



(86) Date de dépôt PCT/PCT Filing Date: 2005/08/31
(87) Date publication PCT/PCT Publication Date: 2006/03/09
(45) Date de délivrance/Issue Date: 2012/04/17
(85) Entrée phase nationale/National Entry: 2007/02/28
(86) N° demande PCT/PCT Application No.: AU 2005/001321
(87) N° publication PCT/PCT Publication No.: 2006/024095
(30) Priorités/Priorities: 2004/08/31 (US60/606,278);
2005/04/12 (US60/670,722)

(51) Cl.Int./Int.Cl. *A61K 9/107* (2006.01),
A61K 9/10 (2006.01), *A61P 17/00* (2006.01),
B01F 3/08 (2006.01), *B01F 3/20* (2006.01),
B01F 3/22 (2006.01)
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(54) Titre : PROCEDE ET COMPOSITIONS A BASE DE MICROEMULSION & EMULSION SUBMICRONIQUE
(54) Title: MICROEMULSION & SUB-MICRON EMULSION PROCESS & COMPOSITIONS

(57) **Abrégé/Abstract:**

There is provided a process for the preparation of an oil in water (O/W) microemulsion or sub-micron emulsion composition for dermal delivery of at least one pharmaceutically active ingredient, the method including the steps of a) Admixing a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxylated alcohols; and one or more lipophilic surfactants, and a second part including water and at least one hydrophilic surfactant to achieve homogeneity, b) heating the mix of step a) to a phase assembly temperature in the range of 40 - 99°C, preferably 45 - 950C, more preferably 65 - 850C with continuous mixing to obtain a microemulsion or sub-micron emulsion, c) allowing said microemulsion or sub-micron emulsion to cool, and d) adding a third part to said microemulsion or sub-micron emulsion at a temperature between 2°C and said phase assembly temperature, said third part if necessary being premixed and heated until the components are dissolved and including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant. The phase assembly temperature can be determined visually by the achievement of translucence in the composition or by measures such as conductivity which peaks and then is maintained at a plateau whilst phase assembly occurs. It has been found that whilst if a non-surfactant amphiphilic type compound such as the polyol is added together with the second part as would conventionally be the case, a microemulsion or sub-micron emulsion is not formed, by adding the so called third part, phase assembly occurs at a lower temperature than would be expected and moreover, this phase appears to assist in maintaining the microemulsion or sub-micron emulsion characteristics of the formulation during storage at normal temperatures.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 March 2006 (09.03.2006)

PCT

(10) International Publication Number
WO 2006/024095 A1

(51) International Patent Classification⁷: **A61K 9/107**,
9/10, 7/48, B01F 3/08, 3/20, 3/22, A61P 17/00

(21) International Application Number:
PCT/AU2005/001321

(22) International Filing Date: 31 August 2005 (31.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/606,278 31 August 2004 (31.08.2004) AU
60/670,722 12 April 2005 (12.04.2005) AU

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

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

Published:

— with international search report

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

(54) Title: MICROEMULSION & SUB-MICRON EMULSION PROCESS & COMPOSITIONS

(57) Abstract: There is provided a process for the preparation of an oil in water (O/W) microemulsion or sub-micron emulsion composition for dermal delivery of at least one pharmaceutically active ingredient, the method including the steps of a) Admixing a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxyated alcohols; and one or more lipophilic surfactants, and a second part including water and at least one hydrophilic surfactant to achieve homogeneity, b) heating the mix of step a) to a phase assembly temperature in the range of 40 - 99°C, preferably 45 - 950C, more preferably 65 - 850C with continuous mixing to obtain a microemulsion or sub-micron emulsion, c) allowing said microemulsion or sub-micron emulsion to cool, and d) adding a third part to said microemulsion or sub-micron emulsion at a temperature between 2°C and said phase assembly temperature, said third part if necessary being premixed and heated until the components are dissolved and including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant. The phase assembly temperature can be determined visually by the achievement of translucence in the composition or by measures such as conductivity which peaks and then is maintained at a plateau whilst phase assembly occurs. It has been found that whilst if a non-surfactant amphiphilic type compound such as the polyol is added together with the second part as would conventionally be the case, a microemulsion or sub-micron emulsion is not formed, by adding the so called third part, phase assembly occurs at a lower temperature than would be expected and moreover, this phase appears to assist in maintaining the microemulsion or sub-micron emulsion characteristics of the formulation during storage at normal temperatures.

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MICROEMULSION & SUB-MICRON EMULSION PROCESS & COMPOSITIONS**FIELD OF THE INVENTION**

This invention relates to a method of formulation of microemulsions and sub-micron emulsions useful in cosmetic and therapeutic applications in the field of dermatology. In particular, the invention relates to methods of formulation of stable microemulsions and sub-micron emulsions which contain ingredients which are known to be disruptive of the physical state of the formulation. The invention also relates to cosmetic and therapeutic microemulsion and sub-micron emulsion compositions arising from these methods. Methods of cosmetic and therapeutic treatment using the microemulsions and sub-micron emulsions are encompassed by this invention as are the uses of the compositions arising from the formulation method in appropriate treatments.

BACKGROUND

The size of a particle is critical to its ability to cross the skin barrier and therefore its ability to deliver a pharmaceutically active ingredient for the treatment of local or systemic medical conditions of the patient concerned. As particles become smaller (particularly below 100 nm), the percentage of exposed surface area of a particle in proportion to its total volume when compared to unrefined material is increased, and hence its potential efficacy is increased.

The characteristics of sub-micron particles in their application to the delivery of pharmaceutically active ingredients across the skin barrier may be summarised as follows:

Particle size	Description	Characteristics
300-1000 nm	Emulsion	Blue-white, milky liquid, reasonable physical stability. Particles reside on skin surface → transdermal delivery.
100-300 nm	Sub-micron Emulsion	Bluish, translucent liquid. Enhanced physical stability. Particles reside on skin surface → enhanced transdermal delivery.
10-100 nm	Microemulsion	Translucent-transparent liquid. Excellent physical stability. Particles reside on skin surface → enhanced transdermal delivery.

<5 nm	Nanoparticles/ Nano-dispersion/ Micelles	Translucent-transparent liquid. Excellent physical stability. Particles reside on skin surface, within stratum corneum and in hair follicles → optimal transdermal delivery.
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Because of the desirable characteristics of so called microemulsions, and sub-micron emulsions, attempts have been made to perfect the means of their manufacture. Essentially, the much higher ratio of emulsifier to disperse phase is that feature which differentiates a microemulsion from a macroemulsion. The aim is to stabilise oil phases in water phases, or vice versa. The nature of the emulsifier (or surfactant) used is clearly very important. Oil in water micro emulsions are particularly difficult to formulate and, generally speaking, simply adapting the mode, or means of homogenization, or increasing the amount of emulsifier present will not guarantee the product is a microemulsion. The choice of emulsifier is reportedly critical to the success of the formulation (BK: MicroEmulsions Theory and Practice, Prince, Leon (ed) pp33-50, Academic Press, NY, USA, 1977).

Water in oil systems are made by blending the oil and emulsifier, with a little heat if necessary, and then adding water. The amount of water that can be added to a given system of emulsifier and oil may not always be high enough for the application in mind. In that event, it becomes necessary to try other emulsifiers. When one is found that permits the desired water uptake, it may be convenient from a processing viewpoint to add the mixture of emulsifier and oil to the water. Again, warming the system may hasten the mixing process. In systems of oil, water and emulsifier that are capable of forming microemulsions, the order of mixing does not affect the end result.

The simplest way to make an oil in water microemulsion is to blend the oil and emulsifier and then pour this liquid mixture into the water with mild stirring. Another technique is to make a crude macroemulsion of the oil and one of the emulsifiers, for example, a soap. By using low volumes of water a gel is formed. This gel is then changed into a clear solution by titration with a second surface active agent like an alcohol. This system may then be transformed into an opalescent oil in water microemulsion of the desired concentration by further addition of water. By far the most common method of making an oil in water

microemulsion, especially in the trial and error stage, however, is by the so-called inversion process.

In actual practice, oils which are capable of being microemulsified, i.e. "emulsifiable oils", as opposed to those which may be dispersed in micellar solution, invert by the slow addition of water from a fluid water in oil dispersion through a viscoelastic gel stage to a fluid oil in water microemulsion. 100% emulsifier on the weight of the oil may be employed. After careful blending, with heat if necessary, water is added to the blend in a beaker. This is done in successive, small aliquots. If the chemistry is right, a clear, transparent water in oil dispersion first forms. This is fluid. As more water is added, at about equal volumes of water and oil/emulsifier blend, the system begins to become more viscous. As more water is added, it becomes very viscous, ultimately becoming a heavy gel. At this point it is frequently helpful to apply heat to thin the gel and facilitate passage through this stage. With the addition of more water, the gel eventually thins out to a fluid oil in water microemulsion which can readily be identified by its clarity or opalescence.

The highly viscous intermediate gel stages are not microemulsions but are sometimes so called, as in the case of ringing gels used as hair pomades. These systems are actually liquid crystalline phases and occur because of the particular sequence of mixing employed in forming the microemulsion.

Given the importance of the emulsifier to the successful formulation of the microemulsion, systems have been developed to assist in selection of the emulsifier. One such system (Shiroda, K., J. Colloid Interface Sci, 24, 4 (1967)) is that based upon the temperature at which an emulsifier causes an oil in water emulsion to invert to a water in oil emulsion. It is known as the Phase Inversion Temperature (PIT) System. It provides information about various oils, phase volume relationships, and the concentration of emulsifier required. The system is established on the proposition that the hydrophilic lipophilic balance (the "HLB") of a non-ionic surfactant changes with temperature and that the inversion of emulsion type occurs when the hydrophilic and lipophilic tendencies of the emulsifier just balance each other. No emulsion forms at this temperature. Emulsions stabilised with non-ionic agents are oil in water types at low temperature and invert to water in oil types at elevated temperature. It goes

without saying that use of more than one emulsifier in a composition may positively influence the formulation of a microemulsion. PIT techniques require a significant input of energy in order to attain a sub-micron emulsion. The process requires high temperature so as to render the ethoxylated surfactant hydrophobic, whereby the oil in water emulsion becomes a water in oil emulsion, and thereafter, the conversion of the water in oil dispersion to a oil in water dispersion is effected upon subsequent cooling of the formulation. At least because of the degradative effect that heat has upon certain active ingredients, it would be desirable to reduce the energy requirements for such processes as this is likely to reduce the risk of crystallisation of poorly soluble active ingredients occurring upon normal temperature cycling of the stored product

Microemulsion technology has been the subject of relatively intense investigation since the late 1950's when hair gels using the technology were first developed.

One patent US 6,333,362 (L'OREAL) describes an ultrafine foaming oil in water emulsion where the particle size of the oil particles constituting the oil phase range from 50-1000 nm. The PIT technique is used to manufacture the formulation. Example 1 describes a formulation as follows:

Phase 1	%
dicapryl ether	7.7
Isocetyl stearate	3.0
cetearyl isononanoate	4.0
beheneth-9	4.5

Phase 2	%
Distilled water	14.7
Preservative	q.s

Phase 3	%
distilled water	q.s.100
sodium lauryl ether sulphate	5.0

where the sodium lauryl ether sulphate in phase 3 acts as the foaming agent on dispensing the product from its pressurised can. To prepare the formulation phases 1 and 2 were heated separately to 60°C and homogenised. Phase 2 was poured slowly, with stirring, onto Phase 1 and the mixture was heated as far as
5 the phase inversion temperature, which was around 85°C. The heating was stopped and Phase 3 was poured in unheated and the mixture was allowed to cool while slow stirring was maintained.

Nanoemulsions which contain an amphiphilic lipid phase composed of phospholipids, water and oil are known in the art. These emulsions exhibit the
10 disadvantage of being unstable on storage at conventional storage temperatures, namely between 0 and 45°C. They lead to yellow compositions and produce rancid smells which develop several days after storage. One example of such an emulsion is described in WO 03/08222 (BEIERDORF AG)

In practice there are challenges in formulating microemulsions. The point
15 at which the composition inverts from an oil in water or water in oil formulation, respectively, to a water in oil or oil in water formulation, known as the "set point" needs to be carefully monitored. If the set point is not reached before the product is poured out, inversion will not occur, and so a microemulsion will not be achieved. High set points in particular can be difficult to achieve and maintain.
20 Additives can be used to lower the set point but these can also have the effect of destabilising the microemulsion resulting in undesirable alteration of the viscosity of the microemulsion, cloudiness, and can also cause loss of invertible character altogether. Furthermore, although high levels of emulsifier can be desirable, on the other hand, high emulsifier content can lead to skin and eye irritation of the
25 user.

Propylene glycol, which is desirably included in dermatological compositions for its capacity as a penetration enhancer, is an additive that has been reported as undesirable in microemulsion technology because of its potential to disrupt or destabilise the formulation. WO 94/08603 (SMITHKLINE
30 BEECHAM CORPORATION) teaches the avoidance of propylene glycol and other polyhydroxyl alcohol cosurfactants because of the processing and stability issues they introduce.

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Another ingredient which is desirable in dermatological applications is petrolatum used for its occlusive and emollient properties. However because of its viscosity it is considered too difficult to incorporate in microemulsion formulations.

5 Another challenge in the application of microemulsions to the field of dermatology is the solubilisation of the pharmaceutically active ingredients in the formulations. Some pharmaceutically active ingredients are highly water soluble, or in the alternative are highly oil soluble. Others are sparingly soluble. A pharmaceutically active ingredient in solution provides better penetration than one
10 in suspension and, both of these provide better penetration than a drug as a solid. In the case where a pharmaceutically active ingredient is not easily solubilised, the need for an additive such as propylene glycol which can assist in penetration, is obvious, but conversely the ease of formation of a microemulsion is diminished.

