EXPERIMENTAL DESIGN

An auxiliary and useful tool for patents

Rafael Pi

Daily examples (1)

A softening composition for the textile industry has been developed and, surprisingly, it shows very good performance properties:

- stability,
- compatibility with anionic resins, and
- softening.

The softener has the following composition:

Component	%
Cationic surfactant	50
Fatty alcohol 40 EO	21
Glycerin monostearate	29

Would it be possible to identify a broader optimum region?

Daily examples (2)

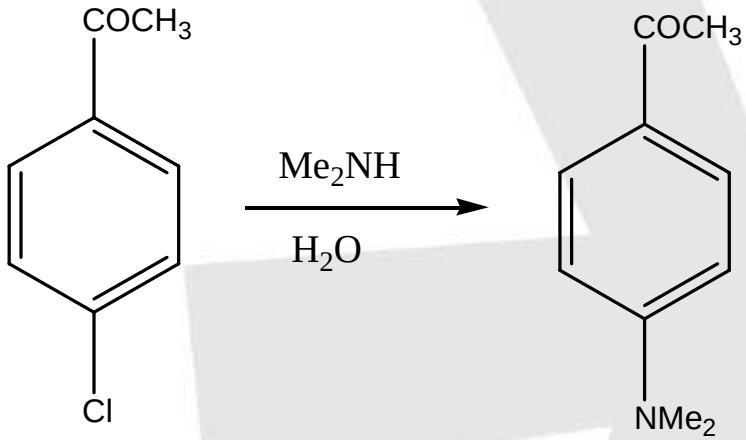
This softener composition is new and, surprisingly, clear at room temperature:

Component	%
Cationic surfactant	15.0
Fatty alcohol 12 EO	15.0
Glycerin monostearate	7.5
Water	62.5

Are any other emulsifiers and solvents, which would also provide clear compositions?

Daily examples (3)

In the synthesis of 4-(N,N-dimehtylaminoacetophenone was reported a yield of 77% in JP79132542.



Would it be possible to improve this yield?

Daily examples (4)

This softener composition has an excellent rewetting capacity:

Component	%
Cationic surfactant A	80.0
Fatty alcohol 20 EO	7.5
Additive M	12.5

Would it be possible to formulate the product using another Cationic surfactant (i.e. B) and Additive M or Additive N?

Would it be possible to identify any other good combination?

Daily examples (5)

The microscopic structure of this cosmetic composition shows a nanoemulsion:

Component	%
Mineral oil	12.0
C12-14 3 EO phosphated	7.5
Glycerin monostearate	5.0
Glycerin	3.0
Cetearyl glucoside	2.0
Water	70.5

Would it be possible to identify other good combinations?

Daily examples (6)

Developing a tablet, the following composition, surprisingly, shows good disintegrating and crushing properties:

Component	%
Lactose monohydrate	15
Starch	42
Anhydrous lactose	43

Would it be possible to broaden this formulation?

Daily examples (7)

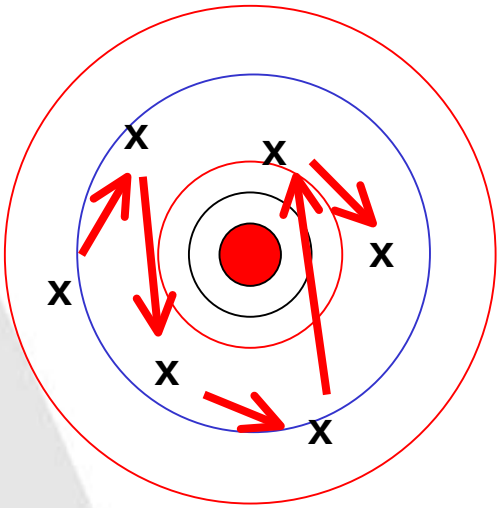
The following excipient mixture surprisingly stabilizes an unstable active ingredient in a tablet formulation:

- Microcrystalline cellulose
- Starch
- Hydroxypropylmethylcellulose
- Magnesium stearate

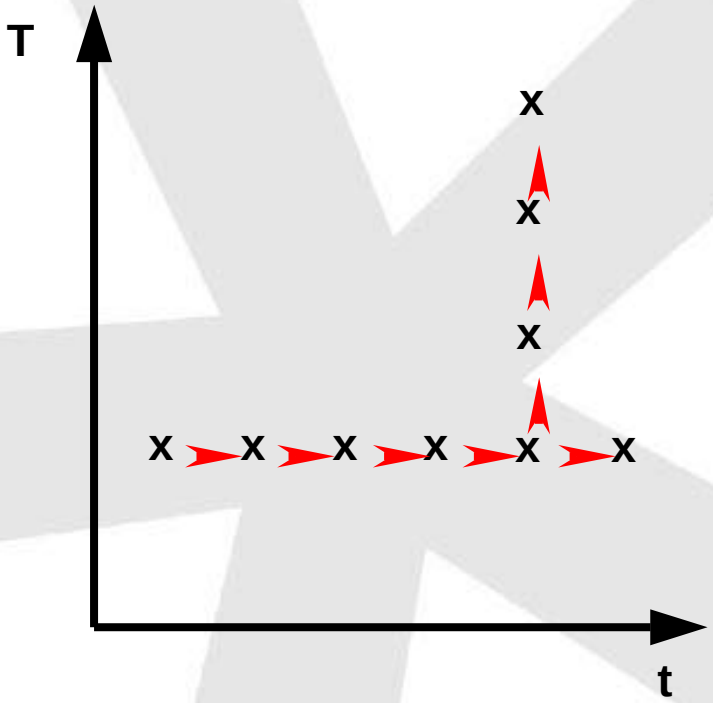
Would it be possible to identify other suitable excipients?

Experimental work - Traditional ways

Feeling driven



One variable each time



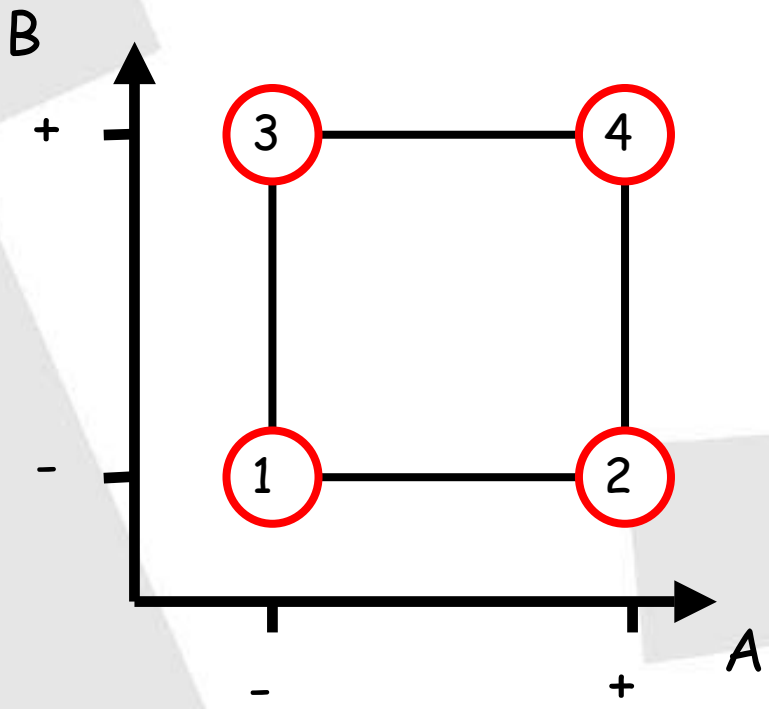
and the eventual interactions?

Experimental work - Now

The alternative is:

EXPERIMENTAL DESIGN METHODOLOGY!!!

2^2 Factorial Design

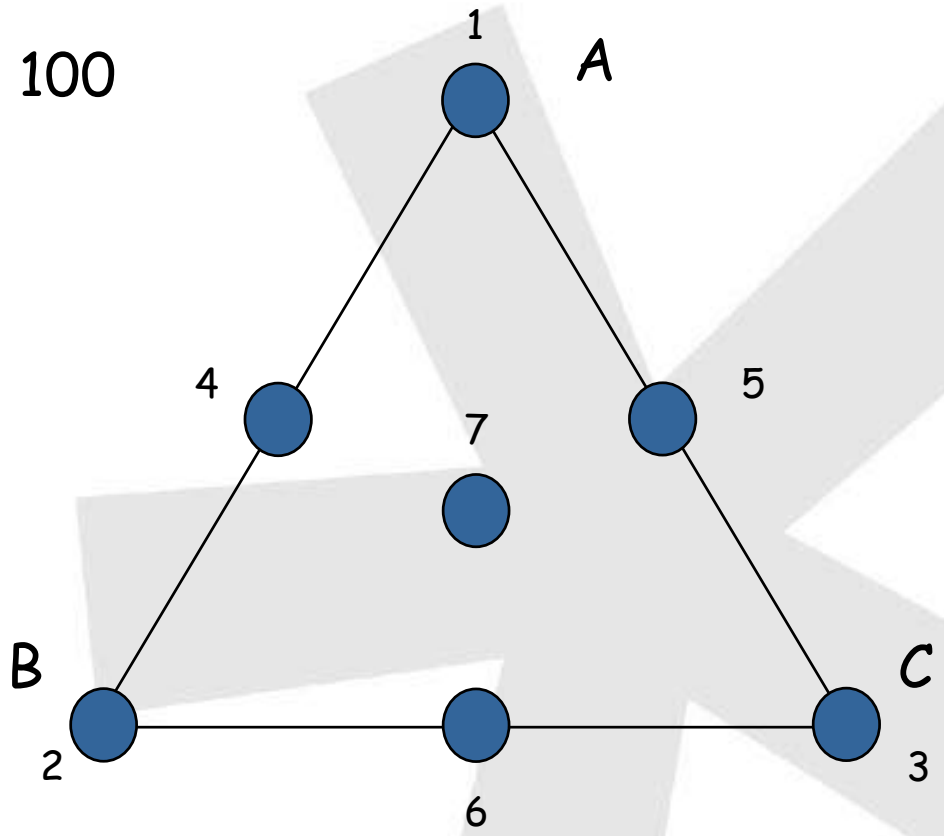


Experiment	A	B
1	-	-
2	+	-
3	-	+
4	+	+

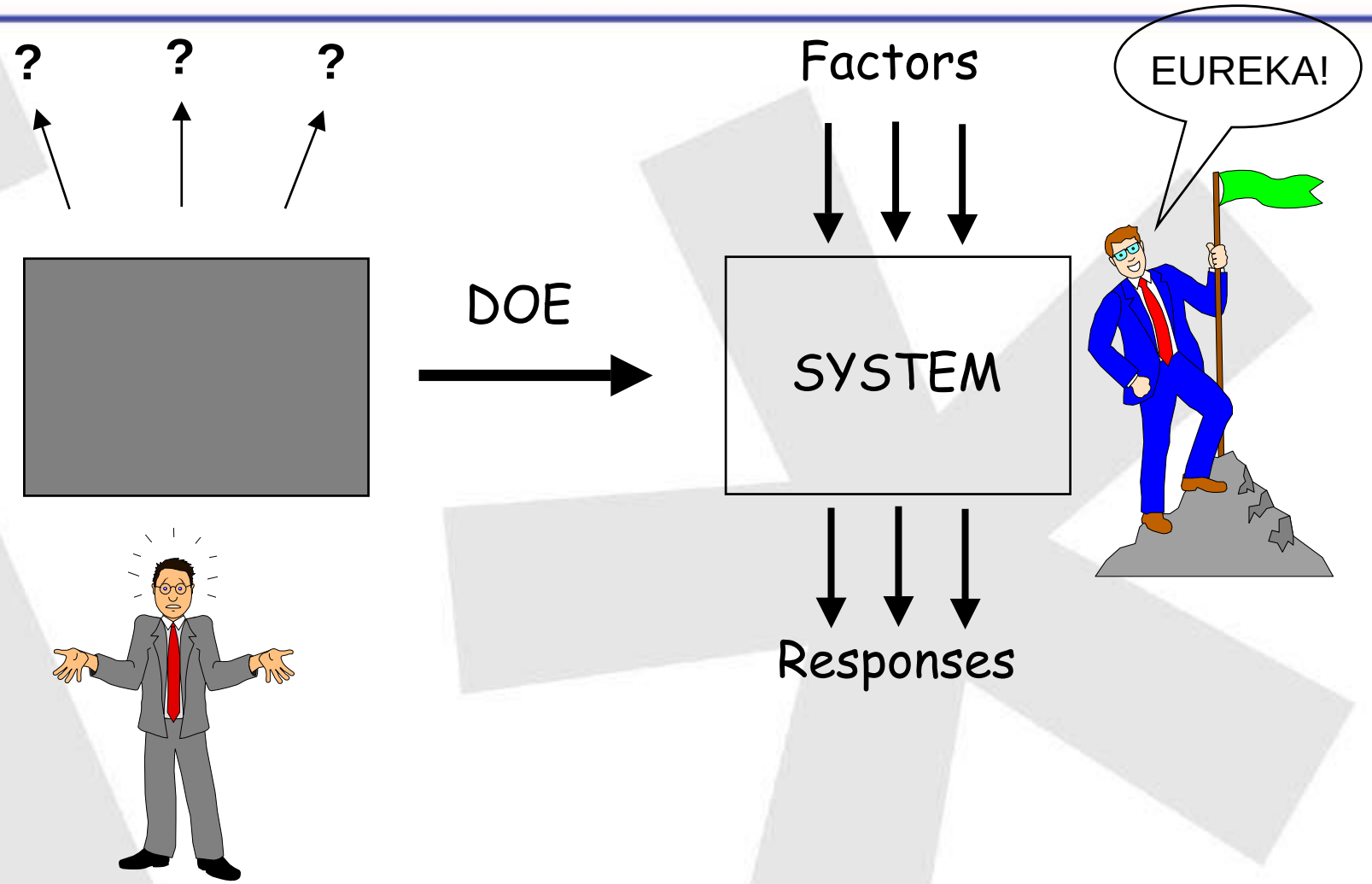
Effects, interactions, ... feasible also in industrial plant

Mixture design

Mixture: A + B + C = 100



Researcher discovery



United States Patent [19]

Ciko et al.

[11] **3,984,335**

[45] **Oct. 5, 1976**

[54] **COMPOSITIONS FOR SOURING AND SOFTENING LAUNDERED TEXTILE MATERIALS AND STOCK SOLUTIONS PREPARED THEREFROM**

[75] Inventors: **John D. Ciko**, Allen Park; **John J. Cramer**, Wyandotte, both of Mich.

[73] Assignee: **BASF Wyandotte Corporation**, Wyandotte, Mich.

[22] Filed: **Jan. 16, 1975**

[21] Appl. No.: **541,448**

[52] **U.S. Cl.** ..... **252/8.6;** 252/8.8; 260/29.6 XA

[51] **Int. Cl.²** **D06M 13/36;** D06M 13/40; D06M 13/46; D06M 15/26

[58] **Field of Search** 252/8.8, 8.6

[56] **References Cited**

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Primary Examiner—Donald E. Czaja
Assistant Examiner—E. A. Nielsen
Attorney, Agent, or Firm—Bernhard R. Swick; L. S. Van Landingham, Jr.; Robert E. Dunn

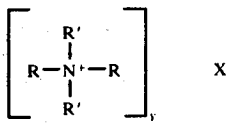
[57] **ABSTRACT**

Liquid and solid compositions are provided for souring and imparting softness to freshly laundered textile materials. When in the form of a stable homogeneous liquid, the composition may contain a quaternized fatty amide, a quaternized fatty amine, an aqueous emulsion of partially oxidized polyethylene or a fatty amphoteric compound as a softening agent, a water soluble organic acid containing about 1–20 carbon atoms and having a primary ionization constant between 10^{-1} and 10^{-5} as the souring agent, and water. When in the form of a stable dry solid, the composition may contain a quaternized fatty amide, a quaternized fatty amine or a fatty amphoteric compound as the softening agent, and a dry solid water soluble organic acid containing 2–20 carbon atoms and having a primary ionization constant between 10^{-1} and 10^{-5} as the souring agent. Stable homogeneous stock solutions are also prepared from the novel liquid or solid compositions of the invention.

44 Claims, No Drawings

lected from the group consisting of halide, sulfate, phosphate, alkyl sulfates having about 1–3 carbon atoms in the alkyl group and alkyl phosphates having about 1–3 carbon atoms in the alkyl group, and Y is an integer having a numerical value equivalent to the valency of X.

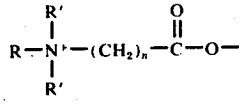
B. Quaternized fatty amines corresponding to the following structural formula



wherein R, R', X and Y are as defined in (A) above.

C. An aqueous emulsion of partially oxidized emulsifiable polyethylene having a molecular weight of about 1000–10,000, and

D. Fatty amphoteric compounds corresponding to the structural formula



wherein R, R', and *n* are as defined in (A) above, the said amphoteric compounds having non-acidic isoelectric ranges.

The liquid composition also contains a water soluble organic acid containing about 1–20 carbon atoms and preferably about 2–10 carbon atoms and having a primary ionization constant between about 10^{-1} and 10^{-5} as an acidic souring agent for the freshly laundered textile materials, or admixtures of two or more of such organic acids. Preferred organic acids include acetic acid, citric acid, glycolic acid, maleic acid, malonic acid, oxalic acid and tartaric acid. Glycolic acid usually produces the best results.

In the foregoing structural formulae, R is preferably a monovalent alkyl radical containing about 12–18 carbon atoms and for still better results about 18 carbon atoms. R' is preferably a monovalent alkyl radical containing one carbon atom, Z is preferably a monovalent alkyl radical containing either about one or about 12–18 carbon atoms, and *n* preferably is an integer having a numerical value of about 1–3 for still better results about 1. X is preferably halide and in many instances is chloride. The numerical value of Y varies with the valence of X and may be 1, 2 or 3 depending upon the selected anion.

The molecular weight of the partially oxidized polyethylene in the aqueous emulsion is preferably about 1,400–5,000 and may be about 2,500 for still better results. The density is preferably about 0.93–1.05 and the carboxyl content may be, for example, about 0.2–2 milliequivalents per gram. The solids content of the emulsion may vary over wide ranges and may be, for example, about 5–50% by weight and preferably about 25% by weight. In calculating the amount of the emulsion to be used as a softening agent, it is understood that the calculations are made on a dry solids basis. The emulsifying agent for the emulsion may be a cationic, anionic or nonionic synthetic surfactant and is preferably a cationic synthetic surfactant. The emulsifying agent may be present in an amount of about 1–25% by weight and preferably about 5–10% by weight based upon the weight of the partially oxidized polyethylene. The partially oxidized polyethylene in one presently preferred emulsion has a ring and ball softening point of 223°F., a penetration (100 grams for 5 seconds) of 0.22 millimeter, a density of 0.940 g/cc, a Brookfield viscosity at 302°F. of 1,300 cps, a molecular weight of 2,500 and an acid number of 14.

The fatty amines and amides and fatty amphoteric compounds disclosed herein are well known commercially available products and may be prepared in accordance with the usual prior art processes. The aqueous emulsion of partially oxidized polyethylene is likewise a commercially available product and it may be prepared by the usual prior art processes. Examples of emulsions of partially oxidized polyethylene and the preparation thereof are disclosed in a number of United States patents including U.S. Patent Nos. 3,442,964 and 3,475,207, the disclosures of which are incorporated herein by reference.

The liquid composition preferably contains a quaternized fatty amine as the softening agent and glycolic acid as the souring agent. In instances where freeze-thaw stability is of importance, then the liquid composition preferably contains a quaternized fatty amide, or a quaternized fatty amine, or a fatty amphoteric compound, or an admixture of two or more thereof as a softening agent, and for best results glycolic acid as the souring agent. These latter liquid compositions reconstitute upon freezing and thawing and a precipitate or other nonhomogeneous phase is not formed.

It is understood that the aforementioned ingredients are present in proportions and in concentrations whereby a stable homogeneous liquid composition is produced. In most instances, the preferred concentrations and proportions of the ingredients may be determined by the Box or Factorial Methods of Experimental Design. Suitable procedures for making such determinations are disclosed in the text *Design and Analysis of Industrial Experiments*, edited by Owen L. Davies, and published by the Hafner Publishing Company, New York, New York (1956), the disclosure of which is incorporated herein by reference. This text has been assigned Library of Congress Card No. T 175.D 3. Chapters 10 and 11, i.e., pages 440–578, are especially pertinent.

The aforementioned solid composition of the invention contains a quaternized fatty amide, or a quaternized fatty amine, or a fatty amphoteric compound, or an admixture of two or more thereof. The quaternized fatty amides, the quaternized fatty amines and the fatty amphoteric compounds correspond to the structural formulae described previously for the liquid composition. The solid composition also contains a dry solid water soluble organic acid containing about 2–20 carbon atoms and having a primary ionization constant between 10^{-1} and 10^{-5} as a souring agent, or admixtures of two or more of such organic acids. The presently preferred organic acids for the solid composition include citric acid, fumaric acid, glycolic acid, maleic acid, malonic acid, oxalic acid and tartaric acid. Citric acid or glycolic acid is usually preferred. Inasmuch as the quaternized fatty amides, the quaternized fatty amines, the fatty amphoteric compounds and the organic acid souring agents are dry solids and are compatible, the solid composition may be prepared by uniformly admixing the ingredients in the proportions and

Experimental design: a tool for research

- Quality tool for medium and long term results, because it operates in the design phase of a product or a process
- Tool to question systematically the product or process in order to observe the responses and to get high quality information
- Systematic change of variables, because the analysis of results is strongly dependent on the experiments layout

Experimental design: advantages

- Minimum number of experiments
- Maximum use of internal know how
- Faster, more innovator and closer to the customer
- Easy work up of the results
- Experts meeting before starting experimentation

Experts meeting

- Collect the available information
- List exhaustively all eventual factors
- List all responses
- Set the most suitable levels of the factors
- Exploratory design
- **The most important: thinking before doing!**

Experimental design: uses

- Screening
- Optimization
- Continuous improvement
- Processes, products and formulations

Diseño de un pintalabios

Componentes:

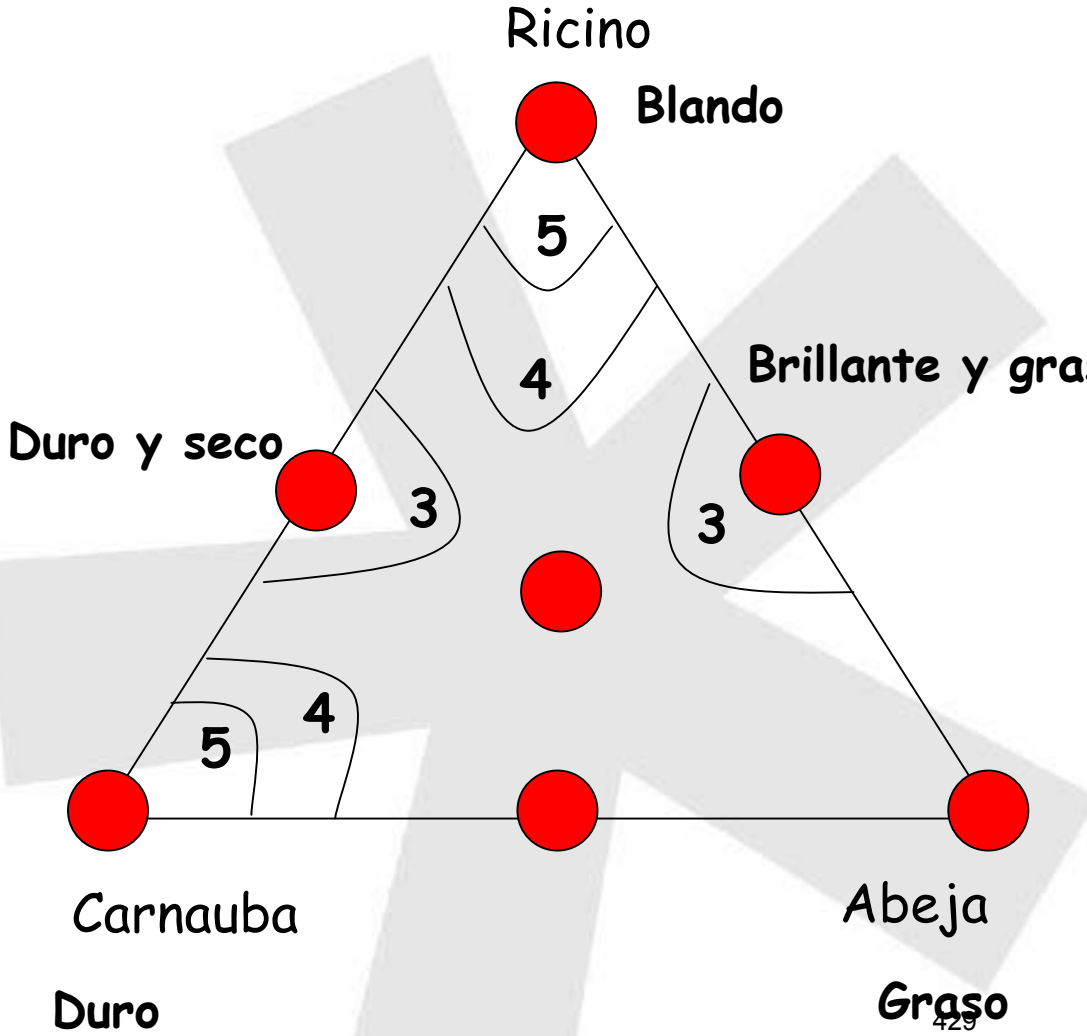
- Aceite de ricino
- Cera de carnauba
- Cera de abeja

Restricciones:

$A_i < X_i < 1$

Valoración por orden de preferencia:

1 mejor que 2



Variables or factors

- Qualitative
  - Product: Coemulsifer 1, Coemulsifier 2
  - Process: Mixer1, Mixer2
- Quantitative:
  - Continuous: any value within determined limits
    - Temperature, Time, pH, Concentration
  - Discontinuous: only discrete levels are available
    - Mixer speed, Sieve, Dielectric constant

Responses

- Qualitative
  - Stable or Unstable
  - OK or NOK
  - ...
- Quantitative:
  - Yield
  - Colour
  - ...

Tools (1)

- Full factorial designs
- 2^f Factorial designs
- 2^f Fraccionated factorial designs
- Taguchi designs
- Plackett-Burman designs
- Latin squares

Tools (2)

- Central composite designs
- Doehlert designs
- Box-Behnken designs
- Mixture designs
- Combined designs
- Graphics, Anova, regression analysis

Also a tool for patents?

- Could experimental design help to define better the scope of the invention?
- Could experimental design help providing coherent experimental data to support the claims?
- Could experimental design help to support inventive step?
- Could experimental design help during examination and opposition procedures?

Daily examples (1)

A softening composition for the textile industry has been developed and, surprisingly, it shows very good performance properties:

- stability,
- compatibility with anionic resins, and
- softening.

The softener has the following composition:

Component	%
Cationic surfactant	50
Fatty alcohol 40 EO	21
Glycerin monostearate	29

Would it be possible to identify a broader optimum region?

Robust softener

Mixture:

Esterquat ≥ 25 %
Non ionic ≥ 10
Ester ≥ 0

} Pseudocomponents

Esterquat + Non ionic + Ester = 100 %

Mixture design

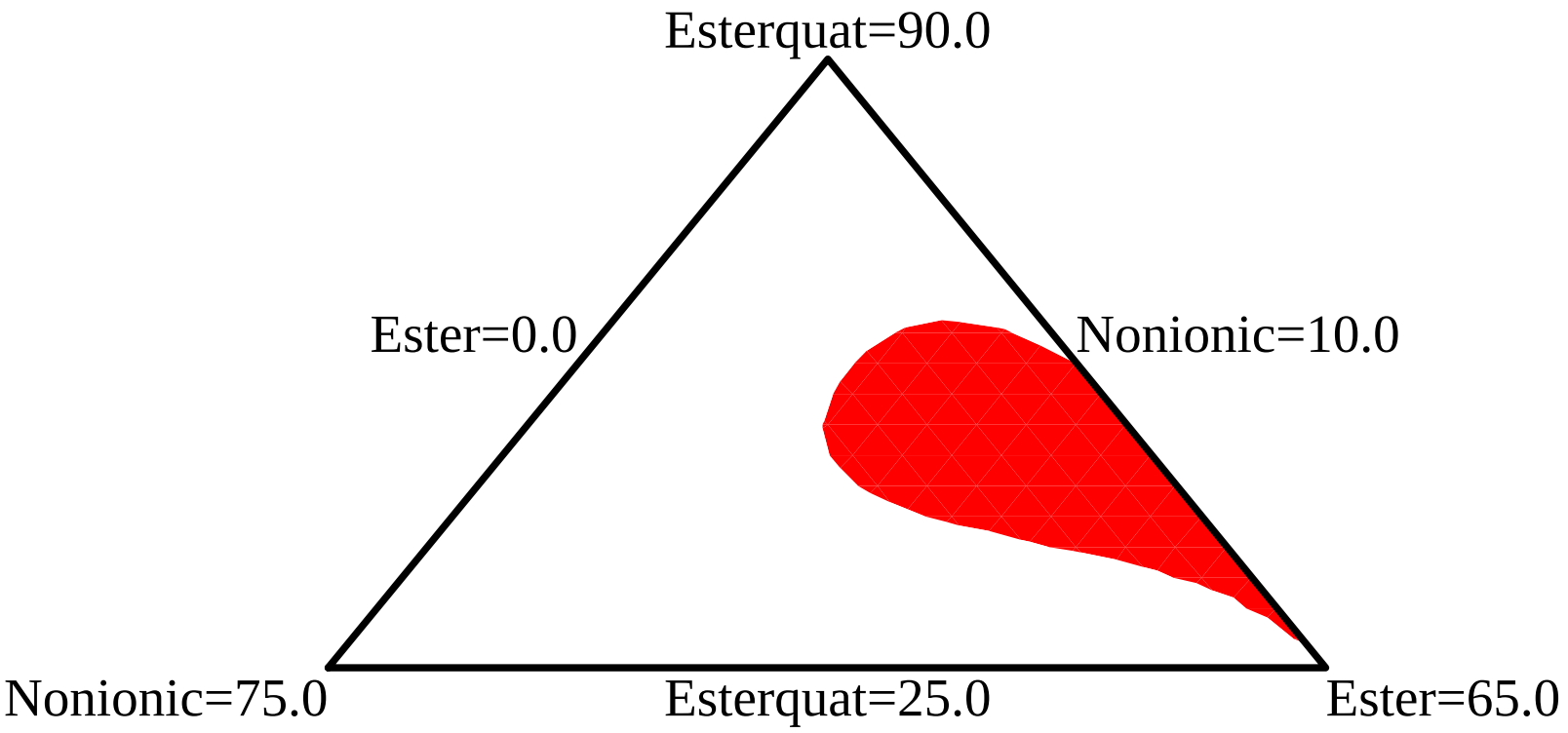
Responses:

Melting point
Emulsion appearance after 28 days
Bath stability
Softness on towel
Softness on shirt

