



(86) **Date de dépôt PCT/PCT Filing Date:** 2009/10/21
(87) **Date publication PCT/PCT Publication Date:** 2011/04/28
(45) **Date de délivrance/Issue Date:** 2018/11/20
(85) **Entrée phase nationale/National Entry:** 2012/04/12
(86) **N° demande PCT/PCT Application No.:** US 2009/005732
(87) **N° publication PCT/PCT Publication No.:** 2011/049547

(51) **Cl.Int./Int.Cl.** **A61K 31/327** (2006.01),
A61K 9/10 (2006.01), **A61P 17/10** (2006.01),
B01F 17/00 (2006.01), **C07C 409/34** (2006.01)
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(54) **Titre :** PROCEDE POUR MOUILLAGE D'UNE POUDRE CONTENANT DU PEROXYDE DE BENZOYLE
(54) **Title:** METHOD FOR WETTING A POWDER CONTAINING BENZOYL PEROXIDE

(57) **Abrégé/Abstract:**

Powder containing benzoyl peroxide is readily wetted by contacting the powder with a liquid containing water and one or more water-soluble organic solvents in a concentration sufficient to reduce the surface tension of the liquid to less than 64 dynes/cm.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 April 2011 (28.04.2011)

(10) International Publication Number
WO 2011/049547 A1

(51) International Patent Classification:

A01N 37/10 (2006.01) *A61K 31/19* (2006.01)

(21) International Application Number:

PCT/US2009/005732

(22) International Filing Date:

21 October 2009 (21.10.2009)

(25) Filing Language:

English

(26) Publication Language:

English

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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

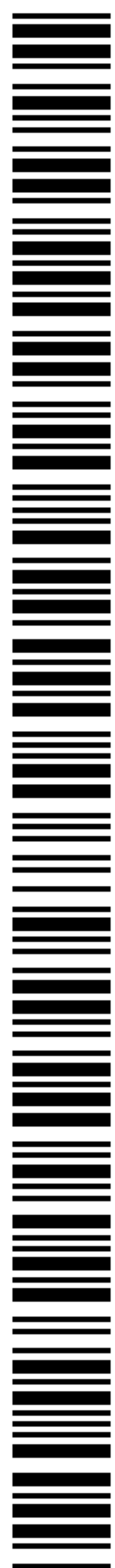
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*

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METHOD FOR WETTING A POWDER CONTAINING BENZOYL PEROXIDE

Field of the Invention

The invention pertains to the field of formulating
5 stable dispersions and microdispersions of benzoyl peroxide.

Background of the Invention

Benzoyl peroxide is used extensively in dermatologic
pharmaceutical compositions. Many compositions for the
10 treatment of acne vulgaris and acne rosacea, for example,
contain between 2.5% and 10% benzoyl peroxide. The
effectiveness of benzoyl peroxide in treating these and other
dermatologic conditions is its usefulness as a keratolytic
agent, thereby increasing skin turnover and clearing pores.
15 Benzoyl peroxide additionally has direct antibacterial
activity as well.

A serious difficulty in obtaining stable dispersions
of benzoyl peroxide in aqueous fluids is that benzoyl peroxide
is a highly hydrophobic organic compound and is not readily
20 wetted by water. This problem has been dealt with by the
prior art in one or more ways.

Benzoyl peroxide may be dissolved in an organic
solvent, thus avoiding the problem of preparing a stable,
homogeneous, cosmetically elegant and efficacious dispersion
25 of benzoyl peroxide for topical administration for treating a
skin affliction. Early products containing benzoyl peroxide in
solution for topical use were gels in which the benzoyl
peroxide was dissolved in an organic solvent such as acetone
or a combination of alcohol and acetone. These products proved
30 to be efficacious, however they suffered from several
disadvantages including flammability, over-drying the skin,
and causing frank skin irritation in many acne sufferers.
More recent developments have used other organic solvents to

solubilize benzoyl peroxide. However these compositions do not solve the problem of severe skin irritation in a significant number of subjects due to the problem of bolus delivery of solubilized benzoyl peroxide into the pilo-sebaceous apparatus of the skin.

For these and other reasons, including increased production of degradation products that occurs with solutions, suspensions of benzoyl peroxide are preferred over solutions. Micro-suspensions, that is suspensions containing micronized benzoyl peroxide, are preferred to standard or non-micronized suspensions of benzoyl peroxide for several reasons, including the following exemplary reasons. First, micronized suspensions provide effective delivery of small particles of benzoyl peroxide into the infundibulum of the pilo-sebaceous apparatus, in which they lodge and from which they provide non-bolus delivery of drug into the sebum and pilo-sebaceous tissue. This delivery provides a proper balance of optimal efficacy and reduction of skin irritation reactions. Second, cosmetic elegance and patient acceptance is improved with the smooth, homogeneous gels, creams or lotions containing suspended benzoyl peroxide. Particularly in treating facial conditions of the skin such as acne or acne rosacea, cosmetic elegance is an important factor in obtaining good patient compliance with treatment instructions. For chronic diseases with ongoing topical drug management, good patient compliance is essential in obtaining overall treatment success.

