Description

1. Field of the Invention

This invention relates to processes for making finely divided solid powders such as pharmaceutical and technical chemicals or explosive agents which are normally difficult to solubilize in aqueous media or to subdivide without extensive chemical or physical treatments such as micronizing or repeated grinding operations, or in the case of explosives, hazardous operations. More particularly, this invention provides a process for producing finely divided solid crystalline or amorphous powders involving the sub- or super critical gases which process is not limited by the solubility of the solid in the pure supercritical gas, per se. The expression "microns" used in the following means "µm".

2. Description of the Related Art

Adding a normally liquid anti-solvent to a liquid solution of a solid to be precipitated or subdivided, or of adding the liquid solution containing the solid to be precipitated or subdivided into the liquid anti-solvent is a well-known chemical plant practice which is often referred to as the "salting out" effect. See Kirk-Othmer's ENCYCLOPEDIA OF CHEMICAL TECHNOLOGY, Third Edition, 7, John Wiley & Son, Publishers (1979), page 261 in a chapter on "Crystallization".

Adding a solution of a solid dissolved in a good liquid solvent therefor to a comparatively large volume of poor liquid solvent is known as controlled microprecipitation and is practiced on an industrial scale for a variety of solid products.

The use of compressed supercritical gas for its solubility effect on some solids is also an old concept referred to in U.S. Patent 4,263,253 (column 1), but has become of more recent interest for the production of fine powders. In their review of supercritical fluid technology, Paulaitis, M.E. et al, "Supercritical Fluid Extraction", Rev. Chem. Eng., 1 (2) (1983), pp. 179-250, describe the redistribution of particle sizes of solids via supercritical fluid nucleation. Krukonis, V. J., "Supercritical Fluid Nucleation of Difficult to Comminute Solids", Paper No. 140f, presented at the Annual Meeting of the AIChE, San Francisco, Nov. 1984, expands upon that work.

In U.S. Patent 4,582,731 there is described a process for making a finely divided solid using a supercritical fluid as a solvent for the solid to be subdivided which solution is then expanded into a low pressure vacuum atmosphere to quickly separate the depressured supercritical gas solvent from the solid. This latter work is further described in a paper by Peterson, R.C. et al, "Rapid Precipitation ... Supercritical Fluid Solutions; The Formation of Thin Films and Powders", J. Am. Chem. Soc., 108, 2100-2103 (1986). The direct application of supercritical fluid extraction to the production of pharmaceutical powders was described by Larson, K.A. et al, "Evaluation of Supercritical ... Industry", Biotech. Prog. 2 (2) (June 1986), pp. 73-82, and independently by Lath, E. et al, "Properties ... Supercritical Gases", Int. J. Pharm., 32, 265-267 (1986).

All of these literature and patent descriptions are similar insomuch as they all teach that the solid compound to be micronized or subdivided must first be dissolved in an appropriate supercritical fluid. The supercritical fluid containing the dissolved solute is then rapidly expanded (flashed) to separate the supercritical gas from the solid and to recover the dry, micronized powder.

It is also disclosed in Ber. Bunsenges, Phys. Chem., 88, 900 (1984) that complex oily, gummy or otherwise highly viscous natural products such as crude lecithin can be stripped of their more volatile components by extraction with a supercritical gas, leaving behind insoluble matter in the form of a recoverable powder (also see U.S. Patent 4,367,178). This phenomenon forms the basis of all supercritical solvent leaching operations, where for example the unextracted mass may be organic matter as in the leaching of coffee (U.S. Patent 4,247,570) or spice (U.S. Patent 4,123,559). If coal is extracted with a mixture of supercritical xylene and tetralin then the undissolved portion is a particulate ash consisting of organic char and inorganic minerals (U.S. Patent 4,192,731).

A similar but opposite process has been described in the literature, see Chemical Engineering, July 1989, p 39. The process is called the "GAS" (gas-anti-solvent) process and is performed by adding a supercritical fluid to a premixed volume of dissolved solute dissolved in an organic liquid solvent. As the supercritical fluid dissolves in the solution, the solid precipitates out. A speech describing the GAS process was given at the American Institute of Chemical Engineers Annual Meeting on November 29, 1988, (Gas Recrystallization: A new Process to Recrystallize Compounds Insoluble in Supercritical Fluids; paper No. 48c).

In addition to the above the following patents may be of interest as illustrating uses or applications of the above background technology.

U.S. Patent 3,981,957 discloses a process for making a high density polymer powder comprising melting a thermoplastic polymer to a melt, mixing the polymer melt with a solvent and discharging the polymer melt/solvent mixture through a nozzle in contact with a blowing gas such as nitrogen. There is no mention of the use of a supercritical solvent or a supercritical anti-solvent procedure.

U.S. Patent 4,012,461 discloses a process for producing polymer powders which includes the step of atomizing a polymer slurry into a vaporization zone on the presence of a drying gas. There is no mention of the use of a supercritical gas anti-solvent procedure.

U.S. Patent 4,124,607 discloses a process for getting difficult to dissolve soluble sterol starting materials into a fermentation medium by dissolving the sterol in an organic solvent with subsequent removal of the organic solvent by heat or by reduced pressure.

U.S. Patent 4,263,253 discloses a process for sterilizing solids, e.g., pharmaceutical active ingredients, by dissolving the non-sterile solid in a gas under supercritical conditions, and then passing the resulting solution through a sterilizing filter to provide a sterile fluid gas/solid mixture.

These above processes are different from the process of this invention which involves adding a solution of the solute to be micronized or subdivided in a *conventional* liquid solvent and then adding this solution to a compressed liquified or supercritical gas atmosphere, which gas is essentially an anti-solvent or non-solvent for the solid to be micronized or subdivided as a solid. Moreover, the processes described above, with the exception of the GAS process described in Chemical Engineering in July of 1989, which involve the use of supercritical or liquified gases are limited in their application to solids which are soluble in the supercritical gas atmosphere. However, many pharmaceutical, agricultural chemicals, commercial chemicals, fine chemicals, food items, photographic chemicals, dyes, explosives, paints, polymers or cosmetics and other solid materials which need to be further subdivided are not very soluble in the common and reasonably-priced supercritical gas solvents such as carbon dioxide, nitrous oxide, ethylene and fluoroform.