Cognis, EP0729450-B1

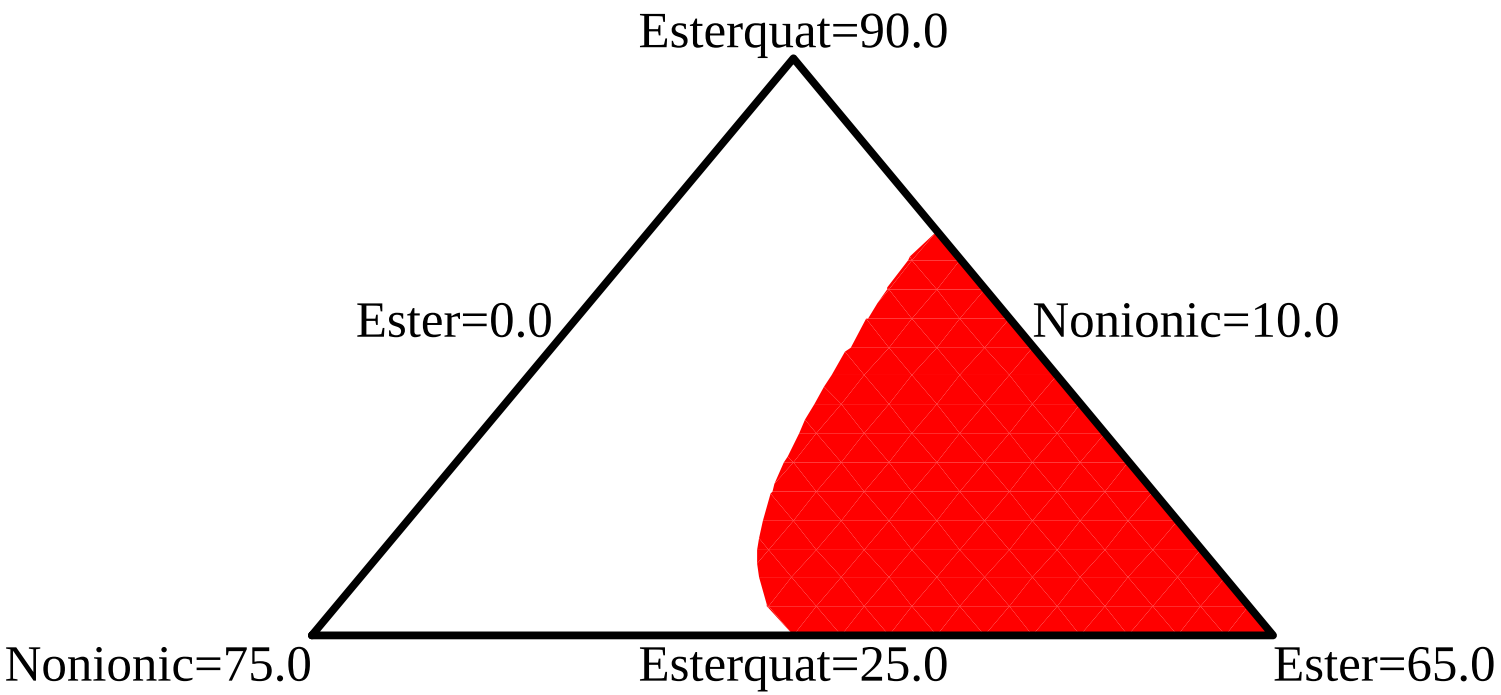
Robust softener

Melting point



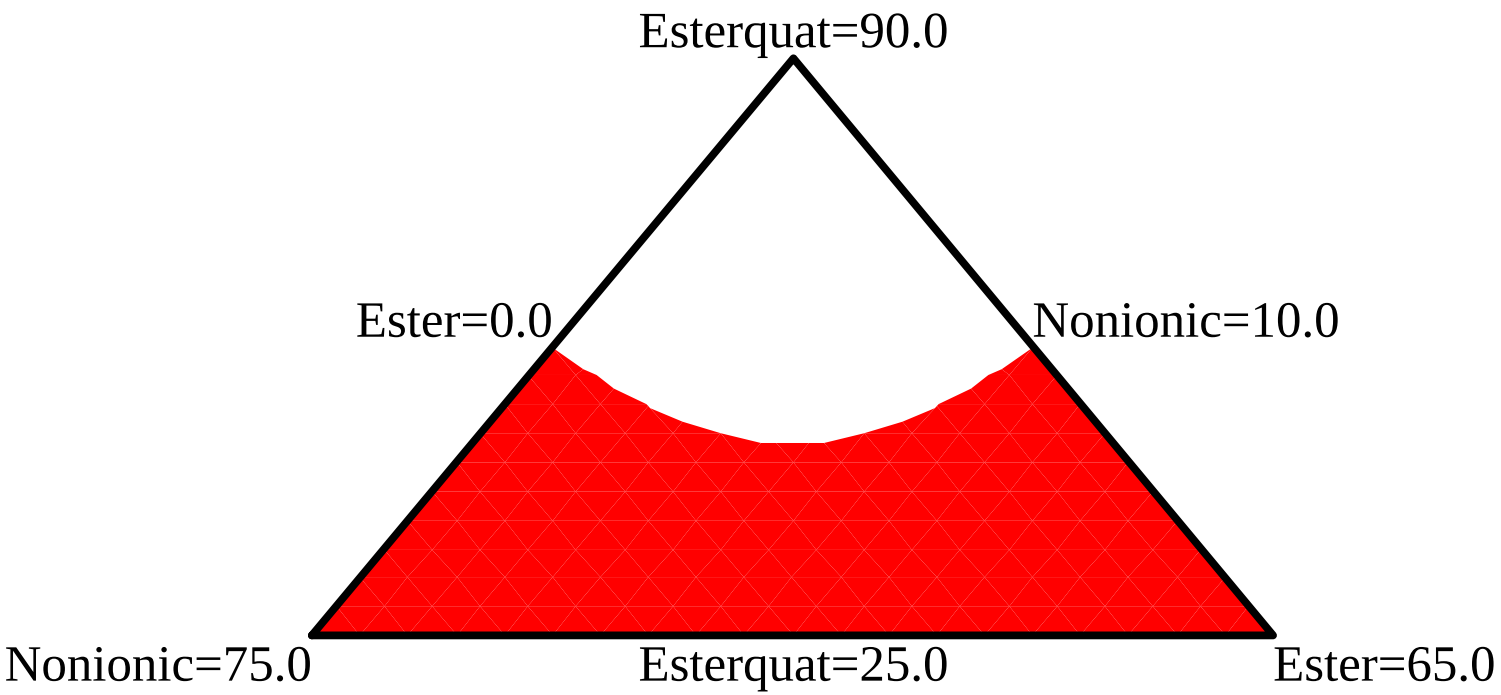
Robust softener

Appearance



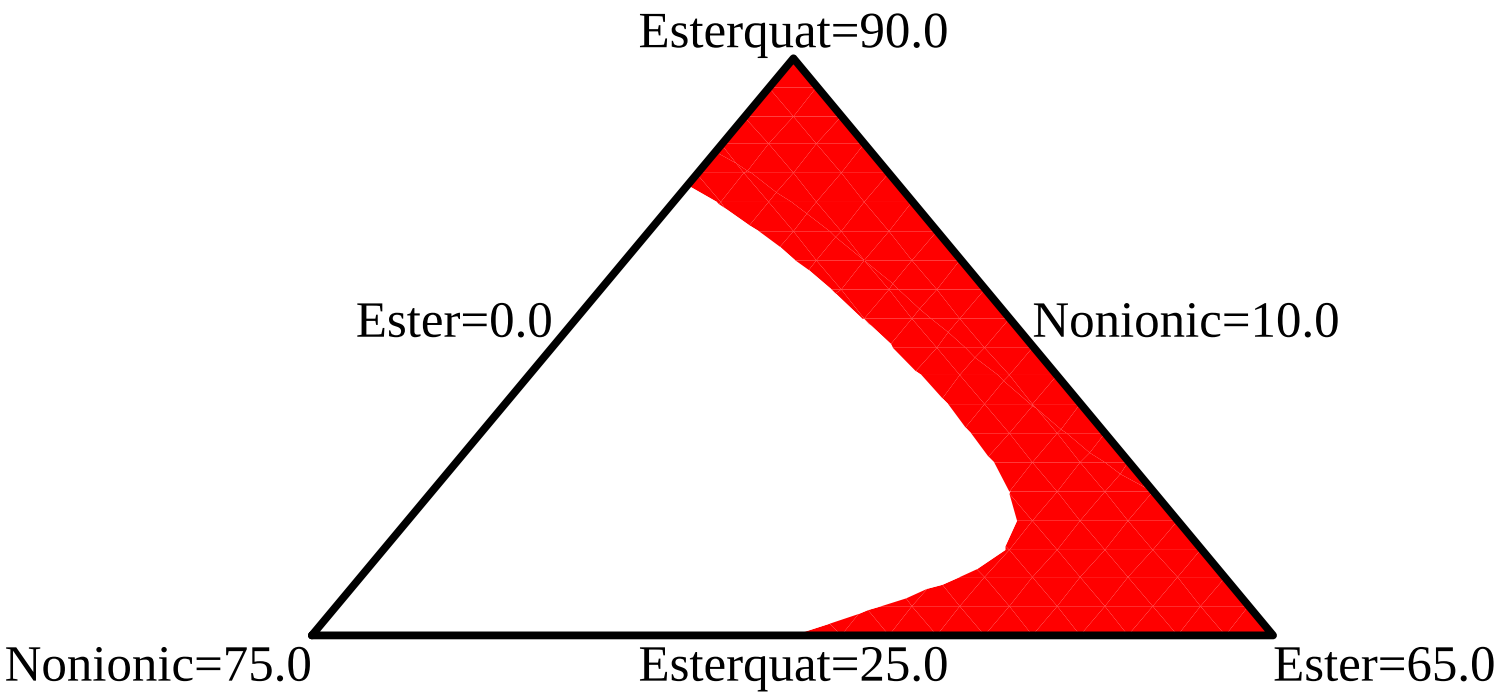
Robust softener

Stability



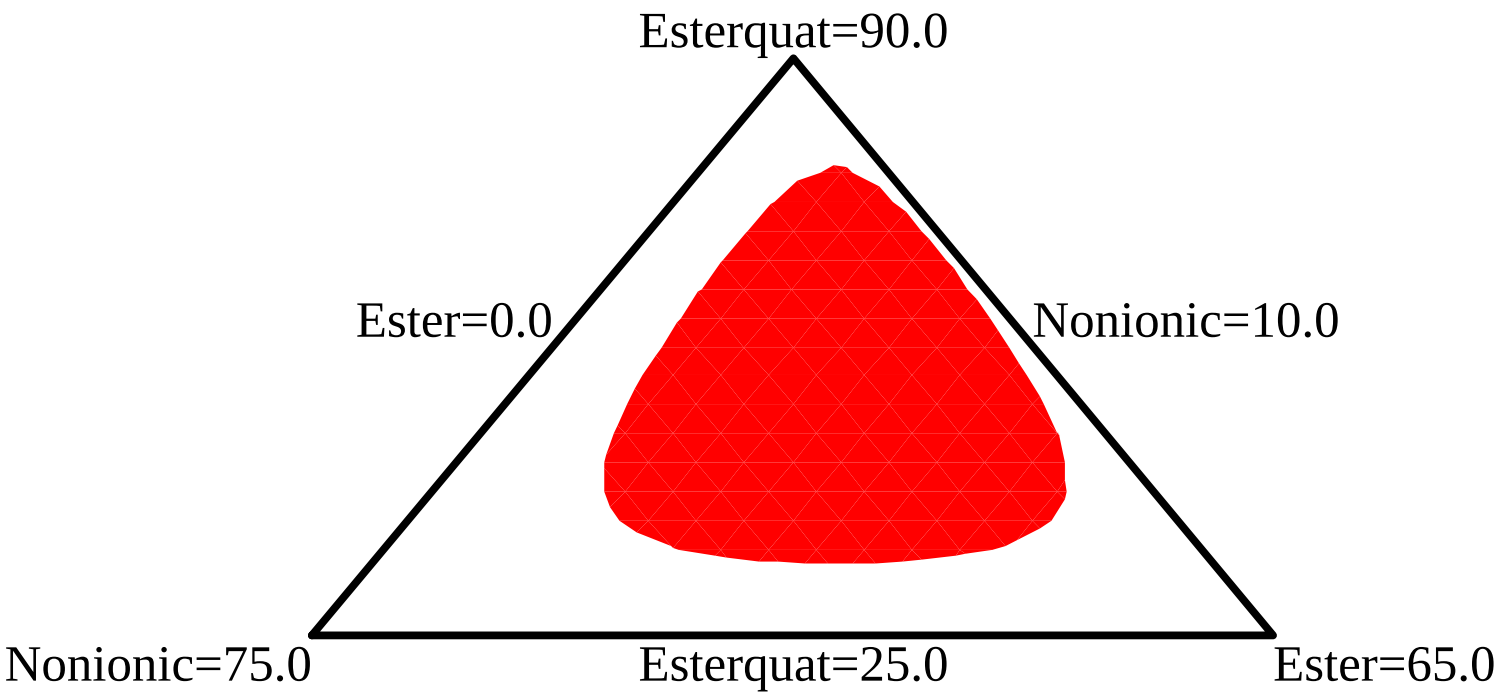
Robust softener

Softness Towel

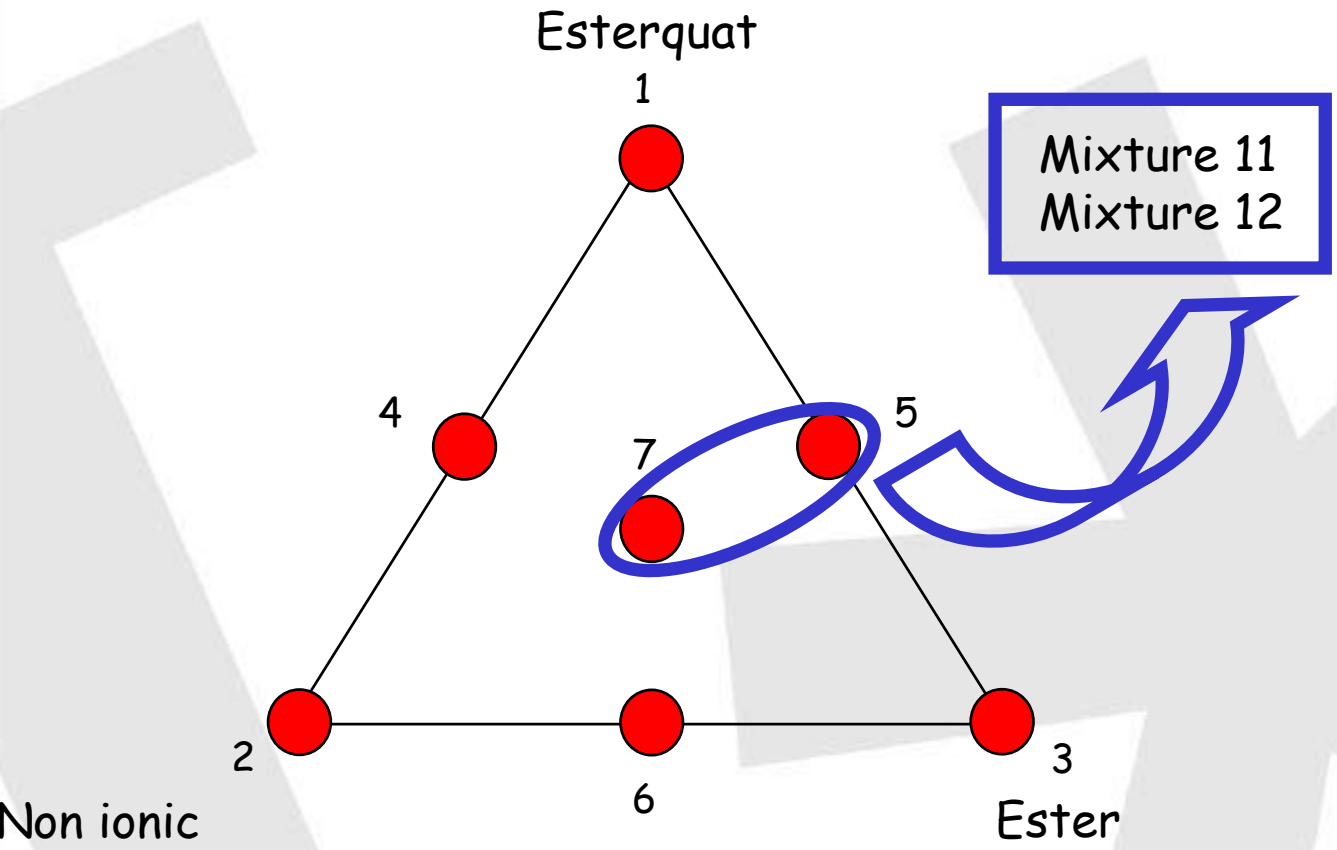


Robust softener

Softness Shirt



Robust softener



Reference	M.P.	Appearance	Stability	Soft.towel	Soft.shirt
11	59	10	10	10	0
12	59	10	10	10	5

(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS

ESPAÑA

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C07C 219/08

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REIVINDICACIONES

1. Procedimiento para la obtención de esterquats sólidos, en el que se cuaternizan trietanolaminoésteres de ácidos grasos de la fórmula (I)

$$R^1CO\text{-}[OCH_2CH_2]_nOCH_2CH_2\text{-}N(\text{-}CH_2CH_2O[CH_2CH_2O]_m\text{-}R^2)(\text{-}CH_2CH_2O[CH_2CH_2O]_pR^3) \quad (I)$$

en la que R^1CO significa un resto alquilo saturado y/o insaturado con 6 a 22 átomos de carbono, R^2 y R^3 significan, independientemente entre si, hidrógeno o R^1CO y n, m y p significan, en suma, 0 o números de 1 a 10, en presencia de

a) poliglicoléteres de alcoholes grasos y

b) glicéridos parciales de ácidos grasos,

en forma en si conocida, con agentes de alquilación.

2. Procedimiento según la reivindicación 1, **caracterizado** porque se emplean poliglicoléteres de alcoholes grasos de la fórmula (II),

$$R^4O\text{-}(CH_2CH_2O)_qH \quad (II)$$

en la que R^4 significa un resto hidrocarbonado alifático lineal o ramificado con 6 a 22 átomos de carbono y 0 y/o 1, 2 o 3 dobles enlaces y q significa números de 10 a 50.

3. Procedimiento según las reivindicaciones 1 y 2, **caracterizado** porque se emplean como glicéridos parciales de ácidos grasos, mezclas industriales de mono- y/o diésteres de la glicerina con ácidos grasos de la fórmula (III)

$$R^5CO\text{-}OH \quad (III)$$

en la que R^5 significa un resto alquilo alifático con 6 a 22 átomos de carbono.

4. Procedimiento según las reivindicaciones 1 a 3, **caracterizado** porque se emplean los trietanolaminoésteres de ácidos grasos, los poliglicoléteres de alcoholes grasos y los glicéridos parciales de ácidos grasos en la proporción en peso de (40 hasta 60) : (10 hasta 25) : (15 hasta 50), con la condición de que los datos sumen 100 partes en peso.

5. Procedimiento según las reivindicaciones 1 a 4, **caracterizado** porque como agentes de alquilación se emplean halogenuros de alquilo, sulfatos de dialquilo u óxido de etileno.

6. Empleo de los esterquats sólidos, obtenibles según el procedimiento de las reivindicaciones 1 a 5, para la fabricación de agentes tensioactivos.

NOTA INFORMATIVA: Conforme a la reserva del art. 167.2 del Convenio de Patentes Europeas (CPE) y a la Disposición Transitoria del RD 2424/1986, de 10 de octubre, relativo a la aplicación del Convenio de Patente Europea, las patentes europeas que designen a España y solicitadas antes del 7-10-1992, no producirán ningún efecto en España en la medida en que confieran protección a productos químicos y farmacéuticos como tales.

Esta información no prejuzga que la patente esté o no incluída en la mencionada reserva.

Daily examples (1)

A softening composition for the textile industry has been developed and, surprisingly, it shows very good performance properties:

- stability,
- compatibility with anionic resins, and
- softening.

Mixture design

The softener has the following composition:

Component	%
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Fatty alcohol 40 EO	21
Glycerin monostearate	29

Would it be possible to identify a broader optimum region?

(19) Europäisches Patentamt
European Patent Office
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(11) EP 0 900 260 B1

(12) # EUROPEAN PATENT SPECIFICATION

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(86) International application number:
PCT/EP97/02239

(87) International publication number:
WO 97/42279 (13.11.1997 Gazette 1997/49)

(54) **HIGH DI(ALKYL FATTY ESTER) QUATERNARY AMMONIUM COMPOUND FROM TRIALKANOL AMINE**

LANGKETTIGE QUATERNÄRE AMMONIUMDIALKYLFETTSÄUREESTER AUS TRIALKANOLAMIN

COMPOSE D'AMMONIUM QUATERNAIRE A BASE DE TRIETHANOLAMINE A HAUTE TENEUR EN DI(ALKYLESTERS D'ACIDES GRAS) PRODUIT A PARTIR DE TRIALKANOLAMINE

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

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WO-A-94/20597
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DE-A- 4 413 431

Opposition case

EP 0 900 260 B1

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[0090] Preheat DI-water to 50-60°C. Charge DI-water to mixing vessel and acidify water to a pH of 2.7 - 3.2 with 1 N HCI. Add the warmed quaternary salt to the acidified water with agitation while maintaining a temperature of 50 - 60°C. After addition of 73% of active, add $CaCl_2$ solution to the stirring dispersion. Make a second salt addition after 84% of active is added, and a third minor salt addition at completion of actives addition. Continue agitation to insure a smooth, homogeneous dispersion. Cool to 40°C with agitation. Solublize fragrance into the softener dispersion. Adjust viscosity to the desired level with addition of $CaCl_2$ solution. Add color and preservative. Adjust weight with DI-water. Dispersion is storage stable within a temperature range of 4 - 50°C. For an even' higher level of softening, dispersions containing 28-40% actives can be easily formulated employing techniques similar to those shown above.

Example 4 Ultra Rinse Cycle Softener Formulation (28% Active)

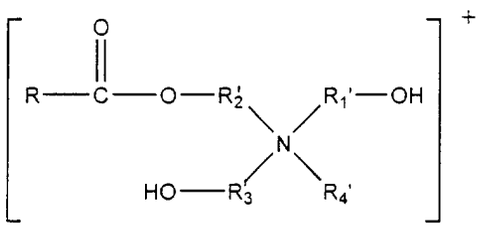
[0091]

Raw Materials:	
Quaternary salt of the present invention	156g
DI-water	315g
1 N HCI	pH 2.7 - 3.2
10% aqueous Calcium Chloride ($CaCl_2$) solution	
Fragrance	q.s.
Dye/Colorant	q.s.
Anti-microbial	q.s.

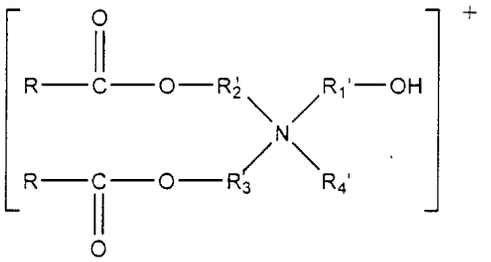
The DI-water is preheated to 50-60°C and charged to the mixing vessel and acidified to a pH of 2.7-3.2 with 1N HCI. The molten quaternary salt is then slowly added to the mixing vessel with mixing while the temperature is maintained at about 60°C. The mixture is then cooled to 40°C with agitation wherein the fragrance solubilized into the softener dispersion. The viscosity is then adjusted to the desired level with addition of $CaCl_2$ solution, and color and preservatives added. Lastly, the weight is adjusted with DI-water. The dispersion is storage stable within a temperature range of 4-50°C.

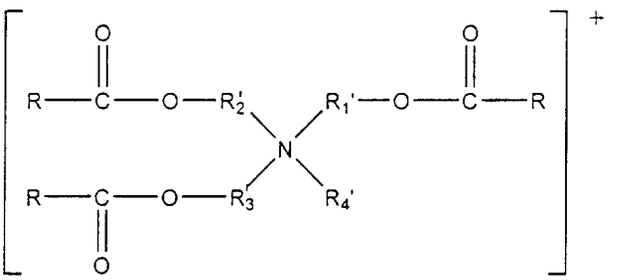
Claims

1. A textile softening composition with improved stability and softening performance which comprises a fabric softening effective amount of a quaternary ammonium salt mixture having mono-, di-, and tri-ester components of the following formulae (I) - (III):

(I) 

Monoester

(II) 

(III) 

Diester

Triester

wherein each R can be the same or different and is represented by a substituted or unsubstituted hydrocarbon radical having from 12-22 carbon atoms and an iodine value of from 20 to 90, R_1', R_2' and R_3' are independently selected from C_2 - C_4 alkyl groups, R_4' is C_1 - C_3 straight or branched chain alkyl or C_7 - C_{10} aralkyl, and wherein said di-ester component (II) comprises greater than 55 wt% and the tri-ester component (III) comprises less than 25 wt%, based on the total amount of the quaternary ammonium salt mixture, X^- represents a softener compatible an ion.

2. The softener composition of claim 1 wherein the cis/trans isomer ratio of said quaternary ammonium salt mixture is the range of from 80/20 to 95/5.

3. The softener composition of claim 1 wherein the cis/trans ratio is greater than 90/10.

4. The softener composition of claim 1 wherein said quaternary ammonium salt mixture comprises 3-50% by weight, based on the total weight of the composition.

5. The composition of claim 1 wherein said quaternary ammonium salt mixture comprises greater than 55 wt% diester component (II) and less than 20 wt% triester (III) component.

6. The composition of claim 1 wherein said quaternary ammonium salt mixture comprises greater than 60 wt% diester component (II) and less than 15 wt% triester (III) component.

7. The composition of claim 1 wherein said R groups represent a hydrocarbon radical having from 16 to 22 carbon atoms and an iodine value from 30 to 60.

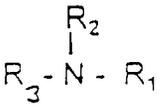
8. The composition of claim 1 wherein said R groups represent a hydrocarbon radical having from 16 to 22 carbon atoms and an iodine value from 45 to 55.

9. A process for the preparation of a quaternary ammonium salt mixture which comprises reacting, at a temperature of from 170°C to 210°C:

I) a C_{12} - C_{22} substituted or unsubstituted fatty acid or mixture of fatty acids having an iodine value of from 20 to 90, and having less than 20% trans double bonds, with
II) an alkanolamine of the formula:

process have a cis to trans isomer ratio of from 80:20 to 95:5. More preferably, the trans isomer content of said fatty acid(s) is less than 10%. An optimum trans-isomer content is between 0.5 - 9.9%. The most preferred fatty acid is a mixture of tallow/distilled tallow having a cis:trans isomer ratio of greater than 9:1.

[0019] The alkanolamines employable in the present invention generally correspond to the formula:



wherein R_3,R_1 and R_2 are independently selected from C_2 - C_4 hydroxyalkyl groups. Preferred alkanolamines include but are not limited to triethanolamine, propanol diethanolamine, ethanol diisopropanolamine, triisopropanol amine and mixtures thereof. Triethanolamine is the most preferred alkanolamine.

[0020] The molar ratio of fatty acid to alkanol amine is preferably in the range of from 1.60 - 1.80, and more preferably, in the range of from 1.65-1.75. Best results are usually obtained when the molar ratio is 1.70.

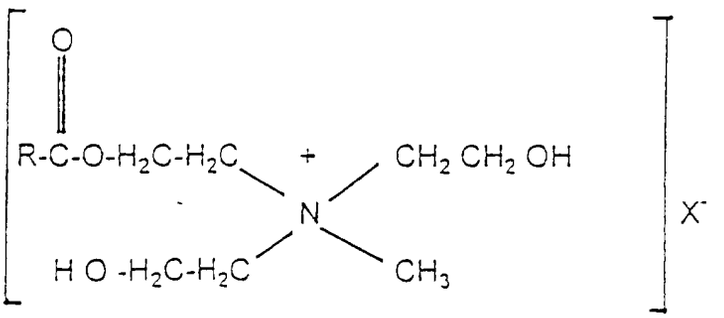
[0021] The acid catalyst employable in the present process inciudes but is not limited to sulphonic acid, phosphorous acid, p-toluene sulphonic acid, methane sulphonic acid, oxalic acid, hypophosphorous acid or an acceptable Lewis acid. A preferred acid catalyst is hypophosphorous acid. Typically, 0.02 - 0.2 % by weight, and more preferably 0.1 to 0.15 % by weight of acid catalyst, based on the weight of fatty acid, in employed in the present process.

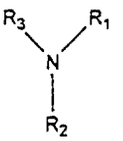
[0022] The esterification of fatty acids with alkanolamines is carried out at a temperature of from 170° - 210°C until the reaction product has an acid value of below 5. Further, triester formation in the final product can be minimized by controlling the heat up rate for forming the esteramine mixture. a heat up rate of 0.8° - 3°C/ minute, preferably 1.25° to 3°C, from a temperature of 70°C to a temperature in a range of from between 170°C to 210°C is effective in minimizing triester formation. After the esterification, the crude product is reacted with alkylating agents in order to obtain the quaternary ammonium product. Preferred alkylating agents include C_1 - C_3 straight or branched chain alkyl halides, phosphates, carbonates, or sulfates, C_7 - C_{10} aralkyl halides, phosphates or sulfates, and mixtures thereof. Examples of preferred alkylating agents include but are not limited to methyl chloride, benzyl chloride, diethyl sulfate, dimethyl carbonate, trimethyl phosphate, dimethyl sulfate or mixtures thereof. Choosing the type and amount of alkylating agent employed is well within the skill of one in the art. Typically, when dimethyl sulfate is the alkylating agent, 0.7 to 1.0 mol dimethyl sulfate per mole of ester is satisfactory in yielding the quaternized product.

[0023] The quaternization may be carried out in bulk or in solvent, at temperatures ranging from 60° - 120°C. If a solvent is employed, then the starting materials and/or product must be soluble in the solvent to the extent necessary for the reaction. Solvents of this type are generally known in the art. Suitable examples include polar solvents such as, for example, lower alcohols, i.e., C_1 - C_6 alcohols. Other solvents which can be employed include, but are not limited to mono-, di-, and tri-glycerides, fatty acid, glycol and mixtures thereof.

[0024] A resultant quaternary ammonium salt mixture comprises a mixture mono - (I), di - (II) and tri-ester (III) components of the following formulae:

I)





wherein R_3, R_1 and R_2 are independently selected from C_2 - C_4 hydroxyalkyl groups, wherein the molar ratio of said fatty acid to alkanol amine preferably is from 1.6 - 1.8, and wherein said reaction temperature is increased from 70°C to a range of from 170° to 210°C, wherein the reaction temperature is maintained within a range of from 170° to 210°C until the reaction product has an acid value of below 5 and wherein the rate of temperature increase is maintained within a range of from 0.8° - 3°C/minute in order to obtain an ester composition with greater than 55 wt% di-ester component and less than 25 wt% tri-ester component, and quatemizing same with C_1 - C_3 straight or branched chain alkyl halides, phosphates, carbonates, or sulfates, C_7 - C_{10} aralkyl halides, phosphates or sulfates, or mixtures thereof in order to obtain a quaternary ammonium salt mixture.

10. The process of Claim 9 wherein the temperature of the reaction is increased at a rate 1.25° - 3°C per minute from a starting temperature of 70°C up a temperature of from 170°C to 210°C.

11. The process of claim 9 wherein said fatty acid is a substituted or unsubstituted C_{16} - C_{22} fatty acid having an iodine value of from 30 to 60.

12. The process of claim 9 wherein said fatty acid is a substituted or unsubstituted C_{16} - C_{22} fatty acid having an Iodine value of from 45 to 55.

13. The process of claim 11 wherein said fatty acid is derived from tallow, soy, palm, palm kernel, rape seed, lard or mixtures thereof.

14. The process of claim 11 wherein said fatty acid is derived from partially hydrogenated tallow, soy, palm, palm kernel, rape seed, lard or mixtures thereof.

15. The process of claim 9 wherein said alkanolamine is selected from the group consisting of triethanolamine, propanol diethanolamine, ethanol diisopropanolamine, triisopropanol amine, and mixtures thereof.

16. The process of claim 9 wherein the molar ratio of fatty acid to alkanol amine is 1.7.

17. The process of claim 9 wherein said fatty acid has less than 10% trans isomer.

18. The process of claim 9 wherein the alkylating agent is selected from the group consisting of methyl chloride, benzyl chloride, diethyl sulfate, dimethyl carbonate, trimethyl phosphate, dimethyl sulfate or mixtures thereof.

19. The process of claim 9 wherein a solvent is not employed during quatemization.

20. The process of claim 9 wherein a solvent is employed during quatemization.

21. The process of claim 20 wherein said solvent is selected from the group consisting of C_1 - C_6 alcohols, glycol, fatty acid, mono-, di-, or triglycerides, and mixtures thereof.

22. A quaternary ammonium salt mixture which comprises mono-, di-, and tri-ester components wherein said quaternary ammonium salt mixture comprises greater than 55 wt% di-ester component and less than 25 wt% tri-ester component, and wherein said quaternary ammonium salt mixture is the reaction product of:

A) an ester which is the reaction product of a substituted or unsubsituted C_{12} - C_{22} fatty acid having an iodine value of from 20 to 90 and having less than 20 % trans double bonds and a trialkanolamine of the formula

Experimental data submitted by the Assignee showing (?) the influence of the temperature ramp rate on mono, di and triester ratio

Target: diester > 55%, triester < 25%

Example and note book #	Reaction temp	temp ramp rate	catalyst loading	Reaction time, under vacuum	mono ester	di ester	tri ester
1. 973-86	140°C	1.75°C/min	1000 PPM	7.75 hr	27.9%	54.3%	11.7%
2. 973-89	140°C	3°C/min	0 PPM	16.5 hr	27.5%	51.7%	14.4%
3. 973-85	210°C	3°C/min	2000 PPM	30 min	23.9%	61.2%	12.3%
4. 805-18	160°C	1.33°C/min	1000 PPM	7.5 hr atmospheric and 0.5 hr under vacuum	25.9%	49.6%	20.3%

Example 3 was performed using reaction conditions according to the invention, favouring diester formation. In all other examples the diester content is considerably lower.

Before giving further arguments, we would like to stress that it is important to distinguish the differences between a diester quaternary compound (DEQ) and a triester quaternary compound (TEQ). A DEQ is generally prepared by reacting a alkyl dialkanol amine (e.g. methyl diethanol amine) with a fatty acid under specific conditions to get primarily a diesteramine, with smaller amounts of monoester amine. No triesteramine is formed. A TEQ is generally prepared by reacting a trialkanol amine (e.g. triethanolamine) with a fatty acid under specific conditions to get a product mixture comprising mono-, di-, and triester components. Under conventional process conditions 40-50 wt% of diester is formed, with triester being formed at least at a 20-30% range. The following table lists the major differences between DEQ and TEQ.

