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(54) **Titre : SUSPENSIONS SOUS-MICRONIQUES PHARMACEUTIQUES STABILISEES ET LEURS PROCEDES DE FORMATION**
(54) **Title: STABILIZED PHARMACEUTICAL SUB-MICRON SUSPENSIONS AND METHODS OF FORMING SAME**

(57) **Abrégé/Abstract:**
The present invention is directed to a pharmaceutical submicron suspension and a method of forming the submicron suspension. The submicron suspension may be useful for delivery of a relatively hydrophobic and/or low solubility therapeutic agent. The submicron suspension and method of forming the submicron suspension typically employ a polymeric material that aids in preventing aggregation of the therapeutic agent.

Abstract

The present invention is directed to a pharmaceutical submicron suspension and a method of forming the submicron suspension. The submicron suspension may be useful for delivery of a relatively hydrophobic and/or low solubility therapeutic agent. The submicron suspension and method of forming the submicron suspension typically employ a polymeric material that aids in preventing aggregation of the therapeutic agent.

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STABILIZED PHARMACEUTICAL SUB-MICRON SUSPENSIONS AND METHODS OF FORMING SAME

Technical Field of the Invention

The present invention is related to pharmaceutical submicron suspensions that employ low molecular weight polymers for stabilization. More specifically, the present invention relates to pharmaceutical submicron suspensions that employ low molecular weight charged polymers for stabilizing a therapeutic agent while that agent is formed into submicron particles and/or while that therapeutic agent exists as submicron particles within the submicron suspension.

Background of the Invention

For many years, the pharmaceutical industry has been developing compositions that include therapeutic agents as well as systems and/or vehicles suitable for delivery of those therapeutic agents. In the ophthalmic, otic and nasal fields, a great deal of energy has been expended in developing fluid pharmaceutical compositions, particularly aqueous solutions, that include systems and/or vehicles suitable for delivery of therapeutic agents to the eye, ear or nose. During such development, many problems and difficulties can be encountered.

As one example, many therapeutic agents that exhibit desired therapeutic properties may also exhibit one or more properties that cause difficulty in developing pharmaceutical vehicles for delivering those agents. For instance, therapeutic agents can exhibit relatively high degrees of hydrophobicity and are formulated as suspensions, which can cause those agents to undesirably aggregate within an aqueous solution. In turn, the overall suspension can lack homogeneity and can, consequently, deliver inconsistent amounts of therapeutic agent to a target.

In efforts to accommodate these undesirable properties, many materials such as surfactants have been added to pharmaceutical vehicles with the objective of developing new stabilization systems. However, more recent discoveries have shown that many of these new systems can lack biocompatibility and can cause irritation or other undesirable effects to human tissue.

In further efforts to accommodate undesirable properties of therapeutic agents, ophthalmic, otic and nasal pharmaceutical compositions have been developed as suspensions. Suspensions can be particularly effective at accommodating therapeutic agents, which exhibit properties such as hydrophobicity, relative water insolubility or the like. However, therapeutic agents delivered as suspensions can also exhibit relatively poor therapeutic activity when delivered to target human tissue.

One way to increase activity of a therapeutic agent is to increase the surface area of that agent. For example, it has been found that providing a therapeutic agent as submicron particles or nanoparticles can increase the surface area of the therapeutic agent and can exhibit significantly increased activity relative to that same therapeutic agent when it is provided as larger particles. It has also been found that such submicron particles can exhibit increased activity when delivered as part of submicron suspensions. However, formation of submicron suspensions can be difficult. For instance, it can be difficult to find suitable materials (e.g., milling agents) to assist in the formation of the submicron particles because such materials typically need to exhibit one or more desirable properties (e.g., wetting ability and/or low foaming) during submicron particle formation and will ultimately also need to exhibit one or more additional desirable properties (e.g., stability and/or biocompatibility) when they ultimately become part of the submicron suspension.

In view of the above, it would be desirable to provide a pharmaceutical submicron suspension (particularly a submicron ophthalmic suspension), a method of forming that suspension and/or materials suitable for forming that suspension, which overcome one or more of the aforementioned difficulties, problems and drawbacks.

