, LHRH, motilin, nafarerlin, neurotensin, oxytocin, relaxin, somatostatin, substance P, tumor necrosis factor, triptorelin, vasopressin, growth hormone, nerve growth factor, blood clotting factors, ribozymes, and antisense oligonucleotides. Analogs, derivatives, antagonists, agonists, and pharmaceutically acceptable salts of each of the above mentioned agents may also be used in formulations of the invention.

[0022] Of particular interest in this invention are interferons. The interferons may be recombinant molecules that can activate the Interferon Type I receptor (α-β receptor) or Interferon Type II receptor. These recombinant molecules may or may not contain sequence homology to native human Type I or Type II interferons. Interferons according to embodiments of the invention may be selected from the group consisting of proteins having the biological activity of recombinant human interferon, interferon analogs, interferon isoforms, interferon mimetics, interferon fragments, hybrid interferon proteins, fusion protein oligomers and multimers of the above, homologues of the above, glycosylation pattern variants of the above, muteins of the above, and interferon molecules containing the minor modifications enumerated above. Interferons according to the invention shall not be limited by method of synthesis or manufacture and shall include those synthesized or manufactured by recombinant (whether produced from cDNA or genomic DNA), synthetic, transgenic, and gene-activated methods. Specific examples of interferons include, but are not limited to, IFN-α, IFN-β, IFN-ω, and IFN-γ.

[0023] Embodiments of the invention provide dry particle formulations including biomolecules. Dry particle formulations of the invention have a low moisture content, typically less than 5 wt%. In accordance with one embodiment of the invention, a dry particle formulation includes an interferon as described above. The dry particle interferon formulation also includes stabilizers. In one embodiment, the stabilizers include a carbohydrate, an antioxidant and/or amino acid. The dry particle interferon formulation also includes a buffer. The amounts of stabilizers and buffer in the dry particle formulation can be determined experimentally based on the activities of the stabilizers and buffers and the desired characteristics of the formulation. In one embodiment, the amount of carbohydrate in the formulation is determined by aggregation concerns. In general, the carbohydrate level should not be too high so as to avoid promoting crystal growth in the presence of water due to excess carbohydrate unbound to interferon. In one embodiment, the amount of antioxidant in the formulation is determined by oxidation concerns. In one embodiment, the amount of amino acid in the formulation is determined by oxidation concerns and/or formability of particles during spray drying. In one embodiment, the amount of buffer in the formulation is determined by pre-processing concerns, aggregation concerns, and formability of particles during spray drying. The buffer may stabilize interferon during processing, e.g., spray drying, when all excipients are solubilized. In general, too much buffer can produce a buffer system in the presence of water, which can then lead to crystallization.

[0024] Examples of carbohydrates that may be included in the dry particle formulation include, but are not limited to, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, and sorbose, disaccharides, such as lactose, sucrose, trehalose, cellobiose, polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, and starches, and alditols (acyclic polyols), such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol, pyranosyl sorbitol, and myoinsitol. Preferred carbohydrates include non-reducing sugars, e.g., sucrose, trehalose, mannitol, and dextrans.

[0025] Examples of antioxidants that may be included in the dry particle formulation include, but are not limited to, methionine, ascorbic acid, sodium thiosulfate, catalase, platinum, ethylenediaminetetraacetic acid (EDTA), citric acid, cysteins,

thioglycerol, thioglycolic acid, thiosorbitol, butylated hydroxanisol, butylated hydroxyltoluene, propyl gallate.

[0026] Examples of amino acids that may be included in the dry particle formulation include, but are not limited to, arginine, methionine, glycine, histidine, alanine, L-leucine, glutamic acid, Iso-leucine, L-threonine, 2-phenylamine, valine, norvaline, praline, phenylalanine, trytophan, serine, asparagines, cysteine, tyrosine, lysine, and norleucine. Preferred amino acids include those that readily oxidize, e.g., cysteine, methionine, and trytophan.