	DEQ (diesterquat)	TEQ (triesterquat)
Esterquat distribution	Mostly Di with some mono present, impossible to make tri.	Broad mixtures are possible due to the chemistry used. Kinetic vs thermodynamic control will influence the esterquat distribution as well as the fatty acid to amine ratio
Fatty acid to amine ratio	Usually slightly less than a 2:1	There is some variation in the ratio depending on the desired properties. The range is between 1.6 – 2.0.
Typical esterquat distribution	Mostly diester is desired for softening, the monoester helps in the formulation	There is a distribution between mono, di and tri. Unlike DEQ, there is also a considerable amount of unreacted starting material, trialkanolamine

Confirmation copy

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Europäisches Patentamt

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AKZO NOBEL N.V.

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Munich,
16 August 2004

OPPO VI: Stepan Europe S.A.

Further to our submission of 5 August 2004, we attach a protocol, which reflects, on the one hand, the data provided in the attacked patent, Example 1 (which allegedly shows the importance of the ramp rate for attaining the desired ester distribution) and, on the other hand, the results of an experiment done by the Opponent, on the basis of said Example 1 of the attacked patent.

The major difference is in the ramp rate, which in Example 1 of the attacked patent is 1.75°C per minute, whereas in the comparison, it was only 0.5°C per minute (30.4°C per hour).

WM:mb

For reasons of practicality, there are some minor deviations in the comparison, from what is described in Example 1, but these are within the ranges given in the patent, as is shown by footnotes.

The ester distribution ratio in the quaternized product according to the comparison was 28.8 weight% mono : 55.3 weight% di : 15.9 weight% tri, thus within the claimed range.

The ramp rate used (0.5°C/minute) is clearly outside of what the Patentee calls critical, which shows the non- criticality of the ramp rate, and thus the fact that the method claimed does not produce anything which is surprising or, for all that, out of the ordinary over what the prior art already had.

Further tests are being carried out, and corresponding results will be submitted in due term.

Maiwald Patentanwalts GmbH
(Walter Maiwald)

Encl.:
6 copies hereof
Protocol, 7-fold

Daily examples (6)

Developing a tablet, the following composition, surprisingly, shows good disintegrating and crushing properties:

Component	%
Lactose monohydrate	15
Starch	42
Anhydrous lactose	43

Would it be possible to broaden this formulation?

Tablet formulation

Components:

A = α-Lactose monohydrate

B = Starch

C = Anhydrous α-lactose

Lubricant = magnesium stearate at constant level

Mixture design

Responses:

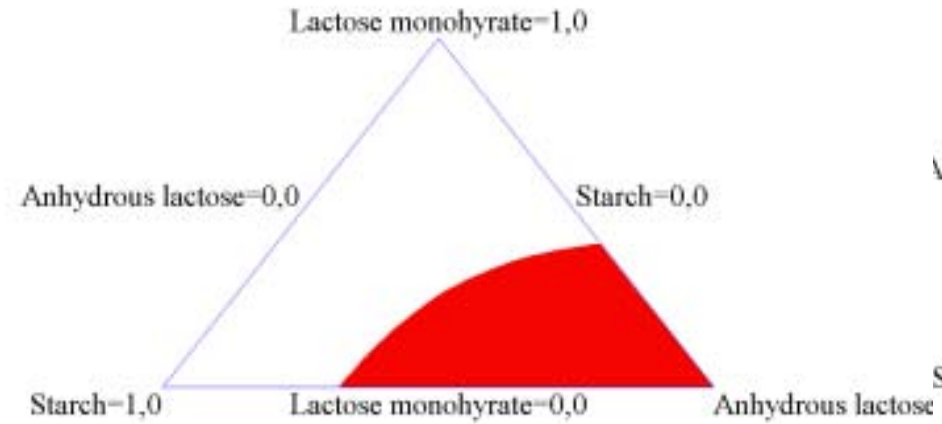
Crushing strength

Disintegration time

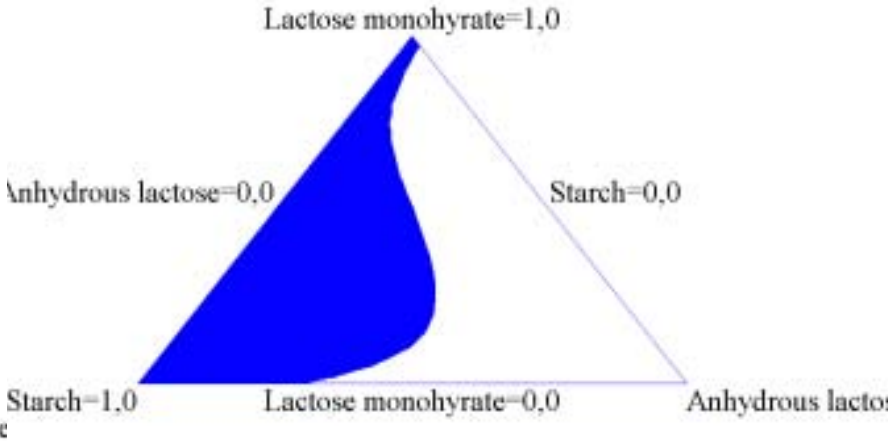
Lewis *et al*, Pharmaceutical experimental design, 1999, Marcel Dekker, New York

Tablet formulation

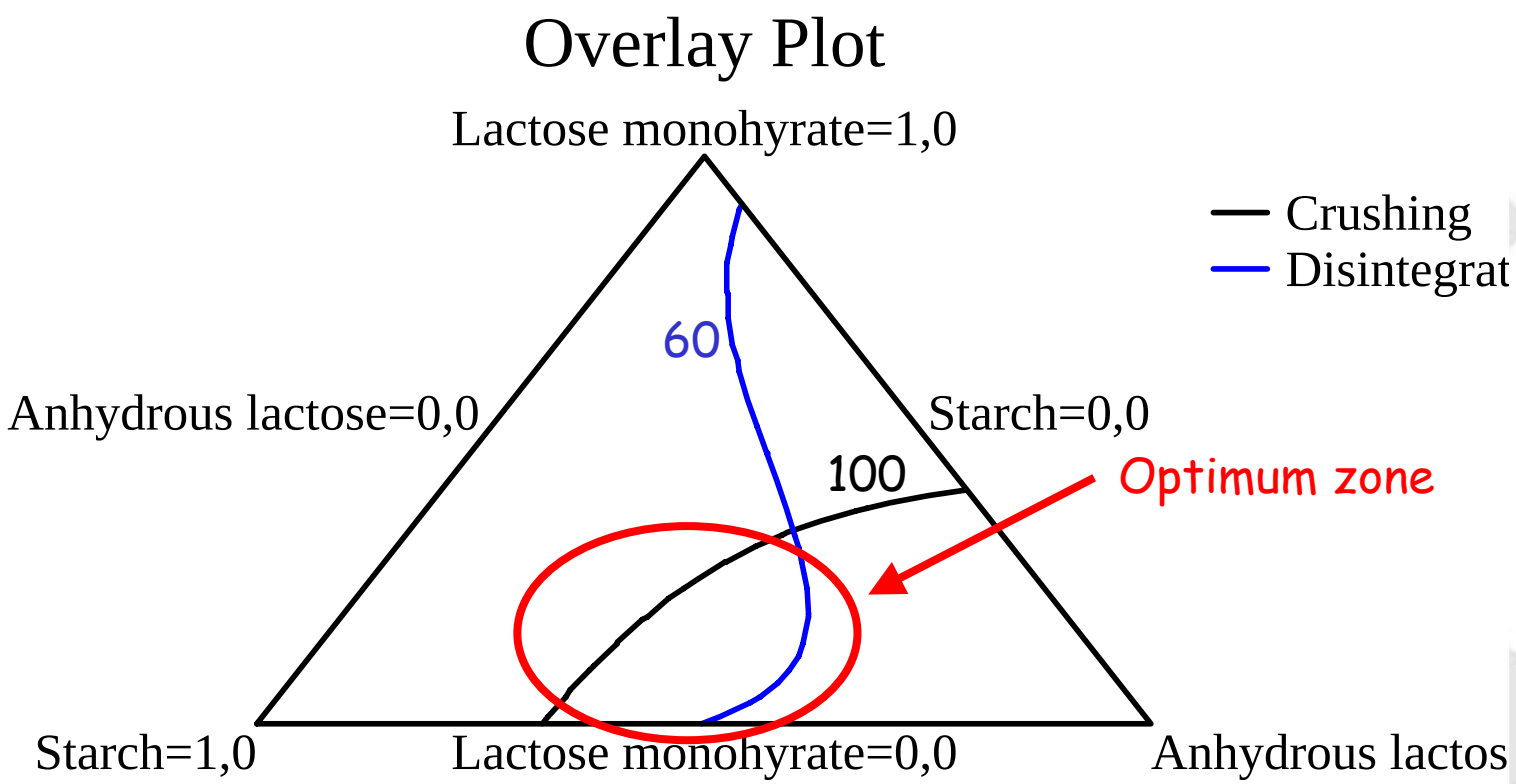
Crushing



Disintegration time



Tablet formulation



Daily examples (6)

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Mixture design

Would it be possible to broaden this formulation?

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Published
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(54) Title: APPARATUS AND PROCESS FOR PREPARING CRYSTALLINE PARTICLES

(57) Abstract

There is provided according to the present invention a process for preparing crystalline particles, especially particles of a pharmaceutical or carrier substance suitable for inhalation therapy, in addition to an apparatus for the preparation of such particles.

experimental design. Appropriate maximum and minimum values for each of the four variables were chosen as shown in Table 1.

Table 1

Variable	Units	Minimum Value	Mid Point	Maximum Value
A Water antisolvent flow rate	Ml/min	12	18	24
B Drug acetone solution flow rate	Ml/min	3.5	5.25	7.0
C Ultrasound Power	%	0	20	40
D Stirring Rate	%	0	20	40

A half factorial design was chosen to model the 4 variable experiment and the software package Design Expert 5 was used to generate the design. Two centrepoints were added to the design bringing the total number of experiments to 10.

Ultrasound Power is given as a percentage of maximum (50W).

Analysis

Samples were analysed using Malvern laser diffraction particle sizing.

Instrument: Malvern Mastersizer X
Lens: 45mm Reverse Fourier
Analysis: 0607 presentation code
Dispersant: Iso Octane / Lecithin 0.05% w/w
Pre dispersion: Sonicate for 10 seconds
Obscuration: 10% to 16%

One analysis per sample was carried out. The median particle size (D50), particle size at 90% undersize (D90) and particle size at 10% undersize (D10) were used as responses to characterise the medium, course, and fine particles.

In addition a fourth response, uniformity index (UI) was calculated as a measure of the breadth of the distribution.

Results

(a) Size Results

Table 2

Run N°	Water ml/min	Acetone ml/min	Stirring %	U/sound %	D50 (μm)	D10 (μm)	D90 (μm)	UI (%)
1	24	3.50	40.00	0.00	4.95	1.07	18.91	5.7
2	18	5.25	20.00	20.00	4.56	1.02	14.29	7.1
3	24	3.50	0.00	40.00	4.2	1	18.3	5.3
4	12	7.00	0.00	40.00	7.52	2.62	20.83	12.6
5	24	7.00	40.00	40.00	4.3	1.05	14.66	7.2
6	18	5.25	20.00	20.00	5.28	0.89	17.16	5.1
7	12	3.50	0.00	0.00	9.34	2.32	28.97	8
8	12	7.00	40.00	0.00	3.46	1.06	9.33	11.4
9	12	3.50	40.00	40.00	3.67	0.97	11.47	8.5
10	24	7.00	0.00	0.00	9.79	1.48	37.62	3.9

Uniformity Index (UI) is calculated as 100xD10/D90.

The particle size distribution for Run 9 is shown graphically in Figure 2.

(b) Analysis of effects

Effect graphs to show the interdependence of pairs of variables A, B, C, D were constructed using Design Expert 5 and are shown in Figures 3-6.

A- and A+ indicate, respectively, the minimum and maximum values of variable A shown in Table 1. B-/B+, C-/C+ and D-/D+ may be interpreted similarly.

R^2 is a measure of closeness of fit; R^2=1 being the measure of perfect fit.

Figure 3 shows the effect of ultrasound power or stir rate on D50; ultrasound has a major effect and stirring rate has a minor effect (R^2=0.72).

Figure 4 shows the effect of anti-solvent flow rate or ultrasound power on D10; ultrasound and anti-solvent flow rate both have a major effect (R^2=0.94).

Claims

1. A process for preparing crystalline particles of substance which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of the substance in a liquid solvent with a flowing liquid antisolvent for said substance, and collecting the resultant crystalline particles generated.

2. An apparatus for preparing crystalline particles of a substance which comprises

(i) a first reservoir of said substance dissolved in a liquid solvent;

(ii) a second reservoir of liquid antisolvent for said substance;

(iii) a mixing chamber having first and second inlet ports and an outlet port;

(iv) means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;

(v) a source of ultrasonic radiation located in the vicinity of the first inlet;

and

(vi) means for collecting particles suspended in the liquid discharged from the mixing chamber at the outlet port.

3. A process according to claim 1 wherein the liquid antisolvent is miscible with the liquid solvent.

4. An apparatus according to claim 2 wherein the liquid antisolvent is miscible with the liquid solvent.

5. An apparatus according to claim 2 or 4 further comprising means to mix the liquids delivered to the mixing chamber via the first and second inlets.

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(54) **BRUSHITE HYDRAULIC CEMENT STABILIZED WITH A MAGNESIUM SALT**

MIT EINEM MAGNESIUMSALZ STABILISIERTER HYDRAULISCHER BRUSHITZEMENT

CIMENT HYDRAULIQUE DE BRUSHITE STABILISE AU MOYEN D'UN SEL DE MAGNESIUM

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- **DRIESSENS ET AL.: "Effective formulations for the preparation of calcium phosphate bone cements" JOURNAL OF MATERIAL SCIENCE: MATERIALS IN MEDICINE, vol. 5, 1994, pages 164-170, XP000929539**

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$MgHPO_4 \cdot 3H_2O$, $MgHPO_4 \cdot 7H_2O$, $Mg_3(PO_4)_2$, $Mg_3(PO_4)_2 \cdot 4H_2O$, $Mg_3(PO_4)_2 \cdot 8H_2O$, $Mg_3(PO_4)_2 \cdot 22H_2O$, $MgCO_3$, $MgCO_3 \cdot 3H_2O$, $MgCO_3 \cdot 5H_2O$, $3MgCO_3 \cdot Mg(OH)_2 \cdot 3H_2O$, $MgCO_3 \cdot Mg(OH)_2 \cdot 3H_2O$, $Mg(C_3H_5O_3)_2 \cdot 3H_2O$, $MgC_2O_4 \cdot 2H_2O$, $MgC_4H_4O_6 \cdot 5H_2O$, $Mg(C_4H_4O_6)_2 \cdot 4H_2O$, $MgCO_3 \cdot CaCO_3$, $Mg_2P_2O_7$, $Mg(C_{12}H_{23}O_2)_2 \cdot 2H_2O$, $Mg(C_{14}H_{27}O_2)_2$, $Mg(C_{18}H_{33}O_2)_2$, $Mg(C_{18}H_{35}O_2)_2$. The amount of the fourth component should be comprised in the range of 0.001 to 60% w/w, more precisely in the range of 1 to 20% w/w, preferably in the range of 2 to 5% w/w. The magnesium salt should not be too soluble to prevent a fast release of Mg ions from the implant site. The solubility in water should preferably be lower than 10 g/L and more preferably lower than 1 g/L.

[0027] Five specific examples are reported below for producing the temporary bone replacement materials according to the invention.

Example 1

[0028] Samples with various cement compositions were prepared. The cement composition was: 1.33g β-TCP (mean particle diameter in volume: 1.1 micrometer), 0.67g MCPM, 25mg $Na_2H_2P_2O_7$, 1g TCP granules (400 to 500 micrometers in diameter) and (x) mg Na_2SO_4 or $MgSO_4$. The mixing liquid was 1g of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). Three repeats were made. The samples were prepared as follow: (i) 30s mixing of the powders with the solution, (ii) insertion of the paste into the tip of a cement syringe, (iii) measurement of the setting time, (iv) ejection of the sample out of the syringe, (v) aging in 2mL d.i. water for 24 hours, (vi) drying. To measure the pH, a sample of each composition was placed into 10 mL d.i. water and the pH was measured at regular intervals. The tensile strength of the samples was determined by means of the Brazilian tensile test. The crystalline composition of the samples was determined by x-ray diffraction (XRD). Results showed that the setting time increased drastically at a sulfate concentration of 0.1 M: from 3 minutes to 15 minutes. Interestingly, the setting time was a little bit longer with magnesium ions than with sodium ions (about 1 minute longer above a concentration of 0.15M). The mechanical properties were not significantly modified by the addition of sodium or magnesium sulfate. However, a sulfate concentration superior to 0.1 M led to finer microstructures. The end-product of the reaction was brushite.

Example 2

[0029] Cement samples were prepared according to a factorial design of experiments 2^3 with 4 repeat. The factors were: (A) Sulfate source (Na_2SO_4 or $MgSO_4$); (B) Sulfate amount (20 or 50mg) and (C) $Ca_2P_2O_7$ amount (0/150mg). The cement composition was: 1.33g β-TCP (mean particle diameter in volume: 1.1 micrometer), 0.67g MCPM, 25mg $Na_2H_2P_2O_7$, 1g TCP granules (400 to 500 micrometers in diameter), 20 or 50mg Na_2SO_4 or $MgSO_4$, and 0 or 150 mg $Ca_2P_2O_7$. The mixing liquid was 1g of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). The samples were prepared and analyzed as explained in the first example. Results show that the setting time of the cement was significantly increased by replacing sodium sulfate with magnesium sulfate, and significantly decreased when $Ca_2P_2O_7$ was added to the cement paste. The latter effect is due to the fact that the powder/liquid ratio was increased. The amount of sulfate ions did only play a minor role at the chosen concentration: the setting time was slightly increased by an increase of sulfate amount. This result is actually similar to what was observed in the first example. The cement tensile strength was decreased when Na_2SO_4 was replaced by $MgSO_4$, and when $Ca_2P_2O_7$ or more sulfate were added to the cement. The cement microstructure was finer with 50mg sulfate salt than with only 20mg.

Example 3

[0030] Cement samples were prepared by mixing for 60 seconds with a spatula the cement powder with the mixing liquid. Afterwards, the paste was poured into a syringe and the paste was injected with the syringe into a cylindrical defect (8 mm diameter) made in the proximal or distal femora/humerus of a sheep. Eight compositions were tested pro sheep according to the factorial design of experiment: (A) Sulfate source (Na_2SO_4 or $MgSO_4$); (B) $MgHPO_4 \cdot 3H_2O$ (0/150mg) and (C) $Ca_2P_2O_7$ amount (0/150mg). The cement composition was: 5.33g β-TCP (mean particle diameter in volume: 1.1 micrometer), 2.66g MCPM, 100mg $Na_2H_2P_2O_7$, 4g TCP granules (400 to 500 micrometers in diameter), 100 mg Na_2SO_4 or $MgSO_4$, 0 or 600 mg $MgHPO_4 \cdot 3H_2O$, and 0 or 600 mg $Ca_2P_2O_7$. The mixing liquid was 4mL of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). Two sheep were operated. The first sheep was killed after 3 weeks. The second after 6 weeks. Results showed that all the samples which did not contain $MgHPO_4 \cdot 3H_2O$ decomposed much quicker than the other. Moreover, after three week implantation, the samples which did not contain $MgHPO_4 \cdot 3H_2O$ had provoked a large inflammatory reaction and partial disappearance of the bone surrounding the implant. Fibrous tissue was found between the implant and bone. In conclusion, it resulted that the presence of a poorly-soluble salt like $MgHPO_4 \cdot 3H_2O$ is necessary to improve the in vivo behavior of brushite cement.

Example 4

[0031] Cement samples were prepared by mixing for 60 seconds with a spatula the cement powder with the mixing liquid. Afterwards, the paste was poured into a syringe and the paste was injected with the syringe into a cylindrical defect (8 mm diameter) made in the proximal or distal femora/humerus of a sheep. Three compositions and one control (empty hole) were tested pro sheep. The first composition was a commercial product, Norian® SRS, which contains as end-product a poorly-crystallized carbonato-apatite. Second composition: 0.96g β-TCP (mean particle diameter in volume: 1.1 micrometer), 1.92g MCPM, 80mg $Na_2H_2P_2O_7$, 6.72g TCP granules (125 to 1000 micrometers in diameter), 100 mg Na_2SO_4, 600 g $CaSO_4 \cdot 1/2H_2O$, and 600 mg $Ca_2P_2O_7$. The mixing liquid was 4mL of an aqueous hyaluronic acid solution (viscosity: 200 mPa·s). The third cement composition was: 5.33g HA (mean particle diameter in volume: 0.08 micrometer), 2.66g MCPM, 20mg $Na_2H_2P_2O_7$, 4g TCP granules (125 to 1000 micrometers in diameter), 100 mg Na_2SO_4, and 600 mg $Mg_2P_2O_7$. The mixing liquid was 6mL of an aqueous xanthan solution (viscosity: 100 mPa·s). Two sheep were operated. The first sheep was killed after 3 weeks. The second after 6 weeks. Norian® SRS cement behaved like an inert material. No resorption could be observed after 6 week implantation. The second cement provoked a large inflammatory reaction and osteolysis after 3 weeks. Fibrous tissue was present between the cement and bone. After 6 weeks, the situation was similar as after 3 weeks, suggesting that only the early reaction provoked by the presence of the cement was detrimental to the sheep bone. The third cement provoked only a mild inflammatory reaction and no osteolysis could be observed. After 6 weeks, 20% of the third cement had resorbed and been replaced by new bone. There was a direct apposition of new bone on the third cement.

Example 5

[0032] Cement samples were prepared according to the following composition: 1.2g HA (mean particle diameter in volume: 2 micrometer), 0.6g MCPM, 1g HA granules (200 to 300 micrometers in diameter), and 0 to 0.1g gentamicin sulfate (powder). The mixing solution (1.2 mL) was a 0.1M aqueous Na_2HPO_4 solution containing 0.5 weigth-% xantham gum. The cement was prepared according to the following scheme: (i) thorougly mixing the different powders with the mixing liquid for 45 seconds; (ii) insertion of the paste into the tip of a syringe, (iii) measurement of the setting time, (iv) ejection of the sample out of the syringe, (v) aging in 2mL d.i. water for 24 hours, (vi) drying. In some cases, the samples were not aged and dried, but placed in 250ml PBS 7.4 and the amount of gentamicin released by the cement sample was measured over time. The setting time was influenced by the presence of gentamicin sulfate: the addition of more than about 300 mg gentamicin sulfate increased the setting time by a factor of 2 (4 to 8 minutes). The mechanical properties were also increased by the addition of gentamicin sulfate: between 400 and 500 mg gentamicin sulfate, the tensile strength increased from 3.2 to 5.8 MPa. The release experiments showed that gentamicin was released according to a first-order reaction from the cement matrix. Small amounts of gentamicin were still released after 5 days.

Claims

1. Brushite cement for surgical purposes comprising

a first component comprising a basic calcium phosphate and
a second component comprising an acidic phosphate and
a third component comprising water, and
a fourth component used to stabilize the end-product of the setting reaction between the components comprising a source of magnesium,

characterized in that

A) the solubility of the source of magnesium is smaller than 100g/L; and
B) the components are chosen in such an amount that

(i) the pH of the cement paste during setting is lower than 6,5; and
(ii) the end-product of the setting reaction comprises dicalcium phosphate dihydrate [$CaHPO_4 \cdot 2H_2O$].

2. Cement according to claim 1, **characterized in that** the first component comprises β-tricalcium phosphate [β-$Ca_3(PO_4)_2$].

3. Cement according to claim 1 or 2, **characterized in that** the first component comprises α-tricalcium phosphate

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(54) **PROCESS FOR THE PREPARATION OF THIAZOLIDINEDIONE DERIVATIVES**

VERFAHREN ZUR HERSTELLUNG VON THIAZOLIDINDION-DERIVATEN

PROCEDE DE PREPARATION DE DERIVES DE THIAZOLIDINEDIONE

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suitably at an elevated temperature, preferably above 70°C, for example in the range of from 80°C to 115°C.

[0014] 5-{4-[2-(N-methyl-N-(2-pyridyl}amino)ethoxy]benzyl}-2,4-thiazolidinedione is isolated from the reaction and subsequently purified by use of conventional isolation and purification methods such as chromatography and crystallization/recrystalliazation.

[0015] Crystalline 5-{4-[2-(N-methyl-N-(2-pyridyl}amino)ethoxy]benzylidene}-2,4-thiazolidinedione is isolated from the present reaction and as such forms a further aspect of the present invention. A suitable crystallization/recrystallization solvent is denatured ethanol, the crystallization is favourably effected from refluxing solvent which is allowed to cool to provide the required compound.

[0016] Suitable salts are pharmaceutically acceptable salts.

[0017] Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

[0018] In addition should be mentioned those pharmaceutically acceptable salts provided by pharmaceutically acceptable acids including mineral acids, including salts provided by mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids, especially tartaric and maleic acid. A preferred salt is a maleate salt.

[0019] Suitable solvates are pharmaceutically acceptable solvates, such as hydrates.

[0020] 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione is prepared according to known methods, for example by use of the appropriate method disclosed in EP 0306228. The contents of EP 0306228 are incorporated herein by reference.

[0021] The following example illustrates the invention but does not limit it in any way.

Example

Reduction of (Z)-5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione to 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benxyl}-2,4-thiazolidinedione.

[0022] To a solution of (Z)-5-{[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione (123 kg) in glacial acetic acid (1232 L) is added 10% palladium on charcoal (Johnson-Matthey type 87L, 123 kg, catalyst contains ~ 50% w/w water and hence the catalyst loading was 50%w/w). The resulting mixture is hydrogenated at 4.8265 x 10^5 to 5.516 x 10^5Pa (70-80 psi) hydrogen pressure at about 95°C. After the starting material is consumed (15 - 20 hours), the reaction mixture is cooled to about 65°C and the catalyst is removed by filtration. The resulting solution is concentrated under reduced pressure to low volume and the residue is dissolved in denatured ethanol (500 L) at 60°C. The solution is heated to reflux and then cooled to ambient temperature to effect crystallisation. The product, 5-{[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]
benzyl}-2,4-thiazolidinedione, is isolated by filtration, and dried *in vacuo* at 45°C. Typical yields are 70-80%.

Effect of Change of Reaction Pressure

[0023] The above reaction can be performed over a range of pressures resulting in a significant reduction in reaction time and catalyst loading, as shown below.

Reaction number	Conditions	Reaction Time (hours.)
1	5.17125 x 10^5Pa (75psi), 100% catalyst	15 - 20
2	68.95 x 10^5Pa (1000 psi), 100% catalyst	< 2
3	68.95 x 10^5Pa (1000 psi), 50% catalyst	7
4	34.475 x 10^5Pa (500 psi), 100% catalyst	4
5	34.475 x 10^5Pa (500 psi), 50% catalyst	ca.12

Claims

1. A process for preparing 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione, or a tautomeric form thereof or a salt thereof, or a solvate thereof, which process comprises catalytically reducing 5-{4-[2-(N-

methyl-N-(2-pyridyl}amino)ethoxy]benzylidene}-2,4-thiazolidinedione or a tautomeric form thereof or a salt thereof, or a solvate thereof, **characterised in that** the reduction reaction is carried out using a hydrogen pressure above 1.379 x 10^5Pa (20psi); and thereafter if required forming a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate.

2. A process according to claim 1, wherein the reaction is carried out using a hydrogen pressure in the range of from 3.4475 x 10^5Pa to 103.425 x 10^5Pa (50 to 1500psi), 4.137 x 10^5 to 103.425 x 10^5Pa (60 to 1500psi), 5.17125 x 10^5 to 103.425 x 10^5Pa (75 to 1500psi), 4.8265 x 10^5 to 68.95 x 10^5Pa (70 to 1000psi) or 13.79 x 10^5 to 68.95 x 10^5Pa (200 to 1500psi).

3. A process according to claim 1 or claim 2, wherein the reaction hydrogen pressure is in the range of from 4.8265 x 10^5 to 68.95 x 10^5Pa (70 to 1000psi).

4. A process according to any one of claims 1 to 3, wherein the reaction hydrogen pressure is 4.8265 x 10^5, 5.17125 x 10^5, 5.516 x 10^5, 34.475 x 10^5, and 68.95 x 10^5Pa (70, 75, 80, 500 or 1000psi).

5. A process according to any one of claims 1 to 4, wherein the hydrogenation catalyst is a 10% palladium-on-carbon catalyst.

6. A process according to any one of claims 1 to 5, wherein the catalyst loading is 5 to 100%, (%w/w of catalyst to substrate).

7. A process according to any one of claims 1 to 6, wherein the reaction solvent is acetic acid, aqueous acetic acid, an alkanol, an alkanol admixed with an aqueous mineral acid, tetrahydrofuran or tetrahydrofuran admixed with an aqueous mineral.

8. A process according to claim 7, wherein the reaction solvent is acetic acid.

9. A process according to any one of claims 1 to 8, wherein the reaction temperature is in the range of from 80°C to 115°C.

Patentansprüche

1. Verfahren zur Herstellung von 5-{4-[2-(*N*-Methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidindion oder einer tautomeren Form davon oder eines Salzes davon oder eines Solvats davon, wobei das Verfahren katalytisches Reduzieren von 5-{4-[2-(*N*-Methyl-*N*-(2-pyridyl)amino)ethoxy]benzyliden}-2,4-thiazolidindion oder einer tautomeren Form davon oder eines Salzes davon oder eines Solvats davon umfasst, **dadurch gekennzeichnet, dass** die Reduktionsreaktion unter Verwendung eines Wasserstoffdrucks von über 1,379x10^5 Pa (20 psi) durchgeführt wird; und danach, falls notwendig, Bilden eines pharmazeutisch verträglichen Salzes und/oder eines pharmazeutisch verträglichen Solvats.

2. Verfahren gemäß Anspruch 1, wobei die Reaktion unter Verwendung eines Wasserstoffdrucks im Bereich von 3,4475x10^5 Pa bis 103,425x10^5 Pa (50 bis 1500 psi), 4,137x10^5 bis 103,425x10^5 Pa (60 bis 1500 psi), 5,17125x10^5 bis 103,425x10^5 Pa (75 bis 1500 psi), 4,8265x10^5 bis 68,95x10^5 Pa (70 bis 1000 psi) oder 13,79x10^5 bis 68,95x10^5 Pa (200 bis 1000 psi) durchgeführt wird.

3. Verfahren gemäß Anspruch 1 oder Anspruch 2, wobei der Wasserstoffdruck der Reaktion im Bereich von 4,8265x10^5 bis 68,95x10^5 Pa (70 bis 1000 psi) liegt.

4. Verfahren gemäß einem der Ansprüche 1 bis 3, wobei der Wasserstoffdruck der Reaktion 4,8265x10^5, 5,17125x10^5, 5,516x10^5, 34,475x10^5 und 68,95x10^5 Pa (70, 75, 80, 500 oder 1000 psi) beträgt.

5. Verfahren gemäß einem der Ansprüche 1 bis 4, wobei der Hydrierkatalysator ein Katalysator aus 10% Palladium auf Kohle ist.

6. Verfahren gemäß einem der Ansprüche 1 bis 5, wobei die Beladung mit Katalysator 5 bis 100% (%Gew./Gew. Katalysator zu Substrat) beträgt.

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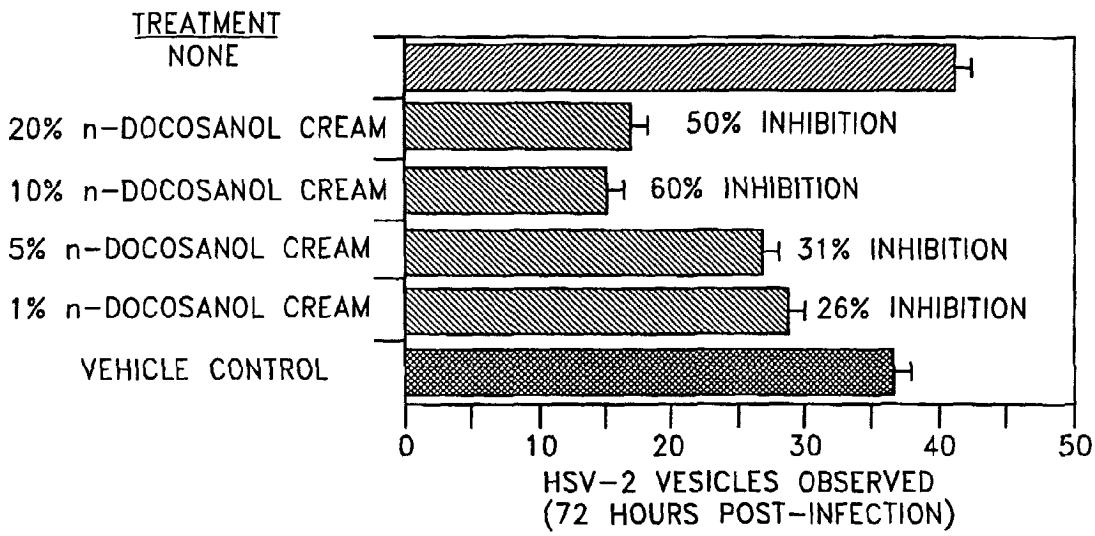

(57) Abstract: This invention relates to topical therapeutic preparations and methods for treating viral and inflammatory diseases and for reducing the pain of topical inflammation of skin and mucous membranes. The preparations include creams containing *n*-docosanol.