Summary of the Invention

The present invention is directed to a sub-micron suspension and a process of forming the sub-micron suspension.

In an embodiment, the present invention relates to an ophthalmic aqueous pharmaceutical submicron suspension, comprising: a hydrophobic therapeutic agent that is formed of submicron particles, wherein the therapeutic agent has a log D greater than 0.1; a low molecular weight charged polymer, wherein the low molecular weight charged polymer includes one or more cellulose polymers that by itself or cooperatively have an average molecular weight that is less than 200,000 kilodaltons (kDa) and wherein the low molecular weight charged polymer has an average degree of polymerization (DP) that is at least 100 and is up to 4,000; and one or more excipients, wherein i) the low molecular weight charged polymer inhibits the aggregation of the submicron particles within the suspension; and ii) the submicron particles have an average or mean hydrodynamic radius that is less than 1 micron.

In another embodiment, the present invention relates to a suspension as described herein wherein the suspension is an ophthalmic suspension suitable for administration to the eye of a human.

In preferred embodiments, the therapeutic agent is a receptor tyrosine kinase inhibitor (RTKi) or a non-steroidal anti-inflammatory agent (NSAID) (e.g., nepafenac). Also in preferred embodiments, the low molecular weight charged polymer is substantially entirely or entirely carboxymethylcellulose.

Detailed Description of the Invention

The present invention is predicated upon the formation of a pharmaceutical composition and particularly a submicron suspension that includes a therapeutic agent in the form of submicron particles and includes a polymeric material (e.g., a charged polymer) that assists in stabilizing the therapeutic agent within the submicron suspension. The polymeric material can also be used to stabilize the therapeutic agent as relatively large particles of therapeutic agent are reduced to submicron or even nano-particles using one or more processing machines. It is contemplated that the pharmaceutical submicron suspension may be applicable in a variety of pharmaceutical contexts but may be particularly useful for otic and nasal

applications. Thus, it is contemplated that the submicron suspension may be applied topically within the ear or nose of a mammal, particularly a human being. Most preferably, however, the submicron suspension is an ophthalmic suspension that may be applied topically or intravitreally to the eye of a human being.

As used herein the term "stabilize" and its conjugations as those terms are used in reference to the polymeric material stabilizing the therapeutic agent at least mean that the polymeric material inhibits the agglomeration of the particles of the therapeutic agent. As used herein, the term "submicron" as it is used to refer to particles means that the particles have a size that is less than one micron, however such particles can also have a size that is no greater than 850 nanometers and even possibly no greater than 700 nanometers. A submicron suspension is a suspension containing such particles suspended in solution. As used herein, the term "nanoparticle" means a particle having a size that is no greater than 200 nanometers, however such particles can also have a size that is no greater than 70 nanometers and even possibly no greater than 50 nanometers. A nanosuspension is a suspension containing such nanoparticles suspended in solution and a submicron suspension of the present invention can be a nanosuspension if the suspended particles are small enough.

Unless otherwise stated, particle size is determined by machine calculation. Several measurement machines are commercially available for measuring particle size within very small tolerances. Such machines measure particle size by, for example, dynamic light scattering and then calculate average or mean particle hydrodynamic radius for a set of particle. Those average or mean particle radii are, unless otherwise stated, the particle sizes discussed herein. One preferred exemplary machine is a ZETASIZER NANO, which is commercially available from Malvern Instruments Ltd., Enigma Business Park, Grovewood Road, Worcestershire WR14 1XZ, United Kingdom.

Measurement with particle sizing machines can require that certain parameters be provided to the machine prior to measurement of particle size in suspensions or other solutions. If required, parameters can be determined as follows: viscosity at zero shear rate (η_0) of a solution can be determined by oscillometer viscometer; refractive index of the particles (RI_p) can be determined using the Becke Line Microscopic method; the refractive index of any diluent (RI_d) can be determined with a refractometer; and dielectric constant (κ) can be determined by capacitance measurements. As a general rule, it is preferable for the

particle size measurement to be determined using solutions having relatively high concentrations of particles before multiple scattering and particle interactions affect the result.