In light of the foregoing, it is an object of this invention to identify methods
15 of formulating microemulsions and sub-micron emulsion formulations which may act as a vehicle for the delivery of a pharmaceutically active ingredient across the skin barrier for cosmetic or therapeutic purposes. It is a secondary object to achieve a means of incorporating one or more microemulsion disrupting substances, such as propylene glycol and/or petrolatum into such a
20 microemulsion or sub-micron emulsion at the same time maintaining the viscosity, appearance, stability and efficacy of the formulation.

Any discussion of documents, devices, acts or knowledge in this specification is included to explain the context of the invention. It should not be taken as admission that any of the information formed part of the prior art base or
25 the common general knowledge in the relevant art on or before the priority date of the present subject matter.

SUMMARY OF INVENTION

There is provided a process for the preparation of an oil in water (O/W) microemulsion or sub-micron emulsion composition for dermal delivery of at least
30 one pharmaceutically active ingredient, the process including the steps of

a) Admixing a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats,

halogen compounds or alkoxylated alcohols; and one or more lipophilic surfactants, and

a second part including water and at least one hydrophilic surfactant to achieve homogeneity,

5 b) heating the mix of step a) to a phase assembly temperature in the range of 40 – 99°C preferably 45 – 95°C; more preferably 65 – 85°C with continuous mixing to obtain an oil in water microemulsion or sub-micron emulsion,

 c) allowing said microemulsion or sub-micron emulsion to cool, and

10 d) adding a third part to said microemulsion or sub-micron emulsion at a temperature between 2°C and said phase assembly temperature, said third part if necessary being premixed and heated until the components are dissolved and including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that
15 when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.

 The phase assembly temperature can be determined visually by the achievement of translucence in the composition or by measures such as conductivity which peaks and then is maintained at a plateau whilst phase
20 assembly occurs.

 It has been found that if a non-surfactant amphiphilic type compound such as the polyol is added together with the second part as would conventionally be the case, a microemulsion or sub-micron emulsion is not formed. However, by adding the so called third part, phase assembly occurs at a lower temperature
25 than would be expected and moreover, this phase appears to assist in maintaining the microemulsion or sub-micron emulsion characteristics of the formulation during storage at normal temperatures.

 The water phase of the microemulsion or sub-micron emulsion is desirably added in two aliquots; in aliquots more preferably of about 70% and 30% by
30 weight of the total water phase. More preferably still, the second aliquot is added after the microemulsion or sub-micron emulsion has formed, at a temperature substantially below the temperature of the first aliquot, and at a rapid rate so as to

reduce the overall temperature of the composition preferably to below about 60°C whereby the microemulsion or sub-micron emulsion structure is fixed.

A pharmaceutically active ingredient may suitably be incorporated in any one or more of the three parts of the formulation during preparation. The most
5 appropriate part of incorporation will depend on the solubility characteristics of the pharmaceutically active ingredient and the preferred release profile of the resulting formulation. The pharmaceutically active ingredient is preferably one which is insoluble or only sparingly soluble in water. Preferably the pharmaceutically active ingredient is one or more water insoluble compounds
10 selected from the group consisting of corticosteroids, desonide, clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.

An occlusive agent which has the effect of adding emollient quality to the formulation is also desirably incorporated in the microemulsions or sub-micron emulsions by inclusion in the preparation of the first part of the composition.
15 Preferably the occlusive agent is petrolatum.

The microemulsion or sub-micron emulsion resulting from the process is desirably gassed using a suitable propellant so as to be deliverable as a foam or mousse.

A preferred form of this process for the preparation of a microemulsion or
20 sub-micron emulsion composition for dermal delivery of at least one pharmaceutically active ingredient, includes the steps of

a) heating a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxyated alcohols, and

25 one or more lipophilic surfactants to a temperature of 40 – 99°C, preferably 45 – 95°C, and more preferably 65 – 85°C and mixing to homogeneity,

b) heating a second part including water and at least one hydrophilic surfactant to a temperature of 40 – 99°C, preferably 45 – 95°C, and more preferably 65 – 85°C and mixing to achieve homogeneity,

30 c) adding said second part to said first part at a temperature of 40 – 99°C, preferably 45 – 95°C, and more preferably 65 – 85°C with continuous mixing whereby a microemulsion or sub-micron emulsion is formed at a phase assembly temperature,

d) allowing said microemulsion or sub-micron emulsion to cool, and
e) adding a third part to said microemulsion or sub-micron emulsion at a temperature between room temperature and said phase assembly temperature, said third part having been premixed, and if necessary heated until the
5 components are dissolved and including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.

There is also provided an oil in water microemulsion or sub-micron
10 emulsion composition for dermal delivery of at least one pharmaceutically active ingredient including an oil phase dispersed throughout a water phase, said oil phase including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxyated alcohols; and at least one lipophilic surfactant; and said water phase
15 including at least one hydrophilic surfactant, water and optionally non-surfactant amphiphilic compound, the weight ratio of the at least one hydrophilic surfactant to the at least one lipophilic surfactant being approximately 9.0:1.0 to 2.0:3.0. Preferably, the composition includes surfactants having an aggregated HLB number between 8.0 and 15.0, more preferably between 10 and 12 and still more
20 preferably between 9.7 and 11.8. More preferably, the lipophilic surfactant has an HLB number of less than 10, and the hydrophilic surfactant has an HLB number of greater than 10.

The pharmaceutically active ingredient may suitably be in either or both said oil and/or water phases. The most appropriate phase of incorporation will
25 depend on the solubility characteristics of the pharmaceutically active ingredient and the preferred release profile of the formulation. The pharmaceutically active ingredient is preferably one which is insoluble or only sparingly soluble in water. Preferably the pharmaceutically active ingredient is one or more water insoluble compounds selected from the group consisting of corticosteroids, desonide,
30 clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.

An occlusive agent is also desirably incorporated in the microemulsions or sub-micron emulsions in the oil phase of the composition. Preferably the occlusive agent is petrolatum.

The microemulsion or sub-micron emulsion is preferably formulated as a foam or mousse by the inclusion of a suitable propellant.

There is further provided an oil in water microemulsion or sub-micron emulsion composition, said composition prepared by a process including the

5 steps of

a) admixing a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxyated alcohols; and one or more lipophilic surfactants, and

10 a second part including water and at least one hydrophilic surfactant to achieve homogeneity,

b) heating the mix of step a) to a phase assembly temperature in the range of 40 – 99°C, preferably 45 – 95°C, more preferably 65 – 85°C with continuous mixing to obtain an oil in water microemulsion or sub-micron

15 emulsion,

c) allowing said microemulsion or sub-micron emulsion to cool, and

d) adding a third part to said microemulsion or sub-micron emulsion at a temperature between 2°C and the phase assembly temperature, said third part if necessary being premixed and heated until the components are dissolved and

20 including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.

The water phase of the microemulsion or sub-micron emulsion is desirably

25 added in two aliquots; in aliquots more preferably of about 70% and 30% by weight of the total water phase. More preferably still, the second aliquot is added after the microemulsion or sub-micron emulsion has formed, at a temperature substantially below the temperature of the first aliquot, and at a rapid rate so as to reduce the overall temperature of the composition preferably to below about 60°C

30 whereby the microemulsion or sub-micron emulsion structure is fixed.

A pharmaceutically active ingredient may suitably be incorporated in one or more of the three parts of the formulation during preparation. The most appropriate part of incorporation will depend on the solubility characteristics of the

pharmaceutically active ingredient and the preferred release profile of the resulting formulation. The pharmaceutically active ingredient is preferably one which is insoluble or only sparingly soluble in water. Preferably the pharmaceutically active ingredient is one or more water insoluble compounds
5 selected from the group consisting of corticosteroids, desonide, clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.

An occlusive agent is also desirably incorporated in the microemulsions or sub-micron emulsions by inclusion in the preparation of the oil phase of the composition. Preferably the occlusive agent is petrolatum.

10 The microemulsion or sub-micron emulsion resulting from the process is desirably gassed using a suitable propellant so as to be deliverable as a foam or mousse.

Preferably, there is provided an oil in water microemulsion or sub-micron emulsion composition, said composition being prepared by a process including
15 the steps of

a) heating a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxyated alcohols, and

one or more lipophilic surfactants to a temperature of 40 – 99°C, preferably
20 45 – 95°C, and more preferably 65 – 85°C and mixing to homogeneity,

b) heating a second part including water and at least one hydrophilic surfactant to a temperature of 40 – 99°C, preferably 45 – 95°C, and more preferably 65 – 85°C and mixing to achieve homogeneity,

c) adding said second part to said first part at a temperature of 40 –
25 99°C, preferably 45 – 95°C, and more preferably 65 – 85°C with continuous mixing whereby a microemulsion or sub-micron emulsion is formed at a phase assembly temperature,

d) allowing said microemulsion or sub-micron emulsion to cool, and

e) adding a third part to said microemulsion or sub-micron emulsion at
30 a temperature between room temperature and said phase assembly temperature said third part having been premixed, and if necessary heated until the components are dissolved and including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and

water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.

The invention further provides a method of medical or cosmetic treatment of a dermal condition including applying to the skin of a patient requiring such
5 treatment an effective amount of oil in water microemulsion or sub-micron emulsion composition including at least one pharmaceutically active ingredient, including an oil phase dispersed throughout a water phase, said oil phase including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxylated
10 alcohols; and at least one lipophilic surfactant, and said water phase includes at least one hydrophilic surfactant, water and optionally a non-surfactant amphiphilic type compound, the weight ratio of the at least one hydrophilic surfactant to the at least one lipophilic surfactant being approximately 9.0:1.0 to 2.0:3.0.

A pharmaceutically active ingredient may suitably be incorporated in one
15 or more of the phases of the composition. The most appropriate phase of incorporation will depend on the solubility characteristics of the pharmaceutically active ingredient and the preferred release profile of the resulting formulation. The pharmaceutically active ingredient is preferably one which is insoluble or only sparingly soluble in water. Preferably the pharmaceutically active ingredient is
20 one or more water insoluble compounds selected from the group consisting of corticosteroids, desonide, clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.

An occlusive agent is also desirably incorporated in the micromulsions or sub-micron emulsions by inclusion in the oil phase of the composition. Preferably
25 the occlusive agent is petrolatum.

The microemulsion or sub-micron emulsion is preferably formulated as a foam or mousse by the inclusion of a suitable propellant.

There is further provided a use of an oil in water microemulsion or sub-micron emulsion composition including an oil phase dispersed throughout a water
30 phase said oil phase including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds or alkoxylated alcohols; and at least one lipophilic surfactant, and said water phase includes at least one hydrophilic surfactant, water and optionally

a non-surfactant amphiphilic type compound, the weight ratio of the at least one hydrophilic surfactant to the at least one lipophilic surfactant being approximately 9.0:1.0 to 2.0:3.0 for manufacture of a cosmetic or medical preparation for treatment of a dermal condition. Preferably, the composition includes surfactants
5 having an aggregated HLB number between 8.0 and 15.0, more preferably between 10 and 12, and still more preferably between 9.7 and 11.8. More preferably, the lipophilic surfactant has an HLB number of less than 10, and the hydrophilic surfactant has an HLB number of greater than 10.

A pharmaceutically active ingredient may suitably be incorporated in one
10 or more of the phases of the composition during preparation. The most appropriate phase of incorporation will depend on the solubility characteristics of the pharmaceutically active ingredient and the preferred release profile of the resulting formulation. The pharmaceutically active ingredient is preferably one which is insoluble or only sparingly soluble in water. Preferably the
15 pharmaceutically active ingredient is one or more water insoluble compounds selected from the group consisting of corticosteroids, desonide, clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.

An occlusive agent is also desirably incorporated in the microemulsions or sub-micron emulsions by inclusion in the preparation of the oil phase of the
20 composition. Preferably the occlusive agent is petrolatum.

The microemulsion or sub-micron emulsion is preferably formulated as a foam or mousse by the inclusion of a suitable propellant.

The invention further provides, in a process for the preparation of an oil in water microemulsion or sub-micron emulsion composition, the use of a third part
25 in the preparation of said composition, said third part including at least one component selected from the group consisting of non-surfactant amphiphilic type compound, surfactant and water with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant compound, said third part being incorporated into said composition
30 subsequent to the establishment of a microemulsion or sub-micron emulsion formed by an oil phase including at least one of the group consisting of animal, mineral or vegetable oils, silanes, silicones, esters, fatty acids, fats, halogen compounds or alkoxylated alcohols; and at least one lipophilic surfactant which is

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emulsified throughout a water phase including water and at least one hydrophilic surfactant by a temperature induced phase assembly process.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic flow diagram showing one preferred
5 embodiment of the invention in which an ethanol-free 0.05% clobetasol propionate microemulsion is prepared. The method is described in detail in Example 6.

Figure 2 is a graphical representation of one preferred method of preparation of formulations according to the invention utilising the corticosteroid clobetasol propionate.

10 Figure 3 is a timeline of one preferred method of preparation of formulations according to the invention utilising the corticosteroid desonide.

Figure 4 is a graphical representation of the method depicted in the timeline of Figure 3.

Figure 5 shows the effect on particle size distribution of varying the ratio
15 of surfactants in betamethasone valerate compositions according to the invention.

Figure 6 shows the conductivity response from heating various compositions according to the invention to the assembly temperature, and then cooling them.

Figure 7 is a schematic flow diagram of the process used to produce
20 the formulation subject of the clinical trials described in Example 14.