Surfactants are often utilized as wetting agents to help disperse benzoyl peroxide in aqueous fluids and to maintain benzoyl peroxide in suspension. Surfactants, however, are often irritating to damaged or diseased skin and, when applied to intact skin repeatedly, surfactants are known to disrupt the normal skin barrier function as evidenced by an increase in trans-epidermal water loss from the skin.

Therefore it is desirable to formulate pharmaceutical compositions, particularly those that will be used daily over extended periods for treating chronic skin conditions, with minimal or no surfactants. In order to facilitate dispersion
5 of benzoyl peroxide and to maintain the dispersion of benzoyl peroxide in suspension, a micronized form of benzoyl peroxide is often utilized, sometimes in conjunction with a surfactant.

Cox, U.S. Patent No. 3,535,422, discloses a stable emulsion containing benzoyl peroxide. Cox discloses two
10 methods to obtain the emulsion containing benzoyl peroxide in suspension. In a first method, Cox forms an emulsion containing water, a surfactant, and up to 25% of a saturated organic compound emollient. Dry micronized benzoyl peroxide is then blended into this emulsion to obtain the composition.

15 In a second method, utilizing non-micronized benzoyl peroxide, coarse crystals of benzoyl peroxide in the form of a powder packaged wet with water are combined with a previously made emulsion containing all of the components of the composition, including a surfactant and a saturated organic compound
20 emollient. The resulting composition is then milled in order to obtain a composition containing micronized benzoyl peroxide.

Young, U.S. Patent No. 4,056,611, discloses a single-phase composition containing benzoyl peroxide in
25 suspension. The composition of Young contains an alcoholic solvent, water, and a surfactant as necessary components. Like Cox, Young discloses that the composition may be made by using dry micronized benzoyl peroxide crystals. Preferably, Young utilizes, as does Cox, a wet-packed powder of coarse
30 crystals of benzoyl peroxide, which powder contains 70% benzoyl peroxide and 30% w/w water. All of the components of the composition are mixed together and then this mixture is milled to obtain a composition containing micronized benzoyl

peroxide in suspension. Young further discloses that the compositions may advantageously contain a suspending agent to maintain the benzoyl peroxide particles in suspension and a viscosity building (gelling) agent.

5 The Cox and Young methods and compositions contain several disadvantages pertaining to compositions containing benzoyl peroxide. In both Cox and Young, surfactants are utilized, which are often irritating to damaged or diseased skin. Further, both Cox and Young disclose combining together
10 all constituents of their compositions containing coarse, non-micronized benzoyl peroxide to form a mixture and then milling this mixture to obtain a composition containing micronized benzoyl peroxide. Although Young discloses that a gelling agent may be combined in the composition, it is well known
15 that the mechanical milling forces used in to micronize benzoyl peroxide will likewise tend to disrupt the polymers utilized as gelling agents. Thus, the milling process results in a reduction of the ability of the gelling agents to provide the viscosity that is desired.

20 Klein, U.S. Patent No. 4,387,107, discloses gel compositions containing benzoyl peroxide. Klein avoids the problem of milling a composition containing benzoyl peroxide by using benzoyl peroxide that is pre-micronized prior to combining with the remaining ingredients. In order to make
25 the composition of Klein, water is combined with a gelling agent to make a first mixture. To this mixture is optionally added an alcohol vehicle and other components such as a perfume and other therapeutic agents such as methyl salicylate. Finally, a second mixture containing micronized
30 benzoyl peroxide, a surfactant, and water is added to the first mixture to obtain the composition. Because micronized benzoyl peroxide is used, there is no need to mechanically mill the composition. Thus, the polymeric gelling agents are

not disrupted. However, the method of Klein requires the use of pre-micronized benzoyl peroxide and the presence of a surfactant.

5 The use of micronized benzoyl peroxide, as disclosed in Klein, provides advantages, particularly regarding the formation of semi-solid compositions containing one or more polymeric gelling agents. Micronized, as opposed to non-micronized benzoyl peroxide, is more readily suspended in a hydrophilic fluid and such suspensions are more physically
10 stable than are similar suspensions made with non-micronized benzoyl peroxide. However, micronized benzoyl peroxide, particularly as pharmaceutical grade material, is often difficult to obtain and, when it is obtainable, micronized benzoyl peroxide is expensive.

15 It would, therefore, be advantageous to be able to purchase non-micronized benzoyl peroxide, which is readily available and is much less expensive than micronized benzoyl peroxide, and to then be able to micronize the benzoyl peroxide for use in manufacturing pharmaceutical formulations.

20 As disclosed in both the Cox and Young patents, benzoyl peroxide, in solid crystalline form, is stable at room temperature but is flammable and capable of exploding when subjected to temperatures associated with grinding. Consequently, dry milling of benzoyl peroxide is not
25 preferred. Rather, it is preferred to wet-mill benzoyl peroxide in order to obtain benzoyl peroxide in a micronized form. Benzoyl peroxide in the presence of water, which is utilized in the preferred wet milling processes, is much safer to process as the risk of fire and explosion is minimized.