Unless otherwise indicated, percentages provided for the ingredients of the pharmaceutical composition of the present invention are weight/volume (w/v) percentages.

Therapeutic Agent

Typically, the submicron suspension of the present invention includes therapeutic agent. The therapeutic agent may be a single therapeutic agent or may be comprised of multiple therapeutic agents. Therapeutic agents include, but are not limited to, any component, compound, or small molecule that can be used to bring about a desired therapeutic effect. For example, a desired effect may include the cure, mitigation, treatment, or prevention of a disease or condition. A therapeutic agent may also affect the structure or function of a body part or organ in a subject.

Generally it is preferred that the therapeutic agent include at least one hydrophobic drug or therapeutic agent. A hydrophobic therapeutic agent includes an agent that is sparingly soluble in aqueous media (e.g., not completely dissolved in the media at the concentration at which it is administered in an aqueous composition) particularly when immersed in such aqueous media without aids to assist in solubilizing the agent. The therapeutic agent is typically at least about 0.001, more typically at least about 0.01 and still more typically at least about 0.1 w/v% of the submicron suspension. The therapeutic agent is typically less than about 10, more typically less than about 5 and still more typically less than about 2.0 w/v% of the submicron suspension.

The therapeutic agent of the present invention is preferably a solid in particle form. However, it is also contemplated that therapeutic agent, such as therapeutic agent in liquid form, could be adsorbed by or otherwise disposed upon particles (e.g., polymeric particles) for use in the present invention.

A preferred class of therapeutic agents includes ophthalmic, otic and nasal drugs, particularly hydrophobic and/or low solubility ophthalmic, otic and nasal drugs. Non-limiting examples include: anti-glaucoma agents, anti-angiogenesis agents; anti-infective agents; anti-inflammatory agents; growth factors; immunosuppressant agents; and anti-allergic agents. Anti-glaucoma agents include

beta-blockers, such as betaxolol and levobetaxolol; carbonic anhydrase inhibitors, such as brinzolamide and dorzolamide; prostaglandins, such as travoprost, bimatoprost, and latanoprost; seretonergics; muscarinics; dopaminergic agonists. Anti-angiogenesis agents include anecortave acetate (RETAANE™, Alcon™ Laboratories, Inc. of Fort Worth, Tex.) and receptor tyrosine kinase inhibitors. Anti-inflammatory agents include non-steroidal and steroidal anti-inflammatory agents, such as triamcinolone actinide, suprofen, diclofenac, ketorolac, nepafenac, rimexolone, and tetrahydrocortisol. Growth factors include EGF or VEGF. Anti-allergic agents include olopatadine and epinastine. The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt.

The submicron suspension of the present invention has been found to be particularly desirable for ophthalmic applications (e.g., topical or intravitreal) when the therapeutic agent includes, is substantially entirely or is entirely receptor tyrosine kinase inhibitor (RTKi). Thus, in one preferred embodiment, the therapeutic agent may be at least 50%, more typically at least 80% and even more typically at least 95% (e.g., 100%) by weight RTKi.

The preferred RTKi contemplated for use in the present invention is a multi-targeted receptor tyrosine kinase inhibitor. Most preferred are RTKi's with multi-target binding profiles, such as N-[4-(3-amino-1H-indazol-4-yl) phenyl]-N'-(2-fluoro-5-methylphenyl) urea, having the binding profile substantially similar to that listed in Table 1 below. Additional multi-targeted receptor tyrosine kinase inhibitors contemplated for use in the compositions of the present invention are described in U.S. application Ser. No. 2004/0235892. As used herein, the term "multi-targeted receptor tyrosine kinase inhibitor" refers to a compound having a receptor binding profile exhibiting selectivity for multiple receptors shown to be important in angiogenesis, such as the profile shown in Table 1, and described in co-pending U.S. application Ser. No. 2006/0189608. More specifically, the preferred binding profile for the multi-targeted receptor tyrosine kinase inhibitor compounds for use in the compositions of the present invention is KDR (VEGFR2), Tie-2 and PDGFR.