DETAILED DESCRIPTION OF THE INVENTION

In compositions traditionally prepared for dermal delivery of pharmaceutically active ingredients it is conventional to add the pharmaceutically active ingredient and any non-surfactant, amphiphilic type compound, including, for

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example, a solvent for the active ingredient or a polyol acting as a solvent, emollient or penetration enhancer to the phase in which they are soluble, before the oil phase and the water phase are mixed together. This results in a product which is an emulsion or dispersion of one phase in the other. Without being limited by theory, it is found that by adding a third part, a microemulsion or sub-micron emulsion may be formed having the advantages discussed in the preamble of this specification. This is a particularly useful phenomenon where it is desirable to use pharmaceutically active ingredients which tend towards insolubility except in solvents including a polyol and/or alcohol. By effectively

lowering the temperature at which phase assembly is achieved, active ingredients which are degraded by exposure to temperature are more preserved than is the case in prior art formulations. It is thus believed that the shelf life of the formulations according to the invention can be prolonged as compared to prior art compositions.

Without being bound by theory, it is thought that when the non-surfactant, amphiphilic components such as propylene glycol, a typical polyol used in dermatological formulations because of its capacity as a penetration enhancer, and a solvent is present in the water phase, it interferes with the assembly or packing formation of the surfactants present in the composition around the oil particles and prevents the formation of microemulsion sized particles. The same is also true of the preservative, phenoxy ethanol. By the process of the invention, it is possible to reproducibly manufacture sub-micron particles at low temperature in the range 100-600 nm with the majority of particles being in the 100-200 nm range. The exclusion of propylene glycol from the initial water/oil phase mixing appears to allow the surfactants present the ability to pack into a microemulsion structure at a lower temperature than would otherwise be achieved and with the assistance of temperature manipulation, to fix in place.

Throughout this specification, the term "non-surfactant, amphiphilic type compound" should be taken to include compounds which are miscible with water and other organic excipients, and which may act as a solvent for a pharmaceutically active ingredient not soluble in water, but may also have other functions in the formulations. Examples of compounds falling into the scope of this term are alcohols including propylene glycol, dichlorobenzyl alcohol, phenoxyethanol, transcitol P, panthenol; polyols such as glycerin; alkoxylated alcohols including polyethylene glycol of varying molecular weight; heterocyclic compounds including methyl pyrrolidine; and aprotic solvents including dimethyl sulfoxide. Preferred non-surfactant, amphiphilic type compounds are phenoxyethanol and propylene glycol. Phenoxyethanol may be present in amounts of up to 2%w/w and propylene glycol is desirably present in amounts of up to 50% w/w, more preferably in amounts of up to 30% w/w, and still more preferably in amounts of up to 25% w/w.

Throughout this specification the term "water soluble" when used in relation to a pharmaceutically active ingredient should be taken to mean compounds which have significant aqueous solubility and which typically exhibit low solubility in non-aqueous solvents.

- 5 The term "water insoluble" when used in relation to pharmaceutically active ingredients should be taken to mean compounds which have no appreciable aqueous solubility and which typically favour hydrophobic solvents.

10 The term "phase assembly temperature" when used throughout this specification should be taken to mean the temperature at which maximum translucency of the dispersion is observed when preparing the oil in water microemulsions or sub-micron emulsions according to the processes described. This temperature point is consistent with the temperature at which tiny particles are assembled.

15 Preferably, in the methods, processes and compositions according to the invention, the oil phase includes an occlusive agent which has the effect of adding an emollient quality to the formulations. One preferred occlusive agent is petrolatum. Although present at room temperature as a solid, using the process of preparation of the invention, it is found that petrolatum can be successfully incorporated into a formulation which is of low viscosity and suitable for
20 pressurised delivery. Other occlusive agents which may be incorporated in the compositions and according to the processes of the invention are microcrystalline wax, bees wax, paraffin wax and lanolin wax. Notably petrolatum, a preferred occlusive agent is made up of approximately 50% w/w mineral oil and approximately 50% w/w microcrystalline and paraffin wax. Desirably the waxy
25 component should not account for more than 25% w/w of the total oil phase.

30 Preferably in the methods, processes and compositions of the invention the water phase of the formulation is added in two aliquots; in aliquots more preferably of about 70% and 30% by weight of the total water phase. More preferably still, the second aliquot is added after the microemulsion or sub-micron emulsion has formed, at a temperature substantially below the temperature of the first aliquot, and at a rapid rate so as to reduce the overall temperature of the composition preferably to below about 60°C whereby the microemulsion or sub-micron emulsion structure is fixed. The two aliquots may both be an homogenous

mix of all components in the phase or may be different components of the phase e.g. water together with non surfactant amphiphilic type compound and/or surfactant alone.

A pharmaceutically active ingredient may be introduced in any one or more
5 of the three parts of preparation with the result that in the microemulsion or sub-micron emulsion according to the invention, the active ingredient may be present in the continuous water phase or the discontinuous oil phase or both. By appropriate manipulation, the formulations of the invention may be designed as slow or delayed release compositions by, for example, the location of the active
10 ingredient in the phase in which it is substantially or completely insoluble.

Where the pharmaceutically active ingredient is introduced in the first part, optionally solvents, co-solvents and coupling agents may also be present. Preferred solvents may include acetyl tributylcitrate, tributyl citrate and other appropriate solvents. Coupling agents help link or improve miscibility of oils that
15 are immiscible with the oil phase and assist in achieving clarity. Suitable coupling agents according to the invention are organic, non-ionic, virtually insoluble in water, miscible with oily/fatty/lipophilic materials and exhibit solubility for pasty and/or solid fatty/lipophilic materials. Isopropyl myristate is one suitable coupling agent. Others include, but are not limited to, polyglyceryl esters, isocetyl alcohol,
20 octyl methoxycinnamate, octyl dimethyl PABA, tocopheryl acetate and lanolin alcohols.

Preferably the pharmaceutically active ingredient is introduced in the second part, and more preferably it is introduced in the third part where it appears that its presence alongside the non-surfactant, amphiphilic type compound serves
25 to improve the transdermal performance of the composition. A non surfactant amphiphilic type compound also appears to assist in distributing the pharmaceutically active agent throughout the desired phase. In particular, where the pharmaceutically active agent is desirably present in both the oil phase and the water phase, non water miscible organic solvent is required in the oil phase
30 and a water miscible organic solvent is required in the water phase. As the amount of water miscible organic solvent is increased, the rate of diffusion of the active agent across the skin barrier is seen to increase. A slower flux is observed when the active is dissolved within the oil phase that contains organic solvent.

Particularly in the case that the pharmaceutically active agent is only sparingly soluble in water or insoluble in water, the addition of an increased amount of organic solvent to the water phase can assist in partitioning the pharmaceutically active agent into the water phase. Thus where the active agent is present in the continuous water phase, the active agent is available for rapid treatment of the patient's condition. Active agent in the oil phase may be available through other skin diffusion pathways for longer term treatment regimes.

The water phase may also include buffers such as, but not limited to, citric acid and potassium citrate, disodium EDTA and tetrasodium EDTA, disodium EDTA and disodium phosphate, and preservatives such as, but not limited to phenoxyethanol and dichlorobenzyl alcohol.

Where the pharmaceutically active ingredient is included in the water phase, this phase may also include a functional water soluble organic component including humectants, solvents for the active ingredient and penetration enhancers. Substances which may be included in the formulations of the invention in the water phase and which fall into one or more of these categories include but are not limited to propylene carbonate, transcitol, ethoxydiglycol, polyhydric alcohols such as glycerol, sorbitol and propylene glycol.

The pharmaceutically active ingredient may be any chemical substance or combination of chemical substances which have registration for the purposes of cosmetic or medical treatment and which are dermally deliverable. The pharmaceutically active ingredients can be present in the composition in different forms, depending on which form yields the optimum delivery characteristics. Thus, in the case of drugs, it can be in its free base or acid form, or in the form of salts, esters, or any other pharmacologically acceptable derivatives, or as components of molecular complexes, analogues, metabolites or pro-drugs.

Preferably the active ingredient is a corticosteroid selected from the group consisting of betamethasone valerate, desonide and clobetasol propionate or vitamin D or vitamin A analogues. The pharmaceutically active ingredient may alternatively be a drug that is normally delivered by oral, parenteral, percutaneous, perungual or rectal route.

Other examples of pharmaceutically active ingredients that can be administered by the compositions of this invention include, but are not limited to:

Cardioactive medications, for example, organic nitrates such as nitroglycerine, isosorbide dinitrate, and isosorbide mononitrates; quinidine sulfate; procainamide; thiazides such as bendroflumethiazide, chlorothiazide, and hydrochlorothiazide; nifedipine; nicardipine; adrenergic blocking agents, such as
5 timolol and propranolol; verapamil; diltiazem; captopril; clonidine and prazosin.

Androgenic steroids, such as testosterone, methyltestosterone and fluoxymesterone.

Estrogens, such as conjugated estrogens, esterified estrogens, estropipate, 17beta estradiol, 17beta-estradiol valerate, equilin, mestranol,
10 estrone, estriol, 17beta-ethinyl estradiol, and diethylstilboestrol. Progestational agents, such as progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17alpha hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol,
15 norgestrel, demegestone, promegestone, and megestrol acetate.

Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anaesthetics, such as chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine,
20 methocaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, and nicotine.

Nutritional agents, such as vitamins, essential amino acids and essential fats.

Anti-inflammatory agents, such as hydrocortisone, cortisone,
25 dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprofen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin,
30 salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.

Antihistamines, such as diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine,

tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, and chlorpheniramine.

Respiratory agents, such as theophylline and beta2-adrenergic agonists such as albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, 5 quinterenol, rimiterol, solmefamol, soterenol, and tetroquinol.

Sympathomimetics, such as dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine and epinephrine. Miotics, such as pilocarpine, and the like. 12 Cholinergic agonists, such as choline, acetylcholine, methacholine, carbachol, 10 bethanechol, pilocarpine, muscarine, and arecoline.

Antimuscarinic or muscarinic cholinergic blocking agents such as atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, and eucatropine. Mydriatics, such as atropine, cyclopentolate, 15 homatropine, scopolamine, tropicamide, eucatropine and hydroxyamphetamine.

Psychic energizers such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

Anti-infectives, such as antivirals, eg acyclovir, allylamines and in particular terbinafine hydrochloride and naftifine hydrochloride antibiotics, including 20 penicillin, tetracycline, chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; antibacterials, such as erythromycin and clarithromycin; and other anti-infectives including nitrofurazone and the like.

Vitamins such as vitamins A, D and E.

25 Humoral agents, such as the prostaglandins, natural and synthetic, for example PGE1, PGF2alpha, and PGF2alpha, and the PGE1 analog misoprostol.

Antispasmodics, such as atropine, methantheline, papaverine, cinnamedrine, and methscopolamine.

Antidepressant drugs, such as isocarboxazid, phenelzine, tranylcypromine, 30 imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, and trazodone.

Anti-diabetics, such as insulin, and anticancer drugs such as tamoxifen and methotrexate.

Anorectic drugs, such as dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, and phentermine. Anti-allergens, such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and pheniramine.

5 Tranquilizers, such as reserpine, chlorpromazine, and antianxiety benzodiazepines such as alprazolam, chlordiazepoxide, clorazepate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

10 Antipsychotics, such as thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone.

Decongestants, such as phenylephrine, ephedrine, naphazoline, Antipyretics, such as aspirin, salicylamide, and the like.

15 Antimigraine agents, such as dihydroergotamine and pizotyline.

Drugs for treating nausea and vomiting, such as chlorpromazine, perphenazine, prochlorperazine, promethazine, scopolamine, hyaline hydrobromide, triethylperazine, triflupromazine, and trimetoprim.

20 Anti-malarials, such as the 4-aminoquinolines, alpha-aminoquinolines, chloroquine, and pyrimethamine.

Anti-ulcerative agents, such as misoprostol, omeprazole, and enprostil.

Peptides and proteins, such as drugs for Parkinson's disease, spasticity, and acute muscle spasms, such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, 25 benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, insulin, erythropoietin and growth hormone.

Anti-estrogen or hormone agents, such as tamoxifen or human chorionic gonadotropin.

Nucleotides and nucleic acids (e.g. DNA).

30 The third part may be present in the compositions according to the invention in an amount from 0.1% w/w to 50% w/w.

The first part of the methods, processes and compositions according to the invention preferably makes up 1 – 30% w/w of the total resulting composition.

Individual components of this phase preferably each have a solubility parameter of approximately 5.7 – 8.1 cal/cc and together, more preferably, when combined, have a calculated solubility parameter of approximately 7.0 – 7.4 cal/cc and should still more preferably be in a liquid state at the phase assembly
5 temperature of the composition.

Oils that may be used in the methods, processes and compositions according to the invention may include but are not limited to one or more of mineral oils, petrolatum, caprylic/capric triglyceride, peanut oil, cyclomethicone, cod liver oil, isopropyl myristate and alkoxyated oils including ethoxylated,
10 propoxylated or ethoxylated-propoxylated oils. Cosmetic grade oils such as dioctyl cyclohexane, cetearyl isonanoate, C12-C15 alkyl benzoate, oleyl oleate, octylhydroxy stearate and octyl dodecanol may also be suitable. In preferred processes, methods and compositions according to the invention, the oil phase includes petrolatum, mineral oil, esters and cyclomethicone. Still more preferably,
15 the oil phase includes petrolatum, mineral oil, an ester being isopropyl myristate, acetyl tributylcitrate, or tributylcitrate and cyclomethicone in an approximate ratio of 1:1:1:1. Still more preferably the oil phase includes approximately 25% petrolatum, 25% mineral oil, 25% isopropyl myristate and 25% cyclomethicone. One of the problems confronted with conventional emulsion formulations is the
20 extent to which they have to be redispersed if, on standing, a separation occurs. The ability to redisperse is important to the commercial acceptability of a product. In the methods, processes and compositions according to the invention, this issue has been addressed by optimising the oil phase to reduce the proportion of petrolatum, introduce co solvents and coupling agents and reduce the presence
25 of any solid surfactants that exhibit solubility in the oil phase whilst ensuring the surfactant remains functional.