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Two active ingredients in two types of formulations

Docosanol and acyclovir were prepared in two types of formulations: a cream formulation and a polyethylene glycol–(PEG) based ointment. The compositions of both formulations are listed in Table 11a (Composition of Docosanol and Acyclovir Creams) and Table 11b (Composition of Docosanol and Acyclovir in PEG).

Table 11a

Ingredient	Formulation (% w/w)		
	Vehicle	Docosanol 10% Cream	Acyclovir 5% Cream
Docosanol	0	10	0
Acyclovir	0	0	5
Cream excipients	100	90	95

Table 11b

Ingredient	Formulation (% w/w)		
	PEG Vehicle	Docosanol 10% in PEG	Acyclovir 5% in PEG
Docosanol	0	10	0
Acyclovir	0	0	5
PEG 3350	30	15	20
PEG 400	70	75	75

Hairless and Hartley guinea pigs (Crl:(HA)BR) were obtained from Charles River laboratories. They were quarantined 7 days before use and fed diet and water ad libitum. The animals were individually caged and housed under strict pathogen-free conditions. Two strains of HSV-1 (Kos strain and MacIntyre strain) and the MS stain of HSV-2 were used. The virus was a cell culture preparation that had been pre-titered in guinea pigs prior to use in these experiments.

Prior to inoculation the haired guinea pigs were shaved with an electric razor, dampened with warm water, then Nair depilatory cream was applied for 3-4 minutes to remove the remaining hair. The backs of both hairless and haired animals were then washed with warm water and thoroughly dried. In Inoculation Method 1, the backs of guinea pigs were marked into a grid of 8 squares and within each area a 10 mm diameter lesion (wound) was induced by applying virus to the skin and scarifying the area with 10 light vertical and horizontal scratches using a 20 gauge inoculation needle. In Inoculation Method 2, a grid of six squares was drawn with a marking pen.

Treatment	Mean Lesion Score ± SD Day 2	Mean Lesion Score ± SD Day 3	Mean Lesion Size ± SD Day 2	Mean Lesion Size ± SD Day 3	Mean Virus Titer Day 4 (log_{10}/g ± SD)
10% Docosanol (PEG)	0.7 ± 0.3	0.8 ± 0.3	32.9 ± 14.5	40.8 ± 18.4	3.7 ± 1.2**
10% Docosanol (Cream)	0.6 ± 0.3	0.8 ± 0.3	34.2 ± 16.1	43.3 ± 18.3	3.6 ± 1.3**
5% Acyclovir (PEG)	0.6 ± 0.3	0.8 ± 0.3	25.8 ± 13.6	35.0 ± 15.7	4.0 ± 1.1**
5% Acyclovir (Cream)	0.4 ± 0.2	0.4 ± 0.2***	13.2 ± 10.3***	13.6 ± 9.0***	3.1 ± 0.8***
Cream Vehicle	0.5 ± 0.2	0.5 ± 0.3	24.0 ± 11.5	29.3 ± 15.7	4.9 ± 0.8
PEG Vehicle	0.7 ± 0.2	0.8 ± 0.3	33.7 ± 14.8	38.0 ± 13.7	4.7 ± 0.8
Untreated	0.6 ± 0.2	0.8 ± 0.3	28.2 ± 9.5	38.6 ± 14.1	5.0 ± 0.7

*tid x 4 beginning 12 h post virus exposure
*P<0.05 **P<0.01 ***P<0.001 compared to appropriate placebo
*P<0.05 **P<0.01 ***P<0.001 compared to untreated controls

The formulations prepared are listed in Tables 11a and 11b above. All samples were subjected to analytical testing prior to experimental use. The cream formulation with docosanol is a white, odorless, non-staining and non-water soluble cream. In the absence of docosanol, the cream vehicle and 5% acyclovir in cream vehicle have watery, lotion-like consistencies. The PEG vehicle is a clear, water-soluble ointment that becomes white in formulations containing docosanol and acyclovir.

The formulations listed in Tables 11a and 11b were evaluated for efficacy in the treatment of cutaneous lesions induced by HSV-1 in hairless models using Inoculation Method 1 (scarification). Topical treatment began 12 hours later and continued every 8 hours for a total 10 treatments. Lesion size and severity were assessed on Day 2 and Day 3 of infection. On Day 4 each lesion was excised and assayed for viral content.

The results are summarized in Table 12. Lesion size and score were not inhibited by docosanol in cream or ointment or by acyclovir ointment. It has been reported that greater inhibition of lesion size and severity is generally observed if treatment is continued past Day 4, and since guinea pigs in this study were sacrificed on Day 4 for determination of viral content, it was not unexpected that effects on lesion size and severity were not observed. The virus titer reduction data indicated that docosanol treatment in both vehicles reduced the mean virus titer/gram by approximately 1 log_{10} when compared to the untreated control mean. This difference was statistically significant ($p < 0.01$). Docosanol in PEG reduced the viral titer by 1.0 log_{10} and acyclovir in PEG reduced the viral titer by 0.7 log_{10}. The differences between acyclovir and docosanol were not statistically significant.

Based on the results in Table 12, and because the PEG vehicle is similar in consistency to that of docosanol in PEG, PEG formulations were selected for further study. The results of tests in hairless guinea pig

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(86) International application number:
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(54) **POTENTIATION OF BIOCIDE ACTIVITY USING AN N-ALKYL HETEROCYCLIC COMPOUND**

BIOZIDE WIRKUNGSSTEIGERUNG DURCH N-ALKYL-HETEROZYKLISCHE VERBINDUNG

POTENTIALISATION DE L'ACTIVITE BIOCIDE A L'AIDE D'UN COMPOSE HETEROCYCLIQUE N-ALKYLE

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
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(56) References cited:
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US-A- 4 661 503
US-A- 5 182 277
US-A- 5 250 194

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spraying an aqueous dispersion containing the microbicide and N-alkyl heterocyclic compound onto the pulp after the pulp leaves the presses in a papermaking process. Or, the microbicide and the N-alkyl heterocyclic compound may be incorporated into a bath used at the wet or size press and the web contacted by nipping the web to incorporate the combination into the web with any other agents applied at the press. Alternatively, the pulp may be contacted by mixing the microbicide and N-alkyl heterocyclic compound into the pulp/white water mixture, preferably prior to the pulp reaching the formation wire.

[0047] When treating paper (which includes paperboard and other cellulosic products or substrates), the microbicide and N-alkyl heterocyclic compound may be added into pulp slurries in the headbox, in the substrate forming solution, or in the white water system to treat the water system itself or for incorporation into the body of the paper. Alternatively, as with other known microbicides, the combination of a specified microbicide and an N-alkyl heterocyclic compound according to the invention may be mixed into a coating used to coat the finished paper.

[0048] The activity of the combinations described above has been confirmed using standard laboratory techniques as discussed below. In many cases, the N-alkyl heterocyclic compound potentiates, or even synergistically enhances, the microbicidal affect of the particular microbicide. The following examples are intended to illustrate, not limit, the present invention.

Examples:

[0049] One procedure for determining a potentiating, or even synergistic, interaction between two compounds utilizes the same technique and apparatus as that used in the basic determination of antifungal activity for a single compound. However, the identification of an interaction between two compounds requires a special arrangement of treatments in an experimental design known as a "factorial" arrangement. This is commonly accomplished using a "checkerboard" design in which each vertical column represents a different concentration of Compound A, and each horizontal row represents a different concentration of Compound B. The concentration series for each compound alone begins at "zero". Thus, the correct factorial design provides:

(a) a "no chemical" control (position row 1, column 1),
(b) results for the concentration series of each chemical alone (on row 1: chemical B = 0, thus chemical A is in a series by itself; on column 1, compound A = 0, thus compound B is in a series by itself), and
(c) each concentration of compound A in a combination with each concentration of compound B.

[0050] In the procedure, each position in the factorial or checkerboard design is occupied by a culture tube containing 5 ml of sterile liquid culture medium. Individual stock solutions for both compounds are prepared, and the appropriate volume (µl) is added to the medium to achieve the required concentration specified by the test protocol. Each tube is inoculated with 100 µl of spore suspension prepared from the test fungus (*Aspergillus niger*). The suspension is prepared by swabbing the surface of a viable culture (agar slant) and introducing the collected spores into a bottle containing 100 ml of sterile water. The spore suspension is complete when the optical density = 0.28 at 686 nm. The inoculated treatments are incubated in the dark at 28°C for seven days. All tubes then are observed for either the presence or absence of fungal mat growing on the surface of the liquid medium.

[0051] The key items of data recorded are:

(1) the lowest concentration (minimum inhibitory concentration, MIC) of each test compound separately for which there was no growth, and
(2) the lowest concentration of compound A in combination with compound B for which there was no growth.

[0052] The above procedure was used to determine the potentiating effect of an N-alkyl heterocyclic compound with various microbicides. Tables 1-12 show the results of the various tests and the potentiation of microbicidal effect using an N-alkyl heterocyclic compound. Tables 1-12 present both the lowest concentrations of each test compound separately for which there was no growth, and the lowest concentration of compound A in combination with compound B for which there was no growth. A plus (+) sign represents the presence of fugal mat and a minus (-) sign represents the absence of fungal mat. The following compounds or formulations were used:

- dodecyl morpholine (DDM), technical grade 85-95% pure;
- dodecyl imidazole (DDI), technical grade 85-95% pure;
- Kathon, Busan® 1078 product, Buckman Laboratories Inc., Memphis, TN;
- iodopropargyl butyl carbamate (IPBC), technical grade 95% pure;
- iodopropargyl carbamate (IPC), technical grade 95% pure;
- 2,2-Dibromo-3-nitrilopropionamide (DBNPA), Busan® 94 product, Buckman Laboratories Inc., Memphis, TN;

Table 10:

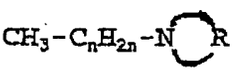
Proxel GXL-20 (compound A) and DDI (compound B)													
													B
	-	-	-	-	-	-	-	-	-	-	-	-	160
	-	-	-	-	-	-	-	-	-	-	-	-	80
	-	-	-	-	-	-	-	+	-	+	-	-	40
	-	-	-	-	+	+	+	+	+	+	+	+	20
	-	-	+	+	+	+	+	+	+	+	+	+	10
	-	+	+	+	+	+	+	+	+	+	+	+	5
	-	+	+	+	+	+	+	+	+	+	+	+	2.5
	-	+	+	+	+	+	+	+	+	+	+	+	0
A	320	160	80	40	20	10	5	2.5	1.25	.625	.3125	0	

Claims

Sinergistic combination

1. A microbicidal composition comprising:

(a) at least one microbicide selected from 5-chloro-2-methyl-4-isothiazolin-3-one, 2-methyl-4-isothiazolin-3-one, iodopropargyl butyl carbamate, iodopropargyl carbamate, 2,2-dibromo-3-nitrilo-propionamide, tribromophenol, 1,2-benzisothiazoline-3-one, and mixtures thereof and
(b) an N-alkyl heterocyclic compound of the formula:



wherein n is from 5 to 17, the heterocyclic ring defined by

is a substituted or unsubstituted ring having four to eight members, and wherein (a) and (b) are present in a combined amount effective to control the growth of at least one microorganism and the N-alkyl heterocyclic compound (b) is present in an amount effective to potentiate the microbicidal activity of the microbicide (a).

2. A microbicidal composition as claimed in claim 1, wherein n is from 9 to 15, and the heterocyclic ring is selected from the group consisting of pyrrolidinyl, 2-pyrrolidinonyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, imidazolidinyl, imidazolinyl, imidazolyl, oxazolidinonyl, piperidinyl, piperazinyl, morpholinyl, hexamethyleneiminyl and heptamethyleneiminyl,

3. A microbicidal composition as claimed in either one of claims 1 or 2, wherein the N-alkyl heterocyclic compound is selected from the group consisting of N-dodecyl morpholine, N-dodecyl imidazole, N-dodecyl-2,6-dimethyl-morpholine, N-dodecyl-5-chloromethyl-2-oxazolidinone, N-dodecyl-2-pyrrolidinone, N-dodecyl hexamethyleneimine, N-dodecyl pyrrolidine, N-dodecyl-3-methyl-piperidine, N-dodecyl piperidine, N-dodecyl-4-methyl-piperidine and N-dodecyl-2-methyl-piperidine.

4. A microbicidal composition as claimed in any one of claims 1 to 3, wherein the N-alkyl heterocyclic compound is N-dodecyl morpholine or N-dodecyl imidazole.

5. A microbicidal composition as claimed in any one of claims 1 to 4 wherein the microorganism is selected from

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

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(54) Title: AN INSTANT DRY MIX COMPOSITION FOR PROVIDING A BEVERAGE

(57) Abstract: An Instant dry mix composition produces a beverage having a two-toned foam on the surface upon reconstitution in a hot liquid. The composition includes a foaming creamer for producing a foam layer and a separately enclosed quick dissolving or dispersing flavor/color component e.g. coffee, tea or chocolate and optional sweetener component. The density of the combined flavor/color component and optional sweetener component is higher than the density of the foam layer. A beverage is prepared by combining the foaming creamer and hot liquid until the foaming creamer dissolves and creates a foamed layer on the surface. The combined flavor/color component and optional sweetener component is then added. Upon stirring the resultant mixture, a two-toned effect results in the foam layer.

[0026] Example 1

[0027] The following experiments were conducted to determine the densities of foam layers produced by gasified foaming creamers having different densities. The creamers used were the standard gasified foaming creamers having a composition of 53.0% Skimmed Milk Solids in the dry state, 4.0% Lactose Monohydrate and 29.5% fat. Each of the creamers was dissolved in water, the resulting foam layer scooped off the surface and the density of the foam was measured.

[0028] The densities of the creamers were as follows:

		Density of Creamer	Density of Foam Layer
[0030]	C1	12.45g/100ml	19.5g/100ml
[0031]	C2	15.19g/100ml	19.5g/100ml
[0032]	C3	19.25g/100ml	19.9g/100ml

[0033] The conclusion from this set of experiments is that foam density is fairly consistent and unrelated to creamer density.

[0034] Example 2

[0035] Tests were conducted using three variables or factors: different density coffees, different density creamers and different density sugars. These tests followed a factorial design, where factors were ranged at 3 levels (3x3), representing a typical product range.

[0036] The coffees used were standard instant, agglomerated coffees as purchased from the supermarket. The coffees were differentiated by densities and the three examples chosen were of a low, medium and high density, where:

[0037] Low = 22.4g/100ml
[0038] Medium = 25.3 g/100ml

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(54) **PROCESS FOR AQUEOUS GRANULATION OF CLARITHROMYCIN**

VERFAHREN ZUR WÄSSRIGEN GRANULIERUNG VON CLARITHROMYCIN

PROCEDE DE GRANULATION AQUEUSE DE LA CLARITHROMYCINE

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(56) References cited:
- **PHARMACEUTICAL RESEARCH, vol. 8, no. 6, 1991, NEW YORK (US), pages 706-712, XP000645421 MOU-YING FU LU; ET AL.: "A polymer carrier system for taste masking of macrolide antibiotics"**

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room temperature.

d. Ether Extractable Analysis: This assay was primarily utilized to assess the concentration of free Clarithromycin after each granulation step. The ether extractable analysis has been developed based on the simple principle that CARBOPOL 947P® and PVP are completely insoluble in ether, while Clarirhromycin molecules have a very high ether solubility. As a result of interaction between Clarithromycin and CARBOPOL 947P® molecules during the granulation process, the Clarithromycin-CARBOPOL 947P® articles will remain insoluble in ether. Filtration of a mixture of these granules in ether leads to entrapment of any Clarithromycin-CARBOPOL 947P® or Clarithromycin-CARBOPOL 947P®-PVP particles, while the free Clarithromycin remains in the solution and is recovered when the solvent part of the filtered solution is evaporated. The detailed procedure may be found under Standard Control Procedure (SCP), list no. 31043, issued at 4/07/92 (Abbott Labs).

e. Loss on rung: Two gravimetric techniques, a vacuum oven at 60°C and a Computrac at 110°C were utilized to verify the concentration of water at different granulation stages.

f. Dissolution: The rate of dissolution for uncoated clarithromycin particles produced with aqueous granulation was compared with current (*i.e.*, alcohol granulated) uncoated particles. The HPLC procedure utilized to assay is described above.

EXAMPLE 1

Formation of Clarithromycin/Carbopol 974P® Granules in a 10 Liter GRAL

[0046]

A. First Granulation: Preliminary experiments were designed to examine the different variables that may affect the first granulation process (of clarithromycin and carbomer). A multiple level factorial design was utilized to examine the aqueous granulation process. In these series of experiments, 625 grams of clarittzromycin and 375 grams of CARBOPOL 974P® (5:3 w/w) were used exclusively. The granulating solvent was 100% water. The effect of jacket temperature, rate of water addition and the total quantity of water added were the variables examined in this study. The effect of these variables on granulation was measured by determining (1) ease of fluidization and (2) % ether extractable material (*i.e.*, Clarithromycin). Table 2 shows a summary of all experiments conducted in the 10 liter GRAL.

1. Effect of Jacket Temperature: As indicated in Table 2, at lower quantities of water (*i.e.*, 1.6 kg of water/1.0 kg of powder), jacket temperature did not significantly effect the ease of fluidization of the granules and a 12°C change in the jacket temperature did not affect the quality of final product (*i.e.*, the extent of interaction between Clarithromycin and CARBOPOL 974P® as measured by ether extractable analysis) for a given granulation time. However, granulation at lower temperatures tended to result in the formation of a more fluid material, (since gel formation was more effectively retarded). At the higher concentrations of water (*i.e.*, 2.0 kg of water/1.0 kg of powder), increasing the jacket temperature improved both the quality of particles formed (*i.e.*, with respect to ease of fluidization) and decreased the concentration of ether extractables measured.

TABLE 2

Exp. No.	Jacket Temp. (°C)	Water Added (Kg)	Granulation Time (Minutes)	Appearance/ Drying Method	% LOD	% Ether Extractable Material
1	0	1.61	60	Easily fluidized	1.0	14.0
2	0	1.61	120	Easily fluidized	1.2	9.0
3	0	2.0	60	Paste/Tray dried	-	-
4	0	2.5	60	Paste/Tray dried	-	-
5	12	1.61	60	Easily fluidized	2.1	15.0
6	12	1.61	120	Easily fluidized	1.0	7.0
7	12	2.0	60	Overwet/ fluidized	0.9	8.0
8	12	2.5	60	Overwet/ flmdized	1.1	1.6

Propanolol sustained release pellets

Target

Investigate the effects of formulation variables upon the release properties of propanolol HCl - containing pellets coated with Eudragit RS.

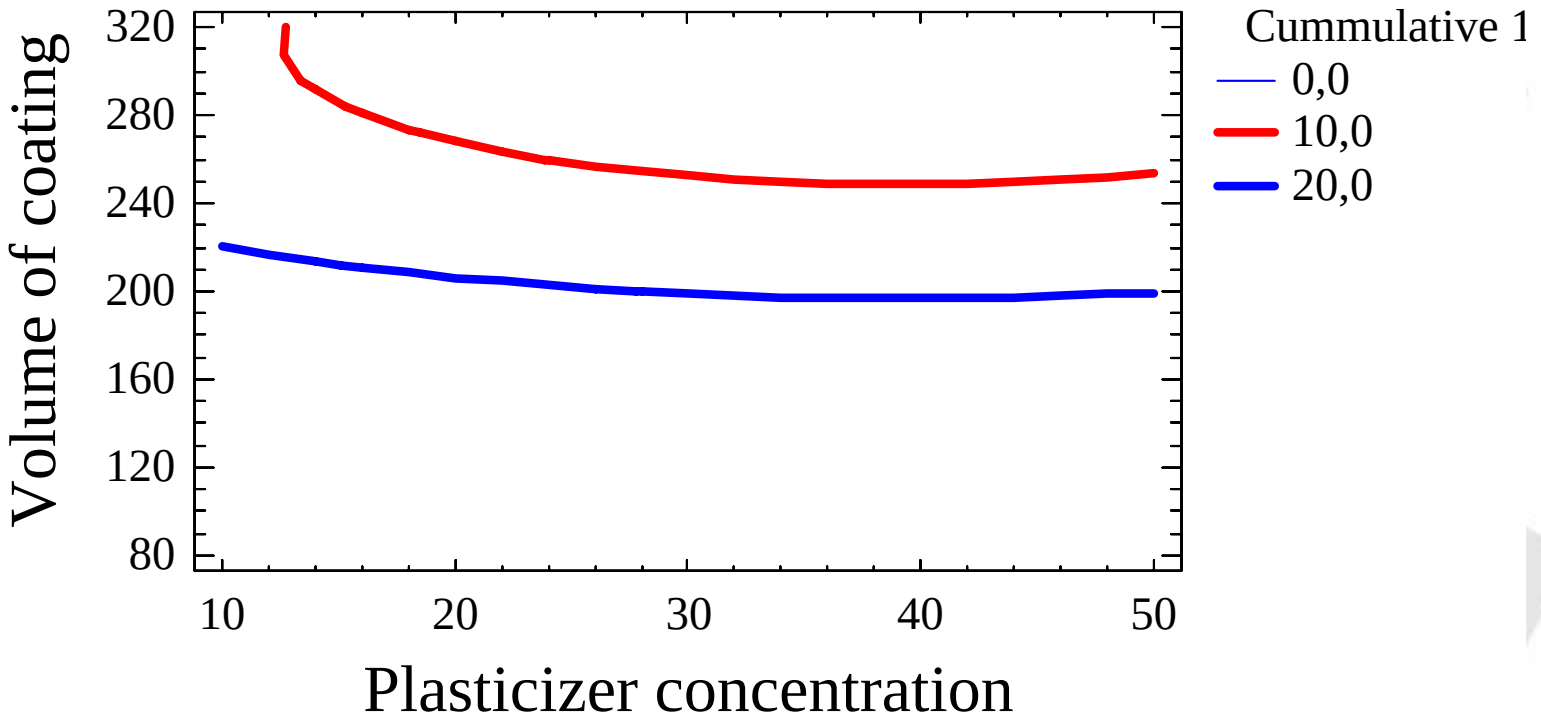
Optimize the release of the active ingredient.

The optimization would aid in the preparation of controlled release pellets with predictable properties.

International Journal of Pharmaceutics, 1997, 154, 49-57

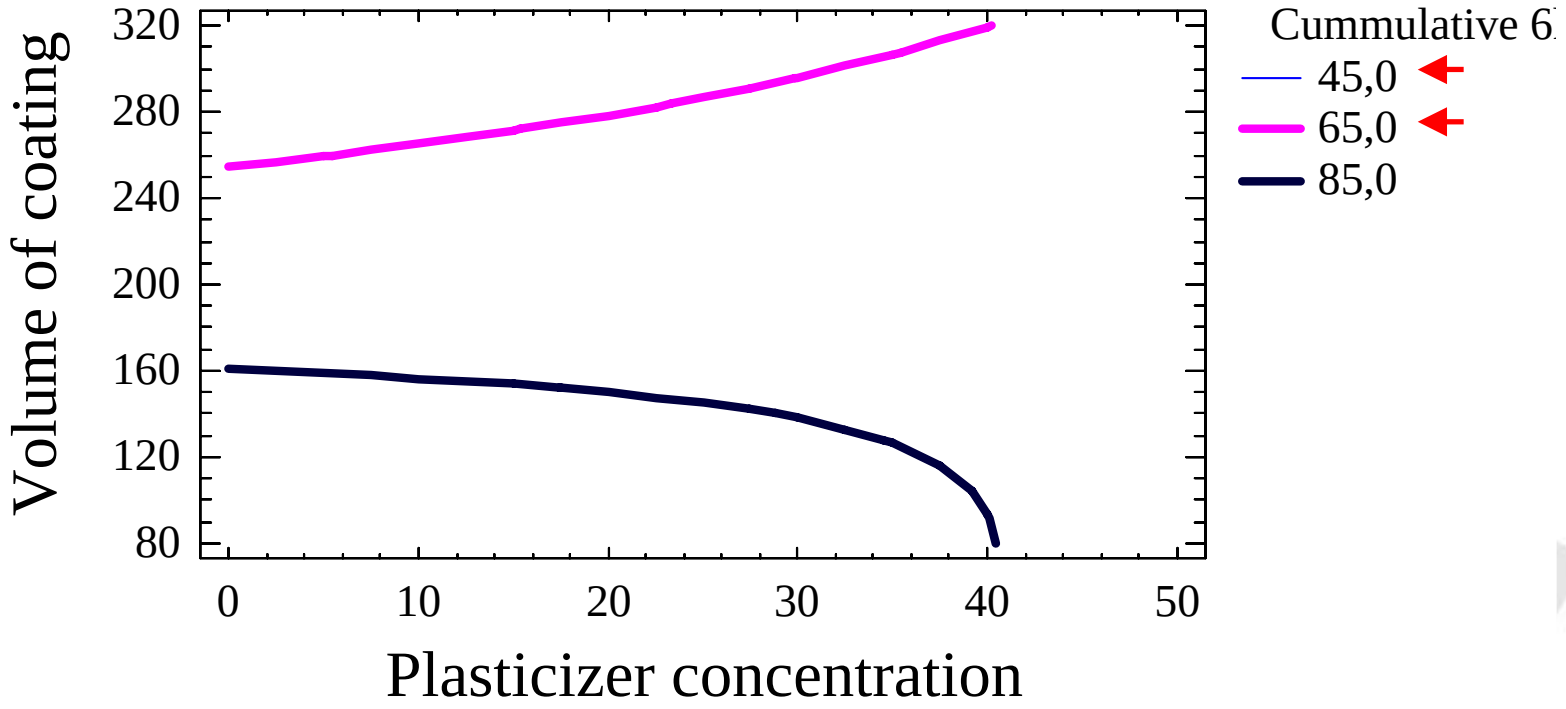
Propanolol sustained release pellets

Cummulative dissolved in 1 h



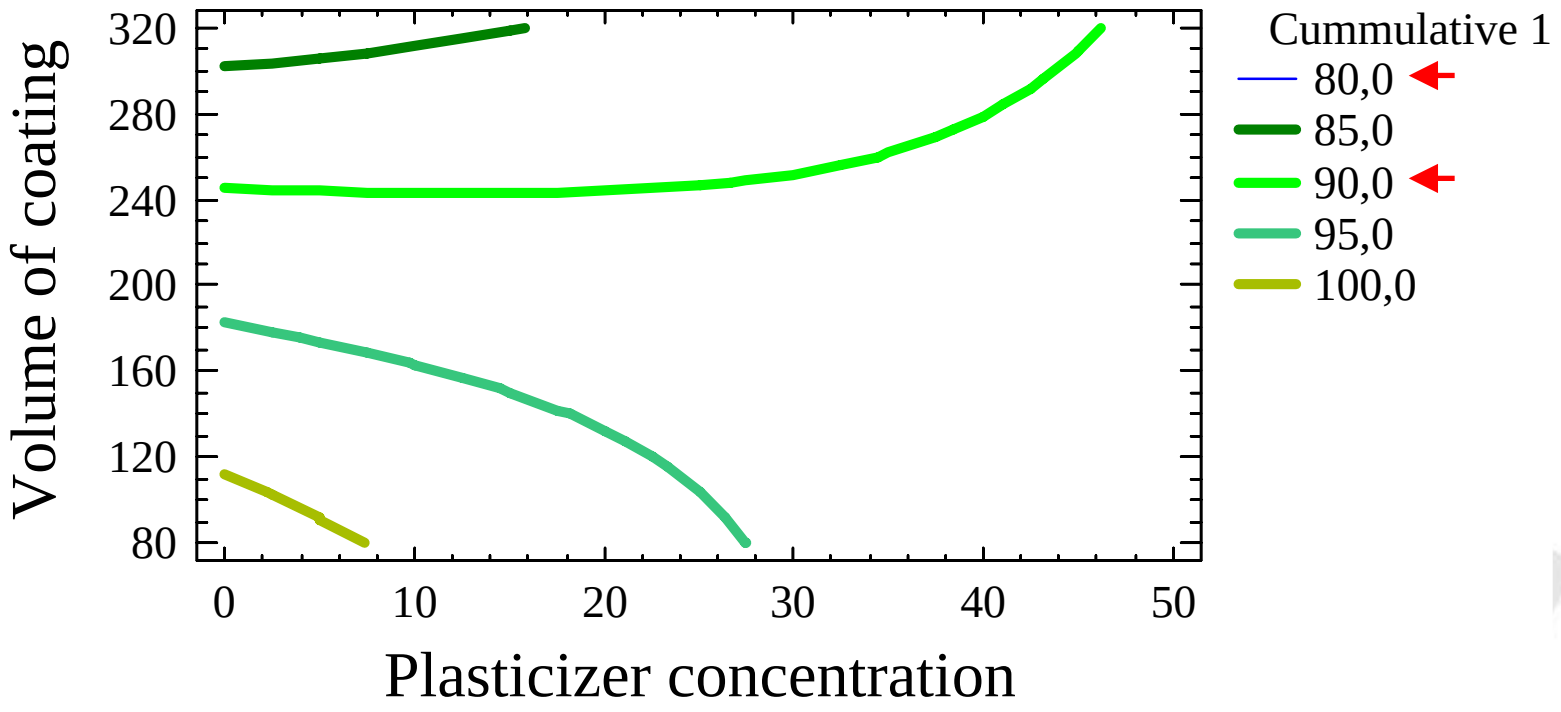
Propanolol sustained release pellets

Cummulative dissolved in 6 h

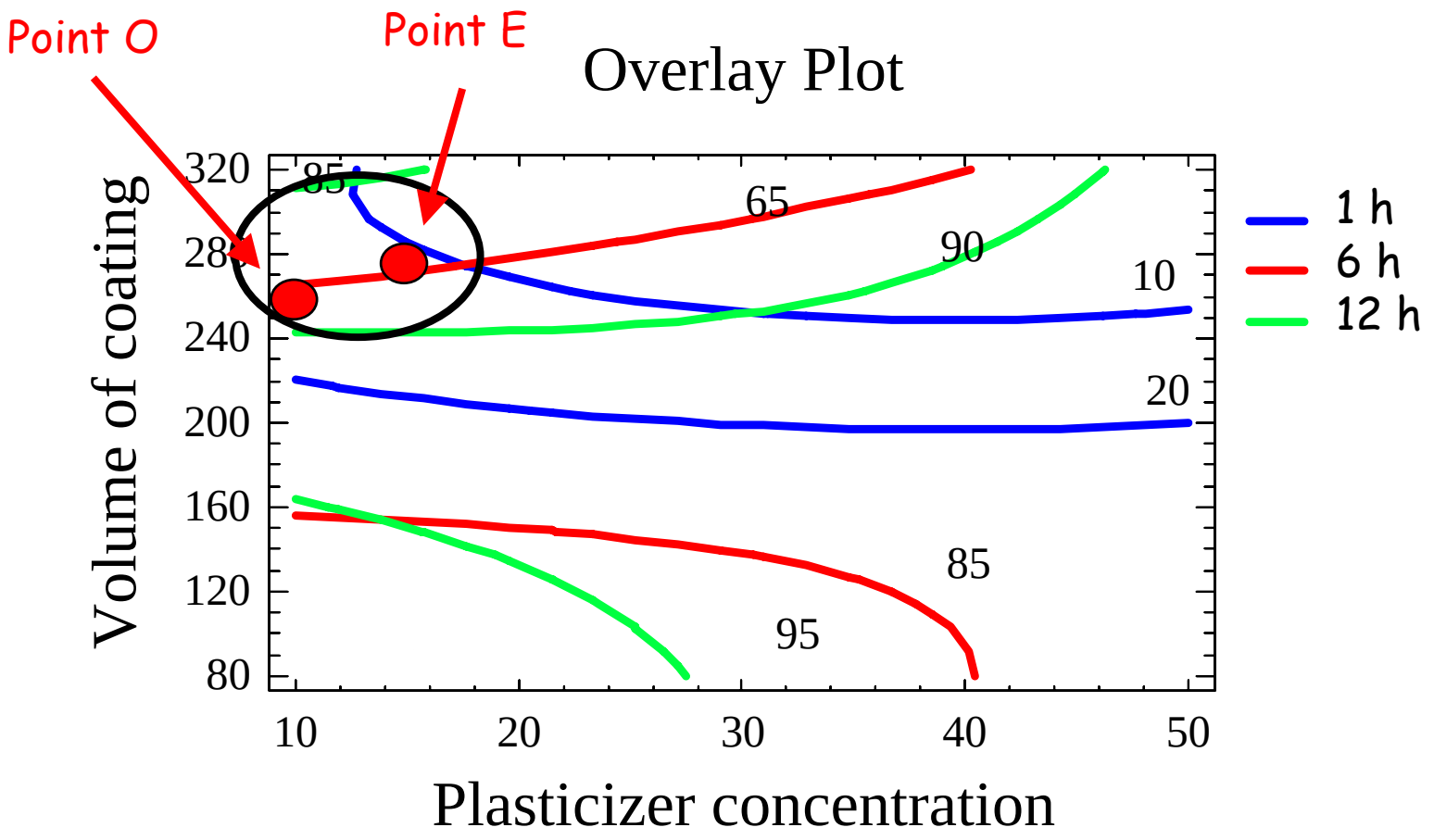


Propanolol sustained release pellets

Cummulative dissolved in 12 h



Propanolol sustained release pellets



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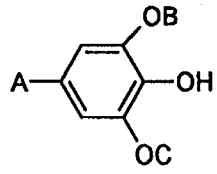
(54) Title: ANTIMICROBIAL ACTIVITY OF LACCASES



(I)

(57) Abstract

A method for antimicrobial treatment of microorganisms and/or viruses comprising treating with an effective amount of a fungal Laccase and one or more enhancers in the presence of oxygen, O_2, the enhancers being of formula (I).

evaluated against *Pseudomonas aeruginosa* which are more resistant than *S. epidermidis*. Acetosyringon was found to be the most bactericidal enhancer against *P. aeruginosa*.