[0027] Examples of buffers that may be included in the dry particle formulation include, but are not limited to, citrate, histidine, succinate, phosphate, maleate, tris, acetate, carbohydrate, and gly-gly. Preferred buffers include citrate, histidine, succinate, and tris.

[0028] The dry particle formulation may include other excipients selected from, for example, surfactants, bulking agents, and salts. Examples of surfactants include, but are not limited to, Polysorbate 20, Polysorbate 80, Tween 20, Tween 80, Pluronic F68, and sodium docecyl sulfate (SDS). Examples of bulking agents include, but are not limited to, mannitol and glycine. Examples of salts include, but are not limited to, sodium chloride, calcium chloride, and magnesium chloride. Possible advantages of incorporating a surfactant into the dry particle formulation will be further discussed in this disclosure.

[0029] Table 1 below shows protein particle formulation composition ranges according to some embodiments of the invention. In one embodiment, a dry particle interferon formulation includes 1:2:1:1.5-2.5 interferon: carbohydrate: antioxidant and/or amino acid: buffer. One example of a dry particle interferon formulation is 1:2:1:1.5-2.5 IFN-ω: sucrose: methionine: citrate. In another specific example, a dry particle interferon formulation includes 1:2:1:1.5-2.5:0.06 interferon: carbohydrate: antioxidant and/or amino acid: buffer: surfactant.

TABLE 1

Loading in dry particle formulation (wt%)	Range	Preferred Range	Most Preferred Range
Protein	0.1 to 99.9%	1 to 50%	1 to 30%
Surfactant	0.0 to 10%	0.01 to 10%	0.01 to 5%
Bulking Agent	0 to 99.9%	0 to 70%	
Salt	0 to 99.9%	0 to 70%	
Stabilizers to protein (wt ratio)	Range	Preferred Range	Most Preferred Range
Carbohydrate	0.1 to 99.9	> 0.5	> 1
Antioxidant and/or amino acid	0.1 to 99.9	> 0.5	
Buffer	Range	Preferred Range	Most Preferred Range
Buffer Concentration	5 mM to 50 mM	5 mM to 25 mM	
Buffer pH	5.0 to 8.0		

[0030] Dry particle formulations according to embodiments of the invention may be prepared by spray drying, lyophilization, or other technique available in the art for forming particles from a mixture of components. A typical spray dry process may include loading a spray solution containing a protein and stabilizing excipients into a sample chamber, which may be maintained at refrigeration to room temperature. Refrigeration generally promotes stability of the protein. A feed pump then sprays the spray solution into a nozzle atomizer. At the same time, atomized gas (typically, air, nitrogen, or inert gas) is directed at the outlet of the nozzle atomizer to form a mist of droplets from the spray solution. The mist of droplets are immediately brought into contact with a drying gas in a drying chamber. The drying gas removes solvent from the droplets and carries the dry particles into a collection chamber.

[0031] Suspension formulations according to embodiments of the invention are prepared by incorporating dry particle formulations according to embodiments of the

invention into non-aqueous, hydrophobic vehicles. The non-aqueous, hydrophobic vehicles may be any combination of solvent, liquid or non-liquid polymer, liquid or non-liquid non-polymer, and surfactant.

[0032] In one embodiment, a non-aqueous, hydrophobic vehicle used in a suspension formulation of the invention is biodegradable, i.e., it disintegrates or breaks down over a period of time in response to a biological environment. This breakdown may take place by one or more physical or chemical processes, such as by enzymatic action, oxidation, reduction, hydrolysis (e.g., proteolysis), displacement, or dissolution by solubilization, emulsion or micelle formation. In one embodiment, the components of the vehicle are selected such that the vehicle has a viscosity in a range from 1 kP to 1,000 kP, preferably 5 kP to 250 kP, more preferably 5 kP to 30 kP. In one embodiment, to maintain stability of the biomolecule at elevated temperature, e.g., 37°C or higher, over a time period, the components of the vehicle are chosen such that the vehicle does not react with the biomolecule. The components of the vehicle may be chosen such that the vehicle has little or no solubility for the selected biomolecule and particle excipients, thereby maintaining the selected biomolecule and excipients as dry particles, thereby achieving stability of the selected biomolecule.