Other components of the oil phase might include but are not limited to lauryl lactate, isosteareth-2-octanoate, alk-oxylated derivatives of lauric, oleic or stearic acid, each of which may act as emulsifiers, humectants, or coupling
30 agents; octyl salicylate and oleyl oleate which may act as skin penetrants; polyglyceryl-3-laurate, diisopropyl sebacate which may act as an emollient, solubiliser or coupling agent or Hydramol PGPL (PEG.PPG – 8/3 laurate).

The total amount of oil in the oil phase may be in the amount of about 1-30% w/w.

The nature of surfactants (also known as emulsifiers) which can be utilised in the compositions resulting from the preferred processes of the invention will vary, and as discussed in the preamble of this specification may be subject to some experimentation before being perfected. Variations may arise as a result of the components of the oil phase selected, the pharmaceutically active ingredient and possibly even the temperature parameters under which the process is conducted.

Generally, commercial microemulsion gels are based on phosphate esters and non-ionic emulsifiers, although it is possible to formulate systems based on non-ionic emulsifiers alone. Ethoxylated fatty alcohols are the most popular non-ionic emulsifiers used. These include ethoxylates of: lanolin alcohols (laneths) oleyl alcohol (oleths), lauryl alcohol (laureths), cetyl alcohols (ceteths), stearyl alcohol (steareths), cetostearyl alcohols (ceteareths) and isocetyl alcohol (isoceteths). Phosphate esters include those based on ethoxylated lauryl alcohol (laureth phosphates) and ethoxylated oleyl alcohol (oleth phosphates). In general, the more ethoxylated a surfactant is, the higher its HLB, the higher the temperature at which a microemulsion or sub-micron emulsion is formed, and the larger the particle size of the resulting formulation. Ethoxylation has a greater effect on the ability of the composition to assemble as a microemulsion or sub-micron emulsion than does the carbon chain length of the surfactant.

When discussing emulsifiers for microemulsion gels, it is helpful to keep in mind that a large molecular weight emulsifier and a small molecular weight oil may be the optimum combination.

In the processes, methods and compositions according to one preferred embodiment of the invention, lipophilic nonionic surfactants may be selected from the group consisting of fatty alcohols such as cetyl alcohol, isocetyl alcohol or stearyl alcohol; glyceryl esters and derivatives thereof such as glyceryl monostearate and glyceryl monooleate; esters such as methyl glucose sesquistearate; sorbitan derivatives such as sorbitan laurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate and sorbitan sesquioleate. Lipophilic anionic surfactants may be selected from the group

consisting of fatty acids such as palmitic acid and stearic acid. Hydrophilic non-ionic surfactants may be selected from the group consisting of alkoxylated carboxylic acids such as PEG 40 stearate; alkoxylated alcohols such as cetareth -12, -20 and -30, oleth 10 and laureth -4 and -23 and steareth-4; sorbitan
5 derivatives such as polysorbate 40, polysorbate 60 and polysorbate 80; glyceryl esters and derivatives thereof such as PEG-40 hydrogenated castor oil and PEG-35 castor oil.

The minimum concentration of surfactant in the methods, processes and compositions according to one form of the invention appears to be about 1.8%
10 w/w using 1% w/w oil phase. The maximum concentration of surfactant in the compositions according to one form of the invention appears to be about 20.1% w/w using 10% w/w oil phase.

It also appears that the ratio of surfactant:oil may also contribute to the ability of the compositions prepared according to the processes of the invention to
15 form sub-micron emulsions and microemulsions. A preferred ratio of surfactant:oil is approximately 1:3 to 3:1

In the compositions of the invention, the surfactant system includes at least two surfactants, one lipophilic and one hydrophilic. Preferably, the surfactant system includes surfactants having an aggregated HLB number between 8.0 and
20 15.0, more preferably between 10 and 12 and still more preferably between 9.7 and 11.8. More preferably, the lipophilic surfactants have an HLB number of less than 10, and the hydrophilic surfactants have an HLB number of greater than 10. Preferred candidates as surfactants in the compositions according to the invention are sorbitan laurate and cetyl alcohol used in the first oil phase, and
25 Cetareth-20 or oleth 10 in the second water phase.

In a two surfactant system (one lipophilic and one hydrophilic), the preferred range of concentration of hydrophilic:lipophilic surfactant is about 9:1 to 1.0:1.0.

In a three surfactant system using one hydrophilic surfactant and two
30 lipophilic surfactants, one preferred ratio of surfactants is 8:1:1 to 4:5:1. That is the total hydrophilic:lipophilic ratio is preferably 4:1 to 2:3.

In a four surfactant system using two hydrophilic surfactants and two lipophilic surfactants, one preferred ratio of surfactants is 2.5:2.5:4.0:1.0 to

3.0:3.0:3.0:1.0. That is the total hydrophilic:lipophilic ratio is preferably 3.0:2.0 to 1:1.

Other additives which may be present in the compositions prepared according to the invention not already mentioned include but are not limited to
5 preservatives such as dichlorobenzyl alcohol; antioxidants such as BHT, humectants such as lactic acid, urea and Ajidew N-50/Sodium PCA; and polymers, thickeners or gums such as Eudragit NE40D. These additives are typically organic and exhibit some miscibility with water and other organic ingredients and may generally be incorporated together with the active agent.

10 The compositions according to the invention may be in any physical form so as to suit their purpose. In a final fourth part of the process of preparation of the microemulsions or sub-micron emulsions of the invention it is possible to introduce a propellant into the microemulsion so that the composition may be dispensed as an aerosol foam or mousse. In this case the propellant may be
15 selected from hydrocarbons such as P70; ethers such as dimethylether and halogen compounds such as Hydrofluorocarbon 134A. The propellant may be present in amounts of about 5-20% w/w.

The microemulsion or sub-micron emulsion may also be formulated as a gel, cream, lotion or patch depending on its purpose. For example, thickening
20 agents such as sodium carboxymethyl cellulose or gelling agents such as the water soluble polymers, carbomer and xanthan may be added when a gel formulation is required.

The following examples are provided so as to illustrate the scope of the invention but should not be considered to limit it as the skilled person will
25 appreciate the means by which the following formulations may be altered whilst still resulting in formulations falling within the broadest scope of the invention.

EXAMPLES

Examples 1 and 1A show a composition having surfactant ratios according to the prior art, and wherein propylene glycol, generally considered disruptive of
30 sub-micron emulsions is added together with other constituents in a single stage aqueous phase of the process. These examples are provided for comparison purposes and do not illustrate the invention.

Examples 2-5A show six different compositions using the pharmaceutically active ingredients clobetasol propionate, desonide or betamethasone-17-valerate in formulations according to preferred embodiments of the invention wherein the surfactant ratios are of the desired ratio range. Examples 4 and 5 in accordance with the invention are compositions which include propellant. The examples 2-5A may be further processed into formulations useful as a lotion, spray, gel, paste, foam or any other suitable dosage form.

Example 1

	20% PG / pH6
Phase 1 - Oil Phase	% w/w
Clobetasol Propionate	0.0475
Petrolatum	7.50
Mineral Oil	5.00
Isopropyl Myristate	7.50
Cyclomethicone	5.00
Cetyl Alcohol	2.00
Sorbitan Laurate	1.50
Phase 2 – Aqueous Phase	
Water	38.7525
Ceteareth-20	6.50
Citric Acid	0.04
Potassium Citrate	0.16
Propylene Glycol	20.00
Phenoxy Ethanol	1.00
Phase 3 - Propellant Phase	
Hydrocarbon Propellant P70	5.00
Total	100.00

Example 1A

	20% PG / pH 6
Phase 1 - Oil Phase	% w/w
Clobetasol Propionate	0.05
Petrolatum	7.90
Mineral Oil	5.26
Isopropyl Myristate	7.90
Cyclomethicone	5.26
Cetyl Alcohol	2.11
Sorbitan Laurate	1.58
Phase 2 – Aqueous Phase	
Water	40.79
Ceteareth-20	6.84
Citric Acid	0.04
Potassium Citrate	0.17
Propylene Glycol	21.05
Phenoxy Ethanol	1.05
Emulsion concentrate Total	100.00

Examples 1 and 1A show a surfactant ratio of Ceteareth-20: sorbitan laurate: cetyl alcohol of 6.5:1.5:2.0 wherein propylene glycol is introduced in one stage to the aqueous phase of the composition. This product separates on standby, has poor in-can redispersability and requires continuous mixing in process which is costly in large scale manufacture.

Example 2

	20% PG / pH 5
Part 1	% w/w
Petrolatum	7.90
Mineral Oil	5.26
Isopropyl Myristate	7.90
Cyclomethicone	5.26
Cetyl Alcohol	1.05
Sorbitan Laurate	4.74
Part 2	
Water	40.79
Ceteareth-20	4.74
Citric Acid	0.04
Potassium Citrate	0.17
Part 3	
Propylene Glycol	21.05
Phenoxy Ethanol	1.05
Clobetasol Propionate	0.05
Emulsion concentrate Total	100.00

Example 2 shows a surfactant ratio of Ceteareth-20 : sorbitan laurate : cetyl alcohol of 4.5:4.5:1.0.

Example 3

	17% PG / pH 5
Part 1	%w/w
Petrolatum	5.26
Mineral Oil	5.26
Isopropyl Myristate	10.53
Cyclomethicone	2.63
Cetyl Alcohol	1.05
Sorbitan Laurate	4.74
Part 2	
Water	46.58
Ceteareth-20	4.74
Citric Acid	0.08
Potassium Citrate	0.13
Part 3	
Propylene Glycol	17.90
Phenoxy Ethanol	1.05
Desonide	0.05
Emulsion concentrate Total	100.00

Examples 3 shows a surfactant ratio of Ceteareth-20 : sorbitan laurate : cetyl
5 alcohol of 4.5:4.5:1.0.

Example 4

	5% PG
Part 1	%w/w
Petrolatum	5.00
Mineral Oil	5.00
Isopropyl Myristate	5.00
Cyclomethicone	5.00
Cetyl Alcohol	1.00
Sorbitan Laurate	4.00
Part 2	
Water	58.686
Ceteareth-20	5.00
Citric Acid	0.20
Potassium Citrate	
Part 3	
Propylene Glycol	5.00
Phenoxy Ethanol	1.00
Betamethasone-17-Valerate	0.114
Part 4	
Hydrocarbon Propellant P70	5.00
Total	100.00

Example 4A

	5% PG
Part 1	%w/w
Petrolatum	5.26
Mineral Oil	5.26
Isopropyl Myristate	5.26
Cyclomethicone	5.26
Cetyl Alcohol	1.05
Sorbitan Laurate	4.21
Part 2	
Water	61.80
Ceteareth-20	5.26
Citric Acid	0.21
Potassium Citrate	
Part 3	
Propylene Glycol	5.26
Phenoxy Ethanol	1.05
Betamethasone-17-Valerate	0.12
Emulsion concentrate Total	100.00

Examples 4 and 4A show a surfactant ratio of Ceteareth-20 : sorbitan laurate :
 5 cetyl alcohol of 5.0:4.0:1.0.

Example 5

	10% PG
Part 1	%w/w
Petrolatum	5.00
Mineral Oil	5.00
Isopropyl Myristate	5.00
Cyclomethicone	5.00
Cetyl Alcohol	1.00
Sorbitan Laurate	4.00
Part 2	
Water	53.686
Ceteareth-20	5.00
Citric Acid	0.20
Potassium Citrate	
Part 3	
Propylene Glycol	10.00
Phenoxy Ethanol	1.00
Betamethasone-17-Valerate	0.114
Part 4	
Hydrocarbon Propellant P70	5.00
Total	100.00

Example 5A

	10% PG
Part 1	%w/w
Petrolatum	5.26
Mineral Oil	5.26
Isopropyl Myristate	5.26
Cyclomethicone	5.26
Cetyl Alcohol	1.05
Sorbitan Laurate	4.21
Part 2	
Water	56.53
Ceteareth-20	5.26
Citric Acid	0.21
Potassium Citrate	
Part 3	
Propylene Glycol	10.53
Phenoxy Ethanol	1.05
Betamethasone-17-Valerate	0.12
Emulsion Concentrate Total	100.00

Examples 5 and 5A show a surfactant ratio of Ceteareth-20 : sorbitan laurate :
 5 cetyl alcohol of 5.0:4.0:1.0.

The examples 2-5A show good physical stability, utilise less expensive
 manufacturing techniques and show good redispersability.

Example 6

Figure 1 shows the preparation of an ethanol-free 0.05% clobetasol
 10 propionate foam of the same type as example 2 according to one preferred
 process according to the invention. This process has been successfully scaled
 up as follows.

Petrolatum, light mineral oil, isopropyl myristate, sorbitan monolaurate and
 cetyl alcohol are added in specified quantities to the primary compounding tank

as the oil phase. This phase is mixed in the tank and heated to 75-80°C. Cyclomethicone is added and mixing is continued at 75-80°C until the oil phase is uniform in consistency.

To make the water phase, purified water, citric acid and potassium citrate
5 are added into a kettle. This water phase mixture is mixed and heated to 80-85°C. Ceteareth-20 is then added and mixing is continued at 80-85°C until complete dissolution of all components occur.

The third part containing the active agent ("the active phase") is prepared by adding specified quantities of propylene glycol and phenoxyethanol into a
10 kettle. Mixing of this part is commenced, the active agent, clobetasol propionate is added and the phase is heated to 55-60°C. Mixing is continued until complete dissolution of all components occur. The temperature of this part is allowed to cool, or is cooled in a waterbath to 30°C.