Example 5:

Synergistic effects by combinations of different enhancers

The sensitivity of various microorganisms depends on the used enhancer, thus a broad spectrum of antimicrobial activity may be obtained by combining the different enhancers and applying them simultaneously. The total antimicrobial activity against a mixed culture of different microorganisms is expected to be significantly increased if a mix of enhancers is used.

It is contemplated that the enhancers are tested in a sub-lethal concentration (less than 100 % bactericidal activity), and tested in different combinations against microorganisms with different physiology. Synergistic effects may be determined by a multi-factorial experiment with a laccase and enhancers like eg acetosyringon, methylsyringate, ethylsyringate, butylsyringate and laurylsyringate.

Example 6:

Synergistic antimicrobial effect by combination of two enhancers.

Antimicrobial activity of laccases with two enhancers was determined against *Pseudomonas aeruginosa* (ATCC 10145) and *Staphylococcus epidermidis* (DSM 20042) at pH 6 as described in example 1. Methylsyringate and acetosyringon was used as enhancers and the laccase was rPpL (1 mg/L) and the antimicrobial activity was determined by use of a 3^2 factorial experimental design.

A synergistic antimicrobial activity was found when combining the two enhancers (fig. 5; A=methylsyringate; B=Acetosyringon). Acetosyringon resulted in a cell reduction of *P. aeruginosa* of approximately 1.5 log units, methylsyringate resulted in a cell reduction of approximately 3 log units, whereas the combination resulted in a total kill of the test

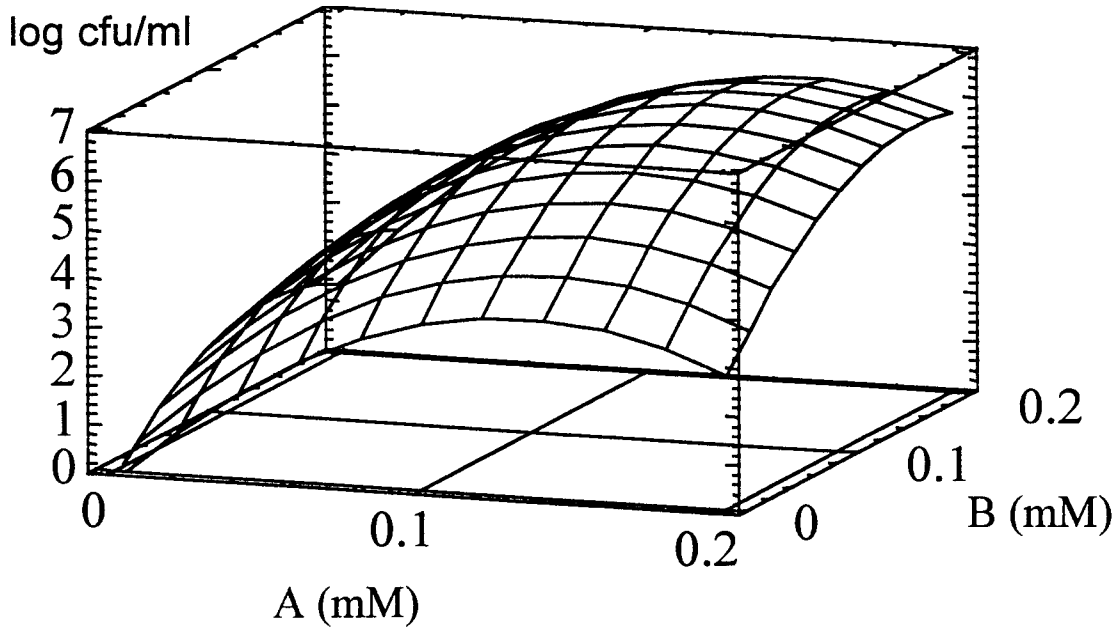
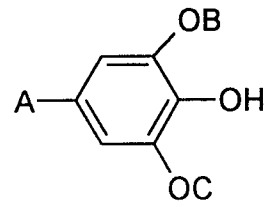


Fig. 5

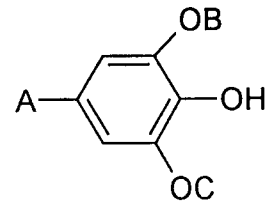
CLAIMS

1. A method for antimicrobial treatment of microorganisms and/or viruses comprising treating said microorganisms and/or viruses with an effective amount of a fungal Laccase (EC 1.10.3.2) enzyme and one or more enhancers in the presence of oxygen, O_2, the enhancers being of the formula:



in which formula A is a group such as -D, -CH=CH-D, -CH=CH-CH=CH-D, -CH=N-D, -N=N-D, or -N=CH-D, in which D is selected from the group consisting of -CO-E, $-SO_2$-E, -N-XY, and $-N^+$-XYZ, in which E may be -H, -OH, -R, or -OR, and X and Y and Z may be identical or different and selected from -H and -R; R being a C_1-C_{16} alkyl, preferably a C_1-C_8 alkyl, which alkyl may be saturated or unsaturated, branched or unbranched and optionally substituted with a carboxy, sulpho or amino group; and B and C may be the same or different and selected from C_mH_{2m+1}; $1 \leq m \leq 5$.

2. An antimicrobial composition comprising a laccase enzyme (EC 1.10.3.2) and at least two different enhancers of the formula:



in which formula A is a group such as -D, -CH=CH-D, -CH=CH-CH=CH-D, -CH=N-D, -N=N-D, or -N=CH-D, in which D is selected from the group consisting of -CO-E, $-SO_2$-E, -N-XY, and $-N^+$-XYZ, in which E may be -H, -OH, -R, or -OR, and X and Y

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(54) **STABLE GEL FORMULATION FOR TOPICAL TREATMENT OF SKIN CONDITIONS**

STABILGELZUSAMMENSETZUNG ZUR TOPISCHEN BEHANDLUNG VON HAUTKRANKHEITEN

COMPOSITION DE GEL STABLE POUR LE TRAITEMENT TOPIQUE DE MALADIES DE LA PEAU

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(56) References cited:
EP-A- 0 290 130 **WO-A-90/14833**

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[0016] The method further includes mixing polyethylene glycol, Polysorbate 40, hexylene glycol, butylated hydroxytoluene and butylated hydroxyanisole and heating to dissolve same. Thereafter, the heated mixture is cooled to room temperature and benzyl alcohol and Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl]nicotinate are added thereto to form a part III.

[0017] Purified water is mixed with tromethamine to form part IV and part III is added to parts I and II while stirring before part IV with mixing until homogeneous.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The advantages and features of the present invention will be better understood by the following description when considered in conjunction with the accompanying drawings indicated as follows:

Figure 1: Plot of residuals vs. fitted values for the solubility data;
Figure 2: Normal plot of. residuals for the solubility data;
Figure 3: Effect of transformation of the response (solubility data);
Figure 4: Response surface fitting the solubility data (with hexylene glycol);
Figure 5: Effect of square root of time on % drug released from gels 1 through 6;
Figure 6: Effect of square root of time on % drug released from gels 7 through 10;
Figure 7: Effect of square root of time on % drug released from gels 11 through 14;
Figure 8: Effect of square root of time on % drug released from gels 15 through 18;
Figure 9: Plot of residuals vs. fitted values for the release data;
Figure 10: Normal plot of residuals for the release data;
Figure 11: Effect of transformation of the response (release data);
Figure 12: Response surface fitting the release data (with hexylene glycol);
Figure 13: Correlation between release rate of drug from gels and the square root of drug solubility;
Figure 14: Release profiles comparing drug release from the prototype gel (H) to drug release from a saturated solution; and
Figure 15: Release profiles showing the effect of increasing the concentration of drug in the gel vehicle on the release rate, 0.025%, 0.05%, and 0.1%.

DETAILED DESCRIPTION

[0019] The following factors must be taken into consideration in the formulation of a suitable pharmaceutical preparation for the treatment of acne and psoriasis:

Formulation and Patient Compliance Issues

[0020]

- Nonirritating and nonstaining
- Odor-free
- Nonoily and nondrying
- Water washable
- Easy application and storage
- Ingredient labeling

Formulation Issues

[0021]

- Development of only one formula for both acne and psoriasis
- Local drug delivery and little systemic effect
- Ease of scaleup
- Stability for a minimum of two years
- Use of safe and compendial excipients
- Paraben-free formulation
- Propylene glycol-free formulation
- Drug having minimal affinity for the base

- Alcohol-free formulation
- Oil-free formulation
- Formula showing minimal placebo effect
- Some portion of drug in solution for immediate release
- Irritation levels comparable to other marketed retinoids

[0022] It has been found that the compound Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl]nicotinate is active in the treatment of acne and psoriasis. However, the solubility of AGN 190168 in water is extremely low. The solubility of Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl]nicotinate in various solutions at 35° ± 0.5 C is shown in Table I.

Table I.

Solubility of AGN in Various Aqueous Solutions at 35° ±0.5 C	
Aqueous Mixtures (v/v)	**Avg. Solubility (mg/ml)**
100% Water	Not Detected
20% Ethanol/Water	Not Detected
40% Ethanol/Water	0.1472 ± 0.0209
60% Ethanol/Water	2:2235 ± 0.000780%
40% Ethanol/Water	0.1472 ± 0.0209
80% Ethanol/Water	8.2248 ± 0.2206
20% PEG-400/Water	Not Detected
40% PEG-400/Water	0.0044 ± 0.0005
60% PEG-400/Water	0.0896 ± 0.0011
80% PEG-400/Water	2.1628 ± 0.0899
1% Oleth-20/Water	0.0733 ± 0.0030
2% Oleth-20/Water	0.1492 ± 0.0006
4% Oleth-20/Water	0.3112 ± 0.007
96% Oleth-20/Water	0.4352 ± 0.0011
0.07% Polysorbate 40	0.0037 ± 0.0006
0.15% Polysorbate 40	0.0092 ± 0.0014
0.30% Polysorbate 40	0.0183 ± 0.0018
0.50% Polysorbate 40	0.0332 ± 0.0003

[0023] As hereinabove noted, a solution dosage form containing AGN is not desirable in view of the aqueous content, the difficulty in handling the solution, and application to skin. A cream formulation is feasible but the oil utilized therein is also not suitable for acne treatment as hereinabove noted.

[0024] The formulation in accordance with the present invention includes a number of ingredients as set forth in Table II.

Table II

Ingredients Used in Formulation of an AGN Gel	
INGREDIENT	**FUNCTION**
AGN	Drug
Purified water	Excipient
Edetate Disodium	Stabilizer
Ascorbic acid	Stabilizer

[0037] **Purified Water** is used as the vehicle in the AGN topical gel formulation.

[0038] Typical concentration of each ingredient in the gel is shown in Table III.

Table III.

Concentration (% w/w) of ingredients in the 0.1% AGN Topical Gel (Formula 8606X)		
INGREDIENT	**FUNCTION**	**CONCENTRATION % W/W**
AGN	Drug	0.1
Purified water	Excipient	49.25
Edetate Disodium	Stabilizer	0.05
Ascorbic acid	Stabilizer	0.05
Carbomer 934P	Thickening agent	1.25
Poloxamer 407	Surfactant	0.2
PEG-400	Co-solvent	45.0
Polysorbate 40	Surfactant	0.2
Hexylene glycol	Co-solvent	2.0
Butylated hydroxytoluene	Stabilizer	0.05
Butylated hydroxyanisole	Stabilizer	0.05
Benzyl alcohol	Preservative	1.0
Triethanolamine/ Tromethamine	Neutralizer	0.8

[0039] The ingredients are combined together to make the following four parts:

Part I:	
INGREDIENT	**FUNCTION**
Purified water	Excipient
Edetate Disodium	Stabilizer
Ascorbic acid	Stabilizer
Carbomer 934P	Thickening agent

Part II:	
Purified water	Excipient
Poloxamer 407	Surfactant

Part III:	
PEG-400	Co-solvent
Polysorbate 40	Surfactant
Hexylene glycol	Co-solvent
Butylated hydroxytoluene	Stabilizer
Butylated hydroxyanisole	Stabilizer
Benzyl alcohol	Preservative
AGN	Drug

Preparation of the gels

design, variations of the prototype gel were prepared which contained different concentrations of three ingredients present in the gel; polysorbate 40 (PS), poloxamer 407 (PX), and hexylene glycol (HG). The purpose was to study the effect of these factors on the release rate and solubility of AGN in the vehicle of the gels. The procedure for the preparation of the gels is described in the formulation record.

Experimental Design

[0048] Experimental design was used to determine the number of formulations necessary to provide the desired information in the most efficient way. The variables studied were the concentrations of hexylene glycol, poloxamer 407, and polysorbate 40. Hexylene glycol was studied at 2 levels and each of the surfactants was studied at 3 levels. Therefore, a $2x3^2$ factorial design was produced which required the preparation of 18 formulations. Table IV shows the actual concentrations used for each of these ingredients. For all ingredients, the concentration of 0 indicates that the ingredient is not present.

Table IV.

The Levels of Poloxamer 407, Polysorbate 40, and Hexylene Glycol Used in the Preparation of Various Experimental Gels			
INGREDIENT	**CONCENTRATION (% W/W)**		
Poloxamer 407	0	0.2	0.4
Polysorbate 40	0	0.2	0.4
Hexylene glycol	0		2

[0049] The experimental design is shown in Table V. This design required the preparation of 18 gels containing all possible combinations of the surfactants and co-solvent at the desired levels. Since the prototype gel (gel B) represented one of the gels, it was necessary to formulate 17 other gels.

Table V.

The $2x3^2$ Factorial Design Used to Prepare the Various Experimental Formulations of the Prototype Gel (Gel B)			
Gel	Hexylene Glycol	Polysorbate 40	Poloxamer 407
10	0.0	0.0	0.0
11	0.0	0.0	0.4
8	0.0	0.0	0.2
12	0.0	0.4	0.0
18	0.0	0.4	0.4
15	0.0	0.4	0.2
9	0.0	0.2	0.0
16	0.0	0.2	0.4
7	0.0	0.2	0.2
3	2.0	0.0	0.0
5	2.0	0.0	0.4
1	2.0	0.0	0.2
6	2.0	0.4	0.0
17	2.0	0.4	0.4
14	2.0	0.4	0.2
2	2.0	0.2	0.0
13	2.0	0.2	0.4
B	2.0	0.2	0.2

Solubility of AGN in the Gels

[0050] To determine the saturated solubility of the drug in the vehicle of each of the 18 gel formulations, solvent systems containing the same ingredients as the gels were prepared. The saturated solubility was determined once in solutions of the vehicle without carbomer and base, and another time by substituting propionic acid for carbomer in order to ease filtration of the solution while keeping the ionic strength of the solution as close to that of the gel as possible. The solutions were filtered through a 0.45 μm filter to remove any crystals which may have formed. The resulting solutions were then diluted and their drug content was assayed using High Performance Liquid Chromatography (HPLC) as described in Method HL036.

Release of AGN from the Gels

[0051] The release of AGN through each of the 0.1% gels was studied using a previously developed release method. The collected fractions were then assayed directly using HPLC Method HL036.

Slopes of the Release Profiles

[0052] The data generated from the assay of the collected fractions for each gel were used to plot the release profile of the drug as the % drug released vs. square root of time. For each release profile, the slope of the linear region containing at least 6 points was calculated using linear regression. The standard deviation and correlation coefficient of each slope was also calculated.

Analysis of Solubility and Release Data

[0053] The saturated solubility values, and slopes of the line obtained from the plot of % drug released vs. square root of time for each gel were analyzed statistically. The difference between the slopes and solubilities from gel to gel were studied using a two tailed t-test to find the gels which resulted in significantly different values. RS/Discover® was used to calculate equations which fit the data and to construct response surfaces.

Maximizing Solubility and Release

[0054] The resulting slope and solubility data were also analyzed using RS/Discover® in order to maximize these responses. Initially the slope was maximized to find the gel exhibiting maximum drug release, then solubility was maximized in order to find the gel which had the highest drug solubility. Finally, both solubility and slope were simultaneously maximized to find the gel which provided optimum drug release and solubility.

Effect of Drug Particle Solubility on Drug Release

[0055] From the solubility data it is apparent that approximately 90% of the drug is present in the aqueous based gel in the form of solid particles. In order to determine if the rate of dissolution of the particles is limiting the rate of drug release, the data obtained form the *in vitro* release study was analyzed.

Effect of Membrane on Drug Release

[0056] In order to investigate the possibility of the silicone membrane being rate limiting, the slope of the release profile for drug diffusion through the gel was compared to the slope of the release profile obtained from a saturated solution of the drug.

Effect of Drug Concentration on Release Rate

[0057] A release study showing the affect of drug concentration on the *in vitro* release of AGN from three gel formulations was conducted. The three gels were formula 8606X (0.1%), 8607X (0.05%), and 8649X (0.025%), and plots of amount of drug release vs. square root of time were compared.

Solubility

Table IX.

Least Squares Coefficients for Solubility (Refined Model)			
Term	Coeff.	Std. Error	Significance
1	76.911	2.135	
PS	17.140	2.615	
PX	13.896	2.615	
HG	7.438	2.135	0.0015
PS*PX	-20.475	3.203	0.0001

[0061] The model became simpler. The equation which fits the data is:

$$\text{Solubility} = 76.91 + 17.14\ PS + 13.90\ PX + 7.44\ HG - 20.48\ PS * PX$$

[0062] The residual values are the difference between the observed values and the fitted values of the response associated with the model. RS/Discover® automatically studentizes the residuals so that they have a constant variance of one. To check whether there is any relationship between the magnitude of the residuals and the fitted values of the response, a plot of absolute values of the studentized residuals versus the fitted values was constructed (Figure 1). Any type of relationship may indicate the need to transform the response. The plot suggests that there is no clear trend in the residuals and the model does not need to be refined.

[0063] A normal probability plot of the residuals shown in Figure 2 indicates that points on the plot fall very close to the line indicating that the model's residuals are normally distributed.

[0064] To determine if the model can be improved by transforming the response, the fit of the model is checked. PS/Discover® produces a graph indicating the possible transformations and their effects on the logarithm of the sum of squares of the residuals (Figure 3). The transformation that results in the smallest value for this number produces the best fit. Transformations below the dashed line are within the 95% confidence interval for the best transformation. Since the untransformed response is below the line, the response was not transformed.

[0065] A three-dimensional response surface is shown in Figure 4. In order to determine the factor levels which result in maximum drug solubility, optimization was performed. As seen in Table X, when preparing a gel which contains between 0 to 0.4 polysorbate 40, poloxamer 407, and hexylene glycol, a maximum solubility of 103.17 µg/ml can be obtained with Polysorbate 40 at level 0.4, Poloxamer 407 at level 0.0, and hexylene glycol at level 2.

Table X.

Optimization of Drug Solubility			
Factor	**Range**	**Initial Setting**	**Optimal Value**
Polysorbate 40	0 to 0.4	0.2	0.4
Poloxamer 407	0 to 0.4	0.2	0.0
Hexylene glycol	0 to 2	2	2
Response			
Solubility	Maximize	97.6 µg/ml	103.17 µg/ml

In vitro Release of Gels

[0066] Drug release was studied from all seventeen formulated gels as described previously. The release profiles for each gel were an average of six runs, and were plotted as % Drug released vs. Square root of time. The release profiles for these gels are shown in Figures 5-8.

Release Studies of Prepared Gels

[0067] From the plots of % Drug Released vs. Square Root of Time, it is seen that the average amount of drug

[0078] A normal probability plot of the residuals shown in Figure 10 indicates that points on the plot fall very close to the line indicating that the model's residuals are normally distributed.

[0079] To determine if the model can be improved by transforming the response, the fit of the model is checked. The graph showing the possible transformations and their effects on the logarithm of the sum of squares of the residuals is shown in Figure 11. Transformations below the dashed line are within the 95% confidence interval for the best transformation. Since the untransformed response is below the line, the response is not transformed.

[0080] A three dimensional plot showing the effect of polysorbate 40 and Poloxamer 407 (when HG=2) on slope is shown in Figure 12.

[0081] In order to determine the levels of surfactants which result in maximum drug release rate, optimization is performed. As seen in Table XVI, when preparing a gel which contains between 0 to 0.4% polysorbate 40 and poloxamer 407, and 0 to 2% hexylene glycol, a slope of 13.53 can be obtained with 0.32% polysorbate 40, 0.18% poloxamer 407, and 2% hexylene glycol.

Table XVI.

Optimization of Drug Release Rate			
Factor	Range	Initial Setting	Optimal Value
Polysorbate 40	0 to 0.4	0.2	0.32
Poloxamer 407	0 to 0.4	0.2	0.18
Response			
Slope	Maximize	13.59	13.53

Correlation Between Solubility and Release

[0082] In order to investigate a possible correlation between drug solubility and the rate of drug release, a plot of slope of release profile vs. square root of solubility of drug in gel was constructed. The highest correlation coefficient obtained was 0.5553 which was for drug solubility in solutions without carbomer or base (Figure 13). Therefore, it was concluded that within the range of surfactant and cosolvent studied there was no correlation observed between drug release and solubility.

Maximizing Solubility and Release

[0083] The final statistical analysis involved the simultaneous optimization of the two responses studied; drug solubility and release rate. This analysis was performed in order to identify the concentration of the two surfactants and cosolvent which could be used in producing a gel with maximum solubility and release. RS/Discover® does not perform simultaneous optimizations, however it is possible to optimize one of the responses while constraining the range of the other response. This is an iterative process.

[0084] For this purpose, slope was maximized while the range of solubility was constrained. The results of the process are shown in Table XVII. It was concluded that a maximum slope of 12.02 can be obtained by preparing a gel containing 0.4% polysorbate 40, 0.0 % poloxamer 407, and 2% hexylene glycol. The range of drug solubility in this gel is calculated to be between 102 to 108 µg/ml.

Table XVII.

Simultaneous Optimization of Drug Solubility and Release Rate			
Factor	Range	Initial Setting	Optimal Value
Polysorbate 40	0 to 0.4	0.2	0.4
Poloxamer 407	0 to 0.4	0.2	0.0
Hexylene glycol	0 to 2	2	2
Response			
Slope	Maximize	13.59	12.02
Solubility	102to108 µg/ml	97.6 µg/ml	107.99 µg/ml

other ingredients were available at the same concentration for both gels.

[0089] Although there has been hereinabove described a stable gel formulation and method suitable for application in topical treatment of acne and psoriasis, in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

Claims

1. A stable gel formulation for topical treatment of skin conditions in humans, said stable gel formulation comprising:

   an active agent having activity for treatment of acne and psoriasis, said active agent comprising:

   Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl)] nicotinate; and
   a plurality of nonaqueous vehicles for both solubilizing said active agent and forming a gel therewith, said nonaqueous vehicles enabling topical application of the gel to a skin condition, said plurality of vehicles each being present in amounts, and in combination, to control solubility of the active agent in the gel and to control release of the active agent from the gel to the skin condition, said plurality of nonaqueous vehicles comprising three vehicles comprising Polysorbate 40, Poloxamer 407 and Hexylene glycol.

2. The formulation according to claim 1 wherein the vehicles are present in amounts selected to produce maximum solubility of the active agent in the gel.

3. A stable gel formulation according to claim 1 comprising:

   (a) water;
   (b) edetate disodium;
   (c) ascorbic acid;
   (d) Carbomer 934P;
   (e) Poloxamer 407;
   (f) polyethylene glycol;
   (g) Polysorbate 40;
   (h) hexylene glycol;
   (i) butylated hydroxytoluene;
   (j) butylated hydroxyanisole;
   (k) benzyl alcohol; and.
   (l) tromethamine.

4. The formulation according to claim 3 wherein the Polysorbate 40 is present in an amount up to about 0.4% by weight, Poloxamer 407 is present in an amount up to about 0.4% by weight, and hexylene glycol is present in an amount up to about 2% by weight.

5. The formulation according to claim 3 wherein the Polysorbate 40 is present in an amount of about 0.32% by weight, the Poloxamer 407 is present in an amount of about 0.18% by weight, and the hexylene glycol is present in an amount of about 2% by weight.

6. A method for preparation of a formulation for topical treatment of both acne and psoriasis comprising the steps of:

   1) mixing purified water, edetate disodium, ascorbic acid and Carbomer 934P until the carbomer is dispersed to form a part I;
   2) mixing purified water, Poloxamer 407 to form a part II;
   3) adding part II to part I and homogenizing part I and part II;
   4) mixing polyethylene glycol, Polysorbate 40, hexylene glycol, butylated hydroxytoluene and butylated hydroxyanisole and heating to dissolve same;
   5) cooling the mixture of step 4) to room temperature and adding benzyl alcohol and ethyl-6-[2-(4,4-dimethylthiochroman-6-yl]nicotinale thereto to form a part III;
   6) mixing purified water and tromethamine to form part IV;

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(54) **STABLE LIQUID INTERFERON FORMULATIONS**

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(21) Appl. No.: **10/397,108**

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(52) **U.S. Cl.** **424/85.6**; 604/500

(57) **ABSTRACT**

Liquid interferon compositions having a pH between 4.0 and 7.2 are described. The compositions comprise interferon-beta and a stabilizing agent at between about 0.3% and 5% by weight which is an amino acid selected from the group consisting of acidic amino acids, arginine and glycine. If needed, salt is added to provide sufficient ionic strength. The liquid composition has not been previously lyophilized or previously cavitated. The liquid is preferably contained within a vessel having at least one surface in contact with the liquid that is coated with a material inert to adsorption of interferon-beta. A kit for parenteral administration of a liquid interferon formulation and a method for stabilizing liquid interferon compositions are also described.

stored at room temperature minus the oxygen partial pressure of the nitrogen purged buffer blank. The percentage dissolved oxygen ("experimental"/"control") is always less than 30%.

[0105] Results:

[0106] IEF/Western blots and SDS-PAGE/Western blots of samples incubated at 37 degrees C. for two weeks indicate band shifting and loss of intensity as well as the presence of interferon multimers in samples containing PEG3350 and glutathione. After an additional week at 37 degrees C., glycerin excipient shows one extra band in our blots. Sucrose excipient shows loss of band intensity. This initial screening procedure allowed us to consider in more detail arginine-HCl, glycine, sodium chloride and mannitol for further studies.

EXAMPLE 5

[0107] Adsorption of Interferon

[0108] Thawed bulk interferon-beta is dialyzed to BG9589-1, 2, 3 and 4 (see Table 1) overnight at 2-8° C. with at least two buffer exchanges, then filtered prior to use. The protein concentrations are determined by absorbance at 280 nm (with extinction coefficient of 1.5 mg^{-1} $ml.cm^{-1}$). All the samples are diluted to final concentrations of approximately of 60 ug/ml. The diluted samples are filtered and filled either 0.5 ml into triplicate, 1.0 ml long, sprayed silicon BD syringes (Type I glass) with nitrogen flushed headspace or 0.75 ml into triplicate, 0.75 ml Type I glass vials with argon flushed headspace. Protein concentrations are determined by reverse phase HPLC (Example 1).

[0109] Results:

[0110] Table 3 below lists the protein concentrations that were determined by reverse phase HPLC. The data indicate that there is less protein for the samples that were filled into the glass vials as compared to the silicon coated prefilled syringes. Thus, siliconized syringes are used for the liquid formulation of interferon-beta.

TABLE 3

	Glass vial (ug/ml) (S.D)	Siliconized Syringes (ug/ml) (S.D)
BG9589-1	59.3 (2.6)	63.3 (2.5)
BG9589-2	58.3 (0.7)	61.7 (0.1)
BG9589-3	56.4 (0.4)	58.8 (1.1)
BG9589-4	55.5 (0.7)	59.3 (0.5)

EXAMPLE 6

[0111] Formulations at Physiological pH

[0112] Ionic Strength/Phosphate. We carried out initial studies in phosphate/sodium chloride, pH 7.2 buffer systems of varying buffer component concentrations in which the phosphate concentration varied between 10, 50 and 75mM with an ionic strength (defined by $I=\Sigma c_1 z_1^2$, where c_1 and z_1 are the molar concentration and valence charge of ionic species I, respectively) of 0.2, 0.4 and 0.6, adjusted by addition of sodium chloride.

[0113] We used a full factorial design on the variables of phosphate concentration (10, 50 and 75 mM) and ionic strength (I=0.2, 0.4, and 0.6). Compositions of sodium phosphate monobasic, sodium phosphate dibasic and sodium chloride (to achieve the desired ionic strength) in the buffers are calculated using a spreadsheet adapted from Ellis and Morrison, "Buffers of Constant Ionic Strength for Studying pH-dependent Processes", *Methods Enzymol.* 87: 405-426 (1982). The equations allowed determination of requisite amounts of each buffer component for specified pH, phosphate concentration and ionic strength. Each of the nine solutions used in the factorial experiment is obtained by buffer exchange of interferon-beta bulk intermediate through Pharmacia PD-10 desalting columns. The pHs of all resulting solutions are at 7.20±0.15. Concentrations are assayed by absorbance at 280 nm and then diluted to 150 ug/ml interferon-beta with the appropriate buffer. The resulting solutions are sterile filtered under argon through 0.22 micron filters, and 1.3 ml is aliquoted into 5 ml glass vials with an argon head space. Samples are incubated at 37 degrees C. for 6 days and run in triplicate. Samples are analyzed by percent transmittance at 580 nm, percent protein recovery, and IEF-PAGE/Western blots.

[0114] Results:

[0115] Analysis of percentage transmittance with respect to varying ionic strength shows a trend toward increasing transmittance (i.e, decreasing amounts of insoluble protein aggregates) with increasing ionic strength. Percent protein recovery data shows a similar trend although IEF-PAGE Western blots show no trend in deamidation with varying ionic strength so that all the samples are equally deamidated. Thus, after storage for six days at 37 C., samples tended to show less aggregation with decreasing phosphate concentration and increasing ionic strength. The results of the experiments on the percentage transmittance and percent recovery as a function of varying phosphate concentration (not presented here) show a weak trend towards decreasing % transmittance with increasing phosphate concentration, but an analysis of variance shows no significant difference in the means of samples with different phosphate concentrations. The percentage recovery data show improved protein recovery for lower phosphate concentrations (a significant difference at the 94% confidence level). IEF-PAGE Western blots display no discernible trend in deamidation with varying phosphate concentration.

[0116] Excipient/Salt Ratio. Preliminary studies (not shown) indicated that some excipients may require salts (e.g., sodium chloride) in order to maintain high ionic strength and in order to exhibit a stabilizing effect at pH 7.2. We designed a factorial study using excipients (glycine, lysine, arginine, sucrose and mannitol) and fraction of sodium chloride contributing to isotonicity (f salt =0, 0.25, 0.75 and 1.0). The fraction is calculated by: $f_{salt}O_{salt}/(O_{salt}+O_{excipient})$, where O_{salt} and $O_{excipient}$ are the osmolalities in mOsmlkg of the sodium chloride and excipient, respectively, in the solution. Salt fraction provides a means of comparing salt effects across different excipients. All samples contained additives to isotonicity, with varying ratios of excipient:salt (as defined by f_{salt}).

[0117] Ten percent (w/v) stock solutions of each excipient in 20 mM phosphate, pH 7.2, are prepared, degassed, and sparged with argon. A stock solution of 250 mM sodium chloride, 20 mM phosphate, pH 7.2 is prepared, degassed and sparged with argon. Bulk interferon-beta intermediate is extensively dialyzed against argon-sparged 20 mM phos-

[0141] Study Conduct. As prophylaxis against interferon-associated flu-syndrome, all subjects will receive acetaminophen immediately before and throughout the dosing periods.

[0142] Pharmacokinetics.

[0143] Serum Interferon beta Determinations. Serum levels are measured as units of antiviral activity by a (CPE) assay. Serum antiviral levels are analyzed for AUC, C_{max} and T_{max}. AUC values will be calculated from time of dosing to the last detectable level (AUC_{0-T}) and through 144 hours post dose (AUC_{0-144}). Standard descriptive analysis of the treatment data are conducted using SAS (version 6.08, SAS Institute, Cary, N.C.).