[0033] In another embodiment, a suspension formulation is made by suspending a dry particle formulation according to an embodiment of the invention in a non-aqueous, single-phase, hydrophobic vehicle including a non-polymer. Examples of non-polymeric materials suitable for use include, but are not limited to, hydrophobic saccharide materials, organogels, or lipid materials that behave as single-phase vehicles, e.g., lipid gels such as dioleoyl phisphatidylcholine (DOPC). Exemplary saccharide materials include, but are not limited to, sucrose esters that exist as fluids at ambient or physiological temperature, such as sucrose acetate isobutyrate (SAIB). The vehicle may or may not include one or more solvents. For example, SAIB, a liquid non-polymer, can be used "neat," i.e., without addition of other excipients. Examples of solvents for creating lipid gel vehicle (with DOPC) include, but are not limited to, n-methyl propanol, cottonseed oil, sesame oil, soybean oil, vitamin E, castor oil, Polysorbate 80, and N dimethylacetamide.

[0034] The non-aqueous, single-phase, hydrophobic vehicle described above may also include excipients such as surfactants, preservatives, and stabilizers. Surfactants may be included in the vehicle to facilitate release of the biomolecule from the vehicle once the formulation is delivered to an environment of use or to help maintain stability of the biomolecule when the biomolecule is suspended in the vehicle. Where included, surfactants will typically account for less than 20 wt%, preferably less than 10 wt%, more preferably less than 5 wt% of the vehicle. Generally, preservatives are included in the vehicle only in amounts sufficient to achieve the desired preservative effect. Examples of surfactants that may be used in the vehicle include, but are not limited to, Tweens, Pluronics, Span 20, Span 40, Span 60, Span 80, glyceryl caprylate, glyceryl laurate, PEG-8 caprylic capric glycerides, polyglyceryl-6 oleate, dioctyly sodium, sulfosuccinate, and Vitamin E TPGS. Preservatives that may be used in the vehicle include, for example, antioxidants and antimicrobial agents. Examples of potentially useful antioxidants include, but are not limited to, tocopherol (vitamin E), ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoulene, and propyl gallate.

[0035] In one embodiment, a suspension formulation according to an embodiment of the invention includes a dry particle interferon formulation, as described above, suspended in a non-aqueous, hydrophobic vehicle. Varying amounts of the dry particle interferon formulation may be loaded into the vehicle to provide a formulation that allows dosing of the interferon at a desired rate over a chosen time period. The suspension formulation may include 0.1 to 40 wt%, preferably 0.1 to 20 wt%, of an interferon. The suspension formulation may include greater than 60 wt%, preferably greater than 80 wt%, of the suspension vehicle.

[0036] Suspension formulations according to embodiments of the invention may be formulated for delivery from an implantable drug delivery device or for use as a depot injection. The implantable drug delivery device may be embodied by any such device capable of delivering a flowable formulation at a controlled rate over a sustained period after implantation within a subject. One example of a suitable implantable drug delivery device is an osmotic pump implant, such as available under the trade name DUROS® implant. Non-osmotic pump implants may also be used. The suspension formulation may be formulated for delivery at flow rates up to 5 ml/day, depending on the

biomolecule to be delivered and the implantable drug delivery device used to deliver the suspension formulation. Where the biomolecule is delivered from an osmotic pump implant designed to provide low flow rates, the formulation is preferably formulated for delivery of between 0.5 and 5 μL/day, with flow rates of about 1.5 μL/day and 1.0 μL/day being particularly preferred. In one embodiment, a suspension formulation according to an embodiment of the invention is formulated to deliver interferon from an implanted device in a range from 1 ng/day to 600 μg/day over one month, preferably over three months, more preferably over one year.

[0037] As previously discussed, non-aqueous, hydrophobic vehicles can behave like a depot when released into a hydrophilic medium. This depot effect may or may not be desirable depending on the application. However, where the depot effect is desirable or acceptable, it is important that the biomolecule suspended in the hydrophobic vehicle remains stable in the hydrophobic vehicle in the presence of the hydrophilic medium and during release from the hydrophobic vehicle into the hydrophilic medium.