This invention is intended to provide a solution to the problem of treatment of solids, particularly those which are not soluble enough in a common supercritical or liquified gaseous solvent, for making large quantities of solids which must be finely-subdivided. Example of such solids are pharmaceuticals, agricultural chemicals, commercial chemicals, fine chemicals, food items, photographic chemicals, dyes, explosives, paints, polymers and cosmetics.

According to the present invention, a process for producing a finely-divided solid comprises

(1) dissolving the solid to be finely-divided in a liquid carrier solvent, to form an injection solution; and

(2) adding the injection solution to a volume of anti-solvent sufficient to precipitate or crystallise the solid, wherein the anti-solvent is a supercritical fluid, a compressed liquefied gas or a dense vapour.

The novel process is very suitable for producing a sterile finely-divided solid, in which case the injection solution and the anti-solvent are each passed through a sterilising filter, and the sterilised solution and the sterilised anti-solvent are then mixed in a sterilised pressure vessel.

Figure 1 is a sketch plan and block symbol view of typical apparatus which can be used to operate the process of this invention.

This invention is a process for producing a finely-divided solid, referred to as "microprecipitation from a compressed gas", or more simply "gas microprecipitation".

The operable solids to be finely-divided in the process of the present invention include almost any solid material which needs to be sub-divided in the solid state and which can be dissolved in some liquid carrier solvent. Operable solids include, for example, a pharmaceutical, agricultural chemical, commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint, polymer or cosmetic. It is preferred that the solid be a pharmaceutical (both prescription and non-prescription drugs). It is preferred that the pharmaceutical be a steroid, benzodiazepene, penicillin, or cephalosporin. The preferred steroids are those set forth in CHART A where

(A-I) R_{10} is α-R_{10-1}:1:β-CH_3, where R_{10-1} and R_5 are taken together are $-CH_2-CH_2-CO-CH=$ or $-CH=CH-CO-CH=$;

(A-II) R_{10} and R_5 taken together are $=CH-CH=COH-CH=$;

R_6 is α-R_{6-1}:β-H where R_{6-1} is -H, -F or $-CH_3$;

R_7 is -H or $-S-CO-CH_3$;

R_9 is -H, -F, -Cl or -Br;

R_{11} is =O or α-H:β-OH;

R_{16} is α-R_{16-1}:β-R_{16-2} where R_{16-1} is -H, -OH or $-CH_3$ and where R_{16-2} is -H or $-CH_3$ with the proviso that one of

R_{16-1} or R_{16-2} is -H;

R_{17} is -H, -CO-R_{17-1} where R_{17-1} is C_1-C_5 alkyl;

R_{21} is -Cl, -OH or -O-CO-R_{21-1} where R_{21-1} is C_1-C_3 alkyl, with the proviso that when R_{16-1} is -OH and when R_{17} is -H, the two groups can form an acetonide.

Examples of pharmaceuticals include triamcinolone acetonide, triamcinolone, dexamethasone, dexamethasone sodium phosphate, methylprednisolone acetate, hydrocortisone, hydrocortisone acetate, medroxyprogesterone acetate, isoflupredone acetate, alprazolam, triazolam, penicillin, glyburide, ampicillin, ibuprofen, spectinomycin, erythromycin, flurbiprofen and their salts.

Examples of commercial chemicals include nylon, polystyrene, benzoic acid, benzene hexachloride and paraffin wax. Examples of fine chemicals includes citric acid, dichlorobenzedine and benzophenone. Examples of food items include cocoa and powdered milk. Examples of explosives include plastic explosives, trinitrotoluene (TNT) and other military munitions. Examples of agricultural chemicals include herbicides and insecticides.

The solid to be finely divided is first dissolved in a suitable liquid carrier solvent. The liquid carrier solvent is selected based on its ability to dissolve the solid to be finely divided, its miscibility with an anti-solvent, toxicity, cost and other factors. The resulting solution of solid dissolved in the liquid carrier solvent is called the injection solution.

The liquid carrier solvent is a conventional liquid solvent (at ambient conditions) in which the solid to be finely divided is quite soluble. In addition the liquid solvent must possess at least partial miscibility with the anti-solvent. Most organic solvents are at least partially miscible with most anti-solvents. Water is only slightly soluble in the anti-solvent carbon dioxide, and even less soluble in ethane, and so, while water may be used as a liquid carrier solvent, the ratio of anti-solvent to injection solution must be kept very high to prevent the formation of a water rich phase in which excessive finely divided solid solute product remains dissolved.

In general, the liquid carrier solvent is chosen for high solubility of the solid to be finely divided, miscibility with the anti-solvent being used, low toxicity, fairly high volatility, non-corrosiveness to the apparatus, and fairly low viscosity for ease of injection. It is understood that for each particular solid there are different preferred liquid carrier solvents which can be readily determined as is known to those skilled in the art. A preferred liquid carrier solvent for any particular solid to be finely divided meets the above criteria and also gives acceptable particle size, crystal form, and low residual solvent levels in the finely divided solid product, for the particular solid being microprecipitated. Suitable liquid carrier solvents include any organic solvent capable of dissolving the solute and mixtures thereof.

In general there are no preferred liquid carrier solvents because each solid has different solubility characteristics. Rather each solid will have its own preferred liquid carriers. Common liquid carrier solvents include:

alcohols of the formula R_a-OH where R_a is C_1-C_6 alkyl or ϕ-CH_2-;

ethers of the formula R_b-O-R_c where R_b and R_c are the same or different and are C_1-C_4 with the proviso that the total number of carbon atoms not be more than 6, and where R_b and R_c can be taken together with the attached oxygen atom to form a heterocyclic ring consisting of 5-8 atoms;

ketones of the formula R_d-CO-R_e where R_d and R_e are the same or different and are -H or C_1-C_4 alkyl with the provisos that (1) R_d and R_e can not both be -H and (2) that the total number of carbon atoms not be more than 6;

amides of the formula R_f-CO-NR_gR_h where R_f is -H, -CH_3 or -C_2H_5 and R_g and R_h are the same or different and are -H, -CH_3 or -C_2H_5 with the proviso that only one of R_g or R_h can be -H when R_f is -CH_3 or -C_2H_5;

esters of the formula R_i-CO-O-R_j where R_i is C_1-C_4 alkyl and R_j is -H or C_1-C_4 alkyl;