30 One difficulty encountered in wet-milling benzoyl peroxide, as mentioned above, is that benzoyl peroxide is highly hydrophobic and resists wetting with water. Further, the strong attractive forces between benzoyl peroxide

particles create a problem of aggregation which compromises both the manufacturing process and the quality of the final pharmaceutical formulation. Surfactants have been utilized for this purpose and to maintain a stable-non-agglomerated
5 micro-suspension of benzoyl peroxide, as disclosed in each of Cox, Young, and Klein patents, but surfactants are not preferred due to their tendency to irritate damaged or diseased skin. Therefore, a method in which benzoyl peroxide may be readily wetted, and preferably placed into suspension,
10 in a hydrophilic or aqueous fluid, and preferably without the use of surfactants, would be of great benefit.

Description of the Invention

It has been unexpectedly discovered that a benzoyl
15 peroxide powder is readily wetted, and a benzoyl peroxide suspension with minimal or no aggregation may be obtained, by combining the benzoyl peroxide, with or without mechanical agitation, with a wetting fluid, preferably aqueous-based, containing a water-soluble organic solvent dissolved in the
20 water-containing fluid at a concentration that is sufficient to decrease the surface tension to about 64 dynes/cm or less. It has further been discovered that this wetting may be obtained without the use of wetting agents, such as a surfactant.

25 As used herein, the term "benzoyl peroxide powder" means any particulate form of benzoyl peroxide. Examples of such particulate forms include granules, crystals, and amorphous powder, whether coarse, fine, or ultrafine such as a nanoparticulate powder.

30 As used herein, the term "powder containing benzoyl peroxide" refers to a powder containing a benzoyl peroxide powder and optionally a particulate form of one or more materials other than benzoyl peroxide. For example, a powder

containing benzoyl peroxide may contain particles of benzoyl peroxide and one or more other particles, wherein the concentration of particles other than benzoyl peroxide in the powder is 50% w/w or less. A powder containing benzoyl peroxide may contain a concentration of benzoyl peroxide between 50% and 100%, for example between 50% and 60%, between 60% and 70%, between 70% and 80%, between 80% and 90%, or between 90% and 100%.

As used herein, the term "non-micronized," when used in reference to a benzoyl peroxide powder, means a powder in which the average benzoyl peroxide particle is 50 microns or greater in size. Conversely, the term "micronized," when used in reference to a benzoyl peroxide powder, means a powder in which the average benzoyl peroxide particle is less than 50 microns in size. Preferably, but not necessarily, substantially all of the benzoyl peroxide particles in a non-micronized powder are 150 microns or larger.

As used herein, the term "wetting" refers to the spreading of a fluid over and through a powder, displacing air adsorbed thereto, so that the particles of the powder are individually and discretely encompassed within the fluid. As is known in the art, a powder is considered to be wetted when almost all, such as about 80% +/- 10% based on visual inspection and estimation, of the particles are encompassed within the fluid. For example, contacting a powder with a suitable wetting fluid results in what is referred to as complete wetting even though a minority of the particles, typically less than about 20% +/- 10% of the particles, does not become wetted.

As used herein, the term "mechanical agitation" refers to the application of kinetic energy to a powder mixture in contact with a liquid in order to facilitate wetting of the powder mixture within the liquid. Examples of

mechanical agitation include but are not limited to mixing, stirring, shearing, shaking, or blending. Other examples include sonication and vortexing.

As used herein, the term "aqueous gel" with regards to a pharmaceutical dosage form for topical application means a single phase semi-solid pharmaceutical dosage form comprising a carrier or carrier system that is gelled with a thickening agent such as a polymer wherein the majority of the carrier or carrier system is water, that is 50% w/w or more.

As used herein, the term "agglomeration" means the strong physical attraction between small solid particles, such that a multiplicity of the particles are aggregated into a single larger mass that appears as a single particle.

In one embodiment, the invention is a method to obtain a wetted powder containing benzoyl peroxide. According to the method of the invention, the powder is placed in contact with a liquid containing water and a water-soluble organic solvent. The solvent is dissolved in the liquid at a concentration sufficient to depress the surface tension to less than 64 dynes/cm at room temperature. In a preferred embodiment, the solvent is present in the liquid at a concentration sufficient to depress the surface tension to less than 62 dynes/cm. In a more preferred embodiment, the solvent is present in the liquid at a concentration sufficient to depress the surface tension to less than 61 dynes/cm. In a most preferred embodiment, the solvent is present in the liquid at a concentration sufficient to depress the surface tension to less than 60 dynes/cm. For example, the solvent may be present in the liquid at a concentration sufficient to reduce the surface tension to between 55 and 60 dynes/cm or even to between 50 and 55 dynes/cm or less.

In the description that follows, the method is described with reference to reducing the surface tension to

less than 64 dynes/cm. As disclosed in the preceding paragraph, preferably, the surface tension is decreased to values even lower than 64 dynes/cm, such as between 50 and 62 dynes/cm or lower.