[0038] The inventors have found that addition of a small amount of surfactant directly into dry particle formulations of the invention and/or into hydrophobic vehicles incorporating the dry particle formulations of the invention can enhance stability of the biomolecules in the dry particle formulations as the dry particle formulations are released from the hydrophobic vehicles into the hydrophilic media. While not wishing to be bound by theory, the inventors believe that addition of the small amount of surfactant directly into the dry particle formulations or suspension vehicles of the invention may have modified the interfacial behavior of the biomolecules in the dry particle formulations, leading to reduction in denaturation and aggregation of the biomolecules as the biomolecules transition from a hydrophobic vehicle into a hydrophilic medium. In particular, the surfactants may have helped to form particles having more hydrophobic excipients on the outside and more hydrophilic excipients on the inside. This biomolecular distribution may have played an important role in biomolecule stability during release from the hydrophobic vehicle into the hydrophilic medium.

[0039] Surfactants that may be incorporated in dry particle formulations and/or suspension vehicles according to embodiments of the invention may be ionic or nonionic. Some examples of surfactants include, but are not limited to, Polysorbate 20, Polysorbate

80, Tweens, Pluronic F68, sodium docecyl sulfate (SDS), Span 20, Span 40, Span 60, Span 80, Vitamin E TPGS, glyceryl caprylate, glyceryl laurate, PEG-8 caprylic capric glycerides, polyglyceryl-6 oleate, Pluronics, and dioctyly sodium sulfosuccinate. Table 2 below shows surfactant loading for dry particle formulations and suspension vehicles according to some embodiments of the invention.

TABLE 2

	Suspension formulation		Surfactant Loading in	
	Suspension Vehicle	Dry particle formulation	Dry particle formulation	Vehicle
Range	> 60 wt%	0.1 to 40 wt%	0.01 to 10 wt%	0.01 to 20 wt%
Preferred Range	> 80 wt%	0.1 to 20 wt%	0.01 to 5 wt%	

[0040] A study was conducted to assess the effect of surfactant on the release of dry particle interferon formulations according to embodiments of the invention from hydrophobic vehicles into hydrophilic release rate media. In the study, the hydrophobic vehicle is SAIB and the hydrophilic release rate medium is phosphate buffer solution. SAIB is a high viscosity, hydrophobic liquid with limited water solubility. It has a viscosity of approximately 3.2 kP at 37°C. SAIB is produced by the controlled esterification of natural sugar (sucrose) with acetic and isobutyric anhydrides. The materials used for the study are listed in Table 3 below.

TABLE 3

MATERIAL	SOURCE
Pluronic F68	BASF
Span 40	Aldrich
Spray dried IFN-ω: Sucrose: Methionine: Citrate (1:2:1:2.15, 25 mM citrate buffer)	
Spray dried IFN-ω: sucrose: Methionine: Citrate: 1% Pluronic F68 (1:2:1:2.15:0.06, 25 mM citrate buffer)	
SAIB	Eastman Chemical Company
Phosphate Buffer Solution (PBS) with 0.2% Na Azide	

EXAMPLE 1

[0041] Solid particles of omega-interferon were obtained by spray drying IFN-ω with sucrose and methionine from 25 mM citrate solution with a solution concentration containing 3.3, 6.6, 3.3 and 7.1 mg/mL of IFN-ω, sucrose, methionine and citrate, respectively to give a final composition of 1:2:1:2.15 (IFN-ω: sucrose: methionine: citrate). The SEM image of the particles is shown in FIG. 1. The average particle size is 6.51 μm.