aromatic compounds such as benzene optionally substituted with 1 or 2 -Cl or with 1 or 2 -CH_3;

methane type compounds of the formula $C(R_k)_4$ where R_k are the same or different and are -H or -Cl;

ethane optionally substituted with 1-3 -Cl;

ethene optionally substituted with 1-3 -Cl;

hydrocarbons of the formula $(CH_3$-$(CH_2)_{n1}$-CH_3 where n_1 is 2-6 optionally substituted with 1-4 -Cl; freons; CH_3-CN, glyme and mixtures thereof. Specific liquid carrier solvents include methanol, ethanol, n- and iso-propanol, n-, sec- and tert-butanol, pentanols, hexanols, heptanols, benzyl alcohol, THF, diethyl ether, methyl-tert-butyl ether, formamide, DMF, N,N-dimethylacetamide, acetone, methylethyl ketone, pentane, hexane, heptane, octane, cyclopentane, benzene, toluene, xylene, pyridine, methylene chloride, chloroform, carbon tetrachloride, chloromethane, ethylene dichloride, butyl chloride, trichloroethylene, 1,1,2-trichlorotrifluoroethanedioxane, chlorobenzene, ethyl acetate, butyl acetate, acetonitrile, glyme, and mixtures thereof.

The anti-solvent to be used is selected based on several factors of which one of the most important is a low solubility of the pure solid to be finely divided in the anti-solvent and a high solubility of the liquid carrier solvent in the anti-solvent. The selected anti-solvent is chosen to minimize cost, maximize product yield, minimize toxicity and on other experimental aspects such as producing the correct crystal form and being easily removed from the crystalline solid, and its being the optimum non-solvent for the solid being finely divided. The selected anti-solvent is one which is at least partially, preferably completely, miscible with the carrier liquid solvent over the range of pressure and temperature encountered during the operation of the process.

Anti-solvent refers to a gas existing at a temperature equal to or above the pure gas critical temperature and at a pressure equal to or above the pure gas critical pressure. Therefore, the term anti-solvent includes supercritical fluids, compressed liquified gases and dense vapors. Because the anti-solvent is chosen which exhibits a small equilibrium solubility for the solid to be microprecipitated, the anti-solvent is an non-solvent in the process. Since the solubility of any solid compound in a anti-solvent is a function of both the temperature and pressure of the supercritical fluid ($T \geq T_c$ and $P \geq P_c$), then optimum yields of finely divided solid may be obtained by adjusting either the temperature or the pressure of the anti-solvent. It is known that lower fluid temperatures favor lower solute solubility. Thus, the process may be run with good results if the temperature of the anti-solvent is less than the critical temperature of the anti-solvent but the pressure is greater than the corresponding vapor pressure of the gas at the selected operating temperature. Under these conditions the supercritical fluid is called a compressed liquified gas, also sometimes referred to as a near-critical liquid (about $0.8T_c < T < T_c$ and $P > P^{vap}$). Thermo-dynamically this criteria is the liquid state. Further, the process also works, though generally not as well, if the anti-solvent is in the dense vapor phase ($T < T_c$ and $P < P_c$), but, for example, injecting the injection solvent into a low pressure vapor ($T < T_c$) or a low pressure gas ($T > T_c$) does not produce satisfactory finely divided solid because the anti-solvent is not capable of rapidly diffusing into the stream of impringent injection solvent and therefore not capable of rapidly solubilizing the liquid carrier solvent.

Anti-solvents include supercritical fluids, compressed liquified gases and dense vapors.

Operable anti-solvents include carbon dioxide, ethane, ethylene, nitrous oxide, fluoroform (CHF_3), dimethyl ether, propane, butane, isobutanes, propylene, chlorotrifluormethane ($CClF_3$), sulfur hexafluoride (SF_6), bromotrifluoromethane ($CBrF_3$), chlorodifluoromethane ($CHClF_2$), hexafluoroethane, carbon tetrafluoride and mixtures thereof.

Preferred anti-solvents include carbon dioxide, ethane, ethylene and $CClF_3$; more preferred is carbon dioxide.

The solid to be finely divided is dissolved in the liquid carrier solvent to form an injection solution which is usually comprised of a slightly less than saturated concentration of the solid in the liquid carrier solvent at the temperature which injection solution is to be maintained. This temperature is usually chosen as ambient temperature (20-25 °) for reasons of operating convenience, but the injection solution can be prepared and maintained at higher or lower than ambient temperature if so desired. Reasons to use other than ambient temperature include the higher solubility loading of the solid in the liquid carrier solvent at higher or lower temperatures, thus improving the rate of finely divided solid product formation, or that the injection solvent temperature influences the particle size, crystal form or habit, residual solvent content, or other physical property of the ultimately produced finely divided solid. Although the liquid carrier solvent may be saturated with solid (now solute), it is generally preferable to inject slightly less than saturated injection solutions as this condition minimizes the plugging of porous filters, check valves, and other process equipment through which the injection solution flows prior to being injected into the anti-solvent.

The injection solution is then added to a comparatively large volume of the anti-solvent which is under the process conditions a supercritical fluid, liquified compressed gas or dense vapor. In the usual method of operation the injection solution is pumped into a stirred autoclave containing the compressed anti-solvent. When the injection solution (liquid carrier solvent containing dissolved solid) contacts the anti-solvent, the injection solution is rapidly permeated with the anti-solvent by the normal process of binary diffusion. Since the solubility of the solid is much lower in the anti-solvent than it is in the liquid carrier solvent, the dissolved solid precipitates from the anti-solvent/liquid carrier solvent mixture soon after the contacting is made. Because the contacting, mixing, and diffusion occur on a fast time scale, the solid precipitates out of the mixture as small, fine particles. If the contacting were made slower (such as might be achieved by slowly adding anti-solvent to a prescribed volume of liquid carrier solvent/dissolved solute solution), then larger sized particles of precipitated solid would be expected to form because of the increased time of good solubility available for kinetically controlled crystal growth. Slow crystallizations generally produce larger crystals than rapid precipitations.