5 Non-micronized benzoyl peroxide is available as Hydrous Benzoyl Peroxide, USP, which is sometimes erroneously referred to as "wet" benzoyl peroxide. Hydrous Benzoyl Peroxide contains not less than 65.0% and not more than 82.0 % benzoyl peroxide, with an average of about 74% benzoyl
10 peroxide and 26% water, in order to reduce flammability and shock sensitivity. The benzoyl peroxide in Hydrous Benzoyl Peroxide is not wetted, as this term is used in the art. Hydrous Benzoyl Peroxide is not a paste and the benzoyl peroxide in Hydrous Benzoyl Peroxide is in a microcrystalline
15 state and behaves as a freely flowing powder. There is no chemical interaction between water molecules and the benzoyl peroxide powder and the water does not make the core or the inside of the benzoyl peroxide powder wet. Thus, commercially available "wet" benzoyl peroxide is not wetted.

20 The benzoyl peroxide in the powder may be micronized or may be non-micronized and, therefore, the description herein pertaining to non-micronized powders will be understood to be applicable also to micronized powders. Micronized benzoyl peroxide powders are often commercially available as a
25 wetted powder containing benzoyl peroxide and water. An example of wetted benzoyl peroxide powders are those marketed under the brand name Benox[®] (Syrgis Performance Initiators, Inc., Helena, Arkansas). Because powders containing micronized benzoyl peroxide are already wetted, such powders
30 are not applicable to the wetting embodiment of the present invention. However, the use of wetted powders containing micronized benzoyl peroxide may be applicable to other embodiments of the invention discussed below.

In accordance with the method of the invention for obtaining a wetted benzoyl peroxide powder, a powder containing benzoyl peroxide is placed in contact with a suitable wetting fluid, which wetting fluid contains water and one or more water-soluble organic solvents having a combined concentration that is sufficient to decrease the surface tension of water to the desired level. Preferably, the wetting fluid is free of surfactants. The powder and the wetting fluid are permitted to remain in contact with one another for a time sufficient for the benzoyl peroxide to become wetted by the wetting fluid. If desired, or if necessary, the powder and the wetting fluid may be mechanically agitated to facilitate or to hasten or to complete wetting.

The organic solvent that is suitable for the method of the invention is one that is "very soluble", "freely soluble", or "soluble" in water as these terms are defined in the U.S.P. 23rd Ed. as shown in Table 1.

Solubility in water	Parts of water required to dissolve 1 part of organic solvent
Very Soluble	< 1
Free Soluble	1 - 10
Soluble	10 - 30
Sparingly Soluble	30 - 100
Slightly Soluble	100 - 1000
Very Slightly Soluble	1000 - 10,000
Practically Insoluble or Insoluble	> 10,000

Table 1

Preferably, but not necessarily, the organic solvent is miscible in water. Examples of organic solvents that are miscible in water and which are suitable for the method of the invention include C₁₋₆ alkanols, such as methanol, ethanol, n-

propanol, isopropanol, n-butanol, sec-butanol, tert-butanol, n-pentanol, cyclopentanol and cyclohexanol; linear amides, such as dimethylformamide or dimethylacetamide; ketones and ketone-alcohols, such as acetone, methyl ethyl ketone, 5 cyclohexanone and diacetone alcohol; water-miscible ethers, such as tetrahydrofuran and dioxane; diols, preferably diols having from 2 to 12 carbon atoms, for example pentane-1,5-diol, ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, hexylene glycol and thiodiglycol and oligo- 10 and poly-alkyleneglycols, such as diethylene glycol, triethylene glycol, polyethylene glycol and polypropylene glycol; triols, such as glycerol and 1,2,6-hexanetriol; mono-C₁₋₄-alkyl ethers of diols, such as mono-C₁₋₄-alkyl ethers of diols having 2 to 12 carbon atoms, such as 2-methoxyethanol, 15 2-(2-methoxyethoxy)ethanol, 2-(2-ethoxyethoxy)-ethanol, 2-[2-(2-methoxyethoxy)ethoxy]ethanol, 2-[2-(2-ethoxyethoxy)-ethoxy]-ethanol and ethyleneglycol monoallylether; cyclic amides, preferably 2-pyrrolidone, N-methyl-2-pyrrolidone, N-ethyl-2-pyrrolidone, caprolactam and 1,3-dimethylimidazolidone; sugar 20 esters such as dimethyl isosorbide; cyclic esters such as caprolactone; and sulfoxides, such as dimethyl sulfoxide and sulfolane.

In addition, the solvent that is suitable for the method of the invention is capable of being dissolved in water 25 at a concentration that is sufficient to reduce the surface tension to less than about 64 dynes/cm at room temperature. The surface tension of water varies slightly with changes in temperature as shown below in Table 2.

Temperature (° C)	Surface Tension of Water (dynes/cm)
0	75.6
5	74.9
10	74.2
15	73.5
20	72.8
25	72.0
30	71.2
40	69.6
50	67.9
60	66.2
70	64.4
80	62.6
100	58.9

Table 2

Preferably, the method of the invention to wet a benzoyl peroxide powder is performed at about room temperature, that is between 20° and 30° C. Less preferably, the method of the invention is performed at a temperature below room temperature, that is between 0° and 20°. Also less preferably, the method of the invention is performed at a temperature above room temperature, that is between 30° and 50° C. Even less preferable, the method of the invention may be performed at high temperatures of between 50° and 100° C. Because one of the advantages of the present invention is the lack of necessity to apply heat, it is preferable to perform the method of the invention at room temperature or below. However, if heat is applied and the temperature is elevated above room temperature, the optimum surface tension for wetting may be slightly higher than 64 dyne/cm.