EXAMPLE 2

[0042] Solid particles of IFN-ω with 1% Pluronic F68 surfactant was obtained by spray drying IFN-ω with sucrose and methionine and Pluronic F68 (Polyethylene oxide-PolyPropylene oxide copolymer) from 25 mM citrate solution with a solution concentration containing 3.3, 6.6, 3.3 7.1 and 0.2 mg/mL of IFN-ω, sucrose, methionine, citrate, and Pluronic F68, respectively to give a final composition of 1:2:1:2.15:0.06 (IFN-ω: sucrose: methionine: citrate: Pluronic F68). Addition of 1% of Pluronic F68 to the IFN-ω/excipient solution was successfully spray dried with a yield of approximately 49% at a batch size of 55 mL (1.1 g solid). The SEM image of the particles is shown in FIG. 2. The particles have a smooth spherical shape. The average particle size is 4.03 μm.

EXAMPLE 3

[0043] Four suspensions (A, B, C, and D) were prepared in the dry box and are listed in Table 4. The appropriate amount of SAIB was weighed and added into a scintillation glass vial. The appropriate amount of surfactant was added into the same vial if specified. The vial was heated to 50°C and hand mixed by a spatula. The appropriate amount of IFN- ω particles (as prepared in Example 1 or 2) was weighed and added into the vial. The vial was heated to 40°C or lower temperature. The suspension was mixed using a spatula.

TABLE 4

	WEIGHT, %	WEIGHT, mg	TOTAL, g
A: Suspension (no surfactant)			
IFN-ω particles	10	150	
SAIB	90	1350	1.5
B: Suspension with 5% Pluronic F68			
IFN-ω particles	10	100	
Pluronic F-68	5	50	
SAIB	85	850	1
C: Suspension with 5% Span-40			
IFN-ω particles	10	100	
Sorbitan monopalmitate (Span-40)	5	50	
SAIB	85	850	1
D: Particles with 1% Pluronic F68 in SAIB	10	100	
IFN-ω particles + 1% Pluronic F68 SAIB	90	900	1

[0044] Stability samples of IFN-ω/SAIB suspension in PBS were obtained by weighing approximately 8 mg of IFN-ω/SAIB suspension into a 5 mL Vacutainer® glass tube and adding 2 mL of PBS to the tube. The samples were stored at 37°C for stability testing. At each stability time point, the sample was taken out from the stability chamber. The liquid was decanted into a HPLC (High Performance Liquid Chromatrogram) vial and was analyzed directly by fast RP-HPLC (Reverse Phase High Performance Liquid Chromatography) method. For the SAIB gel, 0.5 mL of 50% ACN with 0.1% SDS was added into the tube, and the gel was dissolved for 60 minutes, then 2 mL of PBS was added to the tube. The cloudy solution was centrifuged and the liquid layer was transferred into the HPLC vial for fast RP-HPLC analysis. The protein recovery from liquid phase and solid phase and total recovery were calculated.

[0045] Stability samples of IFN-ω/SAIB suspension in implantable device reservoirs in PBS were set up as in Table 5. The samples were analyzed at initial, 3 days and 7 days.

TABLE 5

Formulations (see Table 4)	Stability Sample Prep		Sample Prep for Fast RP-HPLC Assay		
	Suspension (mg)	PBS (mL)	Liquid	Solid (Gel)	
				50% ACN + 0.1% SDS	PBS (mL)
A	8	0		0.5	4
A	8	2	Direct Analysis	0.5	2
B	8	2	Direct Analysis	0.5	2
C	8	2	Direct Analysis	0.5	2
D	8	2	Direct Analysis	0.5	2

[0046] During the release of protein from suspension not all of the protein was instantaneously released into the release rate medium because SAIB is not water soluble. Recovery of the protein from the aqueous phase during select stability time points at 37°C is shown in FIG. 3. For formulation A (IFN-ω/SAIB), fraction of protein recovered after 7 days is about 53%. For formulation B (IFN-ω/SAIB+Pluronic F68), fraction of protein recovered after 7 days is about 73%. For formulation C (IFN-ω/SAIB+Span-40), fraction of protein recovered after 7 days is about 80%. For formulation D (IFN-ω+Pluronic F68/SAIB), fraction of protein recovered after 7 days is about 69%. The results show that addition of surfactants into the SAIB vehicle or dry particle IFN-ω formulation enhanced release of IFN-ω into the aqueous phase after 7 days.