After a desired quantity of injection solvent has been added to the anti-solvent, the precipitated finely divided solid (product), must be separated from the pressured anti-solvent raffinate. This raffinate is a homogeneous mixture of mostly anti-solvent containing typically 2-10 wt % liquid carrier solvent. Thus, it is important that the liquid carrier solvent be miscible with the anti-solvent at all operating temperatures and pressures encountered in the processing while the raffinate is still in contact with the finely divided solid product. If a temperature, pressure, or composition is reached which causes a liquid carrier solvent-rich second phase to form in the raffinate, finely divided solid product may selectively redissolve in this phase and not be recoverable in a finely divided solid state. Two phase gas or liquid formation (a third phase is the solid phase) may be tolerated in the mixture if the finely divided solid is still only sparingly soluble in both phases.

Collection of the finely divided solid product is expediently performed by screening the solid in a sieve filtration operation. The anti-solvent/liquid carrier solvent/finely divided solid precipitate mixture is forced to flow through a fine porosity basket filter located at the bottom of the precipitation chamber while still under full operating pressure. The finely divided solid product is retained by the basket filter while the anti-solvent raffinate passes easily through the bed of collected solid and the sieve filter before being bled from the bottom of the precipitation chamber as clarified filtrate. The low viscosity and low surface tension of the anti-solvent is particularly amenable to fast filtration rates through a packed bed of small particles as opposed to the filtration rate of conventional liquid solvents with their inherently higher viscosities and surface tension effects. In this filtration respect super-critical fluid microprecipitation offers the advantage of rapid filtration rate usually not observed in conventional liquid micro-precipitation, particularly when water is used as the conventional anti-solvent as is common practice.

It is preferred to practice the process of the present invention in a continuous processing mode. In this case the anti-solvent and injection solution are forced into the precipitation chamber and filtered raffinate exits the chamber from the down-stream side of the basket filtration device at such a regulated rate that the chamber pressure remains essentially constant with time. When sufficient solid solute dissolved in the liquid carrier solvent has been added such that the filtration basket is known to be full of product solid, then the inlet flow of injection solution is temporarily halted while pure anti-solvent continues to flow into and out of the precipitation chamber at the operating pressure so as to flush the precipitation chamber of anti-solvent containing miscible carrier solvent. After a few residence volumes of pure anti-solvent are forced through the chamber, the anti-solvent inlet is shut off while the down stream venting of anti-solvent continues. This operation reduces the chamber pressure to ambient pressure so that the chamber may be opened and the filtration basket containing finely divided product solid removed. A thoroughly dry, free flowing finely divided solid product is obtained. The application of vacuum to the precipitation chamber before opening it may facilitate the complete removal (degassing) of residual anti-solvent, and/or residual liquid carrier solvent from the finely divided solid product. Flowing low pressure nitrogen or other inert gas through the depressurized chamber before opening also facilitates the complete removal of the anti-solvent which may be adsorbed on the product solid.

In a batch microprecipitation operation, where no exit stream from the down-stream side of the filtration basket is provided, other factors may influence the logical end of the microprecipitation process besides the complete filling of the product collection basket. The batch operation is typically limited by the fact that as the liquid carrier solvent accumulates in the precipitation chamber, the solubility of the finely divided solid product also increases in the liquid carrier solvent/anti-solvent mixture, up to a point where a significant amount of desired product would be soluble in the raffinate and therefore not collected in the filtration basket assembly. Further, as injection solution is continuously forced into the precipitation chamber to effect a batch microprecipitation, the pressure in the chamber continuously increases which may require termination of the batch operation so that maximum allowable pressure operating limits on the equipment are not exceeded.

Other reasonable methods of depressurizing and collecting the finely divided product solid can be envisioned in either the batch or continuous process operations, and as such do not limit the scope of this invention as the primary process effect is that contacting a solid dissolved in a good liquid carrier solvent with an anti-solvent produces an isolatable finely divided solid product which possesses useful and advantageous properties. One such alternative collection scheme would be to not collect the solid product in a sieve filter basket within the mixing and precipitation chamber, but to have the microprecipitated product/anti-solvent slurry pass through an exit channel which branches into two separate filtration/collection devices such that, with proper valving arrangement, one collection basket device can be depressurized and emptied while the other is collecting the continuously precipitating product solid. In this way intermittent suspension of the mixing and precipitation operation would not have to occur in the mixing chamber to effect emptying the collected product, and a truly continuous anti-solvent microprecipitation process could

be performed.

Operable conditions are where the solid is dissolved in the liquid carrier solvent to the extent of about 1 to about 100% of saturation for that solid in the particular liquid carrier solvent; preferred is from about 50 to about 95%, more preferred is from about 70 to about 95%.

Optionally, if desired, the process can be operated under sterile conditions to produce a finely divided sterile crystalline or powdered product by the use of a sterilizing filter (such as a 0.2 micron average pore size filter) apparatus in the lines leading to the autoclave (1). For example, the dissolved solute/carrier solvent solution can be filtration sterilized by passing that solution from the solution feed tank (3) through a sterilizing filter (14) and passing the compressed liquified or supercritical gas from gas storage tank (7) through a sterilizing filter (15) prior to mixing of the respective component solution and gas streams in a sterilized pressure vessel (1).

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

DEFINITIONS

All temperatures are in degrees Centigrade.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

CO_2 refers to carbon dioxide.

Raffinate refers to the solution or mixture formed containing the liquid carrier solvent dissolved in the anti-solvent with little or no dissolved solid (solute).

Pharmaceutical refers to and includes both prescription and non-prescription drugs.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

Term	P. T Conditions	Precise Thermodynamic State
Supercritical fluid	$T \geq T_c$ & $P \geq P_c$	fluid
Compressed liquified gas	$T < T_c$ & $P > P^{vap}$	liquid
Dense vapor	$T < T_c$ & $P < P^{vap}$	gas (vapor)

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 Batch Crystallization

A solution of triamcinolone acetonide (6.5 g) in THF (140 ml) is prepared.