TABLE 1

Kinase Selectivity Profile of a RTK Inhibitor

KDR	FLT1	FLT4	PDGFR	CSF1R	KIT	FLT3	TIE2	FGFR	EGFR	SRC
4	3	190	66	3	14	4	170	>12,500	>50,000	>50,000

All data reported as IC50 values for kinase inhibition in cell-free enzymatic assays. Values determined @ 1 mM ATP.

Another highly preferred therapeutic agent suitable for use in suspensions of the present invention is, without limitation, a non-steroidal anti-inflammatory agent. The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthesis inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A. CT-2820, PD-168787, CP-293121 DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents known to those skilled in the art. Preferred compounds for use as a prostaglandin synthesis inhibitor in the compositions or methods of the present invention are phenylacetamides selected from 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, of which the most preferred is nepafenac.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation. The concentrations should be those which are sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount

is referred to herein as "an anti-inflammatory effective amount". The compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of from about 0.01 to about 3.0 w/v%, more typically from about 0.05 to about 1.0 w/v% and still more typically from about 0.08 to about 0.5 w/v%.

As suggested, it is preferable for the therapeutic agent (e.g., RTKi or NSAID such as nepafenac) suspended in the suspensions of the present invention to be hydrophobic. As such, the therapeutic agent typically has a log D that is greater than 0.1, more preferably greater than 0.4, more preferably greater than 0.6 and even possibly greater than 1.0 or even greater than 1.5.

As used herein, log D is the ratio of the sum of the concentrations of all forms of the therapeutic agent (ionized plus un-ionized) in each of two phases, an octanol phase and a water phase. For measurements of distribution coefficient, the pH of the aqueous phase is buffered to 7.4 such that the pH is not significantly perturbed by the introduction of the compound. The logarithm of the ratio of the sum of concentrations of the solute's various forms in one solvent, to the sum of the concentrations of its forms in the other solvent is called Log D:

$$\log D_{oct/wat} = \log ([solute]_{octanol} / ([solute]_{ionized\ water} + [solute]_{neutral\ water}))$$

Other agents which may be useful in the suspension and methods of the invention include anti-VEGF antibody (i.e., bevacizumab or ranibizumab); VEGF trap; siRNA molecules, or a mixture thereof, targeting at least two of the tyrosine kinase receptors having IC_{50} values of less than 200 nM in Table 1; glucocorticoids (i.e., dexamethasone, fluoromethalone, medrysone, betamethasone, triamcinolone, triamcinolone acetonide, prednisone, prednisolone, hydrocortisone, rimexolone, and pharmaceutically acceptable salts thereof, prednicarbate, deflazacort, halomethasone, tixocortol, prednylidene (21-diethylaminoacetate), prednival, paramethasone, methylprednisolone, meprednisone, mazipredone, isoflupredone, halopredone acetate, halcinonide, formocortal, flurandrenolide, fluprednisolone, flupredнidine acetate, fluperolone acetate, fluocortolone, fluocortin butyl, fluocinonide, fluocinolone acetonide, flunisolide, flumethasone, fludrocortisone, fluclorinide, enoxolone, difluprednate, diflucortolone, diflorasone diacetate, desoximetasone (desoxymethasone), desonide, descinolone, cortivazol, corticosterone, cortisone, cloprednol, clocortolone, clobetasone, clobetasol,

chloroprednisone, cafestol, budesonide, beclomethasone, amcinonide, allopregnane acetonide, alclometasone, 21-acetoxypregnenolone, tralonide, diflorasone acetate, deacylcortivazol, RU-26988, budesonide, and deacylcortivazol oxetanone); Naphthohydroquinone antibiotics (i.e., Rifamycin).

Polymeric Material

Multiple polymers may be part of the polymeric material of the present invention. Examples of potentially suitable polymers include, without limitation, chondroitin sulfate, low molecular weight hyalouronic acid or other low molecular weight charged polymers that have a desired ability to lower or reduce surface tension. It is also contemplated that the submicron suspension of the present application may include polymers in addition to or not included as part of the polymeric material. Examples of potentially suitable additional polymers include, without limitation, polyols, NIPAM polymers, polyethylene glycol, combinations thereof or the like.