TABLE 5

Dose schedule for Exemplary Study

Dose Group	Route	Dose (MU)	Treatment Period: 1	Treatment Period: 2
1	IM	12	Lyophilized (60 mcg)	Liquid (60 mcg)
2	IM	12	Liquid (60 mcg)	Lyophilized (60 mcg)

[0144] Pharmacodynamics. The biological marker neopterin, a product of the interferon induced enzyme GTP cyclohydrolase which reflects macrophage and T-cell activation (C. Huber et al., *J Exp Med* 1984; 160: 310-314; Sep. 20, 1996; D.Fuchs et al., *Immunol. Today* 9: 150-155, 1988) has been characterized. In both nonclinical and clinical studies of recombinant human interferon beta, induction of neopterin correlates with serum activity levels following administration of various recombinant human interferon beta treatments.

[0145] Neopterin is measured via standard laboratory procedures. The pharmacodynamic profile of interferon-beta is described in a quantitative manner by calculation of three serum neopterin parameters. The first parameter, E_{AUC}, is the area under the neopterin vs time curve normalized to baseline level. The second parameter is E_{MAX}; this parameter is the difference between the observed peak neopterin level and the baseline neopterin level. The third parameter is the induction ratio, R; this parameter is calculated as the peak neopterin level divided by the baseline neopterin level.

[0146] Statistics. The Wilcoxon-Mann-Whitney two, one-sided tests procedure is used on AUC to determine equivalence. To estimate the relative bioavailability of interferon from the liquid formulation relative to the lyophilized formulation and its 90% confidence limits, AUC is submitted to an analysis of variance (ANOVA) after logarithmic transformation. From the "between-subject" variation, the sequences and genders are isolated. From the "within-subjects" variation, components due to periods and treatments are isolated.

[0147] Equivalents

[0148] Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed therein. It is intended that the specification and examples be considered exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

1. A liquid composition comprising an interferon and a stabilizing agent at between about 0.3% and 5% by weight which is an amino acid selected from the group consisting of acidic amino acids, arginine and glycine, wherein the liquid composition has not been previously lyophilized.

2. The liquid composition of claim 1, further comprising a vessel containing said liquid composition, the vessel having at least one surface coated with a material inert to interferon.

3. The liquid composition of claim 1, wherein the interferon is a interferon-beta, or a recombinantly produced interferon.

4. The liquid composition of claim 1 having a pH between about 4.0 and about 7.2.

5. The liquid composition of claim 4, having a pH of 4.8 to 5.2.

6. The liquid composition of claim 5, having a pH of 5.0.

7. The liquid composition of claim 5 wherein the acidic amino acid is glutamic acid.

8. The liquid composition of claim 1, wherein the arginine is arginine-HCl.

9. The liquid composition of claim 1 having an interferon concentration between about 6 IMU/ml and 50 IMU/ml.

10. The liquid composition of claim 2, wherein said at least one surface of the vessel is coated with a material selected from the group consisting of silicone and polytetrafluoroethylene.

11. The liquid composition of claim 10, wherein the vessel is a syringe.

12. A 20 mM acetate buffer at pH 5.0 that includes interferon-beta plus a stabilizing agent selected from the group consisting of: (a) 150 mM arginine; (b) 100 mM sodium chloride and 70 mM glycine; (c) 150 mM arginine and 15 mg/ml human serum albumin; (d) 150 mM arginine and a surfactant; (d) 140 mM sodium chloride; (e) 140 mM sodium chloride and 15 mg/ml human serum albumin; and (f) 140 mM sodium chloride and a surfactant, wherein the buffer has not been previously lyophilized.

13. The buffer of claim 12, wherein the surfactant is 0.1% (w/v) Pluronic F-68.

14. The buffer of claim 12, wherein the arginine is arginine-HCl.

15. The buffer of claim 12, further comprising a vessel containing said buffer, wherein at least one surface of the vessel in contact with the buffer is coated with a material selected from the group consisting of silicone and polytetrafluoroethylene.

16. The buffer of claim 15, wherein the vessel is a syringe.

17. A liquid composition at pH 5.0 that comprises interferon-beta and 170 mM L-glutamic acid, the liquid not previously lyophilized.

18. The liquid composition of claim 1, comprising the amino acid glycine and further comprising a salt.

19. The liquid composition of claim 17, further including ingredients selected from the group consisting of 15 mg/ml human serum albumin and 0.1% (whv) Pluronic F-68.

20. A 20 mM phosphate buffer at pH 7.2 including interferon-beta plus a stabilizing agent selected from the group consisting of: (a) 140 mM arginine; and (b) 100 mM sodium chloride combined with 70 mM glycine, wherein the buffer has not been previously lyophilized.

21. The liquid composition of claim 20, further comprising a vessel containing said liquid, wherein at least one

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(54) **OPHTHALMIC SOLUTION BASED ON DICLOFENAC AND TOBRAMYCINE AND ITS APPLICATIONS**

OPHTHALMISCHE LÖSUNG, DIE DICLOFENAC UND TOBRAMYCIN ENTHÄLT, UND IHRE VERWENDUNG

SOLUTION OPHTALMIQUE A BASE DE DICLOFENAC ET TOBRAMICINE, ET SES APPLICATIONS

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under the same conditions of single solutions with tobramycin (0.3%) or with sodium diclofenac (0.5%) has permitted to observe, that in the former case, a clear and transparent solution was obtained, whilst in the latter case, this was not possible, and only a cloudy solution could be obtained. All the formulations have been studied with the same quantity (0.01%) of one of the quaternary ammoniums used in ophthalmology, benzalkonium chloride (BAC). Solid particles without dissolving have also been observed when preparing a formulation which includes 0.1% of sodium diclofenac, which is the concentration generally used in ophthalmology. The presence of particles in suspension may be due to the following reasons:

- The insolubility of the sodium diclofenac under the experimental conditions used.
- The formation of an interaction between some of the dissolution components, as for example, between the diclofenac and the tobramycin, since when elaborating the formulation which only includes the tobramycin as active principle, a clear and transparent solution is obtained.

[0010] Paying attention to the bibliographic data consulted [(10) Morimoto, Y., Hatanaka, T. and Sugibayashi, K. and Omiya, H. Prediction of Skin Permeability of Drugs: Comparison of Human and Hairless Rat Skin. J. Pharm. Pharmacol 1992; 44:634- 6 39; (11) Kriwet, K. and Müller-goymann, C. binary Diclofenac Diethylamine-water systems: Micelles, vesicle and lyotropic liquid crystals. Eur J.Pharm, Biopharm. 1993; 39 (6) :234-238] the first reason can be emphasized, since at the working pH (7.4 ± 0.4), the diclofenac, presents a greater solubility to the concentration used in the experiments.

[0011] With the object of confirming the second possibility, formulations have been prepared with 0.1% (concentration generally used in ophthalmology) of sodium diclofenac, 0.3% of tobramycin (concentration generally used in ophthalmology), 0.01% of BAC, 1.0% of Octoxynol 40 (maximum concentration claimed in EP-A-0390071) and adjusting the pH to 8.0 (maximum value specified in EP-A-0390071). Two additional formulations have been prepared in parallel, one exclusively with sodium diclofenac as active principle, and the other only with tobramycin as active principle. Samples of the three formulations have been placed at 4 and 22ºC in order to follow the evolution thereof under critical conditions, from the point of view of the appearance of precipitates (4ºC), though realistic from the point of view of the conditions under which a preparation may be found during the life time of a pharmaceutical product, and under normal shelf-life conditions (22ºC). In the case of the formulation with the two active principles, the appearance of precipitates has been observed in a time < than 41 days, whilst in the other two formulations it has not been so. No appearance of precipitates has been observed at environmental temperature in any case whatsoever.

[0012] The precipitate formulated, was separated, and has been analyzed, with the detection in the same, of the presence of sodium diclofenac and tobramycin, both by thin layer chromatography and HPLC and by I.R. spectrography. The IR spectrum of the precipitate shows characteristic bands of each one of the active principles which are not found in the spectra of the individual components (see Figure 1). The DSC analysis of the precipitate shows a profile which is clearly differentiated from the one obtained with the individual components, as well as the profile obtained of the simple physical mixture of sodium diclofenac and tobramycin (see Figure 2).

[0013] The appearance of precipitation in a time < to 3 days has also been observed, even at 22ºC, with a formulation which contains 0.15% sodium diclofenac, 0.45% tobramycin, 1.0% OCTOXYNOL 40 and in which the pH has been adjusted to 8. These concentrations which are included in the claims of EP-A-0390071, were selected because it was considered that they are the maximums at which a formulation may be found with the normal concentrations of diclofenac and tobramycin in ophthalmology, 0.1% and 0.3% respectively, considering the need of having specifications for the elaboration of the formulations, the potential requirement of overdoses of the same, complying with the stability of the molecules [(6) Vademecum International (1993). 34th Edition. Medicom; (12) U.S.P. XXII (1990). United States Pharmacopeial Convention, INC:;(13) Brandl, M. and Gu, L. Degradation of Tobramycin in aqueous solution. Drug Development and Industrial Pharmacy, 1992; 18(3):1423-1436.] and to the concentration of the formulations by losses due to evaporation from the containers used generally for these products.

[0014] With the object of determining more widely, at which experimental conditions a clear and transparent solution cannot be obtained, a study has been conducted on the influence of the sodium diclofenac concentration, the OCTOXYNOL concentration and the pH in the combination of sodium diclofenac-tobramycin in the presence of BAC. As range for the sodium diclofenac concentrations, values comprised within 0.05 and 0.5% have been selected, values which include the values generally used in ophthalmology and which are included in the concentrations claimed in EP-A-0390071. As OCTOXYNOL concentrations, values comprised within 0.01 and 1.0% have been selected, this latter value being the one which corresponds with the maximum value claimed in EP-A-0390071. The pH studied have been 6, 7 and 8, values which coincide with the ones specified in EP-A-0390071. The concentration of tobramycin and BAC has been established in all cases at 0.3 and 0.01% respectively. The rest of the components have been set in all cases and corresponded to the examples specified in EP-A-0390071. The initial experimental plan has corresponded with a factorial design 3^3 and as incidences have been observed, new formulations have been considered in order to limit the experimental conditions under which the formation of a clear and transparent solution containing sodium diclofenac

United States Patent [19]

Katz

[11] **Patent Number: 5,070,107**

[45] **Date of Patent: Dec. 3, 1991**

[54] **SYSTEMIC ANTIVIRAL TREATMENT**

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[73] Assignee: **Lidak Pharmaceuticals**, La Jolla, Calif.

[21] Appl. No.: **430,822**

[22] Filed: **Nov. 2, 1989**

Related U.S. Application Data

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[52] **U.S. Cl.** **514/724**; 514/936; 514/944; 514/965; 514/966; 514/967; 514/969; 424/434; 424/435; 424/436; 424/449

[58] **Field of Search** 514/724, 739, 936, 944, 514/965, 966, 967, 969; 424/434, 435, 436, 449

[56] **References Cited**

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Primary Examiner—Nathan M. Nutter
Attorney, Agent, or Firm—Grant L. Hubbard

[57] **ABSTRACT**

Systemic antiviral treatment using a narrow class of aliphatic straight-chain saturated monohydric alcohols which have from 27 to 32 carbons in the chain in physiologically compatible compositions for injection or trans-mucus membrance introduction into humans and other mammals is disclosed.

13 Claims, 1 Drawing Sheet

Patent strategy

Chain length	Treatment	Patent
C27-C32	Antiviral	US5070107
C20-C26	Antiviral	US5071879
C27-C32	Antiinflammatory	US5166219
C20-C26	Antiinflammatory	US5194451

US006326458B1

(12) **United States Patent**
Gruber et al.

(10) **Patent No.: US 6,326,458 B1**
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(54) **CONTINUOUS PROCESS FOR THE MANUFACTURE OF LACTIDE AND LACTIDE POLYMERS**

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(58) **Field of Search** 528/354, 357, 528/361; 525/415; 526/67, 68; 549/274

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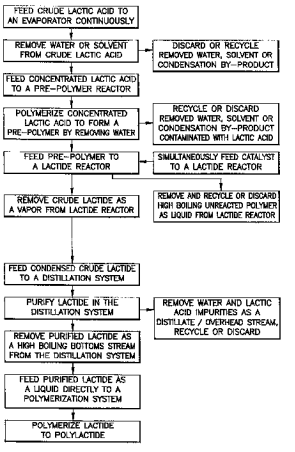
Primary Examiner—Shelley A. Dodson
(74) *Attorney, Agent, or Firm*—Merchant, Gould, Smith, Edell, Welter & Schmidt, P.A.

(57) **ABSTRACT**

A process for the continuous production of substantially purified lactide and lactide polymers from lactic acid or an ester of lactic acid including the steps of forming crude polylactic acid, preferably in the presence of a catalyst means in the case of the ester of lactic acid, to form a condensation reaction by-product and polylactic acid, and depolymerizing the polylactic acid in a lactide reactor to form crude lactide, followed by subsequent purification of the crude lactide in a distillation system. A purified lactide is then polymerized to form lactide polymers.

17 Claims, 6 Drawing Sheets



technique of Example 1. In each case, a projected molecular weight which the polymer would achieve at 100% conversion was determined by GPC analysis of the highest conversion sample and corrected for the unconverted monomer. This method has been shown to give reproducible values and accurately corrects for any effect of sampling at different conversion levels. The results of the experiments are tabulated below and shown graphically in FIG. **3**.

Temperature (° C.)	Hydroxyl impurities meq/mol	Molecular weight, adjusted to 100% conv.
173	4.45	40,100
173	2.52	77,500
186	3.90	37,800
186	2.38	72,100
199	3.98	39,400
199	2.48	74,900

A statistical analysis of variance showed that the molecular weight of the polymer was controlled solely by the level of impurities, with temperature having no effect. Thus, in a preferred embodiment hydroxyl impurities are controlled to desired levels to control the physical properties of the resulting polymer product.

EXAMPLE 3

Polymer Molecular Weight is Controlled by Impurity Level and is Nearly Independent of Catalyst Concentration

The polymers were prepared at 160° C. using the polymerization technique of Example 1. Two levels of water (H=5.9–8.8 meq./mol., L=1.8–3.7 meq./mol.) and two levels of lactic acid (H=0.9–1.3 meq./mol., L=0.1–0.2 meq./mol.) were used in a duplicated factorial design experiment at each of two different levels of catalyst (0.0002 mol/mol; and 0.0004 mol/mol) (eight experiments total). Projected molecular weights were calculated as in Example 2. The results are shown in tabular form below and graphically in FIG. **4**.

Water conc.	Impurity level Lactic acid	Total Hydroxyl Content meq/mol	Molecular weight adjusted to 100% conversion	Catalyst Level
L	L	4.49	133,500	0.002
H	H	11.35	33,900	0.002
L	H	5.36	74,500	0.002
H	L	9.20	29,400	0.002
L	H	4.65	89,800	0.004
H	H	8.31	34,900	0.004
L	L	2.52	160,600	0.004
H	L	8.89	32,700	0.004

An analysis of variance revealed that the change in hydroxyl content accounted for 91% of the variance in the molecular weight, while the change in catalyst concentration accounted for only 4% of the variance. Both effects were found to be statistically significant.

These data show, in a preferred embodiment, the critical need to control the level of hydroxyl containing impurities in the lactide in order to control the molecular weight of the final polymer.

EXAMPLE 4

Equilibrium Concentration of Lactide in Polylactic-Acid

PLA of 650 MW was heated at atmospheric pressure with either 0.00, 0.05, or 0.15 wt % SnO as a catalyst. The mixtures were held at three different desired temperature for 20 minutes, at which time 10 wt % of purified L-lactide was added to the mixture with stirring. The vessel was fitted with a condenser to prevent the loss of water or other volatile components. Samples were removed from the reaction vessel at times ranging from 5 minutes to 450 minutes and were analyzed using an Ultrastyragel® 100A GPC column (Waters Chromatography, a division of Millipore Corp.) with THF as the mobile phase to determine the concentration of lactide. The concentration data were fit to a simple first order decay model using a non-linear regression software package (SAS Institute, Inc.) to determine the equilibrium values. The resulting projected values for the equilibrium concentrations of lactide are shown in the table below and plotted graphically in FIG. **5**. The results show the beneficial effect of rapid removal of lactide from the lactide reactor in preferred embodiments to further drive the lactide generation reaction.

Temperature (° C.)	Catalyst conc., wt %	Equilibrium lactide, wt %
140	0.05	3.50
140	0.15	3.30
170	0.05	4.00
170	0.05	3.57
170	0.15	4.13
170	0.15	3.85
200	0.00	5.12
200	0.05	5.38
200	0.05	4.82
200	0.15	5.47
200	0.15	5.20

EXAMPLE 5

Relative Rates of Racemization

Samples of PLA (with and without SnO as catalyst) and lactide were heated and stirred for four hours at 200° C. at atmospheric pressure in a round bottom flask fitted with a condenser to prevent loss of volatile components. The samples were then allowed to cool and the optical purity of the PLA was determined by saponification followed by a measurement of the optical rotation. The lactide sample was analyzed by GC to determine the meso-lactide content, which was then converted to a measurement of optical purity

	Optical Composition	
Sample	% L	% D
Initial PLA	96.0	4.0
PLA, no catalyst	95.4	4.6
PLA, 0.05 wt % SnO	87.5	12.5
PLA, 0.15 wt % SnO	90.0	10.0
Initial lactide	99.7	0.3
Lactide after heating	97.2	2.8

The results of this experiment demonstrate that racemization occurs fastest in PLA which is exposed to catalyst. Thus, in the most preferred embodiment racemization is controlled in the lactide generating reactor. It is however recognized that another area of racemization control will be the evaporators which are used to prepare PLA, because of the long residence times and the possible inclusion of catalyst and catalyzing impurities. In a preferred embodi-

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(54) Title: ENCAPSULATION OF FOOD INGREDIENTS

(57) Abstract: Oxygen sensitive oils or oils containing oil soluble oxygen sensitive substances are encapsulated in proteins which have been reacted with carbohydrates that contain reducing sugar groups. An aqueous mixture of a protein preferably casein and a carbohydrate preferably a sugar is heated within the range of 60 to 160 °C so that Maillard reaction products are formed in the aqueous mixture. The oil phase, up to 50 % by weight is then emulsified with the aqueous phase to form micro encapsulated oil particles. The formation of MRP may also be done after emulsification prior to drying. The emulsions can be used as food ingredients or dried to form powders.

and this result in the formation of a more uniform protein layer at the interface, which results in a better emulsion.

Table 2.6 Characteristics of emulsions with oil added at different stages during preparation.

Emulsion Total solids	% Protein-% Sugar Concentration at heating	Heat Treatment of Protein solution	Emulsion Size D (0.5) μm
14.3% tuna oil, Na-caseinate-lactose-sucrose system with 0.12% carrageenan (36% total solids)			
Ncas:carra:lac:suc:**oil** [1]	12 - 0	60°-30 min	0.75
Ncas:**oil**:carra:lac:suc[2]	12 - 0	60°-30 min	0.74
14.3% tuna oil, Na-caseinate-lactose-sucrose system with 0.12% pectin (36% total solids)			
Ncas:HMP:lac:suc:**oil**[1]	12 - 0	60°-30 min	0.63
Ncas:**oil**:HMP:lac:suc[2]	12 - 0	60°-30 min	0.53
21.4% tuna oil, Na-caseinate-lactose-sucrose system with 0.12% pectin (36% total solids)			
Ncas:**oil**:HMP:lac:suc[2]	8 - 0	60°-30 min	0.59
21.4% tuna oil, WPI-lactose-sucrose system (36% total solids)			
WPI:lac:suc:**oil**[1]	7 – 0	90°C-30 min	0.77
WPI:**oil**:lac:suc[2]	7 – 0	90°C-30 min	0.74

[1]*Oil was added after all the sugars were added,* *HMP "high methoxy pectin";*

[2]*Oil was added before all the sugars were added* *carra "carrageenan"*

Example 3

To illustrate the effect of different processing conditions on 60% tuna oil powder characteristics with Casein-sugar Maillard reaction products (MRPs) as encapsulant

Powders containing 60% tuna oil, were prepared using Maillard Reaction Products produced from the reaction of casein and sugars as encapsulants. A combination of different processing variables were chosen using fractional factorial design to investigate on the effects of these variable on the powder properties and stability during storage. The oils were emulsified into the protein-sugar mixtures that had been heated for at least 90°C for 30 minutes or by

refluxing the mixture for 90 minutes. The emulsions were then homogenised and subsequently dried into powders. The free fat content of the powders was determined after powder production and these ranged from 1-20% which was greatly affected by the combination of processing variables used. Samples of powder (80g) were stored in 2 litre plastic containers to provide sufficient oxygen in the headspace to accelerate oxidation of the samples. These were stored at 35°C for 4 weeks. Propanal, was determined using gas chromatography (GC) (static headspace analysis).

The encapsulation efficiency and powder stability can therefore be optimised by choosing the right combination of processing variables and formulation (Table 3).

Effect of pH:

The effect of pH (6.5 to 7.5) on propanal headspace concentration was significant ($p<0.001$). This result suggested that pH of the aqueous casein-sugar solution at the time of heating was very important. The results clearly showed this trend where increasing pH from 6.5 to 7.5 reduced the propanal concentration. This pH effect was consistent with the different sugars used, with the change in casein-sugar ratio from 1:1 to 1:2, and also when all or part of the sugar was heated (Table 3)

Effect of sugar concentration at time of heating to form MRP

The effect of sugar concentration at time of heating on powder free fat was significant ($p=0.019$). When sugar concentration at time of heating is increased from 2.5% to 12% the resulting powders had lower propanal during storage. This effect is more significant when the protein to sugar ratio is also much lower (Table 3)

Effect of casein-sugar ratio

The effect of casein-sugar ratio on propanal was significant ($p=0.025$). The results showed lower propanal concentration in stored powders, when the amount of sugars are increased in the formulation. This suggests that powders with casein-sugar ratio of 1:2 were more stable against oxidation than powders with casein sugar ratio of 1:1 (Table 3).

Claims

1. A powder containing an oxygen sensitive oil obtained by drying an emulsion of the oil, wherein the oil is encapsulated within a film forming protein which, prior to drying to form the powder, has been heated in solution, in the presence of a carbohydrate, for a time to provide sufficient Maillard reaction products to provide resistance to oxidation.
2. A method of forming an emulsion of an oxygen sensitive oil which includes the steps of :

a) preparing an aqueous mixture of a protein and a carbohydrate which contains a reducing sugar group

b) heating the mixture from 60°C to 160°C for a period to allow sufficient Maillard reaction products to form without coagulation

c) dispersing said oil in the aqueous phase.

d) homogenising the mixture to obtain an emulsion

3. A method as claimed in claim 2 in which at least some of the carbohydrate is added after the emulsion is formed and step b) is carried out after step d).
4. A method as claimed in claim 2 in which the total solids at homogenisation is less than 50 % and the protein:carbohydrate ratio is between 1:4 and 4:1.
5. A method of forming a powder containing an oxygen sensitive product which includes steps a) to d) defined in any one of claims 2 to 4 followed by drying the emulsion to form a powder
6. Powders obtained by the method of claim 5
7. Powders as claimed in claim 6, which are coated with a substance to alter the release properties of the powder.
8. An emulsion obtained by the method of claim 2.
9. An emulsion of an oxygen sensitive substance encapsulated in a film forming soluble protein which has been reacted with sufficient carbohydrate to form Maillard reaction products in the encapsulation material.
10. An emulsion of an oxygen sensitive substance encapsulated in a mixture of a milk protein containing a major portion of casein and a carbohydrate having a reducing sugar group which has been heated for a time to form sufficient Maillard reaction products to impart antioxidant activity to the encapsulating mixture.

Preformulation work - Input data

Target

Select the best suitable excipients from the point of view of drug stability at an early stage.

Methodology

The active substance is mixed with different excipients in powder form and stored at different temperatures for a given period of time. The drug substance is subsequently analysed for degradation products.

The stability of the active ingredient depends not only on the excipients but also on their interactions.

Sandoz, Pharm.Acta Helv., 1975, 50, 88-91

Preformulation work - Input data

Basic formulation

Filler	70 %
Lubricant	5 %
Disintegrant	20 %
Binder	5 %

Factors

A: Filler (lactose, mannitol)
B: Lubricant (stearic acid, Mg stearate)
C: Disintegrant (maize starch, microcrystalline cellulose)
D: Binder (PVP, gelatine)
E: Humidity (no water added, with 3 % water added)

Response

Y: % intact drug substance after 4 weeks at 50°C

Preformulation work- Results matrix

Exp.	A	B	C	D	E	Y
1	lactose	stearic acid	starch	PVP	Yes	59.6
2	mannitol	stearic acid	starch	PVP	No	86.4
3	lactose	Mg stearate	starch	PVP	No	95.0
4	mannitol	Mg stearate	starch	PVP	Yes	97.0
5	lactose	stearic acid	cellulose	PVP	No	83.4
6	mannitol	stearic acid	cellulose	PVP	Yes	53.8
7	lactose	Mg stearate	cellulose	PVP	Yes	93.7
8	mannitol	Mg stearate	cellulose	PVP	No	99.7
9	lactose	stearic acid	starch	gelatine	No	54.1
10	mannitol	stearic acid	starch	gelatine	Yes	45.8
11	lactose	Mg stearate	starch	gelatine	Yes	92.8
12	mannitol	Mg stearate	starch	gelatine	No	96.1
13	lactose	stearic acid	cellulose	gelatine	Yes	53.6
14	mannitol	stearic acid	cellulose	gelatine	No	64.7
15	lactose	Mg stearate	cellulose	gelatine	No	94.0
16	mannitol	Mg stearate	cellulose	gelatine	Yes	96.3

Experiments carried out in a random order.

Preformulation work - Conclusions

The recommended excipients are:

Lactose, mannitol, Mg stearate, starch, microcrystalline cellulose, PVP.

In the presence of humidity, magnesium stearate has a stabilizing effect on the drug substance.

To improve the compatibility of gelatine, it should be combined with Mg stearate.

The drug substance is incompatible with stearic acid, as well as gelatine and sensitive to moisture.

Excipient compatibility - Input data

Target

Determine the compatibility of the excipients with the active pharmaceutical ingredient and also to find out if the stability is improved or worsened by including one excipient rather than another in the same class.

Factors

A: Diluent (lactose, Ca phosphate, microcrystalline cellulose)
B: Disintegrant (starch, Na starch glycolate, crospovidone)
C: Binder (PVP, HPMC, none)
D: Lubricant (Mg stearate, stearic acid, glyceryl behenate)

Response

Y: degradation in samples stored for 1 month at 50°C and 50% relative humidity

Lewis *et al*, Pharmaceutical experimental design, 1999, Marcel Dekker, New York

Excipient compatibility - Results matrix

Exp.	A	B	C	D	Y
1	lactose	starch	PVP	Mg stearate	4.0
2	lactose	NaSG	HPMC	Glyc. Behenate	3.9
3	lactose	crospovidone	none	stearic acid	3.3
4	Ca phoshate	starch	HPMC	stearic acid	4.0
5	Ca phoshate	NaSG	none	Mg stearate	4.2
6	Ca phoshate	crospovidone	PVP	Glyc. Behenate	3.8
7	cellulose	starch	none	Glyc. Behenate	0.4
8	cellulose	NaSG	PVP	stearic acid	3.1
9	cellulose	crospovidone	HPMC	Mg stearate	1.6

Experiments carried out in a random order.

Excipient compatibility - Conclusions

The most suitable excipients are:

Diluent: cellulose
Disintegrant: starch or crospovidone
Binder: none
Lubricant: glyceryl behenate

Daily examples (7)

The following excipient mixture surprisingly stabilizes an unstable active ingredient in a tablet formulation:

- Microcrystalline cellulose
- Starch
- Hydroxypropylmethylcellulose
- Magnesium stearate

Would it be possible to identify other suitable excipients?

Fractionated factorial design

Tablet optimization – Input data

Target

Develop a tablet composition optimized for direct compression containing DUP753 as active ingredient.

Requirements

Each tablet must be uniform in weight (flowability)
Active component readily available as needed (solubility)
Formulation physically and chemically stable (excipients)
Mechanical integrity
Method of manufacture efficient, reproducible, automation
Elegant appearance and aesthetically pleasing

Merck & Co, EP0511767-A1

Tablet optimization - Input data

Constraints

Manufacturing method: direct compression

Active ingredient DUP753: 33 %

Excipients

Previous trials were used to select excipients and levels:

Microcrystalline cellulose: excellent compactability

Magnesium stearate: excellent lubricant

Lactose: to prevent overlubrication

Pregelatinized starch: improvement of bulk density

Tablet optimization - Input data

Design

2^3 factorial: three factors at two levels

Filler mixture design: one of the factors (filler variable), is allowed to vary such that the % of the remaining factors plus the % of the filler variable equals 100 % of a fixed total.

Factors

Microcrystalline cellulose: 20 – 35 %
Lactose: 10 – 30 %
Magnesium stearate: 0.5 – 0.8 %
Pregel starch: filler to 100 %

Tablet optimization - Input data

Responses

Dissolution rate: % dissolved / minute, desirable 5 %/min

TS/AF: tensile strenght/applied force, high value

Friability: %

ESS: Ejection force/contact area

Dissolution: seconds

Tablet optimization – Effects

Dissolution rate: lactose, microcystalline cellulose

TS/AF: mycrocrystalline cellulose

Friability: no significant factor

ESS: lactose

Dissolution time: microcrystalline cellulose

Tablet optimization

Conclusion

Optimized formulation

Microcrystalline cellulose	35.0 %
Lactose	17.5
Magnesium stearate	0.8
Pregel starch	13.37
DUP753	33.33

Tablets had TS/AF = 257.1 kPa/kN and were suited for film coating

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(54) **Tablets containing compound DUP753.**

(57) An optimized direct compression tablet formulation comprises in parts by weight from about 10% to about 45% of 2-butyl-4-chloro-1[(2'(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole, from about 20% to about 40% microcrystalline cellulose, from about 10% to about 30% lactose, from about 0.5% to about 0.9% magnesium stearate, and from about 5% to about 35% pregel starch.

EP 0 511 767 A1

EXAMPLES 3-12

The following Table shows various additional acceptable formulations of the present invention wherein all ingredients are varied in quantity except DUP 753 which is maintained at 33.3%.

Factorial design using three factors at two levels, including central point

	Avicel (%)	Lactose (%)	Mag. St. (%)	StaRx (%)	Disltn.[1] (% diss/min)	TS/AF (kPa/kN)	Wt. (%)	Friability (%)	ESS[2] (N/cm2)	Disltn. (seconds)
3	20.00	10.00	0.50	36.17	6.45	144	1.16	0.91	641	420
4	20.00	10.00	0.80	35.87	6.23	95	1.09	0.77	605	406
5	20.00	30.00	0.50	16.17	6.27	103	0.95	0.87	1301	382
6	20.00	30.00	0.80	15.87	6.16	165	1.22	0.64	1026	447
7	35.00	10.00	0.50	21.17	5.68	229	0.81	0.80	862	432
8	35.00	10.00	0.80	20.87	5.92	225	0.89	0.85	833	478
9	35.00	30.00	0.50	1.17	3.22	248	1.20	0.59	1204	501
10	35.00	30.00	0.80	0.87	3.31	299	0.82	0.59	1115	500
11	27.50	20.00	0.65	18.52	5.92	212	0.90	0.56	752	446
12	27.50	20.00	0.65	18.52	5.66	214	0.65[a]	0.55	764	436

Fixed Factors: DRUG = 33.33

[a] Due to technical difficulties, weight variation for this run was excluded from the analysis

[1] Disltn. (% diss./min): A dissolution rate at least of 5% dissolved/min. is desirable.

[2] $ESS = \frac{\text{Ejection Force}}{\text{Contact Area}} = \frac{EF}{\int dt}$

Claims

1. A formulation suitable for forming a direct compression tablet comprising in parts by weight from about 20% to about 40% microcrystalline cellulose, from about 10% to about 30% lactose, from about 0.5%

EXAMPLES 3-12

The following Table shows various additional acceptable formulations of the present invention wherein all ingredients are varied in quantity except DUP 753 which is maintained at 33.3%.

	Avicel (%)	Lactose (%)	Mag. St. (%)	StaRx (%)	Disltn.[1] (% diss/min)	TS/AF (kPa/kN)	Wt. (%)	Friability (%)	ESS[2] (N/cm2)	Disltn. (seconds)
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4	20.00	10.00	0.80	35.87	6.23	95	1.09	0.77	605	406
5	20.00	30.00	0.50	16.17	6.27	103	0.95	0.87	1301	382
6	20.00	30.00	0.80	15.87	6.16	165	1.22	0.64	1026	447
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8	35.00	10.00	0.80	20.87	5.92	225	0.89	0.85	833	478
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10	35.00	30.00	0.80	0.87	3.31	299	0.82	0.59	1115	500
11	27.50	20.00	0.65	18.52	5.92	212	0.90	0.56	752	446
12	27.50	20.00	0.65	18.52	5.66	214	0.65[a]	0.55	764	436

Fixed Factors: DRUG = 33.33

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[1] Disltn. (% diss./min): A dissolution rate at least of 5% dissolved/min. is desirable.