Independently and referring to FIGURE 1, the 2-liter autoclave (1) is filled with carbon dioxide at 24° and, by means of the diaphragm compressor, the liquid in the autoclave is compressed to 100 bar. The stirring element (2) is then turned on (power source not shown). The 50 ml vessel (3) is filled with the THF/triamcinolone acetonide solution. At time 0, the high pressure metering pump is turned on which begins to deliver the THF/steroid solution into the agitated carbon dioxide at a flow rate of 7 ml/min. After 5-

1/2 minutes 39 ml of THF/steroid solution is delivered and the metering pump is turned off momentarily. The addition vessel is refilled with more THF/steroid solution and the metering pump is turned back on. After 12-1/2 minutes, the addition vessel is again nearly empty, so the metering pump was turned off. A total of 4.0 g of triamcinolone acetonide is delivered to the autoclave. The pressure in the autoclave (1) is released by slowly venting the contained carbon dioxide/THF high pressure liquid mixture through the bottom valve (5) of the autoclave (the flashed gas was vented to the atmosphere). A wash is then applied to the crystals by refilling the autoclave with liquid carbon dioxide and pressurizing the vessel to 60 bar, stirring for 10 minutes, then releasing the pressure out of the bottom valve (5). The agitator (2) is then turned off. Again carbon dioxide is vented thru the bottom valve (5). The top (8) of the autoclave is then removed and the filter basket (9) taken out. About 1 gram of fine, white powder adheres to the sides of the filter basket and covering most of the bottom 10 micron filter plate (10) in a thin layer.

Upon examination of the powder with a calibrated light microscope, it is found that most of the individual particles are of a size less than 10 microns with a few being as large as 20-30 microns.

EXAMPLE 2 Continuous Microprecipitation

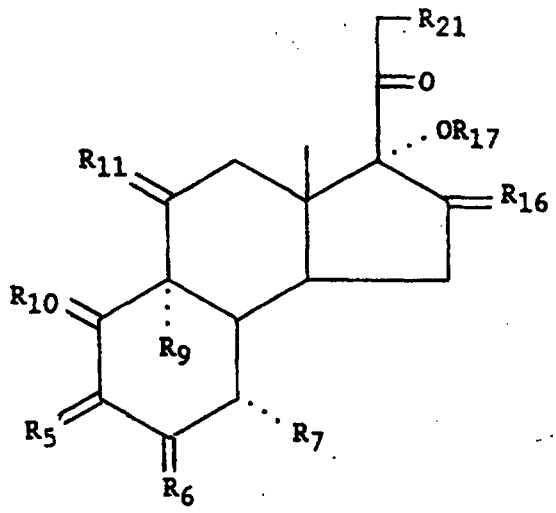
This is the preferred mode of operation. Significantly more product can be made per lot.

A less than saturated injection solution is prepared by dissolving triamcinolone acetonide (8.0 g) in THF (250 ml) at 20-25°. The autoclave (1) with filtration basket in place is then pressurized with CO_2 by means of compressor (11) to 110 bar and heated to 49° while stirring at 2200 RPM. The addition vessel (3) is filled with the triamcinolone acetonide/THF injection solution (250 ml). The bottom valve (5) on the autoclave is then opened and CO_2 is allowed to enter and to vent from the bottom while keeping the autoclave pressure constant at 110-111 bar by means of the back-pressure regulator (12).

With the pure carbon dioxide flowing at a steady state rate of about 30 g/min, the high pressure metering pump (4) is turned on thus forcing the 20-25° THF/triamcinolone acetonide injection solution into the autoclave (1) at a constant rate of 6.8 ml/min. The injection is continued for 34 minutes until about 230 ml of injection solution is added to continuously flowing carbon dioxide (0.90 kg). The injection solution addition is then stopped, but about 0.2 kg of pure carbon dioxide at 49° and 110 bar is allowed to flow through the autoclave chamber and collected solid product to purge the chamber of residual THF.

The carbon dioxide inlet is then shut off but the carbon dioxide venting is continued from the bottom of the autoclave until the pressure is reduced to ambient pressure. The autoclave is opened and the basket filter assembly is removed. The collection chamber contains triamcinolone acetonide as a fine white dry powder (7.05 g) which corresponds to an 88 wt % recovery. The average particle size of the micro-precipitated product is about 5-10 microns by calibrated light microscopy.

CHART A



(steroid)

Claims

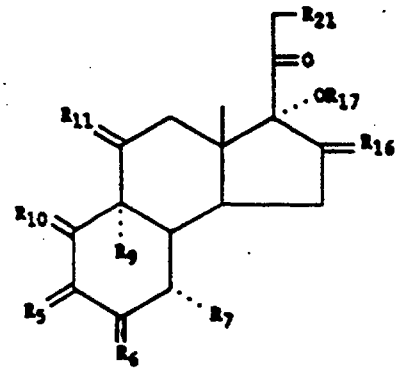
1. A process for producing a finely-divided solid, which comprises
   (1) dissolving the solid to be finely-divided in a liquid carrier solvent, to form an injection solution; and
   (2) adding the injection solution to a volume of anti-solvent sufficient to precipitate or crystallise the solid,
   wherein the anti-solvent is a supercritical fluid, a compressed liquefied gas or a dense vapour.

2. A process according to claim 1, wherein the solid is a pharmaceutical, agricultural chemical, commercial chemical, fine chemical, food item, photographic chemical, dye, explosive, paint, polymer or cosmetic.

3. A process according to claim 1, wherein the solid is a pharmaceutical.

4. A process according to claim 3, wherein the pharmaceutical is a steroid, benzodiazepene, penicillin or cephalosporin.

5. A process according to claim 3, wherein the pharmaceutical is a steroid of the formula



wherein either R_{10} is α-R_{10-1}:β-CH_3, and R_{10-1} and R_5 are taken together and are $-CH_2-CH_2-CO-CH=$ or $-CH=CH-CO-CH=$, or R_{10} and R_5 are taken together and are $=CH-CH=COH-CH=$;
R_6 is H:H, α-F:β-H or α-CH_3:β-H;
R_7 is H or $-S-CO-CH_3$;
R_9 is H, F, Cl or Br;
R_{11} is $=O$ or α-H:β-OH;
R_{16} is H:H, α-OH:β-H, α-CH_3:β-H or α-H:β-CH_3;
R_{17} is H or $-CO-(C_1-C_5$ alkyl); and
R_{21} is Cl, OH or $-O-CO-(C_1-C_3$ alkyl);
or an acetonide thereof when R_{16} is α-OH:β-H and R_{17} is H.

6. A process according to claim 3, wherein the pharmaceutical is selected from triamcinolone acetonide, triamcinolone, dexamethasone, dexamethasone sodium phosphate, methylprednisolone acetate, hydrocortisone, hydrocortisone acetate, medroxyprogesterone acetate, isoflupredone acetate, alprazolam, triazolam, pencillin, glyburide, ampicillin, ibuprofen, spectinomycin, erythromycin, flurbiprofen and their salts.