Typically, however, the polymeric material will be comprised of one or more low molecular weight polymers, which are preferably charged. As used herein, the phrase "low molecular weight" as it is used to describe polymers of the polymeric material means that those polymers of the polymeric material cooperatively have an average molecular weight that is less than 500,000, more typically less than 200,000 and even more typically less than 100,000 kilodaltons (kDa). The viscosity of a solution of 1% polymeric material in purified water is typically at least 3.0, more typically at least 4.5 and still more typically at least 6.0 centipoise at 25 °C and the viscosity of that solution is typically less than about 100, more typically less than about 20 and even more typically less than about 8.0 centipoise at 25 °C.

Cellulose polymers such as carboxymethyl cellulose (CMC) polymers are particularly desirable for the polymeric material of the submicron suspension. As used herein, cellulose polymer includes any polymer that has two or more groups according to the formula ($C_6H_{10}O_5$). Such polymers can be charged when they are in salt form. Particularly desirable cellulose polymers are salts carboxymethyl cellulose polymer such as sodium carboxymethyl cellulose. Sodium carboxymethyl cellulose suitable for use in the present invention has a degree of substitution (DS) of at least 0.2 and preferably at least about 0.5. The degree of substitution of the sodium carboxymethyl cellulose can be up to about 2.5,

preferably up to about 0.9. The degree of polymerization (DP) of the sodium carboxymethylcellulose is at least about 100, preferably at least about 200. The sodium carboxymethylcellulose degree of polymerization can be up to about 4,000, preferably up to about 1,000. One exemplary suitable cellulose polymer is sodium carboxymethyl cellulose is sold under the tradename AQUALON 7L2P and 7LF CMC, which is commercially available from Hercules Inc.

The submicron suspension of the present invention has been found to be particularly desirable for ophthalmic applications (e.g., topical or intravitreal) when the polymeric material includes, is substantially entirely or is entirely cellulose polymer (e.g., salt cellulose polymer such as sodium carboxymethylcellulose). Thus, the polymeric material may be at least 50%, more typically at least 80% and even more typically at least 95% (e.g., 100%) by weight cellulose polymer (e.g., salt cellulose polymer such as sodium carboxymethylcellulose).

Additional Ingredients

Various additional ingredients may be included in the sub-micron suspension of the present invention. The sub-micron suspensions of the present invention are typically aqueous and typically include a substantial amount (e.g., at least 80 or 90 w/v%) of water. The inclusion of other additional ingredients will typically depend upon how the submicron suspension is to be administered.

If the submicron suspension is to be administered topically to the eye or other human tissue, then the suspension may typically include a variety of additional ingredients. Such ingredients include, without limitation, additional therapeutic agents, antimicrobials, suspension agents, surfactants, tonicity agents, buffering agents, anti-oxidants, viscosity-modifying agents, any combinations thereof or the like.

If the submicron suspension is to be administered within the body, particularly intravitreally, by injection (e.g., needle) or otherwise, then it is typically desirable to minimize the amount of additional ingredients included in the submicron suspension. In such instance, it may be the case that the submicron suspension consists of or consists essentially of only the following ingredients: the polymeric material; the therapeutic agent and water.

Processing

The submicron suspension can be formed according to a variety of techniques within the scope of the present invention. According to a preferred protocol, the submicron suspension is formed using the following steps: i) the therapeutic agent is mixed as particles with the polymeric material and possibly excipients to form an admixture; ii) the admixture is supplied to a machine (e.g., a milling machine) that is configured to lower the particle size of the therapeutic agent; and iii) the admixture is combined with water and possibly excipients to form the submicron suspension.

The amounts of polymeric material and therapeutic agent in the admixture can vary and can depend upon the processing to be used for the admixture. However, it is generally preferable that the admixture be aqueous such that the polymeric material and therapeutic agent are added to water. In preferred embodiments, and particularly in embodiments that include a substantial portion of RTKi as therapeutic agent and a substantial portion of cellulose polymer as the polymeric material, the weight ratio of therapeutic agent to polymeric material is typically in a range from about 10:1 to about 1:10, more typically from about 5:1 to about 1:4 and even more typically from about 1.5:1 to about 1:1. In such embodiments, the admixture will typically include at least about 0.5, more typically at least about 1.5 and even more typically at least about 3.0 w/v% and will typically include less than about 12, more typically less than about 8 and even more typically less than about 4.0 w/v% therapeutic agent. Furthermore, in such embodiments, the admixture will typically include at least about 0.5, more typically at least about 1.2 and even more typically at least about 2.5 w/v% and will typically include less than about 12, more typically less than about 7 and even more typically less than about 3.8 w/v% polymeric material.