Approximately 70% of the water phase mixture is then added to the oil
15 phase mixture in the primary compounding tank. The two phases are mixed together and heated to 85-90°C. The approximately 30% remaining of the water phase is cooled to 20-25°C in a chilled waterbath. After continued mixing of the oil/water phase in the primary compounding tank and cooling of the mixture to 72-78°C, the remainder of the water phase mixture (approximately 30%) is added to
20 the oil/water phase in the primary compounding tank. Simultaneously, cooling is commenced to achieve a temperature of 35-40°C.

The content of the active phase kettle is added to the oil/water phase mixture in the primary compounding tank. Mixing is continued and the temperature is lowered to 20-25°C.

25 The resultant composition is dispensed into cans at ambient temperature.

Example 7

This example details the preparation of a Desonide formulation according to one preferred process of the invention. The method results in a 17% Propylene Glycol and Desonide composition. This process has not been scaled
30 up.

The item numbers in the following composition listing correspond to the item numbers in the process description which follows.

Item No.	Ingredient	%w/w	%w/w without Propellant
	Part 1		
1	Snow White Petrolatum	5.00	5.263
2	Lt Mineral Oil (Drakeol 5)	5.00	5.263
3	Isopropyl Myristate	10.00	10.526
4	ST-Cyclomethicone 5-NF	2.50	2.632
5	Cetyl Alcohol	1.00	1.053
6	Sorbitan Laurate (Crill 1)	4.50	4.737
	Part 2 (Part 2A = 70%, Part 2B = 30%)		
7	Purified water	44.2525	46.582
8	Ceteareth-20	4.50	4.737
9	Citric Acid, anhydrous	0.076	0.080
10	Potassium Citrate, monohydrate	0.124	0.131
	Part 3		
11	Propylene Glycol	17.00	17.895
12	Phenoxyethanol	1.00	1.053
13	Desonide	0.0475	0.050
	Part 4		
14	Propellant P70	5	
	TOTAL	100.00	100.00

Items 1 to 6 are added to the mixing vessel, stirred and heated to 60-80°C to form the oil phase. The temperature is maintained or re-established before adding the water phase (see below).

To prepare the water phase, water at room temperature, anhydrous citric acid and potassium citrate, monohydrate are added to a suitably sized vessel and stirred together. Ceteareth-20 is added, and the mixture is heated to a maximum of 50°C until the ceteareth-20 is completely dissolved.

The water phase is separated into two parts. About 30% of the water phase mixture is cooled to 20-30°C. The remaining 70% of the water phase mixture is added to the oil phase mixing vessel at its existent temperature. The mixing vessel containing the oil phase and most of the water phase is heated to

80-85°C with thorough mixing to ensure uniformity. The temperature should be held at this level for about 10 minutes to assist in obtaining uniformity. The mixture will be a water in oil emulsion and will be very white in colour. The conductivity will be less than 100 $\mu\text{s}/\text{cm}$.

- 5 The oil in water mixture should be allowed to cool to about 73°C. When approaching the assembly temperature the rate of cooling should be no more than 1° per minute. At the assembly temperature the Δ conductivity changes from a large negative value to an almost constant value.

10 When the mixing vessel reaches about 73°C as described, the remaining 30% of the water phase which is at 20-30°C is added and the mixing vessel is immediately cooled. Rapid addition of the remaining quantity of water phase is desirable, and the temperature of the mixture should be approximately 60°C at the completion of the addition of the remaining water phase mixture.

15 Phase 3 containing propylene glycol is prepared by adding items 11 to 13 to a suitable vessel and heating until the Desonide is dissolved. After dissolution of the Desonide, the mixture should be cooled to less than 30°C. The oil in water emulsion mixture should be cooled to about 35 – 40°C by stirring and phase 3 is then added at a rate so that the entire mixture is not added until at least 5-10 minutes has elapsed. An unsatisfactory addition rate will be evidenced by the
20 presence of a bilayered product having an oily film on top upon standing.

 The mixing vessel containing all components is cooled by stirring to about 25 – 30°C. The resultant emulsion should be maintained at about 20 – 25°C before filling and should remain homogenous for at least 48 hours without stirring.

25 Temperatures may vary up to about 5°C depending on the sorbitan laurate (oil phase) used. Conductivity tests are recommended to determine the set point or assembly temperature of the microemulsion.

Example 8

30 This example demonstrates the effect on the compositions of varying the parameters of surfactant ratio, pre set point temperature variation and post set point cooling rate.

 Table 1 summarises the effects of varying the parameters of the preparation of mainly 1.5 kg batches of compositions according to preferred

aspects of the invention. As is shown in the table, the ratio of Cetearth-20 : sorbitan laurate is adjusted, the temperature of the phase 1 and phase 2 mixes prior to combination, and subsequent to combination, is adjusted and the cooling rate of the combination of the two phases is adjusted and observations of the appearance, stability and particle size are made. Batch numbers 367-14, 367-16, 367-22, E207/1/1 and 328-68 were considered successful. Figure 2 is a graphical representation of the method of this example charting the rate of addition of the various components of the compositions.

TABLE 1

Summary of Scale-up Process Development E foams in 1.5 kg Batches:

Desonide P1 = 442 g P2 = 773 g P3 = 285 g Clobetasol propionate P1 = 482 g P2 = 686 g P3 = 332 g								
Batch No	Ceteareth-20 to Sorbitan laurate	Temp P1 – P2	P2 addition	Cooling Rate to 40°C	Observations during P2 addition	Size (Microscope)	Emulsion appearance	Stability at R.T.
Desonide E								
367-12	5.0:4.0	82°C – 82°C Maintained	100 ml pipette	Quickly to 40°C with tap water, 5-10 min	Went translucent then white before P2 completely added	Many 1-2 µm	White, leaves white residue on glass	< 12 hr
367-14	4.5:4.5	82°C – 82°C Maintained	50 ml pipette	Quickly to 40°C with tap water, 5-10 min	Went translucent later than for 367-12, stayed longer before going white before P2 completely added	≤ 1 µm	White but less residue on glass than 367-12	> 5 days
367-16	4.5:4.5	75°C – 75°C (65°C)	Pump – 130 ml min ⁻¹	35 min to cool to 40°C	Same as 367-14	< 1 µm	White, but quite clear on glass	> 5 days
367-18	4.0:5.0	75°C – 75°C (65°C)	Pump – 130 ml min ⁻¹	35 min to cool to 40°C	Went translucent later than for 367-14, went white just after P2 added	≤ 1 µm		< 1 day, just see
367-22	4.5:4.5	72°C – 80°C (68°C)	Pump – 112 ml min ⁻¹ for 6 m 6 s High speed for remainder, < 1min	Cooling begun immediately – 25 min to 40°C.	Went translucent at 6 min, then remained quite translucent after P2 added.	<< 1 µm	Blue-White V clean on glass, looks very transparent	> 5 days
Clobetasol propionate								
E207/1/1 500ml	4.5:4.5	75°C – 75°C not maintained	Hand poured	Air cooled in about 45 min	Stayed quite translucent.	<< 1 µm	Blue-White V clean on glass, looks very transparent	> 5 days
328-68	4.5:4.5	72°C – 80°C (68°C)	Pump – 112 ml min ⁻¹ for 5 min High speed for remainder (2 min)	Cooling begun immediately – 25 min to 40°C.	Went translucent at 5 min, then remained quite translucent after P2 added.	<< 1 µm just see dots	Blue-White V clean on glass, looks transparent	> 5 days

KEY: P1 – Phase 2 (oil)

P2 – Phase 2 (aqueous)

P2 addition: 100ml pipette - Constant, stop start using a 100 ml pipette

Pump – constant addition using a peristaltic pump. P2 would cool in the tubing giving resulting in the temperature shown in brackets.

Example 9

Figure 3 shows the timeline of a preferred process of preparation of a large scale 15 kg Desonide composition according to one aspect of the invention. The timeline shows a slow addition of the water phase until inversion of the phases occurs, determined by conductance measurements, whereupon rapid addition of the remainder of the water phase is effected.

The resultant composition is a blue white emulsion which leaves no residue on glass. Only a small amount of foaming occurs mostly during the rapid addition of the remainder of the water phase. Temperature of the mix was maintained between 70-75°C during mixing but cooling was initiated immediately the addition of the water phase had been completed. The majority of particles reviewed under a microscope were much less than 1 µm in diameter. The composition remained stable at 3 days.

Figure 4 is a graphical representation of the process of this example changing the rate of addition of the various components of the composition.

Example 10

This example demonstrates the effect of varying the ratio of emulsifiers in one composition prepared according to an embodiment of the invention wherein the pharmaceutically active ingredient is betamethasone valerate and the emulsifiers are Cetareth-20, sorbitan laurate and cetyl alcohol. It also shows the effect of varying the manner of addition of the water phase; either all at once, or in two separate stages, the first stage being added at a slower rate than the second stage. Figure 5 shows the results of this example graphically. The acronym "BMV" is Betamethasone valerate.

The compositions E208/2/1 – E208/2/8 are prepared as follows in accordance with differing preferred embodiments of the invention:

E208/2/1 - 4.0:5.0:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol,
all water phase added in one hit - heated to 81°C

E208/2/2 - 4.5:4.5:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol,
all water phase added in one hit - heated to 82°C

E208/2/3 - 5.5:3.5:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol,
all water phase added in one hit - heated to 94°C

E208/2/4 - 5.0:4.0:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol, all water phase added in one hit - heated to 84°C

E208/2/5 - 4.5:4.5:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol, all water phase added in one hit - heated to 92°C

5 E208/2/6 - 4.5:4.5:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol, all water phase added in one hit - heated to 78°C

E208/2/7 - 5.0:4.0:1.0 ratio of Cetareth-20: sorbitan laurate:cetyl alcohol, water phase added in two portions (70/30 hot:cold) propylene glycol stirred when added - heated to 74°C

10 E208/2/8 - 5.0:4.0:1.0 ratio, of Cetareth-20: sorbitan laurate:cetyl alcohol water phase added in two portions (70/30 hot:cold) propylene glycol not stirred when added -heated to 74°C

This example shows that a microemulsion meeting the objects of the invention can be made at varying surfactant ratios.

15 In order to determine the point at which a microemulsion is formed, conductance tests are recommended. The conductivity will drop dramatically immediately phase assembly occurs at the set point of the microemulsion.

Utilising the compositions E208/2/7, E208/2/8, E208/2/6 and E208/2/4 (left to right across the key), figure 6 graphs conductivity of the compositions against the temperature of the water/oil phase mix and shows the conductivity response from heating to the assembly temperature and subsequent cooling and addition of active phase. The uppermost section, or assembly temperature range, of the conductivity plot demonstrates the trend that the set point of compositions according to the invention can be reduced by decreasing the relative proportion of hydrophilic surfactant in the surfactant system. The assembly temperature is also lowered when the water phase is split into two aliquots. It is postulated that splitting the water phase has the same effect as reducing the relative proportion of hydrophilic surfactant and subsequently lowering the assembly temperature for the microemulsion.

30 Example 11

This example demonstrates the effect on the appearance and particle size of varying the parameters of the processes hereinbefore described. Table 2 shows that the phase in which the surfactant is added, and the presence or

absence of non-surfactant, amphiphilic substances in the composition prior to emulsification of the compositions, has an effect on the particle size of the composition. In the context of the example, it will be appreciated that the compositions meeting the objects of the invention are those wherein the water phase is added to the oil phase, Cetareth-20 is present in the water phase, and the remaining surfactants are present in the oil phase, and wherein the addition of the non-surfactant amphiphilic components of the composition are added after emulsification of the composition at the phase assembly temperature. In this case, the composition appears to have acceptable stability, and a particle size of less than 0.2 μm .

TABLE 2

Process description	Surfactant addition			Polyol & Phenoxy ethanol addition	Appearance	Particle size (μm)	Comments
	Ceteareth-20	Sorbitan laurate	Cetyl alcohol				
Water phase added to oil phase	Oil phase	Oil phase	Oil phase	Water phase (before emulsification)	White liquid	< 20	Creaming observed within 24 hours
Water phase added to oil phase	Split between oil phase and water phase	Oil phase	Oil phase	Water phase (before emulsification)	White liquid	< 20	Creaming observed within 24 hours
Water phase added to oil phase	Water phase	Oil phase	Oil phase	Water phase (before emulsification)	White liquid	< 20	Creaming observed within 24 hours
Water phase added to oil phase	Water phase	Oil phase	Oil phase	Emulsion (after emulsification)	Bluish-white, translucent liquid	< 0.2	No creaming observed over several days
Oil phase added to water phase	Oil phase	Oil phase	Oil phase	Water phase (before emulsification)	White liquid	< 20	Creaming observed within 24 hours
Oil phase added to water phase	Water phase	Oil phase	Oil phase	Water phase (before emulsification)	White liquid	< 20	Creaming observed within 24 hours

Example 12

In order to demonstrate the chemical and physical stability of compositions prepared according to the process of the invention compared to those of the prior art, the following tests were carried out. In the compositions prepared according to the process of the invention (12B) the polyol and/or alcohol are added in a third phase after emulsification and cooling of the oil in water emulsion formed in the first stage of the process. In the compositions prepared according to prior art processes (12A) the polyol and/or alcohol are added to the oil or water phase prior to emulsification and cooling of the composition. Table 3 shows the 6 month stability data associated with a composition according to example 12A; a prior art type composition.