[0047] The total IFN-ω recovered from both aqueous phase and SAIB solid (gel) phase is shown in FIG. 4. For formulation A (without surfactant), the total recovery decreased over time, e.g., average drops of approximately 10% after 3 days and 25% after 7 days in PBS at 37°C were observed. Addition of surfactants into the suspension vehicle or dry particle formulation (formulations B-D) resulted in approximately 90-100% total recovery after about 7 days. The study shows that surfactants can be added into a dry particle IFN-ω formulation or suspension vehicle to enhance release of IFN-ω from the suspension vehicle into release rate medium.

[0048] While the invention has been described with respect to a limited number of embodiments, those skilled in the art, having benefit of this disclosure, will appreciate that other embodiments can be devised which do not depart from the scope of the invention as disclosed herein. Accordingly, the scope of the invention should be limited only by the attached claims.

[0049] A reference herein to a patent document or other matter which is given as prior art is not to be taken as an admission or a suggestion that that document or matter was, known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

[0050] Throughout the description and claims of the specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

The Claims Defining The Invention Are As Follows:

1. A suspension formulation that is deliverable via an implantable delivery device comprising:
a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics; and
a dry particle formulation comprising a biomolecule dispersed in the vehicle;
characterized in that a first surfactant is incorporated in the vehicle and a second surfactant is incorporated in the dry particle formulation.

2. The suspension formulation of claim 1, wherein the hydrophobic vehicle is non-polymeric.

3. The suspension formulation of claim 2, wherein the hydrophobic vehicle comprises substantially sucrose acetate isobutyrate.

4. The suspension formulation of any one of claims 1 to 3, wherein the biomolecule is an interferon.

5. The suspension formulation of claim 4, formulated to deliver the interferon from an implantable drug delivery device at 1 ng/day to 600 μg/day over at least one month.

6. The suspension formulation of any one of claims 1 to 5, wherein the biomolecule is an interferon omega.

7. The suspension formulation of any one of claims 1 to 6, wherein the biomolecule is spray dried with the surfactant.

8. The suspension formulation of any one of claims 1 to 7, wherein the dry particle formulation further comprises one or more stabilizers and a buffer.

9. The suspension formulation of claim 8, wherein the stabilizers are selected from the group consisting of carbohydrate, antioxidant, and amino acid.

10. The suspension formulation of any one of claims 1 to 9, wherein the hydrophobic vehicle is present in an amount greater than 60 wt%.

11. The suspension formulation of any one of claims 1 to 9, wherein the dry particle formulation is present in a range from 0.01 to 40 wt%.

12. The suspension formulation of any one of claims 1 to 9, wherein a surfactant loading in the dry particle formulation is in a range from 0.01 to 10 wt%.

13. The suspension formulation of any one of claims 1 to 9, wherein a surfactant loading in the vehicle is in a range from 0.01 to 20 wt%.

14. An implantable delivery device comprising:

a suspension formulation comprising a non-aqueous, hydrophobic vehicle exhibiting viscous fluid characteristics and a dry particle formulation comprising an interferon dispersed in the vehicle, characterized in that a first surfactant is incorporated in the vehicle and a second surfactant is incorporated in the dry particle formulation; and

a reservoir containing the suspension formulation in an amount sufficient to provide continuous delivery of the interferon in a therapeutically effective dose in an environment of use over at least one month.

15. A method of enhancing release of interferon omega in a hydrophilic release rate medium, comprising:

suspending a dry particle formulation of interferon omega in a non-aqueous, non-polymeric, hydrophobic vehicle; and

incorporating a first surfactant in the dry particle formulation and a second surfactant in the hydrophobic vehicle.

16. A suspension formulation of claim 1, substantially as hereinbefore described with reference to the Figures and/or Examples.

17. An implantable delivery device of claim 14, substantially as hereinbefore described with reference to the Figures and/or Examples.