Examples of machines for lowering particle size include, without limitation, machines that perform high pressure homogenization and/or high-shear mixing. A preferred machine for lowering the particle size of the therapeutic agent is a wet milling machine. Such a machine can include a chamber filled with milling beads that are typically from about 0.05 mm to about 1 mm (e.g., 0.2 mm) in diameter. The chamber can then be rotated at a speed that is typically from about 2000 to about 4000 revolutions per minute (RPM). One exemplary suitable wet milling machine is a MINICER High Grinding System, commercially available from Netzsche Fine Particle Technology, Exton, PA, USA. It should be understood that

the particles may need to be machined (e.g., milled) multiple times before the desired submicron or nano- particle size is achieved.

The particles of the therapeutic agent, prior to machining or processing, typically have an average particle size that is greater than 500 nanometers, more typically greater than 1.0 micron and even more typically greater than about 1.3 microns. After machining or otherwise processing the particles, the particles either become submicron particles or become smaller submicron particles with a particle size that is less than about 900 nanometers, more typically less than about 820 nanometers and even more typically less than about 730 nanometers. For certain embodiments (e.g., for RTKi therapeutic agent), it may be desirable for the particle size of the therapeutic agent, after machining, to be greater than a particular size (e.g., nanoparticle size) with the aim of providing a therapeutic effect over an extended period of time for the agent. Thus, the submicron particles can have a size greater than about 200 nanometers, more typically greater than about 350 nanometers and even possibly greater than about 400 nanometers. In still other embodiments where it is desirable for the delivery of a greater therapeutic effect over a shorter period of time, it may desirable for the therapeutic agent to be still smaller after machining. In such embodiment, the submicron particles can have a particles size that is less than about 200 nanometers, more typically less than about 150 nanometers and even more possibly less than about 100 nanometers.

For other therapeutic agents, particularly NSAIDS such as nepafenac, the average particle size may be different. Such particle size is typically at least about 50 nanometers, more typically at least about 200 nanometers and even more typically at least about 250 nanometers. Such particle size is typically less than 820 nanometers, more typically less than 500 nanometers and even more typically less than 350 nanometers.

At some point before, during or after the processing of the therapeutic agent to achieve smaller particle size, excipients and/or active agents are added to the therapeutic agent, the polymeric material, the admixture thereof or a combination thereof for forming the submicron suspension. Thus, it is contemplated that excipients or additional active agents can be added before or after the polymeric material is combined with the therapeutic agent, before or after the particle size has been reduced or at any time during the processing. In a preferred step, the admixture is further diluted, preferably with purified water, after the desired particle size has been achieved such that final weight volume percents of polymeric

material and therapeutic agent are achieved for the submicron suspension. At completion, the submicron suspension will typically include at least about 0.1, more typically at least about 0.5 and even more typically at least about 1.0 w/v% and will typically include less than about 7, more typically less than about 5 and even more typically less than about 2.5 w/v% therapeutic agent. Also, the submicron suspension will typically include at least about 0.1, more typically at least about 0.5 and even more typically at least about 1.0 w/v% and will typically include less than about 7, more typically less than about 5 and even more typically less than about 2.5 w/v% polymeric material.

Advantageously, the polymeric material of the present invention provides an aid to processing (e.g., machining such as milling) of the therapeutic agent into submicron particles and, at the same time, tends to inhibit aggregation of the particles of therapeutic agent and/or tends to exhibit a relatively low degree of foaming during such processing. Moreover, the polymeric material can act to inhibit aggregation of the submicron particles in the submicron suspension. Without being bound by theory, it is believed that the charge of the low molecular weight charge polymer assists in closely associating the polymer with the therapeutic agent, which is typically oppositely charged. In turn, this association is believed to assist in preventing agglomeration of the therapeutic agent. As an added advantage, the polymeric material of the present invention tends to be biocompatible.