7. A process according to any preceding claim, wherein the liquid carrier solvent is an organic solvent capable of dissolving the solute.

8. A process according to any preceding claim, wherein the liquid carrier solvent is selected from
   C_1-C_6 alkanols;
   benzyl alcohol;
   R_b-O-R_c or R_b-CO-R_c where R_b and R_c are the same or different and are C_1-C_4 alkyl, with the proviso that the total number of carbon atoms is not more than 6;

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cyclic ethers consisting of 5-8 ring atoms;
C_2-C_5 alkanals;
R_f-CO-NR_gR_h where R_f, R_g and R_h are the same or different and are H, CH_3 or C_2H_5, with the proviso that R_g and R_h are not both H when R_f is CH_3 or C_2H_5;
R_f-CO-O-R_j where R_j is C_1-C_4 alkyl and R_j is H or C_1-C_4 alkyl;
benzene, chlorobenzene, dichlorobenzenes, toluene or xylenes;
methane optionally substituted with 1-4 Cl;
ethane optionally substituted with 1-3 Cl;
ethene optionally substituted with 1-3 Cl;
C_3-C_8 n-alkanes optionally substituted with 1-4 Cl;
freons;
CH_3CN;
glyme; and mixtures thereof.

9. A process according to any preceding claim, wherein the liquid carrier solvent is selected from water, C_1-C_7 alkanols, benzyl alcohol, THF, diethyl ether, methyl tert-butyl ether, formamide, DMF, N,N-dimethylacetamide, acetone, methyl ethyl ketone, pentane, hexane, heptane, octane, cyclopentane, benzene, toluene, xylenes, pyridine, methylene chloride, chloroform, carbon tetrachloride, chloromethane, ethylene dichloride, butyl chloride, trichloroethylene, 1,1,2-trichlorotrifluoroethane, dioxane, chlorobenzene, ethyl acetate, butyl acetate, acetonitrile, glyme, and mixtures thereof.

10. A process according to any preceding claim, wherein the anti-solvent is selected from carbon dioxide, ethane, ethylene, nitrous oxide, CHF_3, dimethyl ether, propane, butane, isobutanes, propylene, $CClF_3$, SF_6, $CBrF_3$, $CHClF_2$, hexafluoroethane, carbon tetrafluoride and mixtures thereof.

11. A process according to any preceding claim, wherein the solid is dissolved in the liquid carrier solvent to a level of 1 to 100% by weight saturation.

12. A process according to any preceding claim, wherein the liquid carrier solvent and the anti-solvent are completely miscible.

13. A process according to any preceding claim, which comprises sterilising the solution and the anti-solvent by passing each through sterilising filters, and then mixing the sterilised solution and the sterilised anti-solvent in a sterilised pressure vessel.

14. A process according to any preceding claim, which comprises adding the injection solution continuously to the anti-solvent, and collecting the finely-divided solid in a continuous manner.

15. A process according to any of claims 1 to 13, which comprises adding the injection solution to the anti-solvent and collecting the finely-divided solid in a batch manner.

16. A process according to any preceding claim, which comprises collecting the finely-divided solid, and aiding the collection by the application of heat, vacuum, forced low pressure inert gas or a combination thereof.

Patentansprüche

1. Verfahren zur Herstellung eines feinverteilten Feststoffes, umfassend
(1) Auflösen des feinzuverteilenden Feststoffes in einem flüssigen Trägerlösungsmittel, um eine Injektionslösung zu bilden, und
(2) Zugeben der Injektionslösung zu einem zur Fällung oder Kristallisation des Feststoffes ausreichenden Volumen eines Antilösungsmittels,
wobei das Antilösungsmittel aus einem superkritischen Fluidum, einem komprimierten verflüssigten Gas oder einem dichten Dampf besteht.

2. Verfahren nach Anspruch 1, wobei der Feststoff aus einem Arzneimittel, einer Chemikalie für die Landwirtschaft, einer handelsüblichen Chemikalie, einer Feinchemikalie, einem Nahrungsmittel, einer photographischen Chemikalie, einem Farbstoff, einem Sprengstoff, einer Farbe, einem Polymeren oder

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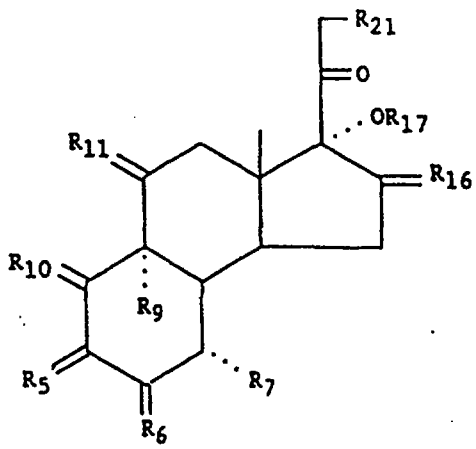
einem kosmetischen Stoff besteht.

3. Verfahren nach Anspruch 1, wobei der Feststoff aus einem Arzneimittel besteht.

4. Verfahren nach Anspruch 3, wobei das Arzneimittel aus einem Steroid, Benzodiazepin, Penicillin oder Cephalosporin besteht.

5. Verfahren nach Anspruch 3, wobei das Arzneimittel aus einem Steroid der Formel:



worin entweder R_{10} für α-R_{10-1}:β-CH_3 mit R_{10-1} und R_5 zusammengenommen gleich -CH_2-CH_2-CO-CH= oder -CH=CH-CO-CH= steht oder R_{10} und R_5 zusammengenommen =CH-CH=COH-CH= bedeuten,
R_6 für H:H, α-F:β-H oder α-CH_3:β-H,
R_7 für H oder -S-CO-CH_3,
R_9 für H, F, Cl oder Br,
R_{11} für =O oder α-H:β-OH,
R_{16} für H:H, α-OH:β-H, α-CH_3:β-H oder α-H:β-CH_3,
R_{17} für H oder -CO-(C_1-C_5-Alkyl) und
R_{21} für Cl, OH oder -O-CO-(C_1-C_3-Alkyl)
stehen,
oder einem Acetonid davon, wenn R_{16} für α-OH:β-H und
R_{17} für H stehen, besteht.