18. A method of claim 15, substantially as hereinbefore described with reference to the Figures and/or Examples.

FIG. 1

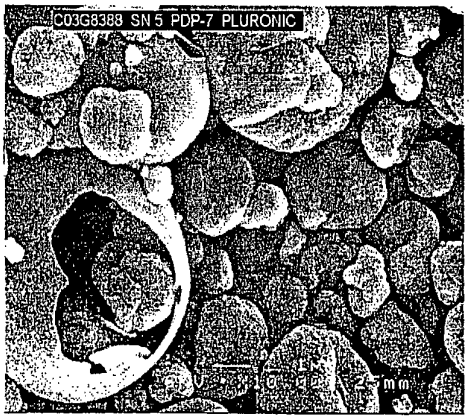

FIG. 2

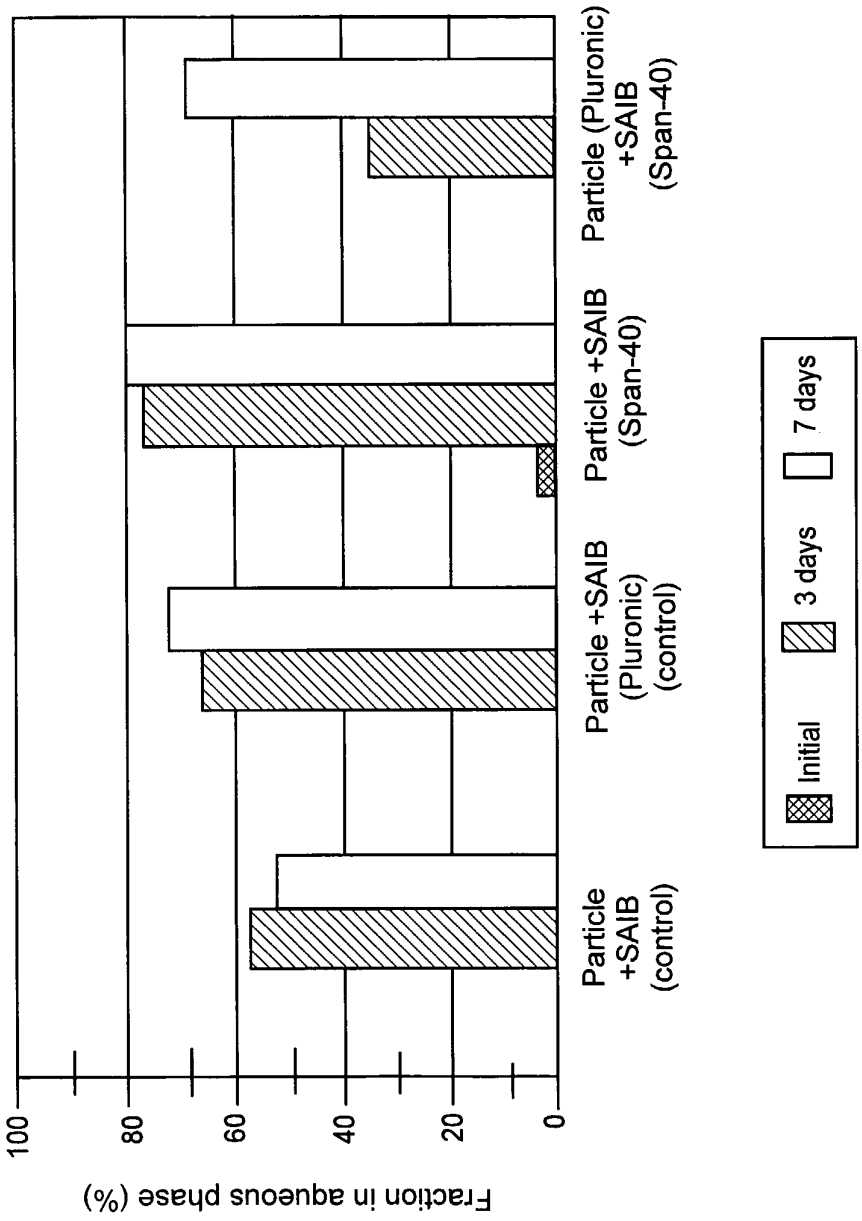
Fraction in aqueous phase (%)
0
20
40
60
80
100
Particle +SAIB (control)
Particle +SAIB (Pluronic) (control)
Particle +SAIB (Span-40)
Particle (Pluronic) +SAIB (Span-40)
Initial
3 days
7 days