Example 12A

Item No.	Ingredient	%w/w	%w/w without Propellant
	Part 1		
1	Clobetasol Propionate	0.0475	0.050
2	Snow White Petrolatum	7.50	7.895
3	Lt Mineral Oil (Drakeol 5)	5.00	5.263
4	Isopropyl Myristate	7.50	7.895
5	ST-Cyclomethicone 5-NF	5.00	5.263
6	Cetomacrogol 1000 BP	6.50	6.842
7	Cetyl Alcohol	2.00	2.105
8	Sorbitan Laurate (Crill 1)	1.50	1.579
	Part 2		
9	Purified water	38.7525	37.803
10	Citric Acid, anhydrous	0.04	0.042
11	Potassium Citrate, monohydrate	0.16	0.168
12	Propylene Glycol	20.00	21.053
13	Phenoxyethanol	1.00	1.053
	Part 3		
14	Propellant P70	5	
	TOTAL	100.00	100.00

Manufacturing Method

1. **Part 1 preparation:** Add Items 2 to 8 into the mixing vessel. Heat to 60°C and stir to combine. Maintain temperature before adding Clobetasol Propionate. Stir until dissolved then increase the temperature to 80-85°C in preparation for part 2 addition.
2. **Part 2 preparation:** Add items 9 to 13 to a mixing vessel and heat to 80-85°C* with stirring until a clear solution is formed.
3. **Emulsification:** Stir part 1 well (without introducing air) then add part 2. Initially add part 2 at a slower rate. During part 2 addition, a period of higher viscosity will occur that may require an increased stirring speed, for a short time, to ensure thorough mixing.
4. **Homogenisation:** Stir cool the emulsion to 40°C (cool at a reasonably fast rate). Homogenise the emulsion if the average particle size is > 2.5 μm or the maximum particle size is > 15 μm . Stir cool the emulsion to 25°C.

TABLE 3

Storage temperature °C	Test time point	Clobetasol %	% of T=0	Phenoxy-ethanol %	% of T=0	Weight loss (g)	Pressure psig @ 25°C	Foam pH @ 25°C	Re-disp. at 10°C	Re-disp. at 15°C	Foam at 15°C	Foam at 25°C	Foam at 35°C	Spay Rate gs ⁻¹ 21°C
5°C	Initial	0.0502	-	1.060	-	-	44	6.04	-	-	0.5	1.0	-	4.2
	1 month	0.0499	99.4	1.051	99.2									
	2 months	0.0500	99.6	1.050	99.1									
	3 months	0.0501	99.8	1.053	99.3									
	6 months	0.0502	100.0	1.046	98.7									
	9 months													
25°C	12 months													
	3 months	0.0502	100.0	1.047	98.7	0.023 ± 0.009	43	6.07	5	4	0.5	1.0	1.5	4.2
	6 months	0.0495	98.6	1.043	98.4	0.043 ± 0.007	43	6.05	6	5	0.5	0.5	1.5	2.9
	9 months													
	12 months													
	2 months	0.0498	99.1	1.045	98.5	0.024 ± 0.006	44	6.03	5	3	0.5	1.0	-	4.3
30°C	3 months	0.0499	99.3	1.045	98.6	0.030 ± 0.008	45	6.12	6	5	0.5	1.0	1.5	3.1
	6 months	0.0496	98.8	1.040	98.1	0.076 ± 0.007	42	6.07	6	5	0.5	0.5	1.5	4.4
	9 months													
	12 months													
	1 month	0.0497	98.9	1.046	98.6	0.039 ± 0.006	43	6.04	5	4	0.5	1.0	-	4.6
	2 months	0.0496	98.7	1.045	98.6	0.057 ± 0.005	43	6.03	6	5	0.5	1.0	-	4.1
40°C	3 months	0.0496	98.8	1.043	98.3	0.083 ± 0.007	45	6.13	6	5	0.5	1.0	1.5	4.6
	6 months	0.0490	97.5	1.045	98.5	0.162 ± 0.011	42	6.06	6	6	0.5	0.5	1.5	4.2

Example 12B

Item No.	Ingredient	%w/w	%w/w without Propellant
	Part 1		
1	Snow White Petrolatum	7.50	7.895
2	Lt Mineral Oil (Drakeol 5)	5.00	5.263
3	Isopropyl Myristate	7.50	7.895
4	ST-Cyclomethicone 5-NF	5.00	5.263
5	Cetyl Alcohol	1.00	1.053
6	Sorbitan Laurate (Crill 1, USA)	4.50	4.737
	Part 2 (Part 2A = 70%, Part 2B = 30%)		
7	Purified water	38.7525	40.792
8	Cetomacrogol 1000 BP	4.50	4.737
9	Citric Acid, anhydrous	0.040	0.042
10	Potassium Citrate, monohydrate	0.160	0.168
	Part 3		
11	Propylene Glycol	20.00	21.053
12	Phenoxyethanol	1.00	1.053
13	Clobetasol Propionate	0.0475	0.050
	Part 4		
14	Propellant P70	5	
	TOTAL	100.00	100.00

Manufacturing Method

1. **Part 1 preparation:** Add Items 1 to 6 into the mixing vessel. Heat to 60 – 80°C and stir to combine. Maintain temperature before adding Part 2A.

2. **Part 2 preparation:** Add Item 7 (Water) at room temp, Item 9 (Citric acid, anhydrous) and Item 10 (Potassium Citrate, monohydrate) to a suitably sized vessel. Stir well and add all of Item 8 (Cetomacrogol 1000 BP). Heat to a maximum of 50°C until the Cetomacrogol has completely dissolved (above 50°C the cetomacrogol melts and will clump to form a large mass).

3. Part 2 separation: Perform a weight check on part 2 then split into

Part 2A - containing 70% of Part 2

Part 2B - containing 30% of Part 2

Cool part 2B to 20 – 30°C (ideally 20-25°C).

4. Part 2A addition: Add part 2A to the mixing vessel. Part 2A may be added immediately after dissolving the Cetomacrogol when hot, or if it was previously prepared and had cooled to room temp.

5. Heat the mixing vessel to at least 80 – 85°C (part 1 + part 2A), with good mixing and hold for 10 min. When measuring the conductivity, this will be $<100 \mu\text{S/cm}$, if not, increase the temperature.

Allow the mixing vessel to slowly cool to 73.0°C. When approaching the target temperature (73.0°C) the cooling rate should be no more than 1°C per min. This should correspond to the maximum clarity of the emulsion. It is also the point where $\Delta\text{Conductivity}$ changes from a large negative value to almost constant zero.

6. Addition of Part 2B: When the mixing vessel reaches 73.0°C, pump in part 2B (which is at 25°C) and immediately begin cooling the mixing vessel. Addition of part 2B should be completed within 90 s. The temperature of the mixture should be about 60°C at the completion of part 2B addition.

7. Addition of Part 3: Stir cool the mixing vessel to 35 – 40°C. Part 3 should be previously prepared by adding Items 11 to 13 into a suitable vessel and heating until the Clobetasol is dissolved. Cool part 3 to $<30^\circ\text{C}$ after the Clobetasol has dissolved and add to the mixing vessel at a rate to take at least 5-10 min.

8. Stir cool the mixing vessel to 25 – 30°C (25°C preferable). Perform a weight check. Base emulsion should be maintained at 20 – 25°C before filling. Base emulsion should remain homogeneous for at least 48 hr without stirring.

Table 4 shows 3 month stability data associated with a composition according to example 12B; a composition prepared in accordance with one form of the invention.

TABLE 4

Storage temperature °C	Test time point	Clobetasol Propionate %	% of T=0	Phenoxy-ethanol %	% of T=0	Weight loss (g)	Pressure psig @ 25°C	Foam pH @ 25°C	Re-disp. at 5°C	Foam at 15°C	Foam at 25°C	Foam at 35°C	Package interaction
	Initial	0.0497	-	1.034	-	-	31	6.20	-	3.0	1.5	2.0	-
25°C	3 months	0.0491	98.8	1.0409	100.7	0.03	30	6.23	1	4.5	2.0	1.0	Lining – no change. Gasket, spring, valve cup - no change, valve body and stem-Slightly yellowed. No signs of attack on scratch (clean and bright)
	6 months												
40°C	1 month	0.0491	98.8	1.0288	99.5	0.01	28	6.21	1	1.5	1.0	1.5	Lining – no change. Gasket, spring, valve cup, valve body and stem- no change. No signs of attack on scratch (clean and bright)
	3 months	0.0487	98.0	1.0262	99.2	0.06	30	6.20	¹ (10°C)	4.0	1.5	2.5	Lining – no change. Gasket, spring, valve cup - no change, valve body and stem-Slightly yellowed. No signs of attack on scratch (clean and bright)
	6 months												

Comparing Tables 3 and 4 it can be seen that the active ingredient, clobetasol propionate and the preservative, phenoxyethanol, which are both routinely analysed, are not affected by the physical form of the emulsion (i.e. prior art versus a composition according to the invention).

5 Example 13

The physical stability of the formulation prepared according to the methods of the invention has been confirmed using a Turbiscan Transmission Plot which shows that after 4 days, the dispersed phase is homogenously distributed throughout the sample meaning that no phase separation has occurred.

10

Surfactant Ratio (Ceteareth-20:Sorbitan Laurate:Cetyl Alcohol)	4.0:5.0:1.0	4.5:4.5:1.0	5.0:4.0:1.0	5.5:3.5:1.0	6.0:3.0:1.0
Part 1					
Petrolatum	5.00	5.00	5.00	5.00	5.00
Mineral Oil	5.00	5.00	5.00	5.00	5.00
Isopropyl Myristate	5.00	5.00	5.00	5.00	5.00
Cyclomethicone	5.00	5.00	5.00	5.00	5.00
Cetyl Alcohol	1.00	1.00	1.00	1.00	1.00
Sorbitan Laurate	5.00	4.50	4.00	3.50	3.00
Part 2					
Water	58.80	58.80	58.80	58.80	58.80
Ceteareth-20	4.00	4.50	5.00	5.50	6.00
Citric Acid	0.12	0.12	0.12	0.12	0.12
Potassium Citrate	0.08	0.08	0.08	0.08	0.08
Part 3					
Propylene Glycol	5.00	5.00	5.00	5.00	5.00
Phenoxy Ethanol	1.00	1.00	1.00	1.00	1.00
Part 4					
Hydrocarbon Propellant P70	5.00	5.00	5.00	5.00	5.00
Total	100.00	100.00	100.00	100.00	100.00
Turbiscan @ > 4 days	Creaming	Creaming	Slight Creaming	Stable	Stable

Example 14

Using the formulation set out below and made using the procedure
15 illustrated in figure 7, a phase II clinical trial was conducted as described.

	17% PG / pH 5
Part 1	%w/w
White Petrolatum	5.26
Light Mineral Oil	5.26
Isopropyl Myristate	10.53
Cyclomethicone	2.63
Cetyl Alcohol	1.05
Sorbitan Monolaurate	4.74
Part 2	
Purified Water	46.58
Polyoxyl 20 Cetostearyl Ether	4.74
Citric Acid Anhydrous	0.08
Potassium Citrate	0.13
Part 3	
Propylene Glycol	17.90
Phenoxy Ethanol	1.05
Desonide (micronized)	0.05
Emulsion concentrate Total	100.00

The randomized phase II clinical trial involved 106 patients demonstrating mild to moderate atopic dermatitis who underwent a 4 week treatment and were followed up three weeks subsequently. Patients aged 3 months to 17 years were administered the above composition formulated as a foam in a ratio of 2:1 (desonide composition: vehicle absent desonide). The primary endpoints of the study were determined to be as follows:

Investigator's Static Global Assessment; clear (0) or almost clear (1), and

Erythema; 0 or 1, and

Induration/Papulation; 0 or 1, and

ISGA; minimum improvement of 2 grades.

There were multiple secondary endpoints.

The Part 2 results showed that were the primary endpoint was validated, there was a 53% response rate in patients treated with the desonide formulation and a 12% response rate in patients treated with the vehicle lacking the active agent

desonide (placebo). The response rate to the placebo was as expected. The response rate to the desonide formulation was nearly double the expected rate (53% versus 27%). The formulations according to the invention show surprising and unexpected advantages over the expected response.

5 Example 15

A 0.12% betamethasone valerate sub-micron emulsion formulation was prepared to demonstrate the ability to dissolve a pharmaceutically active agent in the oil phase. The following formulation was prepared.

Item No.	Ingredient	Trade Name	
1	Octyl dimethyl PABA	Escalol 507	10.00
2	Betamethasone Valerate	BMV	0.12
3	Mineral Oil	Drakeol 9	10.00
4	Sorbitan Laurate	Crill 1	4.00
5	Ceteareth-20	Cetomacrogol 1000BP	5.00
6	Cetyl Alcohol	Cetyl Alcohol	1.00
7	Purified Water	Water	64.18
8	Citric Acid	Citric Acid Anhydrous	0.11
9	Potassium Citrate	Potassium Citrate	0.09
10	Phenoxyethanol	Phenoxyethanol	0.50
11	P70	Propellent 70	5.00*
		Total:	100.00

10

The formulation was prepared according to the following protocol:

- Combine items 1 and 2. Stir until completely dissolved.
- Add items 3, 4, 5 and 6. Heat to 60°C and stir until dissolved.
- In a separate beaker, combine items 7, 8, 9 and 10. Stir until dissolved.

- With stirring add 70% of the water phase to the warm, clear oil phase. Continue stirring and heating while recording the temperature and the conductivity.
- Continue heating and stirring to just past the assembly temperature (approx. 74°C). Remove the emulsion from heat and place on a cool stirrer.
- Continue stirring and add the remaining water phase at the temperature when conductivity is at a maximum (approx. 70 – 72°C).
- Stir cool to 30°C. Top up with water to account for evaporative loss.
- Test pH and adjust to pH 4 (if required)

The physical characteristics the formulation is summarised as follows

Formulation	SME
Appearance	Translucent , water thin emulsion
pH (@RT)	3.97
DLS mean diameter (nm)	64.0
SPOS (% volume > 0.5um)	0.109

In conclusion it will be appreciated that the process of the invention allows the formation of a stable oil-in-water microemulsion or sub-micron emulsion which allows for the inclusion of a hydrocarbon propellant so that a foam may be dispensed when the resulting product is in use. Moreover, the resultant foam appears stable and effective. It will be appreciated that the scope of the invention described herein is not limited to the specific embodiments described herein in the examples but extends to the general principles of the invention as set out in the summary and detailed description of the invention hereinabove.