As used herein, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and

examples be considered as exemplary only with a true scope of the invention being indicated by the following claims.

Experiments and Comparative Examples

For determining the effect on aggregation of particles, a submicron suspension that included RTKi and Carboxy Methyl Cellulose (CMC) was prepared according to the teachings of the present invention. In particular, an admixture of water, CMC and RTKi were milled using a MicroCer Netzch High Energy Grinding System. Then, additional water was added to the admixture to form the submicron suspension as a 4 centipoise solution. The particle size within the submicron suspension was measured shortly after formation of the suspension. Thereafter, the submicron suspension was refrigerated and then the particle size was again measured at one week, six weeks and eight weeks after formation of the suspension. Each of these measurements was performed using a ZETASIZER NANO particle size measurement machine, commercially available from Malvern Instruments. The results are in Table A which are shown in conjunction with polydispersity index (Pd I) as follows:

Storage Time	Particle	Size
	Z-average, nM	Pd I
Initial	110	0.275
6 Weeks	99	0.295
8 Weeks	100	0.279
18 Weeks	99	0.297
20 Weeks	102	0.344

TABLE A

As can be seen, there is no significant changes in particle size. This suggests that little or no agglomeration of particles has occurred at each of the time intervals. In particular, the measurement machine used to measure particle size produces larger particle size measurements when particles agglomerate. Since the measure of particle size in Table A remained substantially unchanged, the particles within the submicron suspension did not significantly agglomerate in the time intervals indicated. It should be noted that the particle size in Table A may not be exact depending on the accuracy of the inputs to the particle size measurement machine, however, the low degree of change in sizes is still quite reflective of the

low agglomeration level since the inputs to the particle size measurement machine were consistent for subsequent measurements of the same solution.

Experiments were also performed on a variety of different potential milling aids and compared to CMC.

Milling Aid %	Level of Foaming	Submicron suspension Homogeneity
Sodium CMC, 0.8 - 2.0%	Very Low	High Homogeneity
Polysorbate (PS) 80, 0.2%	Intermediate	High Homogeneity
Polystyrene Sulfonic Acid (PSSA), 4%	Low	Non-Homogeneous, Non-Wetting
PSSA 3.5%/PS 80 0.2%	Intermediate	High Homogeneity
Hyalouronic Acid, Na Salt, 0.7%	High	Non-Homogeneous
Polyvinyl pyrrolidone, 0.6%	Intermediate	Non-Homogeneous

TABLE B

As can be seen, CMC minimizes foaming and provides for a desirable level of wetting.

For further determining the effect on aggregation of particles, Nepafenac and Carboxy Methyl Cellulose (CMC) were milled using a High Energy Grinding System. Then other ingredients were added to form the ophthalmic suspension in table C:

Nepafenac	0.3
Sodium Carboxymethycellulose 7LF	0.06
Carbopol 974P	0.5
Sodium Chloride	0.4
Propylene glycol	1.1
Benzalkonium Chloride	0.01
Disodium Edetate	0.01
NaOH/HCl	pH to 7.4
Purified water	Qs to 100%

TABLE C

The submicron suspension was monitored as a function of time up to 13 weeks at 25 and 40 °C. The particle size was evaluated by dynamic light scattering (Zatasizer) and reported below. The particle size is not siginificantly changed up to 13 weeks at either temperatures.

	Storage Condition	Mean Particle Size (nm)
Initial	-	586
4 week	40 °C	667
4 week	25 °C	643
13 week	40 °C	564
13 week	25 °C	565

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CLAIMS:

1. An ophthalmic aqueous pharmaceutical submicron suspension, comprising:

a hydrophobic therapeutic agent that is formed of submicron particles, wherein the therapeutic agent has a log D greater than 0.1;

a low molecular weight charged polymer, wherein the low molecular weight charged polymer includes one or more cellulose polymers that by itself or cooperatively have an average molecular weight that is less than 200,000 kilodaltons (kDa) and wherein the low molecular weight charged polymer has an average degree of polymerization (DP) that is at least 100 and is up to 4,000; and

one or more excipients, wherein

i) the low molecular weight charged polymer inhibits the aggregation of the submicron particles within the suspension; and

ii) the submicron particles have an average or mean hydrodynamic radius that is less than 1 micron.