[2] $ESS = \frac{\text{Ejection Force}}{\text{Contact Area}} = \frac{EF}{\int dt}$

Claims

1. A formulation suitable for forming a direct compression tablet comprising in parts by weight from about 20% to about 40% microcrystalline cellulose, from about 10% to about 30% lactose, from about 0.5%

to about 0.9% stearic acid, magnesium or calcium stearate, sodium stearyl fumarate or talc from about 5% to about 35% pregel starch, and from about 10% to about 45% 2-butyl-4-chloro-1-[(2'(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)-imidazole.

2. A tablet formed from a formulation according to claim 1.

3. A formulation according to claim 1 wherein the amount of 2-butyl-4-chloro-1-[(2'(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-5-hydroxymethyl)-imidazole is about 33.33%.

4. A tablet formed from a formulation according to claim 3.

5. A formulation according to claim 3 containing about 35% microcrystalline cellulose, from about 17% to about 17.5% lactose, from about 0.7% to about 0.8% magnesium stearate from about 13.37 to about 13.97 pregel starch, and about 33.33% 2-butyl-4-chloro-1-[(2'(1H- tetrazol- 5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole.

6. A tablet formed from a formulation according to claim 5.

7. A composition according to claim 5 containing about 35% microcrystalline cellulose, about 17.5% lactose, about 0.8% magnesium stearate, about 13.37% pregel starch and about 33.33% 2-butyl-4-chloro-1-[(2'(1H- tetrazol- 5-yl)biphenyl-4-yl)-methyl]-5-hydroxymethyl)imidazole.

8. A tablet formed from a formulation according to claim 7.

9. A composition according to claim 5 containing about 35% microcrystaline cellulose, about 17% lactose, about 0.7% magnesium stearate, about 13.97% pregel starch and about 33.33% 2-butyl-4-chloro-1-[(2'-(1H- tetrazol- 5-yl)biphenyl- 4-yl)-methyl]-5-hydroxymethyl)imidazole.

10. A tablet formed from a formulation according to claim 9.

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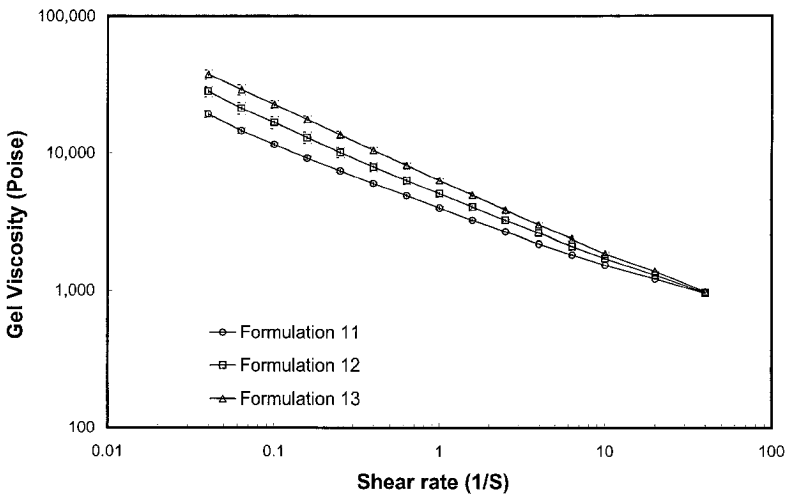
(54) **Title:** INJECTABLE DEPOT COMPOSITIONS AND USES THEREOF



(57) **Abstract:** Injectable depot compositions are provided that include a bioerodible, biocompatible polymer, a solvent having a miscibility in water of less than or equal to 7 wt. % at 25 °C, in an amount effective to plasticize the polymer and form a gel therewith, a thixotropic agent, and a beneficial agent. The solvent comprises an aromatic alcohol, an ester of an aromatic acid, an aromatic ketone, or mixtures thereof. The compositions have substantially improved the shear thinning behavior and reduced injection force, rendering the compositions readily implanted beneath a patient's body surface by injection.

WO 2004/012703 A1

Example 16

Parameters affecting the injection force

[000157] The following parameters affect the injection force for a given formulation at pre-set temperature: the radius of syringe (r); inner radius of needle (R); needle length (L); injection speed (Q). The effect of these four parameters on the injection force was determined using a fractional factorial design approach (8 trials) with one near center point for confirmation. The details of the design are summarized in Table 6 (trials 1-9). The injection force was tested using the following formulation (n = 3): the vehicle containing PLGA RG502/BB/BA (40/45/15 wt%), loaded with lysozyme particles (10 wt% 30 μm). The correlation between the injection force and testing parameters was established using JMP software (which is very similar to the Power Law prediction) as follows:

$$F = 0.028 \bullet \frac{r^{2.475} \bullet L^{0.770} \bullet Q^{0.716}}{R^{2.630}}$$

Table 6

Trial	Needle ID [a] (mm)	Needle length [b] (mm)	Syringe ID [c] (mm)	Injection speed (mL/min)	Injection Force (N)	
					Avg	SD
1	0.191	12.7	2.3	0.05	14.6	0.8
2	0.292	50.8	3.25	0.5	172.2	5.3
3	0.292	12.7	3.25	0.05	8.6	0.2
4	0.191	12.7	3.25	0.5	176.0	2.6
5	0.292	50.8	2.3	0.05	13.4	0.3
6	0.292	12.7	2.3	0.5	30.0	2.5
7	0.191	50.8	3.25	0.05	127.0	2.3
8	0.191	50.8	2.3	0.5	161.4	4.5
9	0.241	25.4	2.3	0.25	48.8	0.5

[a] Needles having following gauges were used: 24G (ID = 0.292 mm), 25G (ID = 0.241 mm) and 27G (ID = 0.191 mm);
[b] Needle having following lengths were used: 0.5 inch (12.7 mm), 1 inch (25.4 mm), 2 inches (50.8 mm);
[c] Two different syringes (Hamilton): 250 μL (ID = 2.30 mm); 500 μL (ID = 3.25 mm).

Extrusion process - Input data

Target

Determine the effects of the factors, which may affect the yield of the pellets.

Factors and levels

A: amount of binder (0.5, 1.0 %)

B: amount of water (40, 50 %)

C: granulation time (60, 120 s)

D: spheronization charge (1, 4 kg)

E: spheronization speed (700, 1000 rpm)

F: extruder rate (15, 60 rpm)

G: spheronization time (120, 300 s)

Lewis *et al*, Pharmaceutical experimental design, 1999, Marcel Dekker, New York

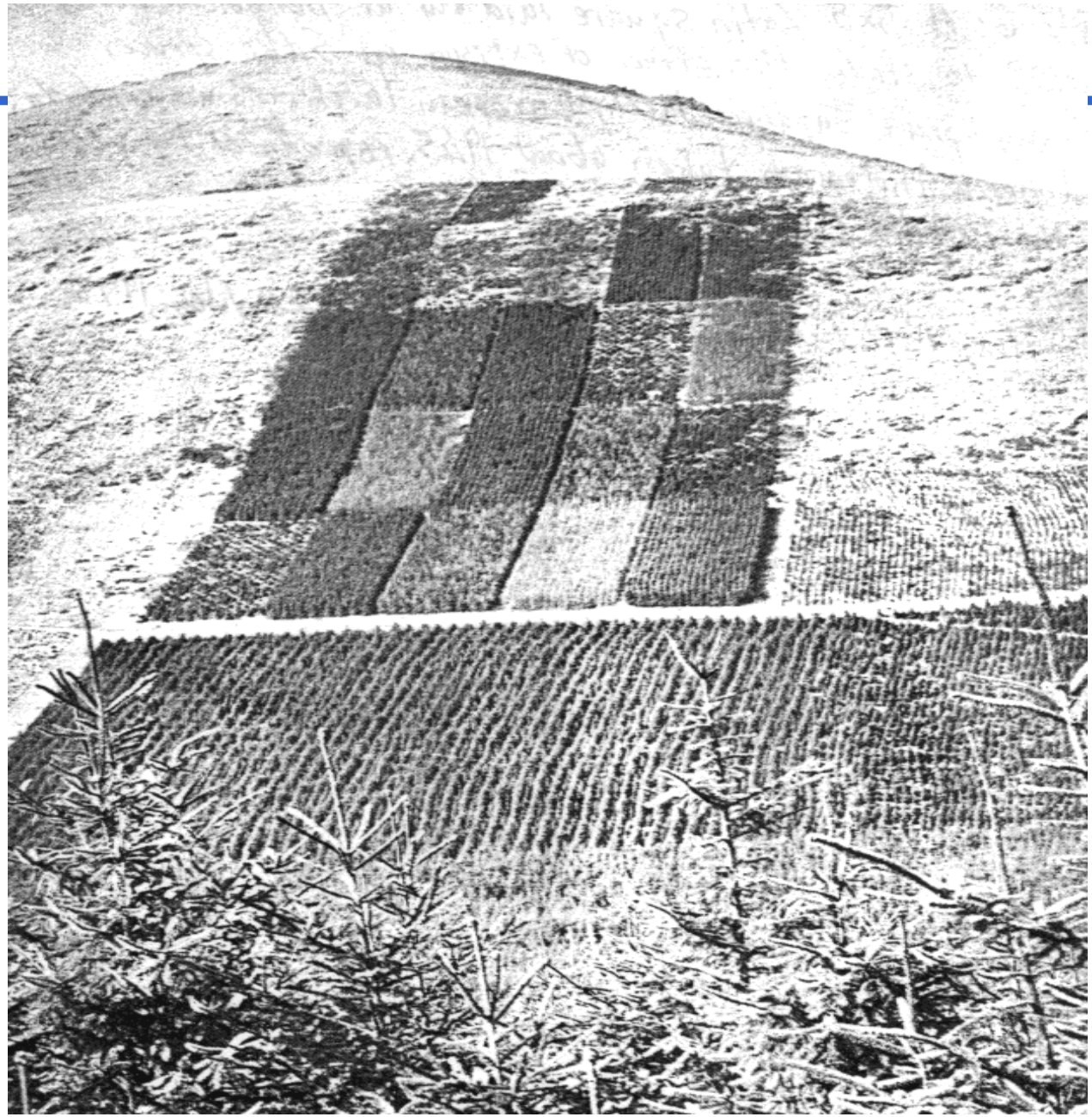
Extrusion process - Conclusions

The factors:

Granulation time
Spheronization charge
Extruder rate

do not affect the yield of the pellets and may be set to the most convenient levels.

Additional experiments may supply a detailed quantitative study of the influence of the main factors and the detection of eventual factors interactions.



Latin Squares

	A1	A2	A3	A4
B1	1 E1 D1 C1	2 E2 D2 C2	3 E3 D C	E4 D4 C4
B2	6 E4 D3 C2	5 D	E2 D1 C4	7 E1 D2 C3
B3	11 C3	12 E1 D3 C4	9 E4 D2 C1	10 E3 D1 C2
B4	16 E3 D2 C4	15 E4 D1 C3	14 E1 D4 C2	13 E2 D3 C1

Up to 5 factors at 4 levels in only 16 experiments!

Daily examples (7)

The following excipient mixture surprisingly stabilizes an unstable active ingredient in a tablet formulation:

- Microcrystalline cellulose
- Starch
- Hydroxypropylmethylcellulose
- Magnesium stearate

Would it be possible to identify other suitable excipients?

Daily examples (2)

This softener composition is new and, surprisingly, clear at room temperature:

Component	%
Cationic surfactant	15.0
Fatty alcohol 12 EO	15.0
Glycerin monostearate	7.5
Water	62.5

Are any other emulsifiers and solvents, which would also provide clear compositions?

Clear softener: Results

	NI1	NI2	NI3	NI4
S1	Translucent	Clear	Clear	Clear
	Translucent	Clear	Translucent	Clear
S2	Clear	Clear	Clear	Clear
	Clear	Clear	Clear	Clear
S3	Turbid	Clear	Clear	Clear
	Clear	Clear	Clear	Clear
S4	Clear	Clear	Clear	Clear
	Translucent	Clear	Translucent	Clear

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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(21) Internationales Aktenzeichen: PCT/EP00/12811

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199 62 874.2 24. Dezember 1999 (24.12.1999) DE

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *Mit internationalem Recherchenbericht.*
— *Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** TRANSPARENT SOFTENING AGENTS

(54) **Bezeichnung:** TRANSPARENTE AVIVAGEMITTEL

(57) **Abstract:** The invention relates to transparent softening agents containing: (a) ester quaternaries, which are obtained by reacting alkanolamines with a mixture consisting of fatty acids and of dicarboxylic acids, whereby the resulting esters are optionally alkoxylated and subsequently quaternized in a known manner, and containing; (b) auxiliary agents selected from the group formed by: (b1) fatty acid amidoamines and/or quaternization products thereof; (b2) betaines; (b3) nonionic surfactants; (b4) polyols and/or derivatives thereof; (b5) alcohols and/or; (b6) hydrotropes.

(57) **Zusammenfassung:** Vorgeschlagen werden transparente Avivagemittel, enthaltend (a) Esterquats, dadurch erhältlich, dass man Alkanolamine mit einer Mischung aus Fettsäure und Dicarbonsäuren umsetzt, die resultierenden Ester gegebenenfalls alkoxyliert und anschliessend in an sich bekannter Weise quaterniert und (b) Hilfsstoffe ausgewählt aus der Gruppe, die gebildet wird von (b1) Fettsäureamidoaminen und/oder deren Quaternierungsprodukten, (b2) Betainen, (b3) nichtionischen Tensiden, (b4) Polyolen und/oder deren Derivate (b5) Alkohole und/oder (b6) Hydrotrope.

WO 01/47489 A1

Daily examples (2)

This softener composition is new and, surprisingly, clear at room temperature:

Component	%
Cationic surfactant	15.0
Fatty alcohol 12 EO	15.0
Glycerin monostearate	7.5
Water	62.5

Latin squares

Are any other emulsifiers and solvents, which would also provide clear compositions?

Daily examples (5)

The microscopic structure of this cosmetic composition shows a nanoemulsion:

Component	%
Mineral oil	12.0
C12-14 3 EO phosphated	7.5
Glycerin monostearate	5.0
Glycerin	3.0
Cetearyl glucoside	2.0
Water	70.5

Would it be possible to identify other good combinations?

Phosphoric esters: Appearance results

Nanoemulsions Vesicules Multiple emulsion

	Oil 1	Oil 2	Oil 3	Oil 4
E 1	1 D1 C1	2 D2 C2	3 C3	4 D4 C4
E 2	6 D3 C2	5 C1	8 4	7 D2 C3
E 3	1 4	1 3	9 1	10 1
E4	16 D2 C4	1 1	14 1	13 3

Daily examples (5)

The microscopic structure of this cosmetic composition shows a nanoemulsion:

Component	%
Mineral oil	12.0
C12-14 3 EO phosphated	7.5
Glycerin monostearate	5.0
Glycerin	3.0
Cetearyl glucoside	2.0
Water	70.5

Latin squares

Would it be possible to identify other good combinations?

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

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60/348,150 14 January 2002 (14.01.2002) US

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

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

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

WO 02/096191 A2

(54) Title: METHOD AND FOR INCREASING THE EFFICIENCY OF RUMINARY

(57) Abstract: The present invention relates to a method and for enhancing productivity of ruminant animals. Particularly, a method comprising determining particular corn hybrids of specific endosperm type and NDF content for use as silage and/or a grain supplement and combining other dier components to form a feed ration that optimizes the site of starch digestion, and a feed made using the method of the invention.

DM, CP (Nebraska only), OM, NDF, and starch are determined by multiplying the concentrations of each component by the ruminal digesta DM weight. Turnover rate of digesta in the rumen is calculated by dividing intake of a feed component by ruminal pool size of the component:

Turnover rate in the rumen (%/h) =
(intake of component, g/ruminal pool of component, g) / 24 x 100.

All cows are observed every 5 min for a 24-h period on one day per period (d 23 for Nebraska, d 22 for Michigan) for chewing activity. Cows are recorded as ruminating, eating, or neither. From this data, eating and ruminating times per day and per kilogram of NDF intake are calculated, as well as number of meals and rumination bouts.

Statistical Analysis:

The combined data (for both locations) is analyzed as a replicated 4 x 4 Latin square design with a 2 x 2 factorial arrangement of the diets and model effects for location, period, square, processing method, endosperm type, and all possible interactions. Statistical analysis is conducted by the use of the Mixed Model procedure of SAS (1998) and the fit-model procedure of JMP (2000). In addition, data for each location is analyzed using the same model with the location effect removed. Discussion of the data focuses on the combined data set except when significant location effects occurred. Significance is declared at $P < 0.10$ unless otherwise noted.

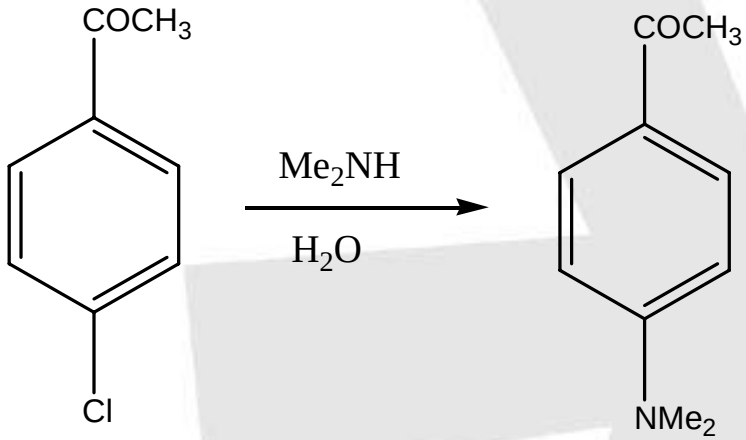
Chemical Composition, Particle Size, and Kernel Integrity:

At one site, the DM content of the silages averaged 42 ± 2%, although the DM content of the nonprocessed, vitreous endosperm corn is greater ($P < 0.01$) than all other corn silages at harvest (Table 1). The NDF, acid detergent fiber (ADF), starch, and CP contents are similar among all silages.

Table 1 shows the effectiveness of processing of the corn silage. Every kernel evaluated contained some degree of damage to the pericarp when the kernel processor is installed. Table 1 also shows the distribution of corn silage particles using the Penn State Particle

Daily examples (3)

In the synthesis of 4-(N,N-dimehtylaminoacetophenone was reported a yield of 77% in JP79132542.



Would it be possible to improve this yield?

Synthesis optimization

Strategy

Hexagonal design based on Doehlert matrix

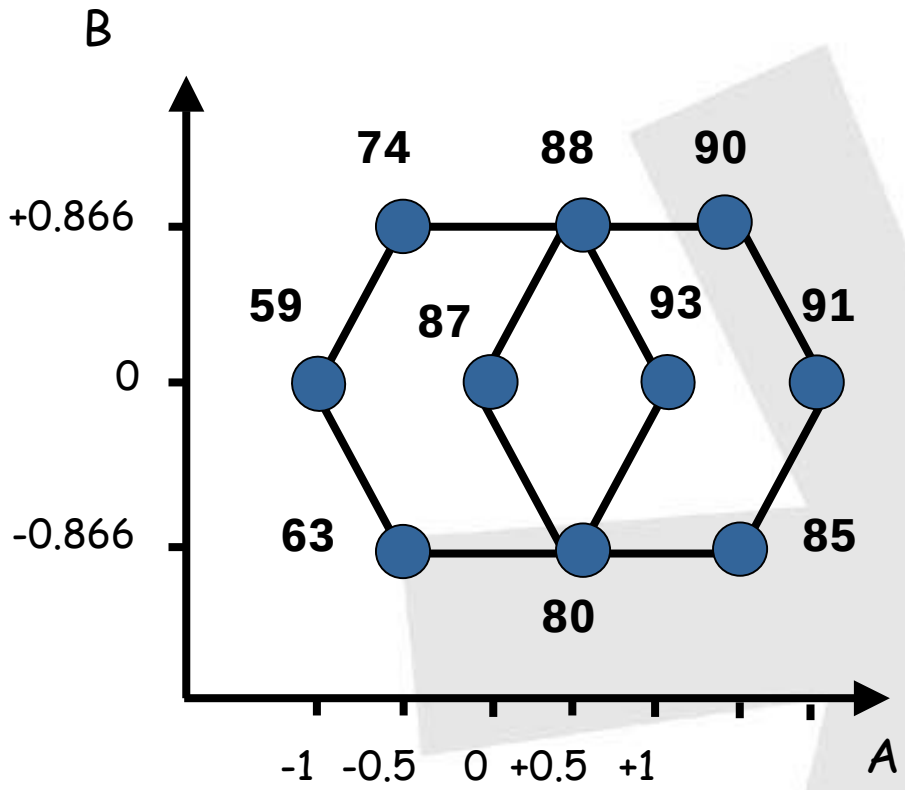
Factors

	Center	Variation
A: Ratio dimethylamine/ketone	3.00	1.00
B: Reaction temperature (° C)	230	20

Response

Yield of 4-(N,N-dimehtylamino)acetophenone(%)

Synthesis optimization: Results



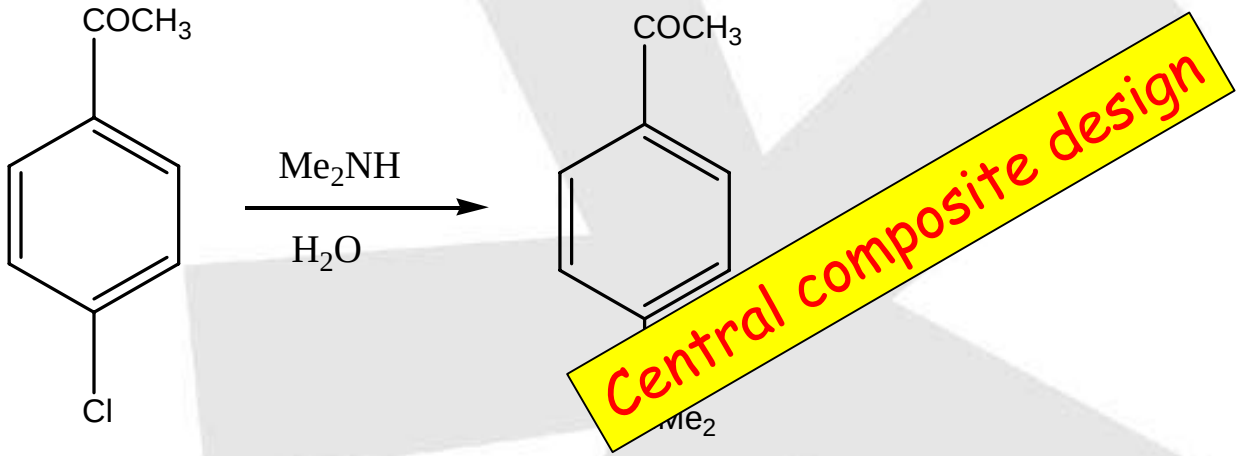
Synthesis optimization - Conclusions

The yields were considerably improved compared to the original procedure given in the patent (91 vs 77 %).

The model predicted a yield of 78.5 % for the conditions given in the patent. This is quite close to the reported yield of 77 %.

Daily examples (3)

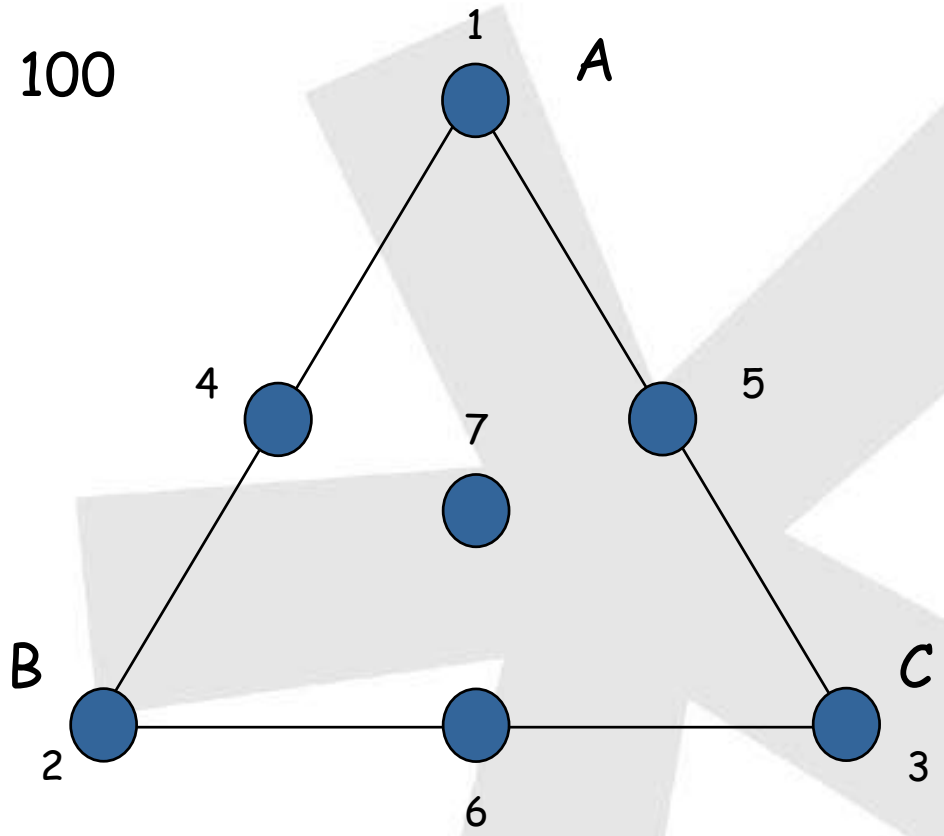
In the synthesis of 4-(N,N-dimehtylaminoacetophenone was reported a yield of 77% in JP79132542.



Would it be possible to improve this yield?

Mixture design

Mixture: A + B + C = 100



US006180026B1

(12) **United States Patent**
Rieger et al.

(10) **Patent No.: US 6,180,026 B1**
(45) **Date of Patent: Jan. 30, 2001**

(54) **NEMATIC LIQUID CRYSTAL MIXTURES AND A MATRIX LIQUID CRYSTAL DISPLAY**

(75) Inventors: **Bernhard Rieger**, Yokohama (JP); **Volker Reiffenrath**, Rossdorf; **Reinhard Hittich**, Modautal, both of (DE)

(73) Assignee: **Merck KGaA**, Darmstadt (DE)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **08/067,154**

(22) PCT Filed: **Mar. 27, 1991**

(86) PCT No.: **PCT/EP91/00595**

§ 371 Date: **May 15, 1991**

§ 102(e) Date: **May 15, 1991**

(87) PCT Pub. No.: **WO91/15554**

PCT Pub. Date: **Oct. 17, 1991**

Related U.S. Application Data

(63) Continuation of application No. 07/688,481, filed on May 15, 1991, now abandoned.

(30) **Foreign Application Priority Data**

Apr. 2, 1990 (EP) 90106252
Aug. 13, 1990 (EP) 90115501

(51) **Int. Cl.**[7] **C09K 19/30**; C09K 19/12; C09K 19/02

(52) **U.S. Cl.** **252/299.63**; 252/299.66; 349/182

(58) **Field of Search** 252/299.63, 299.66; 349/182

(56) **References Cited**

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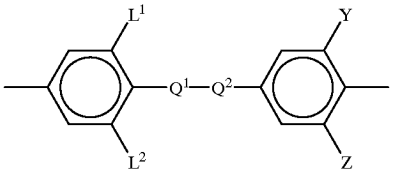
0256636 * 2/1988 (EP) .
9001056 * 2/1990 (WO) .

* cited by examiner

Primary Examiner—C. H. Kelly
(74) *Attorney, Agent, or Firm*—Millen White Zelano & Branigan

(57) **ABSTRACT**

The invention relates to a nematic liquid crystal mixture having a positive dielectric anisotropy $\Delta\epsilon$ of at least +4 and a birefringence Δn of at least 0.12, characterized in that the mixtures comprises one or more components having the core structure



wherein L^1, L^2, Y and Z are each independently of one another H or F, one of Q^1 and Q^2 is 1,4-phenylene, 3-fluoro-1,4-phenylene or 3,5-difluoro-1,4-phenylene and the other residue Q^1 or Q^2 is —CH_2CH_2—, —$CH_2CH_2CH_2CH_2$— or —if at least one of L^1, L^2, Y and Z denotes F—also a single bond, whereby this core structure can be optionally further fluorinated in the benzene rings.

8 Claims, No Drawings

NEMATIC LIQUID CRYSTAL MIXTURES AND A MATRIX LIQUID CRYSTAL DISPLAY

This application is a continuation of application Ser. No. 07/688,481, filed May 15, 1991 abandoned.

SUMMARY OF THE INVENTION

The invention relates to an active matrix liquid crystal display (AMD) being operated in the second or a higher transmission minimum of the Gooch-Tarry curve and to stable nematic liquid-crystal compositions with high optical anisotropy for use in such AMD's, e.g. for projection systems.

Active matrix displays (AMD) are highly favored for commercially interesting displays with a high information content. Such AMDs are used for TV application and also for displays for, e.g., laptops, automobiles and airplanes.

AMDs have non-linear electrical switching elements which are integrated at each picture element. As non-linear driving elements thin film transistors (TFT) [Okubo, U., et al., 1982, SID 82 Digest, pp. 40–41] or diodes (e.g.: metal insulator metal: MIM) [Niwa, K., et al., 1984, SID 84 Digest, pp. 304–307] can be applied. These non-linear driving elements allow to use an electro-optical effect with a rather flat electro-optical characteristic if a good viewing angle characteristic can be obtained. So a TN-type LC cell [Schadt, M. and Helfrich, W., 1971, Appl. Phys. Lett., 18, 127] with a twist angle in the region of 90° can be used. To provide the good contrast over a wide viewing angle, operation in the region of the first minimum of transmission [Pohl, L., Eidenschink, R., Pino, F., del. and Weber, G., 1980, German Pat., DBP 30 22 818, and 1981, U.S. Pat. No. 4,398,803; Pohl, L., Weber, G., Eidenschink, R., Baur, G., and Fehrenbach W., 1981, Appl. Phys. Lett., 38, 497; Weber, G., Finkenzeller, U., Geelhaar, T., Plach, H. J., Rieger, B., and Pohl, L., 1988, Int. Symp. on Liq. Cryst., Freiburg, to be published in Liq. Crys.] is favored. These AMDs are very well suited for direct view and projection type TV-displays and consequently are of high commercial interest. For these applications some physical properties of the liquid crystals become more important than for passive TN displays. Some of the decisive properties for the performance of an AMD are resistivity and UV- and thermal stability of the liquid crystal [Togashi, S., Sekiguchi, K., Tanabe, H., Yamamoto, E., Sorimachi, K. Tajima, E., Watanabe, H., Shimuzu, H., Proc. Eurodisplay 84, September 1984: A 210–288 Matrix LCD Controlled by Double Stage Diode Rings, p. 141 ff, Paris; Stromer, M., Proc. Eurodisplay 84, September 1984: Design of Thin Film Transistors for Matrix Addressing of Television Liquid Crystal Displays, p. 145 ff, Paris]. A problem often encountered is the adverse influence of UV-illumination on the resistivity and therefore on the general performance of the liquid crystal mixture in the display.

In an AMD the non-linear switching elements are addressed in a multiplex scheme. So they charge the electrodes of a pixel in the limited time they are active. Then they become inactive until they are addressed again in the next cycle. Consequently, the change of the voltage on an activated (charged) pixel is a nondesired but a very decisive feature of such a display. The discharge of a pixel is determined by two factors. These are the capacity of the pixel element including liquid crystal and the resistivity of the dielectric material between the electrodes, namely the liquid crystal. The characteristic time constant of the decay of the voltage at a pixel (RC-time) has to be significantly bigger than the time between two addressing cycles ($t_{adr.}$). A parameter frequently used to describe the performance of an AMD is the voltage holding ratio HR of a picture element:

$$HR = \frac{V(to) + V(to + tadr.)}{2V(to)}$$

As the voltage at a pixel decays exponentially an increase of the holding ratio necessitates liquid crystal materials with exceptionally high resistivities.

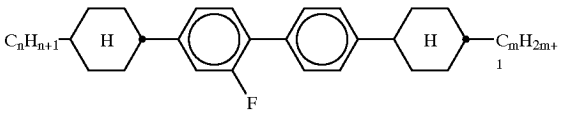
There are several points of importance for the resistivity of the liquid crystal inside a display, e.g., orientation layers, curing condition of the orientation material. But by no means less important are the electrical properties of the liquid crystal used. Especially the resistivity of the liquid crystal in the display determines the magnitude of the voltage drop at the pixel.

Earlier investigations with low-An materials have shown, that the requirements with regard to resistivity and UV-stability and temperature dependence of the resistivity for TFT-applications cannot be met with materials containing cyano moieties as terminal groups. Non-cyano materials containing halogenated terminal groups can show far better resistivity values and UV-stability as well as superior viscosity values than conventionally used cyano materials. However, in general these non-cyano materials unfortunately show a strong tendency towards forming smectic phases, especially at low temperatures. Also, the clearing points and the dielectric anisotropy values of non-cyano materials with halogenated terminal groups are much lower.

Modern commercial mixtures have to operate over a wide temperature range; therefore, crystallization or formation of smectic phases at low temperatures has to be excluded. Good solubility is one of the most important preconditions for the usability of liquid crystalline materials in the development of nematic mixtures. Compounds with high melting temperatures or a tendency to form smectic phases are for this reason not suitable.