6. Verfahren nach Anspruch 3, wobei das Arzneimittel aus Triamcinolonacetonid, Triamcinolon, Dexamethason, Dexamethasonnatriumphosphat, Methylprednisolonacetat, Hydrocortison, Hydrocortisonacetat, Medroxyprogesteronacetat, Isoflupredonacetat, Alprazolam, Triazolam, Penicillin, Glyburid, Ampicillin, Ibuprofen, Spectinomycin, Erythromycin, Flurbiprofen und ihren Salzen ausgewählt ist.

7. Verfahren nach einem der vorhergehenden Ansprüche, wobei das flüssige Trägerlösungsmittel aus einem organischen Lösungsmittel mit der Fähigkeit zur Auflösung des Lösungsstoffes besteht.

8. Verfahren nach einem der vorhergehenden Ansprüche, wobei das flüssige Trägerlösungsmittel aus der Gruppe C_1-C_5-Alkanole,
Benzylalkohol,
R_b-O-R_c oder R_b-CO-R_c, mit R_b und R_c, die gleich oder verschieden sein können, gleich C_1-C_4-Alkyl, wobei gilt, daß die Gesamtzahl der Kohlenstoffatome nicht mehr als 6 beträgt,
cyclische Ether mit 5 - 8 Ringatomen,
C_2-C_5-Alkanale,
R_f-CO-NR_gR_h mit R_f, R_g und R_h, die gleich oder verschieden sein können, gleich H, CH_3 oder C_2H_5, wobei gilt, daß R_g und R_h nicht beide H bedeuten, wenn R_f für CH_3 oder C_2H_5 steht,
R_f-CO-O-R_j mit R_f gleich C_1-C_4-Alkyl und R_j gleich H oder C_1-C_4-Alkyl,
Benzol, Chlorbenzol, Dichlorbenzole, Toluol oder Xylole,

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gegebenenfalls mit 1 - 4 Cl substituiertes Methan,
gegebenenfalls mit 1 - 3 Cl substituiertes Ethan,
gegebenenfalls mit 1 - 3 Cl substituiertes Ethen,
gegebenenfalls mit 1 - 4 Cl substituierte C_3-C_8 n-Alkane,
Freone,
CH_3CN,
Glyme und Mischungen daraus
ausgewählt ist.

9. Verfahren nach einem der vorhergehenden Ansprüche, wobei das flüssige Trägerlösungsmittel aus Wasser, C_1-C_7-Alkanolen, Benzylalkohol, THF, Diethylether, Methyl-tert.-butylether, Formamid, DMF, N,N-Dimethylacetamid, Aceton, Methylethylketon, Pentan, Hexan, Heptan, Octan, Cyclopentan, Benzol, Toluol, Xylole, Pyridin, Methylenchlorid, Chloroform, Tetrachlorkohlenstoff, Chlormethan, Ethylendichlorid, Butylchlorid, Trichlorethylen, 1,1,2-Trichlortrifluorethan, Dioxan, Chlorbenzol, Ethylacetat, Butylacetat, Acetonitril, Glyme und Mischungen daraus ausgewählt ist.

10. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Antilösungsmittel aus Kohlendioxid, Ethan, Ethylen, Distickstoffoxid, CHF_3, Dimethylether, Propan, Butan, Isobutane, Propylen, $CClF_3$, SF_6, $CBrF_3$, $CHClF_2$, Hexafluorethan, Kohlenstofftetrachlorid und Mischungen daraus ausgewählt ist.

11. Verfahren nach einem der vorhergehenden Ansprüche, wobei der Feststoff im flüssigen Trägerlösungsmittel bis zu einem Grad von 1 - 100 Gew.-% Sättigung gelöst ist.

12. Verfahren nach einem der vorhergehenden Ansprüche, wobei das flüssige Trägerlösungsmittel und das Antilösungsmittel vollständig mischbar sind.

13. Verfahren nach einem der vorhergehenden Ansprüche, umfassend ein Sterilisieren der Lösung und des Antilösungsmittels durch Durchleiten der beiden durch Sterilisationsfilter und anschließendes Mischen der sterilisierten Lösung und des sterilisierten Antilösungsmittels in einem sterilisierten Druckkessel.

14. Verfahren nach einem der vorhergehenden Ansprüche, umfassend ein kontinuierliches Zugeben der Injektionslösung zu dem Antilösungsmittel und Sammeln des feinverteilten Feststoffes in einer kontinuierlichen Weise.

15. Verfahren nach einem der Ansprüche 1 bis 13, umfassend ein Zugeben der Injektionslösung zu dem Antilösungsmittel und ein chargenweises Sammeln des feinverteilten Feststoffes.

16. Verfahren nach einem der vorhergehenden Ansprüche, umfassend ein Sammeln des feinverteilten Feststoffs und Unterstützen des Sammelns durch Einwirkenlassen von Wärme, Vakuum, eines durch Zwang auf niedrigen Druck gebrachtes Inertgases oder einer Kombination daraus.

Revendications

1. Procédé de production d'une substance solide finement divisée, qui comprend
(1) la dissolution de la substance solide à diviser finement dans un solvant liquide servant de véhicule, pour former une solution d'injection ; et
(2) l'addition de la solution d'injection à un volume d'anti-solvant suffisant pour la précipitation ou la cristallisation de la substance solide,
dans lequel l'anti-solvant est un fluide surcritique, un gaz liquéfié comprimé ou une vapeur dense.

2. Procédé suivant la revendication 1, dans lequel la substance solide est un produit pharmaceutique, une substance chimique utilisée en agriculture, une substance chimique à usage commercial, une substance chimique de grande pureté, un produit alimentaire, une substance chimique utilisée en photographie, un colorant, un explosif, une peinture, un polymère ou un produit cosmétique.

3. Procédé suivant la revendication 1, dans lequel la substance solide est un produit pharmaceutique.

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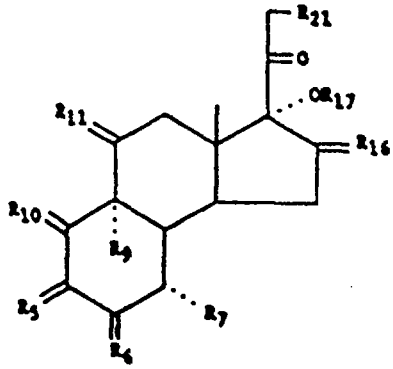
4. Procédé suivant la revendication 3, dans lequel le produit pharmaceutique est un stéroïde, une benzodiazépine, une pénicilline ou une céphalosporine.