FIG. 3

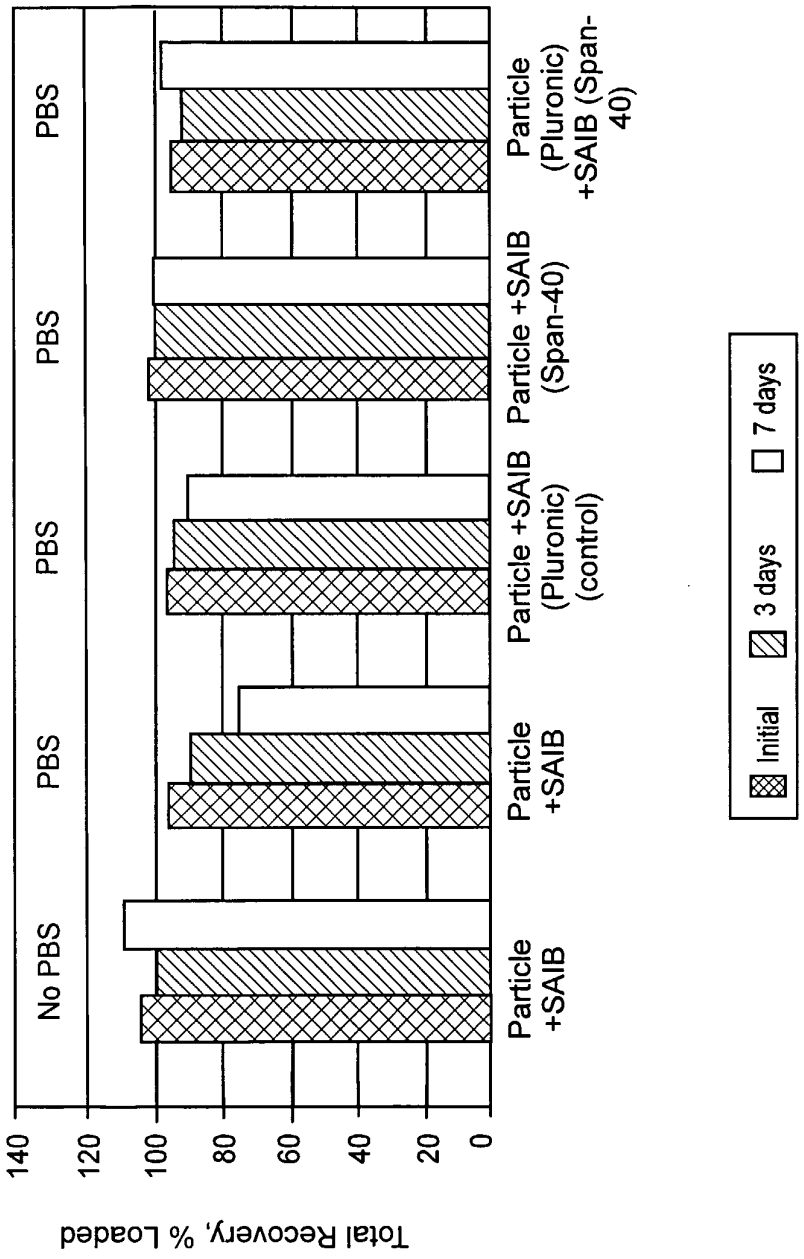
Total Recovery, % Loaded
140
120
100
80
60
40
20
0
No PBS
PBS
PBS
PBS
PBS
Particle +SAIB
Particle +SAIB
Particle +SAIB (Pluronic) (control)
Particle +SAIB (Span-40)
Particle (Pluronic) +SAIB (Span-40)
Initial
3 days
7 days

FIG. 4