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CLAIMS:

1. A process for the preparation of an oil in water (O/W) microemulsion or sub-micron emulsion composition for dermal delivery of at least one pharmaceutically active ingredient, the process including the steps of:
 - 5 a) admixing a first part including at least one of the group consisting of animal, mineral or vegetable oils, siloxanes, esters, fatty acids, fats, halogen compounds, and alkoxyated alcohols; and one or more lipophilic surfactants, and a second part including water and at least one hydrophilic surfactant to achieve homogeneity,
 - 10 b) heating the mix of step a) to a phase assembly temperature in the range of 40-99°C with continuous mixing to obtain an oil in water microemulsion or sub-micron emulsion,
 - c) allowing said microemulsion or sub-micron emulsion to cool, and
 - d) adding a third part to said microemulsion or sub-micron emulsion at a
15 temperature between 2°C and said phase assembly temperature, said third part including at least one component selected from the group consisting of nonsurfactant amphiphilic type compound, surfactant and water, with the proviso that when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.
- 20 2. The process according to claim 1, wherein in step b) the mix of step a) is heated to a phase assembly temperature in the range of 45 - 95°C.
3. The process according to claim 1 or 2, wherein in step b) the mix of step a) is heated to a phase assembly temperature in the range of 65 - 85°C.
4. The process according to any one of claims 1 to 3, wherein said second
25 part is added in two aliquots.

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5. The process according to claim 4, wherein said aliquots are of about 70% and 30% by weight of the second part, respectively.
6. The process according to claim 4 or 5, wherein the second aliquot is added after said microemulsion or sub-micron emulsion has formed, at a temperature substantially below the first aliquot's temperature, and at a rapid rate so as to reduce the overall temperature of the composition to below about 60°C whereby the microemulsion structure is fixed.
7. The process according to any one of claims 1 to 6, wherein an occlusive agent is present in said first part.
- 10 8. The process according to claim 7, wherein said occlusive agent is petrolatum.
9. The process according to any one of claims 1 to 8, wherein a pharmaceutically active agent is included in at least one of said first part, said second part, and said third part.
- 15 10. The process according to claim 9, wherein said pharmaceutically active ingredient is insoluble or only sparingly soluble in water.
11. The process according to claim 9, wherein said pharmaceutically active ingredient is one or more water insoluble compounds selected from corticosteroids, desonide, clobetasol, betamethasone, vitamin D analogues and vitamin A analogues.
- 20 12. The process according to any one of claims 1 to 11, wherein the third part is premixed and heated until all the components are dissolved.
13. A process for the preparation of a microemulsion or sub-micron emulsion composition for dermal delivery of at least one pharmaceutically active agent, the process including the steps of:

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a) heating a first part including at least one of the group consisting of animal, mineral or vegetable oils, silanes, siloxanes, esters, fatty acids, fats, halogen compounds, and alkoxylated alcohols; and one or more lipophilic surfactants to a temperature of 40 - 99°C and mixing to homogeneity,

5 b) heating a second part including water and at least one hydrophilic surfactant to a temperature of 40 - 99°C and mixing to achieve homogeneity,

c) adding said second part to said first part at a temperature of 40 - 99°C with continuous mixing whereby a microemulsion or sub-micron emulsion is formed at a phase assembly temperature,

10 d) allowing said microemulsion or sub-micron emulsion to cool, and

e) adding a third part to said microemulsion or sub-micron emulsion at a temperature between room temperature and said phase assembly temperature, said third part having been premixed and including at least one component selected from non-surfactant amphiphilic type compound, surfactant and water, with the proviso that
15 when the third part includes water it also includes a non-surfactant amphiphilic type compound and/or surfactant.

14. The process according to claim 13, wherein in step a) the temperature is 45 - 95°C.

15. The process according to claim 13 or 14, wherein in step a) the
20 temperature is 65 - 85°C.

16. The process according to any one of claims 13 to 15, wherein in step b) the temperature is 45 - 95°C.

17. The process according to any one of claims 13 to 16, wherein in step b) the temperature is 65 - 85°C.

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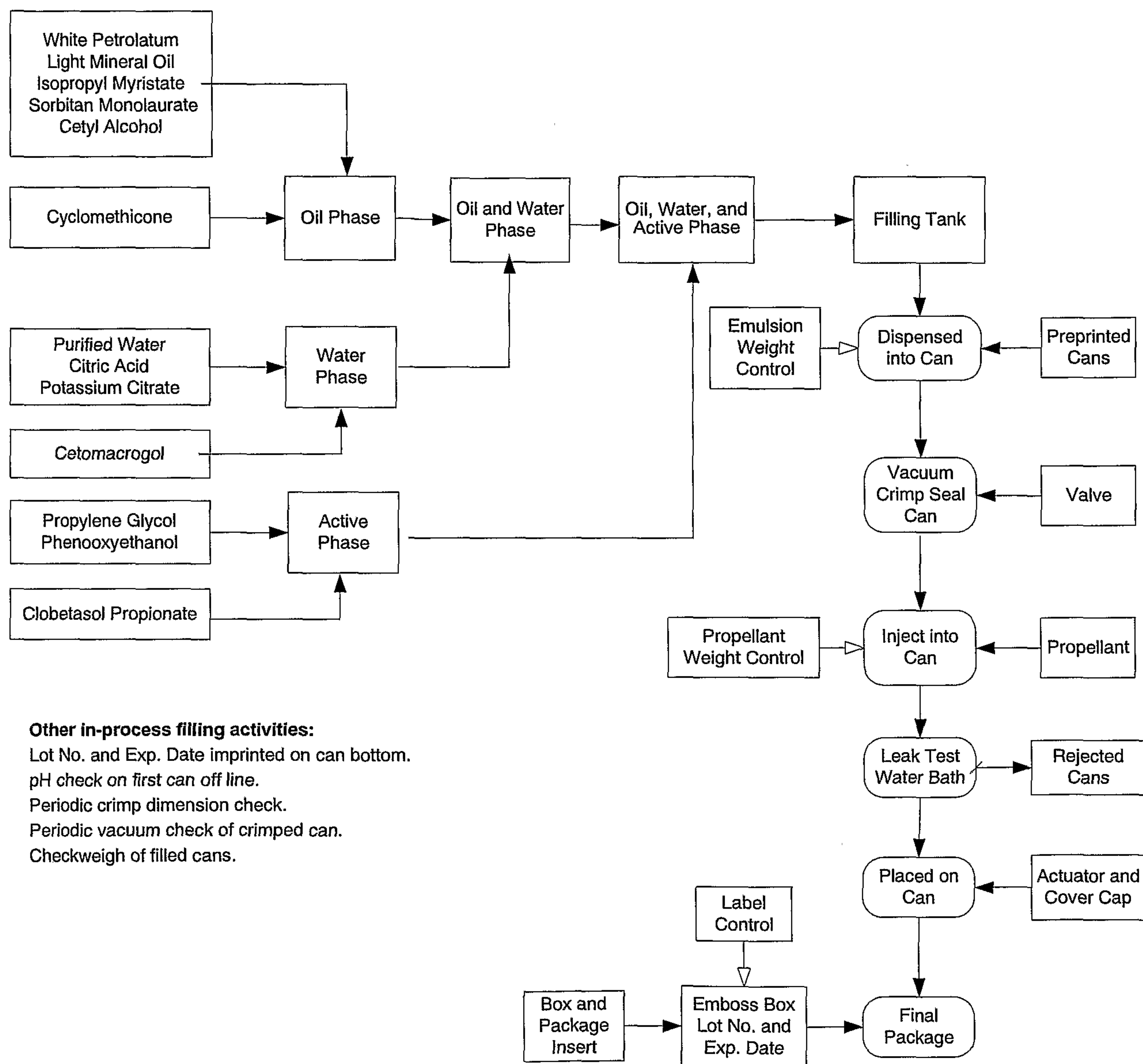
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18. The process according to any one of claims 13 to 17, wherein in step c) the temperature is 45 - 95°C.

19. The process according to any one of claims 13 to 18, wherein in step c) the temperature is 65 - 85°C.

5 20. The process according to any one of claims 13 to 19, wherein the third part is heated until the components are dissolved.

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FIGURE 1**Ethanol-Free Clobetasol Propionate Foam, 0.05% Process Flow Diagram**

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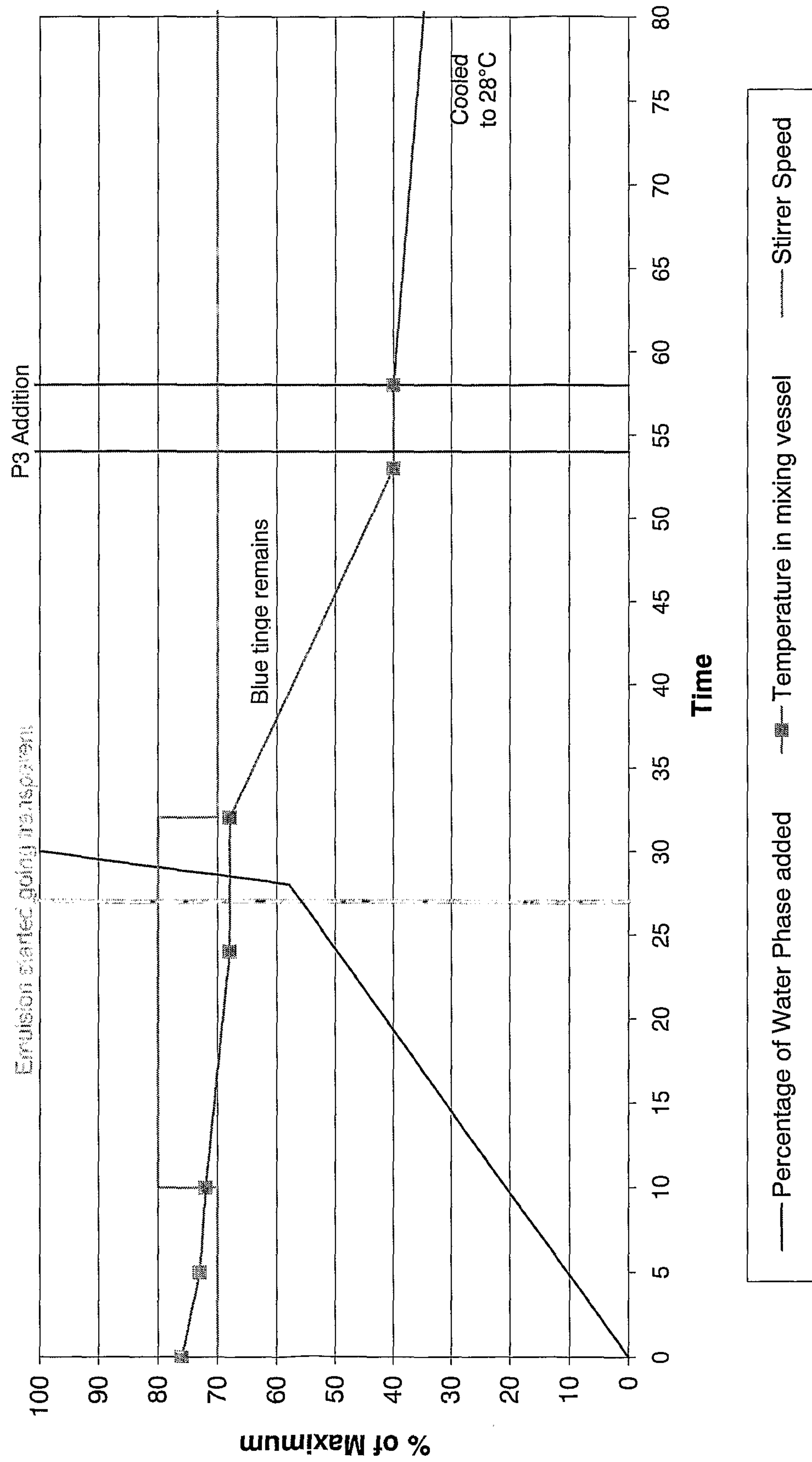
FIGURE 2**Clobetasol propionate E 15 Kg**