5. Procédé suivant la revendication 3, dans lequel le produit pharmaceutique est un stéroïde de formule



dans laquelle R_{10} représente un groupe α-R_{10-1}:β-CH_3, et R_{10-1} et R_5 sont pris conjointement et représentent un groupe -CH_2-CH_2-CO-CH= ou -CH=CH-CO-CH=, ou bien R_{10} et R_5 sont pris conjointement et représentent un groupe =CH-CH=COH-CH= ;

R_6 représente un groupe H:H, α-F:β-H ou α-CH_3:β-H ;

R_7 représente H ou un groupe -S-CO-CH_3 ;

R_9 représente H, F, Cl ou Br ;

R_{11} représente =O ou un groupe α-H:β-OH ;

R_{16} représente un groupe H:H, α-OH:β-H, α-CH_3:β-H ou α-H:β-CH_3 ;

R_{17} représente H ou un groupe -CO-(alkyle en C_1 à C_5) ; et

R_{21} représente un groupe Cl, OH ou -O-CO-(alkyle en C_1 à C_3) ;

ou une de ses combinaisons acétoniques lorsque R_{16} *représente un groupe* α-OH:β-H *et* R_{17} représente H.

6. Procédé suivant la revendication 3, dans lequel le produit pharmaceutique est choisi entre une combinaison acétonique de triamcinolone, la triamcinolone, la dexaméthasone, le phosphate sodique de dexaméthasone, l'acétate de méthylprednisolone, l'hydrocortisone, l'acétate d'hydrocortisone, l'acétate de medroxyprogestérone, l'acétate d'isofluprédone, l'alprazolam, le triazolam, la pénicilline, le glyburide, l'ampicilline, l'ibuprofène, la spectinomycine, l'érythromycine, le flurbiprofène et leurs sels.

7. Procédé suivant l'une quelconque des revendications précédentes, dans lequel le solvant liquide servant de véhicule est un solvant organique capable de dissoudre le soluté.

8. Procédé suivant l'une quelconque des revendications précédentes, dans lequel le solvant liquide servant de véhicule est choisi entre

des alcanols en C_1 à C_5 ;

l'alcool benzylique ;

un composé de formule R_b-O-R_c ou R_b-CO-R_c, dans laquelle R_b et R_c sont identiques ou différents et représentent des groupes alkyle en C_1 à C_4, sous réserve que le nombre total d'atomes de carbone soit non supérieur à 6 ;

des éthers cycliques consistant en 5 à 8 atomes dans le noyau ;

des alcanols en C_2 à C_5 ;

un composé de formule R_f-CO-NR_gR_h dans laquelle R_f, R_g et R_h sont identiques ou différents et représentent H, des groupes CH_3 ou C_2H_5, sous réserve que R_g et R_h ne représentent pas l'un et l'autre H lorsque R_f représente un groupe CH_3 ou CH_2H_5 ;

un composé de formule R_f-CO-O-R_j dans laquelle R_f représente un groupe alkyle en C_1 à C_4 et R_j représente H ou un groupe alkyle en C_1 à C_4 ;

le benzène, le chlorobenzène, les dichlorobenzènes, le toluène ou les xylènes ;

le méthane, facultativement substitué avec 1 à 4 Cl ;

l'éthane, facultativement substitué avec 1 à 3 Cl ;

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l'éthène, facultativement substitué avec 1 à 3 Cl ;
des n-alcanes en C_3 à C_8, facultativement subsitués avec 1 à 4 Cl ;
des fréons ;
CH_3CN ;
le glyme ; et leurs mélanges.

9. Procédé suivant l'une quelconque des revendications précédentes, dans lequel le solvant liquide servant de véhicule est choisi entre l'eau, des alcanols en C_1 à C_7, l'alcool benzylique, le THF, l'éther diéthylique, l'éther méthyltertiobutylique, le formamide, le DMF, le N,N-diméthylacétamide, l'acétone, la méthyléthylcétone, le pentane, l'hexane, l'heptane, l'octane, le cyclopentane, le benzène, le toluène, les xylènes, la pyridine, le chlorure de méthylène, le chloroforme, le tétrachlorure de carbone, le chlorométhane, le dichlorure d'éthylène, le chlorure de butyle, le trichloréthylène, le 1,1,2-trichlorotrifluoréthane, le dioxanne, le chlorobenzène, l'acétate d'éthyle, l'acétate de butyle, l'acétonitrile, le glyme et leurs mélanges.

10. Procédé suivant l'une quelconque des revendications précédentes, dans lequel l'anti-solvant est choisi entre l'anhydride carbonique, l'éthane, l'éthylène, l'oxyde nitreux, CHF_3, l'éther diméthylique, le propane, le butane, les isobutanes, le propylène, $CClF_3$, SF_6, $CBrF_3$, $CHClF_2$, l'hexafluoréthane, le tétrafluorure de carbone et leurs mélanges.

11. Procédé suivant l'une quelconque des revendications précédentes, dans lequel la substance solide est dissoute dans le solvant liquide servant de véhicule en une quantité allant de 1 à 100 % en poids de la saturation.

12. Procédé suivant l'une quelconque des revendications précédentes, dans lequel le solvant liquide servant de véhicule et l'anti-solvant sont totalement miscibles.

13. Procédé suivant l'une quelconque des revendications précédentes, qui comprend la stérilisation de la solution et de l'anti-solvant par passage de chaque substance à travers des filtres stérilisants, puis le mélange de la solution stérilisée et de l'anti-solvant stérilisé dans un récipient stérilisé résistant à la pression.

14. Procédé suivant l'une quelconque des revendications précédentes, qui comprend l'addition de la solution d'injection de manière continue à l'anti-solvant, et la séparation de manière continue de la substance solide finement divisée.

15. Procédé suivant l'une quelconque des revendications 1 à 13, qui comprend l'addition de la solution d'injection à l'anti-solvant et la séparation de manière discontinue de la substance solide finement divisée.

16. Procédé suivant l'une quelconque des revendications précédentes, qui comprend la séparation de la substance solide finement divisée et l'amélioration de la séparation par chauffage, mise sous vide, application forcée d'un gaz inerte sous basse pression ou une association de ces opérations.

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