The wetting fluid may contain, in addition to the one or more water soluble organic solvents, additional components that may be additional solvents. Such additional components are preferably liquid at the temperature at which the wetting process is performed and are preferably soluble in

the water soluble organic solvents that are utilized. Optionally the wetting fluid may contain dissolved solutes such as additional wetting agents, film-forming agents, or de-aggregation agents.

5 It has been surprisingly discovered that a wetting fluid that is a liquid containing water and one or more water soluble organic solvents as described above is capable of wetting a powder containing benzoyl peroxide. The concentration of the water miscible organic solvent or
10 solvents in the wetting fluid will vary depending on factors such as the particular solvent or solvents used, and on the relative volumes of benzoyl peroxide powder and wetting fluid used. Generally, the concentration of the water soluble organic solvent in the wetting fluid is between 1% and 100%
15 w/w. Preferably, the concentration is about 5% or higher, more preferably about 10% or higher, and most preferably at least about 15%. The term "about" in the preceding sentence is intended to mean an amount that is rounded to be the amount stated. Thus, about 5% means 4.5% or more, about 10% means
20 9.5% or higher, and about 15% means 14.5% or higher. The powder and the wetting fluid may be mechanically agitated to facilitate, to hasten, or to complete wetting.

 In another embodiment, the invention is a wetted benzoyl peroxide powder that is in combination with a liquid
25 containing water and one or more water soluble organic solvents as described above, wherein the concentration of the water soluble organic solvent in the liquid is sufficient to decrease the surface tension to less than 64 dynes/cm at room temperature as described above.

30 In another embodiment, the invention is a wetted benzoyl peroxide powder that is in combination with a liquid containing one or more water soluble organic solvents as disclosed above, wherein the concentration of the organic

solvent or solvents in the liquid is sufficient decrease the surface tension to less than 64 dynes/cm at room temperature.

In another embodiment, the invention is a wetted benzoyl peroxide powder that is in combination with a liquid
5 containing one or more water soluble organic solvents as disclosed above, wherein the concentration of the organic solvent or solvents in the liquid is sufficient decrease the surface tension to less than 64 dynes/cm at room temperature and result in wetting of the benzoyl peroxide powder, thereby
10 reducing and controlling agglomeration of the benzoyl peroxide particles, whether micronized or not, during the manufacturing process of a topical drug product or component thereof.

In another embodiment, the invention is a method for preparing micronized benzoyl peroxide, such as for use in
15 making a topical pharmaceutical formulation containing benzoyl peroxide as an active ingredient. According to this embodiment of the invention, a wetting fluid containing water and a water soluble organic solvent at a concentration sufficient to reduce the surface tension to less than 64
20 dynes/cm at room temperature is combined with a powder containing non-micronized benzoyl peroxide. The wetting fluid is permitted to wet the majority of the benzoyl peroxide particles in the powder. The wetted benzoyl peroxide is then subjected to an appropriate micronization procedure to obtain
25 micronized benzoyl peroxide.

In another embodiment, the invention is a suspension of benzoyl peroxide. According to this embodiment, the suspension is a single phase composition containing benzoyl peroxide at a concentration of between 1% and 30% w/w,
30 preferably 10% or less, and most preferably 5% or less. The benzoyl peroxide is suspended in a suspending fluid that contains one or more water soluble organic solvents at a concentration sufficient to reduce the surface tension to less

than 64 dynes/cm at room temperature. The suspending fluid may contain only the one or more organic solvents.

Alternatively, the suspending fluid may contain one or more vehicle fluids that are other than a water soluble organic

5 solvent that is capable of reducing the surface tension to less than 64 dynes/cm at room temperature.

It is preferred that the suspending fluid contains only one or more of the above-described water soluble organic solvents in addition to water. If a vehicle fluid other than

10 a water soluble organic solvent that is capable of reducing the surface tension of water to less than 64 dynes/cm at room temperature is utilized, such vehicle fluid should be

pharmaceutically acceptable and miscible with the one or more of the water soluble organic solvents used. Further, the

15 concentration of the one or more water soluble organic solvent that is capable of reducing the surface tension to less than 64 dynes/cm at room temperature in the suspending fluid should

be that which is sufficient, in the absence of the vehicle fluid that is other than such water soluble organic solvent,

20 to wet a benzoyl peroxide powder therewith combined.

The benzoyl peroxide in the suspension may be micronized or may be non-micronized. If the benzoyl peroxide is non-micronized, the suspension may be treated by a process by which the benzoyl peroxide in the suspension becomes

25 micronized. Suitable micronization processes include milling, grinding, crushing, cutting, impinging, cavitating, and shearing the suspension.