FIGURE 3 - Desonide E 15 kg Batch No. 367-24

Slow addition of P2 until inversion then fast addition of remaining P2

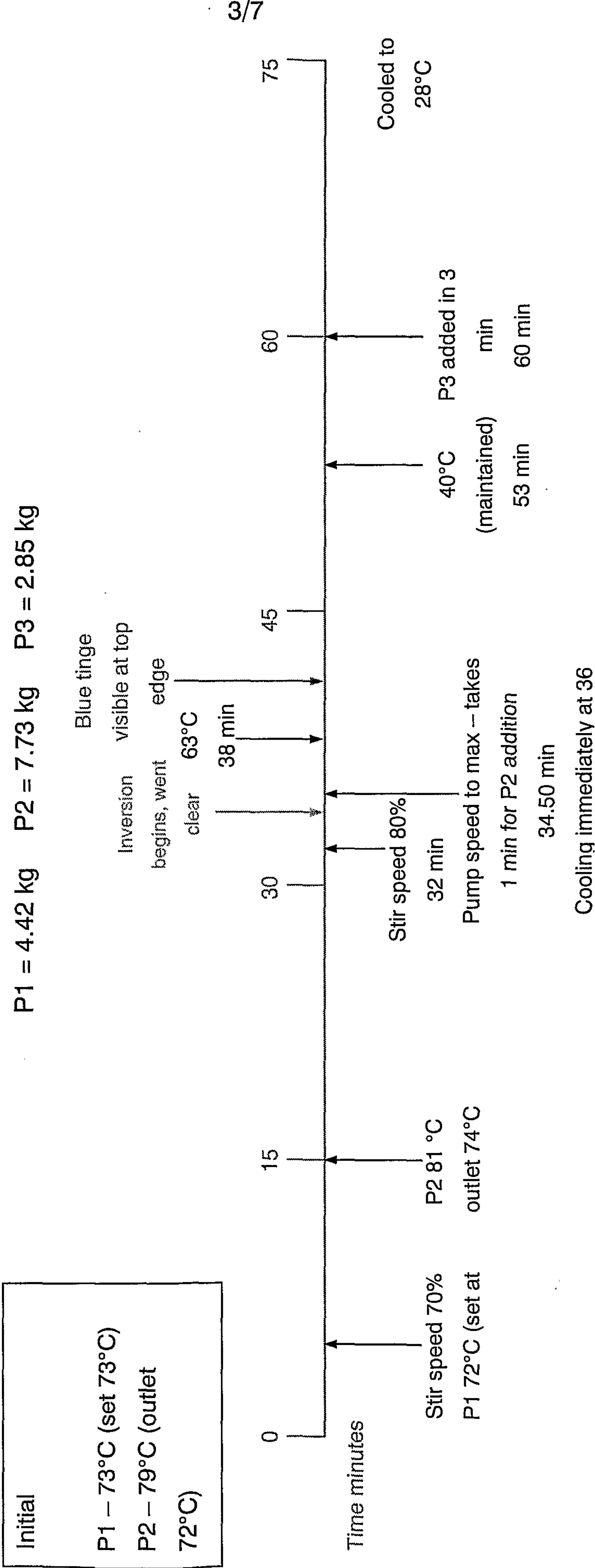


FIGURE 4

Desonide E 15 Kg Batch

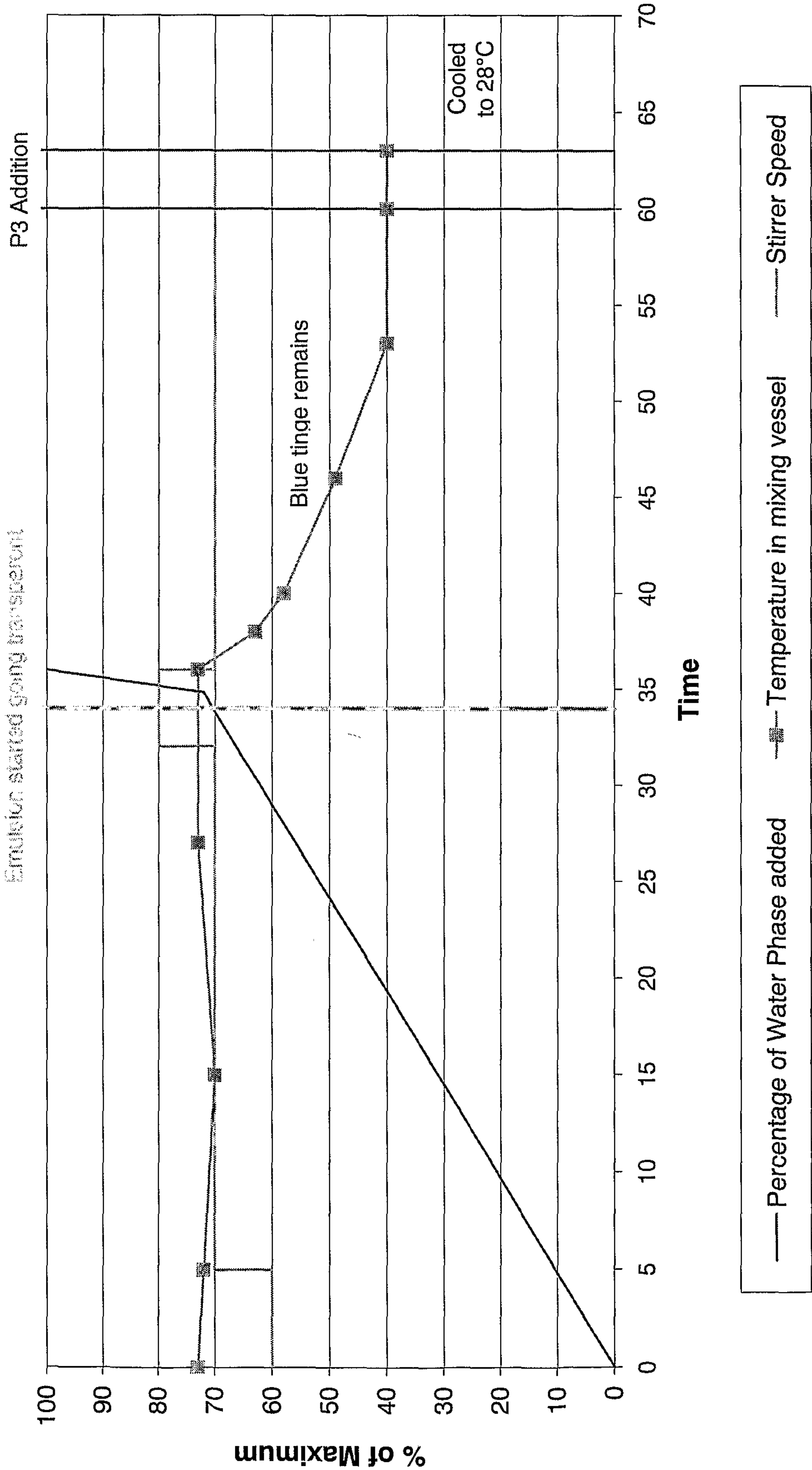
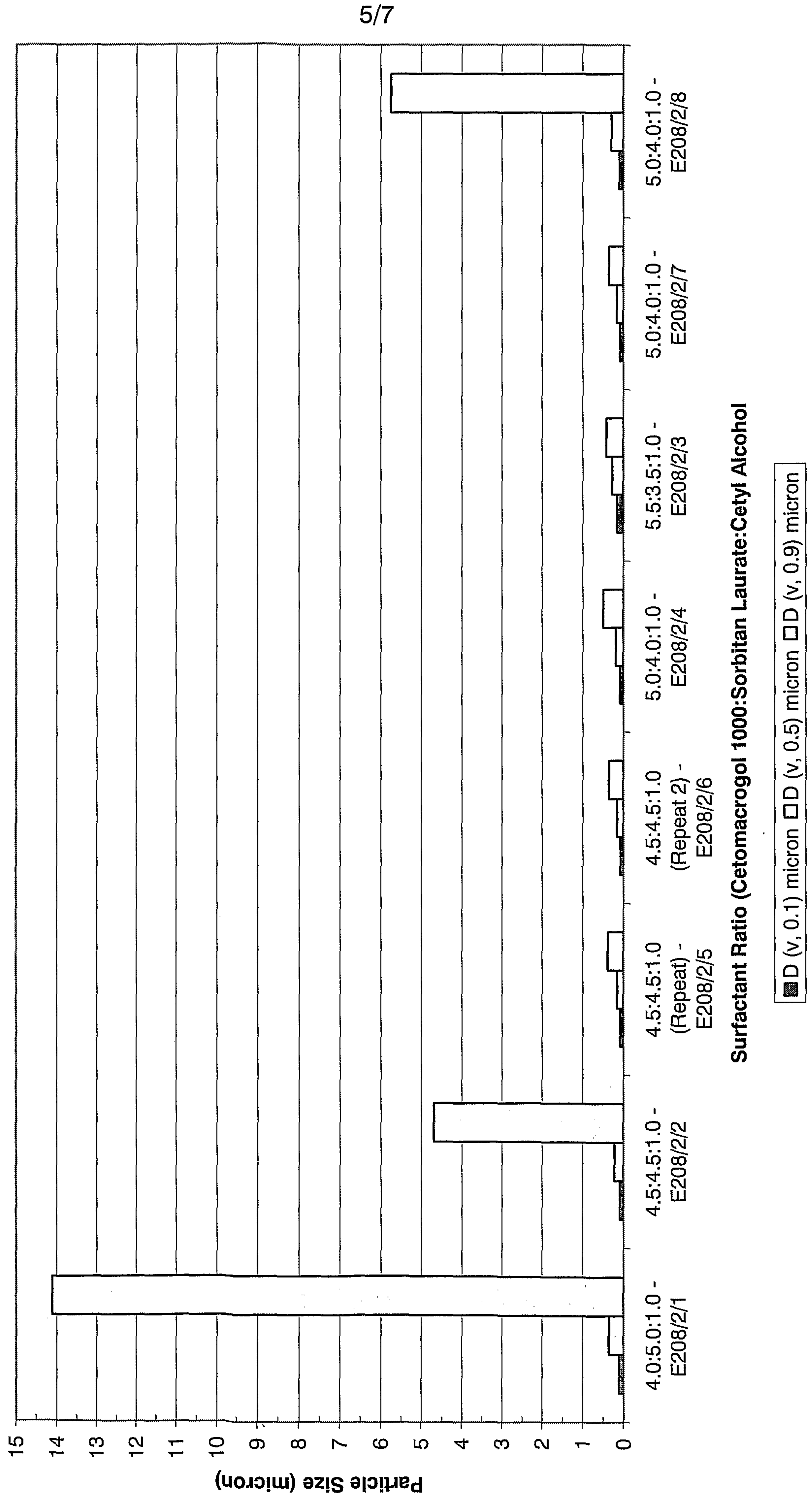


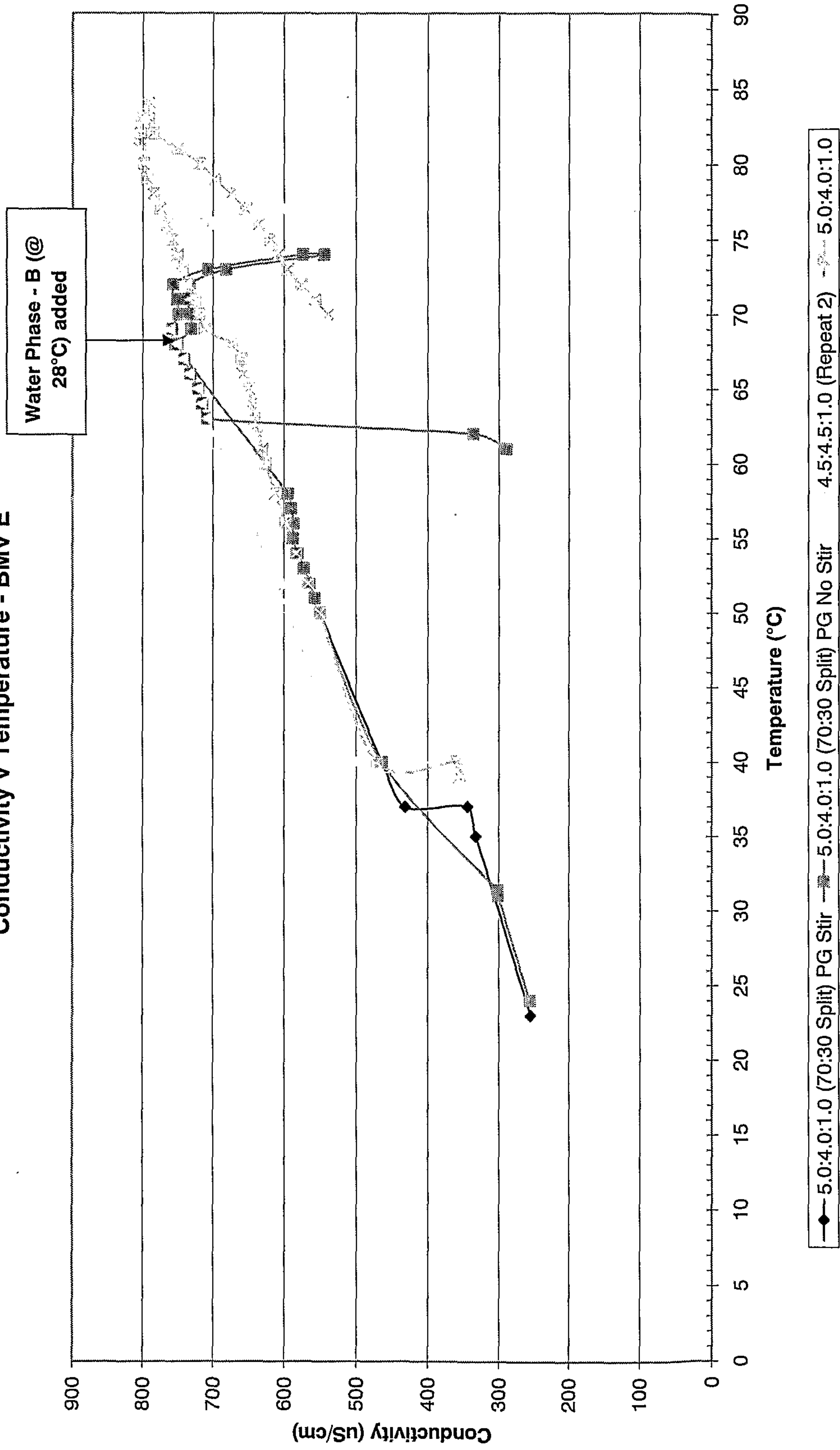
FIGURE 5 BMV E - Particle Size Distribution vs Surfactant Ratio



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FIGURE 6

Conductivity V Temperature - BMV E



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FIGURE 7