2. A suspension as in claim 1 wherein the therapeutic agent is an RTKi or an NSAID.

3. A suspension as in claim 1 or 2 wherein the low molecular weight charged polymer is substantially entirely or entirely carboxymethylcellulose.

4. A suspension as in any one of claims 1-3 wherein the one or more excipients include water.

5. A suspension as in any one of claims 1-4 wherein the therapeutic agent has a log D greater than 0.6.

6. A suspension as in any one of claims 1-5 wherein the viscosity of a solution of 1% of the low molecular weight charged polymer in purified water is at least 4.2 centipoise at 25 °C and the viscosity of that solution is less than about 20 centipoise at 25 °C.

7. A suspension as in any one of claims 1-6 wherein the therapeutic agent has a log D greater than 1.0.

8. A suspension as in any one of claims 1-7 wherein the average degree of polymerization is at least 200.

9. A suspension as in any one of claims 1-8 wherein the average degree of polymerization is up to 1000.

10. A suspension as in any one of claims 1-9 wherein the therapeutic agent is nepafenac.

11. A suspension as in claim 10 comprising 0.3 w/v% nepafenac.

12. A suspension as in claim 10 or 11 wherein the low molecular weight charged polymer is substantially entirely or entirely sodium carboxymethylcellulose 7LF.

13. A suspension as in claim 12 comprising 0.06 w/v% sodium carboxymethylcellulose 7LF.

14. A suspension as in any one of claims 1-13 wherein the suspension is an ophthalmic suspension suitable for administration to the eye of a human.

15. A suspension as in claim 14 wherein the suspension is formulated as an intravitreal injection.

16. A method of forming an ophthalmic aqueous pharmaceutical submicron suspension, the method comprising:

providing a hydrophobic therapeutic agent in the form of particles, wherein the particles have an average or mean hydrodynamic radius of at least 1 micron and wherein the therapeutic agent has a log D greater than 0.1;

combining the particles of therapeutic agent with a low molecular weight charged polymer to form an admixture, wherein the low molecular weight charged polymer includes one or more cellulose polymers that by itself or cooperatively have an average molecular weight that is less than 200,000 kilodaltons (kDa);

processing the admixture to transform the particles of therapeutic agent into submicron particles of the therapeutic agent, the submicron particles of therapeutic agent having an average or mean hydrodynamic radius of less than 900 nanometers wherein the step of processing the admixture includes wet milling of the admixture; and

combining the admixture with one or more excipients thereby forming the pharmaceutical submicron suspension, wherein the low molecular weight charged polymer inhibits the aggregation of the particles and submicron particles during the processing or upon formation of the suspension.

17. A method as in claim 16 wherein the therapeutic agent is an RTKi or an NSAID.

18. A method as in claim 16 or 17 wherein the low molecular weight charged polymer is carboxymethylcellulose.

19. A method as in claim 16, 17 or 18 wherein the therapeutic agent has a log D greater than 0.6.

20. A method as in any one of claims 16-19 wherein the wet milling of the admixture occurs multiple times.

21. A method as in any one of claims 16-20 wherein the one or more excipients include water.

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22. A method as in any one of claims 16-21 wherein the therapeutic agent has a log D greater than 1.0.

23. A method as in any one of claims 16-22 wherein the therapeutic agent is nepafenac.

24. A method as in claim 23 wherein the suspension comprises 0.3 w/v% nepafenac.

25. A method as in claim 23 or 24 wherein the low molecular weight charged polymer is substantially entirely or entirely sodium carboxymethylcellulose 7LF.

26. A method as in claim 25 wherein the suspension comprises 0.06 w/v% sodium carboxymethylcellulose 7LF.

27. A method as in any one of claims 16-26 wherein the suspension is an ophthalmic suspension suitable for administration to the eye.

28. A method as in claim 27 wherein the suspension is formulated as an intravitreal injection.