Non-micronized benzoyl peroxide, when wetted and suspended in accordance with the method of the invention, has
30 a very low tendency to agglomerate or aggregate on the liquid surface and, therefore, there is little or no problem of benzoyl peroxide particles becoming stuck in the small orifices of the micronizing equipment such as a Gaulin mill

(Delavan, WI). Benzoyl peroxide particles that have been wetted in accordance with the method of the invention and then micronized remain in stable suspension and do not agglomerate or aggregate on the liquid surface to a significant extent prior to being incorporated into a pharmaceutical formulation such as a gel, cream or lotion. The stable micro-suspension obtained according to the invention thus results in good pharmaceutical homogeneity and optimal non-bolus delivery into the skin, particularly the pilo-sebaceous apparatus, thus minimizing irritation potential without compromising efficacy.

In another embodiment, the invention is a method for preparing micronized benzoyl peroxide, such as for use in making a topical pharmaceutical formulation containing benzoyl peroxide as an active ingredient. In accordance with this method, a benzoyl peroxide powder is wetted and in suspension as described above, and the benzoyl peroxide suspension is then subjected to appropriate micronization treatment to obtain a suspension containing micronized benzoyl peroxide.

In another embodiment, the invention is a suspension containing micronized benzoyl peroxide, which benzoyl peroxide has been micronized according to the method described above. The micronization process and suspension of benzoyl peroxide of the invention are useful in formulating topical pharmaceutical products containing benzoyl peroxide as an active ingredient, especially topical products that are semi-solid dosage forms. The methods of the invention maintain the dispersed micronized benzoyl peroxide in a stable non-agglomerated and non-aggregated state for optimal pharmaceutical acceptability without a "shake well before using" label in lotions and other pourable topical dosage forms and for optimal drug delivery.

In another embodiment, the invention is a pharmaceutical formulation containing benzoyl peroxide in

suspension in a liquid containing one or more water-soluble organic solvents that is, or are in combination, capable of reducing the surface tension of water to less than 64 dynes/cm at room temperature, wherein the concentration of the water-soluble organic solvents together with the water in the pharmaceutical formulation is sufficient to wet a powder containing benzoyl peroxide at a concentration of the benzoyl peroxide present in the formulation in the absence of all other liquid components of the formulation. Preferably, the benzoyl peroxide is micronized. Preferably, the benzoyl peroxide has been micronized according to the present invention. If desired, the pharmaceutical formulation may contain one or more additional vehicle fluids, as described above. The pharmaceutical formulation may further contain excipients commonly utilized in pharmaceutical formulations, such as humectants, emollients, pH stabilizing agents, chelating agents, film forming agents, preservatives, and anti-oxidants.

The concentration of benzoyl peroxide in the pharmaceutical formulation is preferably between 1% and 10% w/w, with a preferred concentration being between 2% to 5%. If desired, an additional agent that is useful in the treatment of dermatologic disorders such as acne vulgaris or acne rosacea may be included in the formulation. Preferably, the additional anti-acne compound is soluble in the solvent or multiplicity of solvents and so is dissolved in the formulation.

One such preferred anti-acne compound is an antibiotic. Preferred antibiotics include those of the macrolide family of antibiotics such as erythromycin, azithromycin, clarithromycin, tilmicosin, and tylosin, and those of the lincomycin family of antibiotics such as clindamycin and lincomycin. A particularly preferred

antibiotic to be used in combination with benzoyl peroxide in the formulation of the invention is clindamycin, such as clindamycin hydrochloride or clindamycin phosphate.

Additional topical anti-acne active ingredients that may be contained in the formulation of the invention, either with or without the inclusion of an antibiotic, include salicylic acid, azelaic acid, sulfur, sulfacetamide, resorcinol, alpha-hydroxy acids such as glycolic acid, niacinamide, urea, and retinoids such as tretinoin, adapalene, and tazarotene.

The additional anti-acne compound, if present in the formulation of the invention, is preferably present in a concentration in which there is a demonstrable anti-acne effect in the absence of benzoyl peroxide. For example, if clindamycin is present in the formulation of the invention, the concentration of the clindamycin is preferred to be at least 0.5%, such as 1%. Concentrations of clindamycin lower than 0.5% or higher than 1%, such as 2.5% to 5.0% or higher, may be utilized in the formulation.

It is preferred, although not required, that the formulation be in the form of a gel, preferably an aqueous gel. Accordingly, the formulation of the invention may contain a gelling or thickening agent. Any gelling agent that is water-dispersible, is suitable for use on epithelial tissue such as skin, and forms an aqueous gel of substantially uniform consistency, is suitable for use in the composition of the invention. One preferred gelling agent is hydroxypropylcellulose, such as that sold under the tradename KLUCEL® (Hercules Incorporated, Wilmington, DE, USA). Another preferred gelling agent is hydroxyethylcellulose, such as that sold under the tradename NATROSOL® (Hercules Incorporated). Other suitable gelling agents include carboxyvinyl polymers, also known as carbomers, such as are sold under the tradename CARBOPOL® 934, 940, 941, 980, and 981 (B.F. Goodrich Co.,

Akron, OH, USA), ETD 2020™, and ULTREZ® (Noveon, Inc., Cleveland, OH, USA). Additional suitable gelling agents are polyvinyl alcohol, polyethylene oxides, propylene glycol alginates, methylcellulose, hydroxypropylmethylcellulose and
5 natural polymeric gums such as xanthan, and carrageenan. The concentration of gelling agent in the composition may be varied depending on several factors, including the desired viscosity of the gel composition. For example, a gel may be pourable and dispensed from a bottle, such as a plastic
10 squeeze bottle, or it may be more viscous such that it is preferably dispensed from a collapsible tube or wide mouth jar.

If desired, the formulation of the invention may further include additional pharmaceutically acceptable
15 excipients typically used in formulations and known to those skilled in the art. Such excipients include, for example, humectants, emollients, pH stabilizing agents, chelating agents, film formers, penetration enhancers, preservatives, and anti-oxidants.

20 The semi-solid dosage form of the pharmaceutical formulation of the invention may also be in the form of an emulsion, such as a cream or lotion. Preferably, such creams or lotions are formulated without low molecular weight surfactants due to the tendency of such surfactants to be
25 irritating to the skin or to impair the skin barrier function. Thus, it is preferred that the cream or lotion formulations of the invention are made with high molecular weight polymeric emulsifiers which do not exhibit such detrimental effects on skin, such as disclosed in Dow, U.S. Patent No. 7,368,122, or
30 with low levels of mild emulsifiers such as poloxamers.

The invention is further described in the following non-limiting examples. In the examples that follow, the invention is illustrated primarily with an organic solvent

that are miscible with water. However, it is understood that the examples are illustrative and that the invention may be practiced with water soluble solvents that are not miscible with water, as described above.

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Example 1 - Wetting of a benzoyl peroxide powder utilizing various water soluble organic solvents

A benzoyl peroxide wettability study was conducted as follows. 1.5 grams of a benzoyl peroxide powder was spread
10 on the surface of each of four test fluids contained in glass beakers having about a 5 cm diameter, containing either 30 ml of purified water having a surface tension of 72.0 dynes/cm (Sample A), 30 ml of a fluid composed of 7.5% ethanol and 95% purified water having a surface tension of 51.4 dynes/cm
15 (Sample B), 30 ml of a fluid composed of 20% polyethylene glycol (PEG 200) and 80% purified water having a surface tension of 51.9 dynes/cm (Sample C), and 30 ml of a fluid composed of 20% dimethyl isosorbide (DMI) and 80% purified water having a surface tension of 50.1 dynes/cm (Sample D).
20 At the bottom of each beaker was a 12 mm x 8 mm magnetic stir bar. Each of the fluids, with the benzoyl peroxide powder on the surface, was stirred at 1200 rpm. After 5 and 10 minutes of stirring at room temperature, the samples were visually inspected for the degree of wetting of the benzoyl peroxide.
25 It was determined that the wetting of the benzoyl peroxide in Sample A was poor, with little or no visual evidence of wetting. The wetting of the benzoyl peroxide in each of Samples B, C, and D was determined to be good, with visual evidence of wetting of at least 90% of the benzoyl peroxide
30 powder.

Example 2 - Effect of various solvents on water surface tension

Surface tension of a fluid containing water was determined prior to and after mixing with various concentrations of various water soluble organic solvents in water. The study was performed at room temperature and the results are shown in Table 3. Values for surface tension are in dynes/cm.

Conc. of Solvent % w/w	Propylene Glycol	Ethanol (200 proof)	Hexylene Glycol	Ethoxy Diglycol	PEG 400	Dimethyl Isosorbide	Glycerin
0	71.0	72.0	71.9	71.8	72.8	72.8	72.6
1.0	70.8	67.4	60.1	66.2	64.2	66.0	
2.5	68.7	62.0	54.2	62.5	60.9	61.7	
5	65.9	55.9	48.9	56.8	56.6	52.8	
7.5	63.6	51.4	45.5	55.3	56.0	52.1	
10	61.7	47.8	43.0	53.1	52.5	47.9	
12.5	59.7	44.6	41.1	50.4	50.6	46.4	
15.0	58.3	42.2	39.4	49.7	49.7	43.5	
17.5	56.5	40.2	37.8	47.6	48.1	41.9	
20	55.2	38.0	36.5	43.2	46.2	38.6	
22.5	54.1	36.6	35.5	43.1	45.6	40.5	
25	52.8	34.9	34.7	43.8	45.2	41.7	69.8
30	50.6						
50							68.9
75							66.4
100	36.1	22.3	28.6	32.0	45.0	39.3	62.0

Conc. of Solvent % w/w	PEG 200	Poly propylene Carbonate	Isopropyl Alcohol	1,3 Propanediol	Polypropylene Glycol (PPG-9)
0	71.7	71.5	71.9	72.4	72.3
1.0	65.9	68.5	62.1	69.8	50.3
2.5	64.2	63.8	54.2	68.1	47.5
5	61.1	56.8	47.3	64.6	45.2
7.5	58.7	49.6	42.0	64.4	43.6
10	56.1	45.9	38.6	61.2	42.4
12.5	54.8	46.5	35.7	61.1	41.3
15.0	53.0	44.1	33.1	61.0	40.2
17.5	52.2	43.5	31.1	58.9	39.5
20	51.9		29.5	60.4	38.9
22.5	49.9		28.1	58.2	38.3
25	48.7		27.3	58.3	37.5
100	45.4		21.1		32.5

Table 3

5

As shown in Table 3, each of the organic solvents tested, with the exception of glycerin, decreased the surface tension of the water-containing fluid to less than 64 dynes/cm at room temperature. Each of ethanol, hexylene glycol, ethoxy diglycol, polyethylene glycol 400, and dimethyl isosorbide is suitable for use in the method of the invention in a

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concentration less than 5% w/w and higher, such as at any concentration between 1% and 5%. Propylene glycol is shown by the data of Table 3 to be suitable at a concentration of about 7.5% or higher. Glycerin, by itself, is shown by the data of
5 Table 3 to be not suitable for the present method.

Example 3 - Wetting benzoyl peroxide powder with a fluid comprising propylene glycol and water to facilitate the preparation of a stable micronized suspension to be used in
10 manufacturing a 3.13% benzoyl peroxide topical gel

A suspension was prepared containing 24.8% w/w hydrous benzoyl peroxide utilizing a dispersing fluid containing 9.4% w/w propylene glycol and 90.6% w/w water. Into a stainless steel tank, 36 kg of purified water and 3.75
15 kg of propylene glycol were combined. The combination was agitated with a propeller mixer to form a mixture. While mixing, 13.12 kg of hydrous benzoyl peroxide (74.5% benzoyl peroxide) was added. Mixing continued at 1450 rpm for about 10 minutes to wet and disperse the benzoyl peroxide powder at
20 room temperature and to obtain a benzoyl peroxide suspension.

Upon visual inspection, the suspension appeared to be smooth and free of lumps, with uniformly wetted benzoyl peroxide. This suspension was passed through a Gaulin Mill for micronization using a wet-milling method. The milling
25 procedure proceeded efficiently and without problems (i.e., there was no mill plugging) and a stable micro-suspension was produced. This suspension was set aside for a short time before being incorporated into the final topical dosage form, a 3.13% benzoyl peroxide gel, with the active benzoyl peroxide
30 drug substance present as a stable micro-suspension without the use of surfactants.

This example shows that a concentration of propylene glycol of about 9% in water is sufficient to provide wetting of a benzoyl peroxide powder.

5 The above examples show that a hydrophobic benzoyl peroxide powder is easily wetted in water containing a water soluble organic solvent that is capable of reducing the surface tension of the aqueous fluid to less than 64 dynes/cm. The wettability of the benzoyl peroxide powder increases with
10 increased concentrations of the organic solvent and is further facilitated with mechanical agitation. If desired, the benzoyl peroxide powder that has been wetted according to the method of the invention may be effectively and safely micronized by a wet-milling or other process in order to
15 manufacture pharmaceutical formulations containing micronized benzoyl peroxide.

 Various modifications of the above described invention will be evident to those skilled in the art. It is intended that such modifications are included within the scope
20 of the following claims.

Claims:

1. A method for making micronized benzoyl peroxide comprising:
suspending benzoyl peroxide in a suspending fluid comprising water and one or more water-soluble organic solvents,
wherein the benzoyl peroxide is non micronized,
wherein the one or more water-soluble organic solvents are selected from the group consisting of propylene glycol and hexylene glycol,
wherein the concentration of propylene glycol in the suspending fluid is at least 10% (w/w),
wherein the concentration of hexylene glycol in the suspending fluid is at least 1% (w/w), and
wherein the suspending fluid is free of gelling agents and surfactants; and
subjecting the suspension to a micronization treatment to obtain the micronized benzoyl peroxide.
2. The method of claim 1, wherein the benzoyl peroxide is Hydrous Benzoyl Peroxide, USP.
3. The method of claim 1, wherein the concentration of propylene glycol in the suspending fluid is at least 12.5% (w/w).
4. The method of claim 1, wherein the concentration of propylene glycol in the suspending fluid ranges from 12.5% (w/w) to 20% (w/w).

5. The method of claim 1, wherein the concentration of propylene glycol in the suspending fluid ranges from 20% (w/w) to 30% (w/w).

6. The method of claim 1, wherein the concentration of propylene glycol in the suspending fluid ranges from 10% (w/w) to 30% (w/w).

7. The method of claim 1, wherein the suspending fluid consists of water and propylene glycol.

8. The method of claim 7, wherein the concentration of the propylene glycol in the suspending fluid is greater than 30% (w/w).

9. The method of claim 1 which further comprises combining one or more pharmaceutically acceptable excipients with the suspension of micronized benzoyl peroxide to obtain a topical pharmaceutical dosage form, wherein the concentration of benzoyl peroxide in the dosage form is between 1% and 10% w/w.

10. The method of claim 9 wherein the concentration of benzoyl peroxide in the dosage form is between 2% and 5% w/w.