By very careful selection of the components and an appropriate mixture design it was possible to find low birefringence non-cyano mixtures having a broad nematic temperature range for first mininmum application [B. Rieger et al., Proc. 18. Freiburger Arbeitstagung Flüssigkristalle, Freiburg 1989, 16 (1989)]. Non-cyano materials with high birefringence, which are essential for the mixture concept of this invention unfortunately show in many cases even more unfavorable properties such as high melting points and/or strongly smectogenic behavior than similar materials with lower birefringence:

TABLE B-continued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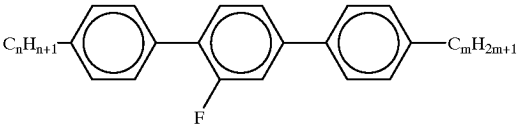
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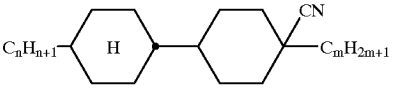
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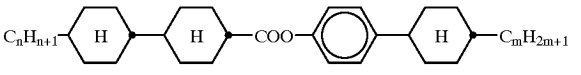
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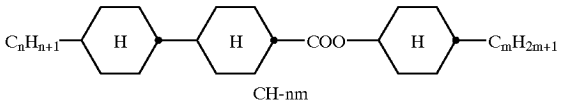
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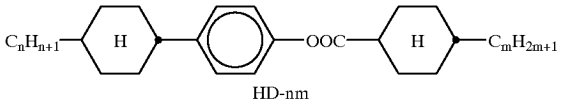
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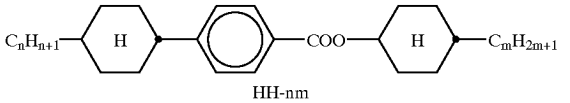
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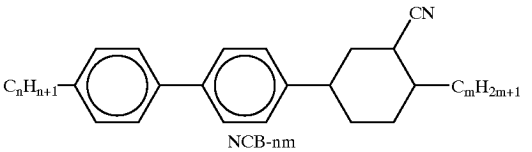
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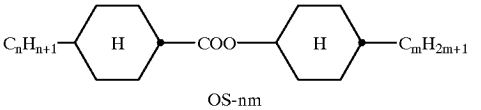
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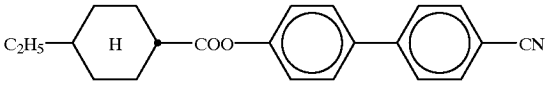
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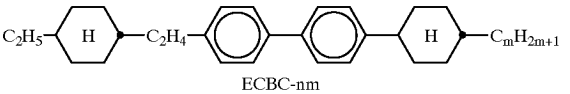
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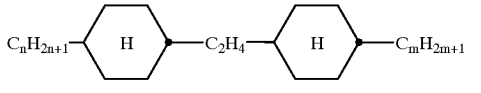
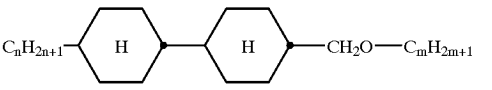


TABLE B-continued

ECCH-nm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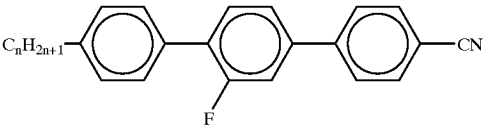
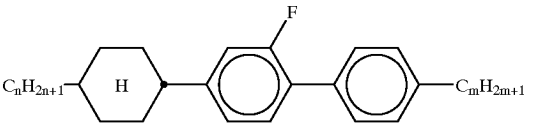

T-nFn


BCH-nmF

Example 1		Example 2		Example 3	
CFET-5F	20%	CFET-5F	17%	CFET-5F	17%
CFET-5Cl	10%	CFET-5Cl	8.5%	CFET-5Cl	8.5%
FET-5F	30%	FET-5F	25.5%	FET-5F	25.5%
FET-5Cl	30%	FET-5Cl	25.5%	FET-5Cl	25.5%
EBCH-3F	10%	EBCH-3F	8.5%	EBCH-3F	8.5%
		FET-3F	15%	EBCH-5F	8.5%
				EBCH-3Cl	8.5%

Example 4		Example 5		Example 6	
CFET-5F	17%	CFET-5F	10%	CFET-5F	10%
CFET-5Cl	8.5%	CFET-5Cl	10%	CFET-5Cl	10%
FET-5F	25.5%	FET-5F	25%	FET-5F	20%
FET-5Cl	25.5%	FET-5Cl	15%	FET-5Cl	10%
EBCH-3F	8.5%	PCH-5Cl	20%	PCH-5Cl	10%
PCH-5Cl	7.8%	PCH-5Cl	20%	PCH-7Cl	10%
PCH-7Cl	7.2%			T-3F2	15%
				T-2F3	15%

Example 7		Example 8		Example 9	
CFET-5F	16.9%	CFET-5F	17%	CFET-5F	12.5%
CFET-5Cl	8.5%	CFET-5Cl	8.5%	CFET-5Cl	6.2%
FET-5F	25.3%	FET-5F	25.5%	FET-5F	18.6%
FET-5Cl	25.3%	FET-5Cl	25.5%	FET-5Cl	18.6%
EBCH-3F	8.5%	EBCH-3F	8.5%	EBCH-3F	6.2%
ECCP-3Cl	15.5%	PCH-5F	7.6%	T-2F3	4.7%
		PCH-6F	7.4%	T-3F2	4.7%
				EBCH-5F	9.5%
				PCH-5Cl	9.5%
				FET-3F	9.5%

Example	Melting point/ S→N (° C.)	Clearing point (° C.)	Δn	Δε
1	−13	104	0.189	
2	−10	95	0.187	
3	−24	98	0.176	5.0
4	<−40	87	0.171	
5	<−40	63	0.145	

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(54) Title: STABLE HYDROALCOHOLIC COMPOSITIONS

(57) Abstract

Disclosed is a composition including a lower alcohol and water in a weight ratio of about 35:65 to 100:0, between at least 0.5 % and 8.0 % by weight thickener system comprised of at least two emulsifiers, each emulsifier present in at least 0.05 % by weight wherein the composition free of auxiliary thickeners has a viscosity of at least 4,000 centipoise at 23 degrees C and wherein each emulsifier is comprised of at least one hydrophobic group and at least one hydrophilic group. The composition is useful as a presurgical scrub replacement, a lotion or other hand preparation.

Composition	A	B	C	D	E	F	G
Tm(°C)	37-39	39	39	39	42	38	38
Heat cycle *	HS	HS	HS	HS	HS	HS	HS

* Once the samples were melted, they were allowed to very slowly cool to room temperature by simply turning off the water bath. The time to cool was several hours. The samples were judged as heat stable (HS) if macroscopically they appeared the same as the original sample.

Example 13: Long Chain Alkylpolyglucoside/Polyethoxylated alkyl alcohol/Quaternary Amine Thickener System

A series of 10 formulations were prepared using a three component mixture design with the total emulsifier level fixed at 2% by weight. The following concentration ranges were investigated using a solvent ratio of 68:32 ethanol:water further containing 0.5% by weight CHG.

Emulsifier	Percent by weight
Eassi 624MP	0.25 - 1.5% by weight
Nikkol BB5	0.25 - 1.5
Incroquat DBM-90	0.25 - 1.5

Eassi 624MP is an alkylpolyglucoside prepared from an alcohol feed stock of 92% by weight behenyl alcohol and was obtained from Seppic Inc., Fairfield, NJ. The product had a melting point of 83°C and a 5% aqueous solution had a pH of 6.4. Each formulation was prepared by adding 49 grams solvent at 80°C to 2 grams thickener system at 80°C followed by 45 seconds of homogenization followed by 3 minutes of overhead mixing while immersed in a 15°C water bath. The samples were subsequently diluted to 2% solids by adding 49 grams solvent mixture. Each composition was subsequently tested for viscosity and Tm. The viscosities of the resulting formulations ranged from less than 165,000 cps to 309,000 cps. Examples of several preferred formulations appear below:

	Sample					
Component	A	B	C	D	E	F
	Amount (grams)					
Eassi 624MP	1.5	1.08	0.25	0.66	0.25	0 87
Nikkol BB5	0.25	0.46	1.5	0.67	0.88	0.88
Incroquat DBM 90(90%)	0.25	0.46	0.25	0.66	0.87	0.25
Viscosity (cps)	309,000	192,000	175,000	227,000	252,000	220,000
Tm (°C)	>57°C	52-57	52	52-57	44	52-57

The results show that the behenylpolyglucoside increases the melt temperature. Comparing the melt temperatures of this example with those of Example 12F shows that increasing the chain length of the hydrophobes in the thickener system increases the Tm. The thickener system of the formulations in this example produce homogenous viscous creams with varying ratios of the emulsifiers.

Example 14: Disinfectant Hand Lotion based on Alkylpolyglucoside /Polyethoxylated alkyl alcohol/Quaternary Amine Thickener System

Disinfectant hand creams/lotions were prepared based on the thickener system of Example 13F. The compositions are shown below:

Daily examples (4)

This softener composition has an excellent rewetting capacity:

Component	%
Cationic surfactant A	80.0
Fatty alcohol 20 EO	7.5
Additive M	12.5

Would it be possible to formulate the product using another Cationic surfactant (i.e. B) and Additive M or Additive N?

Would it be possible to identify any other good combination?

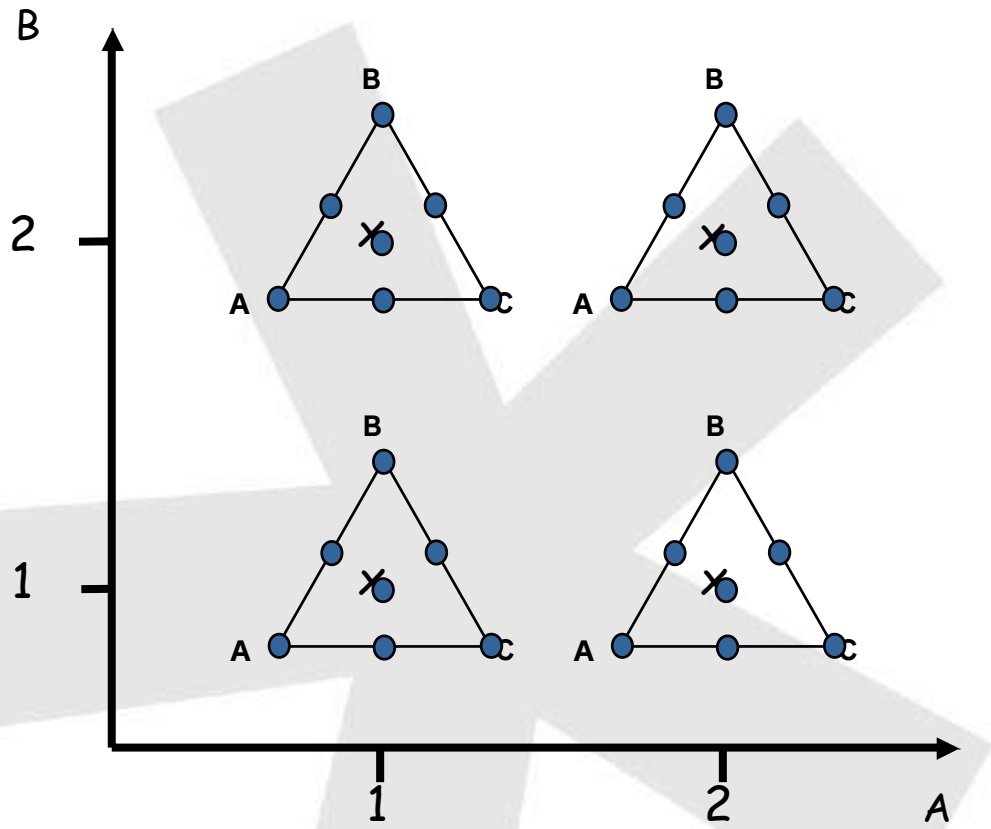
Combined design (2)

Raw materials:

A (1, 2)
B (1, 2)

Mixture:

A + B + C = 100



Hydrophylic Softener

Combined design

Mixture

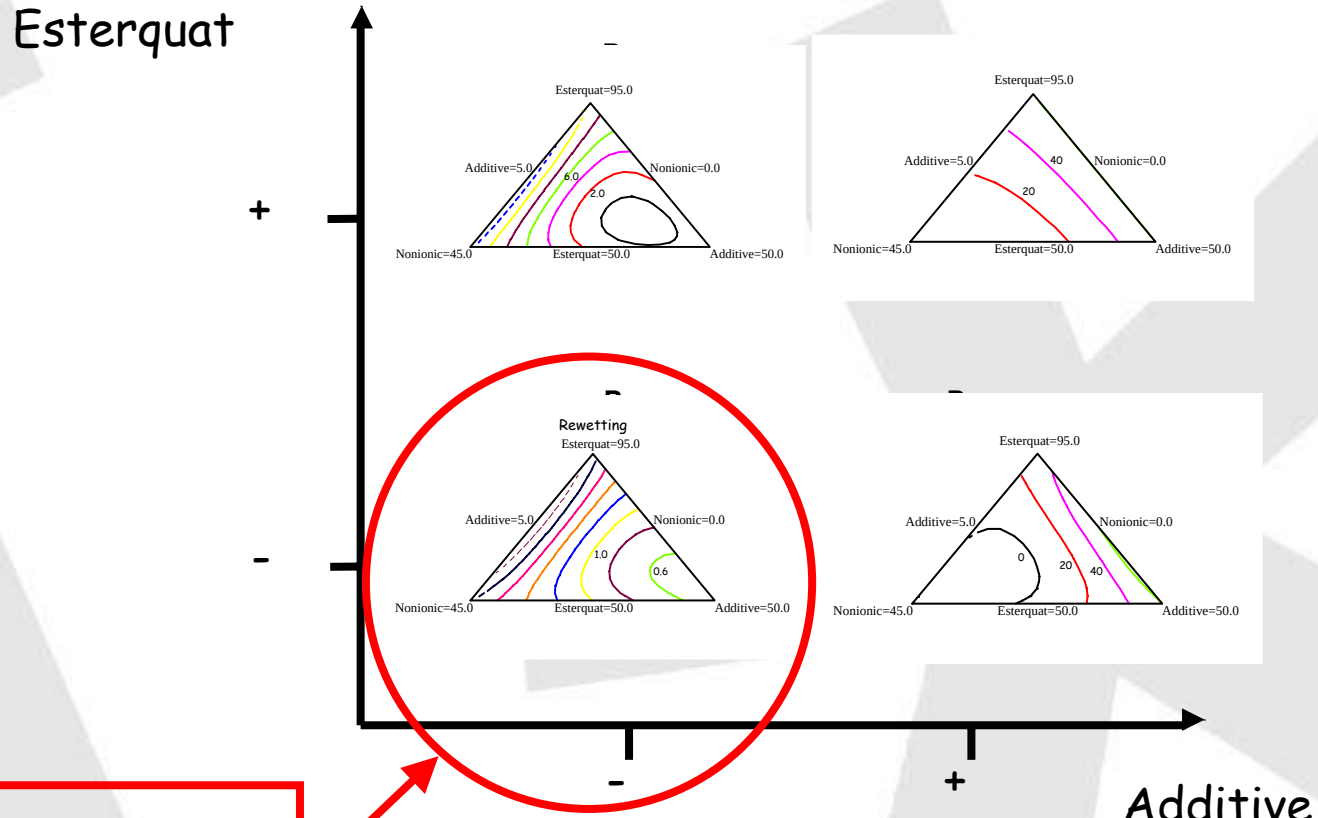
Factor	Level -	Level +	Constraints
Esterquat (A)	Type X	Type Y	> 50 %
Non ionic (B)	-	-	>0
Additive (C)	Non ionic	Ionic	> 5

Factorial

Reference	Esterquat	Additive
1	-	-
2	+	-
3	-	+
4	+	+

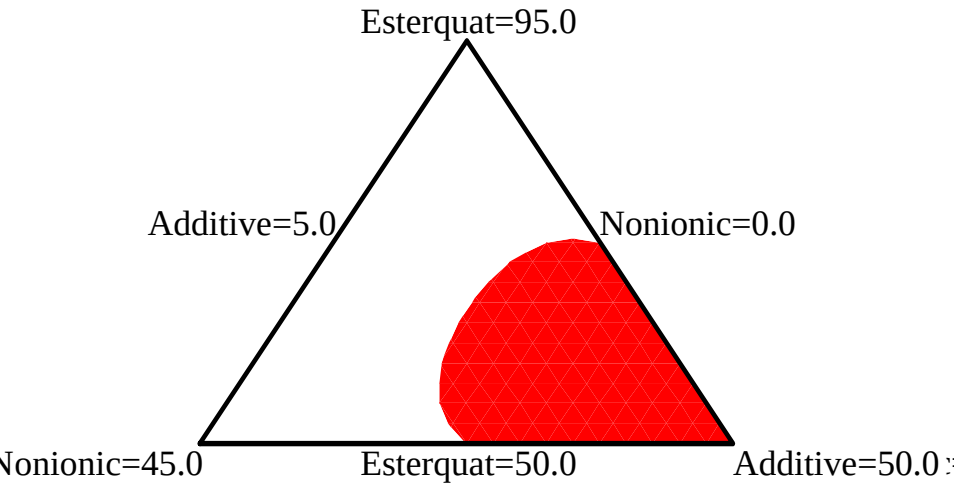
Cognis EP0869168-A2

Hydrophylic Softener

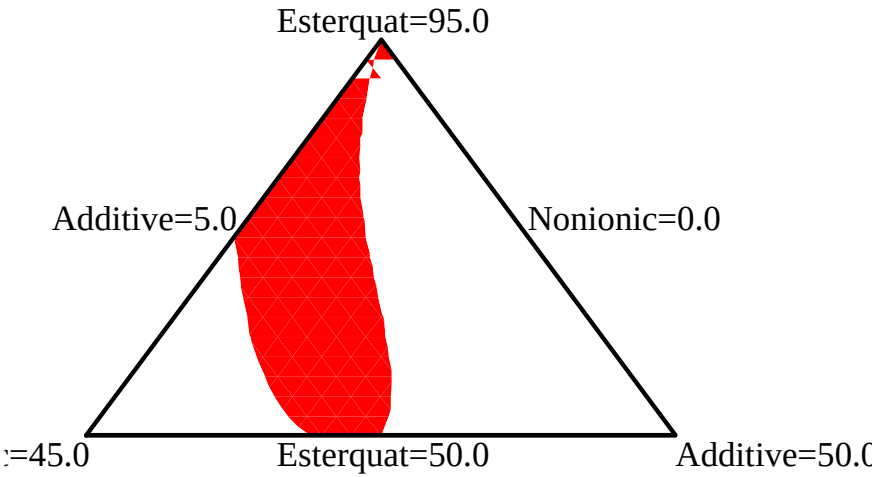


Esterquat: Type X
Additive: Non ionic

Hydrophylic Softener



Rewetting



Softening

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(54) Hydrophile Avivagemittel

(57) Vorgeschlagen werden neue polyolefinwachsfreie Avivagemittel, enthaltend Esterquats und Siliconverbindungen sowie gegebenenfalls weitere Tenside. Die Zubereitungen verleihen Textilien nicht nur einen angenehmen Weichgriff und vermindern die elektrostatische Aufladung zwischen den Fasern, sondern verbessern insbesondere die Hydrophilie und damit die Wiederbenetzbarkeit der Gewebe.

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Beispiele

Zur Bestimmung des Weichgriffs und der Wiederbenetzbarkeit wurden die Avivagemittel nach dem Foulardverfahren auf Baumwollgewebe zwangsappliziert. Der Weichgriff wurde anschließend von einem Panel bestehend aus 6 erfahrenen Personen auf einer Skala von 1 = „sehr weich" bis 4 = „hart" bewertet. Die Wiederbenelzbarkeit bzw. Hydrophilie wurde im bekannten Steighöhentest nach DIN 53924 bestimmt, bei dem man Streifen des Baumwollgewebes von 1 cm Breite in Wasser eintaucht und die Höhe mißt, auf die das Wasser aufgrund der Kapillarkräfte in dem Gewebe innerhalb von 1 min steigt; je größer die Steighöhe um so höher ist auch die Hydrophilie des Gewebes. Die Ergebnisse sind in Tabelle 1 zusammengefaßt. Die Beispiele 1 bis 4 sind erfindungsgemäß, die Beispiele V1 bis V4 dienen zum Vergleich.

Tabelle 1

Weichgriff und Wiederbenetzbarkeit								
Zusammensetzung/Performance	**1**	**2**	**3**	**4**	**V1**	**V2**	**V3**	**V4**
Ditalgfettsäuretriethanolaminester, methylquaterniert,Methylsulfat-Salz	95	-	90	80	95	-	-	-
Ditalgfettsäuremethyldiethanolaminester, methylquaterniert, Methylsulfat-Salz	-	90	-	-	-	95	-	-
Dimethyldisteaylammoniumchlorid	-	-	-	-	-	-	95	90
modifiziertes Dimethylpolysiloxan*	5	7	5	12	-	-	5	4
Isododecanol+6EO	-	3	5	-	5	-	-	6
Kokosalkylpolyglucosid	-	-	-	8	-	5	-	-
Weichgriff	1,0	1,0	1,0	1,5	2,0	2,0	3,0	2,5
Wiederbenetzbarkeit [mm]	11	12	12	15	10	9	8	8

*) Hansa Finish 2883, Th.Goldschmidt

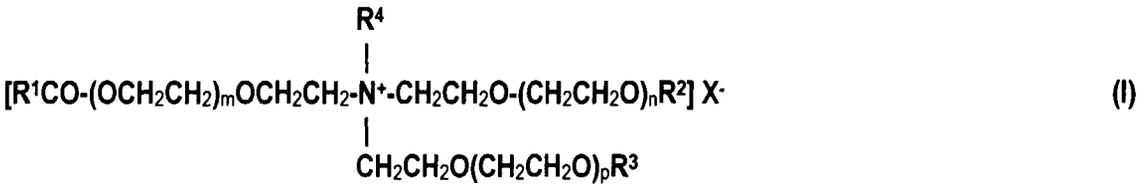
Patentansprüche

1. Hydrophile Avivagemittel, enthaltend

   (a) Esterquats und
   (b) Siliconverbindungen sowie gegebenenfalls
   (c) weitere Tenside,

   mit der Maßgabe, daß die Mittel frei von Polyolefinwachsen sind.

2. Avivagemittel nach Anspruch 1, **dadurch** gekennzeichnet, daß sie Esterquats der Formel **(I)** enthalten,

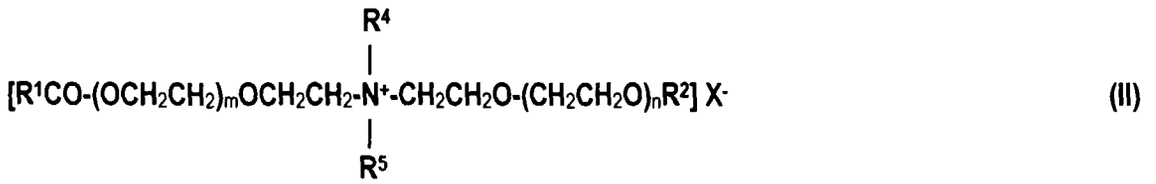


(I)

in der R^1CO für einen Acylrest mit 6 bis 22 Kohlenstoffatomen, R^2 und R^3 unabhängig voneinander für Wasserstoff oder R^1CO, R^4 für einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder eine $(CH_2CH_2O)_qH$-Gruppe, m, n und p in Summe für 0 oder Zahlen von 1 bis 12, q für Zahlen von 1 bis 12 und X für Halogenid, Alkylsulfat oder Alkylphosphat steht.

3. Avivagemittel nach den Ansprüchen 1 und 2, **dadurch gekennzeichnet**, daß sie Esterquats der Formel **(II)** enthal-

ten,



(II)

in der R^1CO für einen Acylrest mit 6 bis 22 Kohlenstoffatomen, R^2 für Wasserstoff oder R^1CO, R^4 und R^5 unabhängig voneinander für Alkylreste mit 1 bis 4 Kohlenstoffatomen, m und n in Summe für 0 oder Zahlen von 1 bis 12 und X für Halogenid, Alkylsulfat oder Alkylphosphat steht.

4. Avivagemittel nach den Ansprüchen 1 bis 3, **dadurch gekennzeichnet**, daß sie Esterquats der Formel **(III)** enthalten,

(III)

in der R^1CO für einen Acylrest mit 6 bis 22 Kohlenstoffatomen, R^2 für Wasserstoff oder R^1CO, R^4, R^6 und R^7 unabhängig voneinander für Alkylreste mit 1 bis 4 Kohlenstoffatomen, m und n in Summe für 0 oder Zahlen von 1 bis 12 und X für Halogenid, Alkylsulfat oder Alkylphosphat steht.

5. Avivagemittel nach den Ansprüchen 1 bis 4, **dadurch gekennzeichnet**, daß sie Siliconverbindungen enthalten, die ausgewählt sind aus der Gruppe, die gebildet wird von Dimethylpolysiloxanen, Methylphenylpolysiloxanen, cyclischen Siliconen sowie amino-, fettsäure-, alkohol-, polyetherepoxy-, fluor- und/oder alkylmodifizierten Siliconen.

6. Avivagemittel nach den Ansprüchen 1 bis 5, **dadurch gekennzeichnet**, daß sie nichtionische Tenside enthalten.

7. Avivagemittel nach den Ansprüchen 1 bis 6, **dadurch gekennzeichnet**, daß sie Fettalkoholpolyglycolether der Formel **(IV)** enthalten,

(IV)

in der R^8 für einen linearen oder verzweigten Alkyl- und/oder Alkenylrest mit 6 bis 22 Kohlenstoffatomen und n für Zahlen von 1 bis 50 steht.

8. Avivagemittel nach den Ansprüchen 1 bis 7, **dadurch gekennzeichnet**, daß sie

(a) 70 bis 95 Gew.-% Esterquats,
(b) 5 bis 30 Gew.-% Siliconverbindungen und
(c) 0 bis 20 Gew.-% weitere Tenside

mit der Maßgabe, daß sich die Mengenangaben gegebenenfalls mit Wasser und weiteren üblichen Hilfs- und Zusatzstoffen zu 100 Gew.-% ergänzen.

9. Verwendung von Mischungen, enthaltend Esterquats und Silicionverbindungen zur Herstellung von hydrophilen Avivagemitteln, die frei von Polyolefinwachsen sind.

Daily examples (4)

This softener composition has an excellent rewetting capacity:

Component	%
Cationic surfactant A	80.0
Fatty alcohol 20 EO	7.5
Additive M	12.5

Combined design

Would it be possible to formulate the product using another Cationic surfactant (i.e. B) and Additive M or Additive N?

Would it be possible to identify any other good combination?

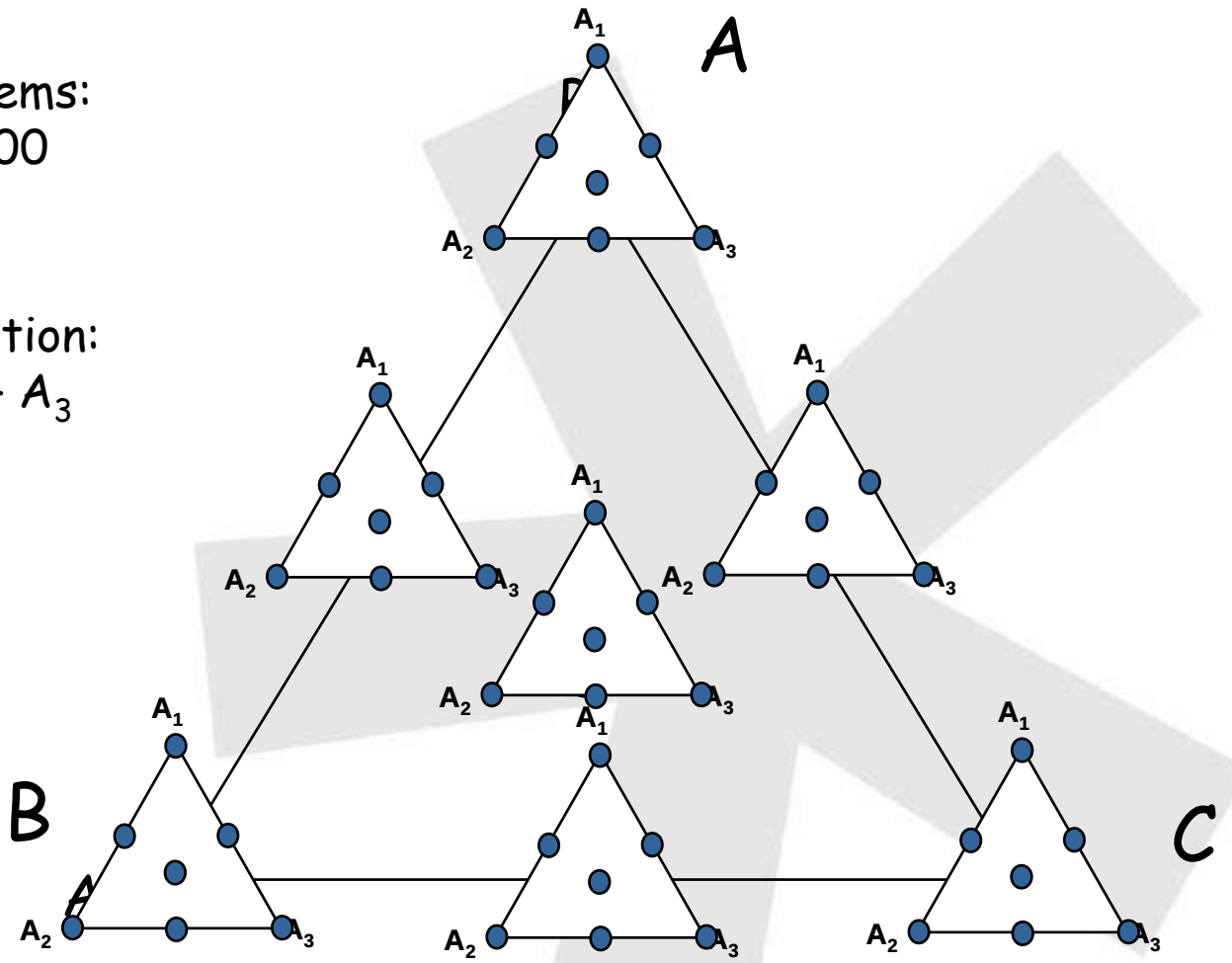
Combined design (3)

Mixture of sub-systems:

$A + B + C = 100$

Sub-system composition:

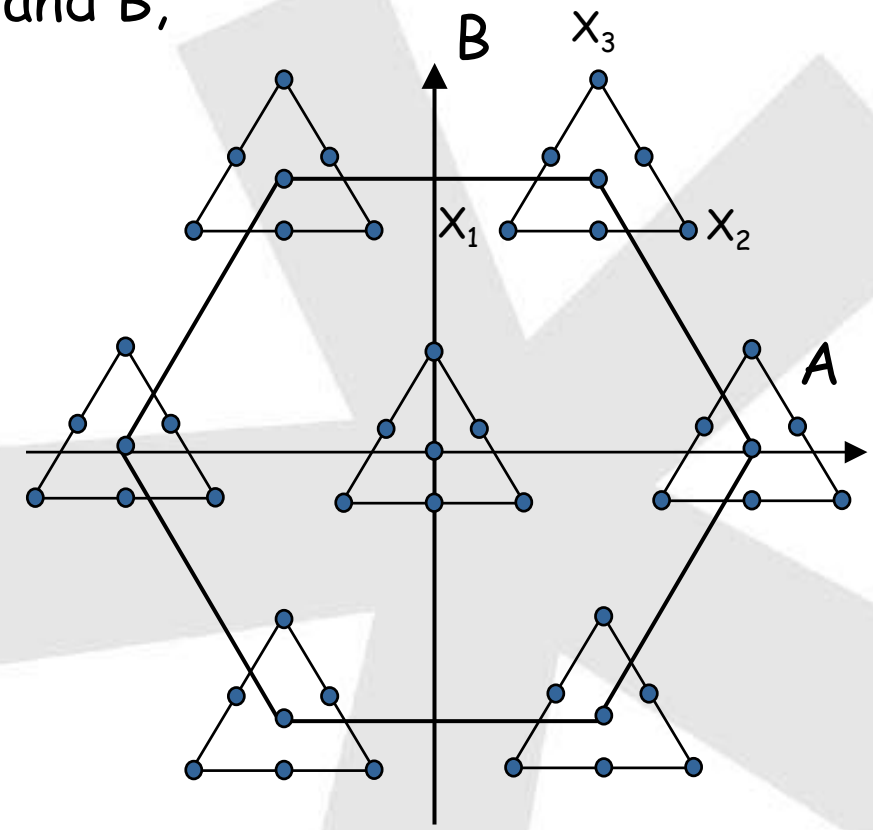
$A = A_1 + A_2 + A_3$



Combined design (4)

Sub-system comprising A and B, and mixture comprising:

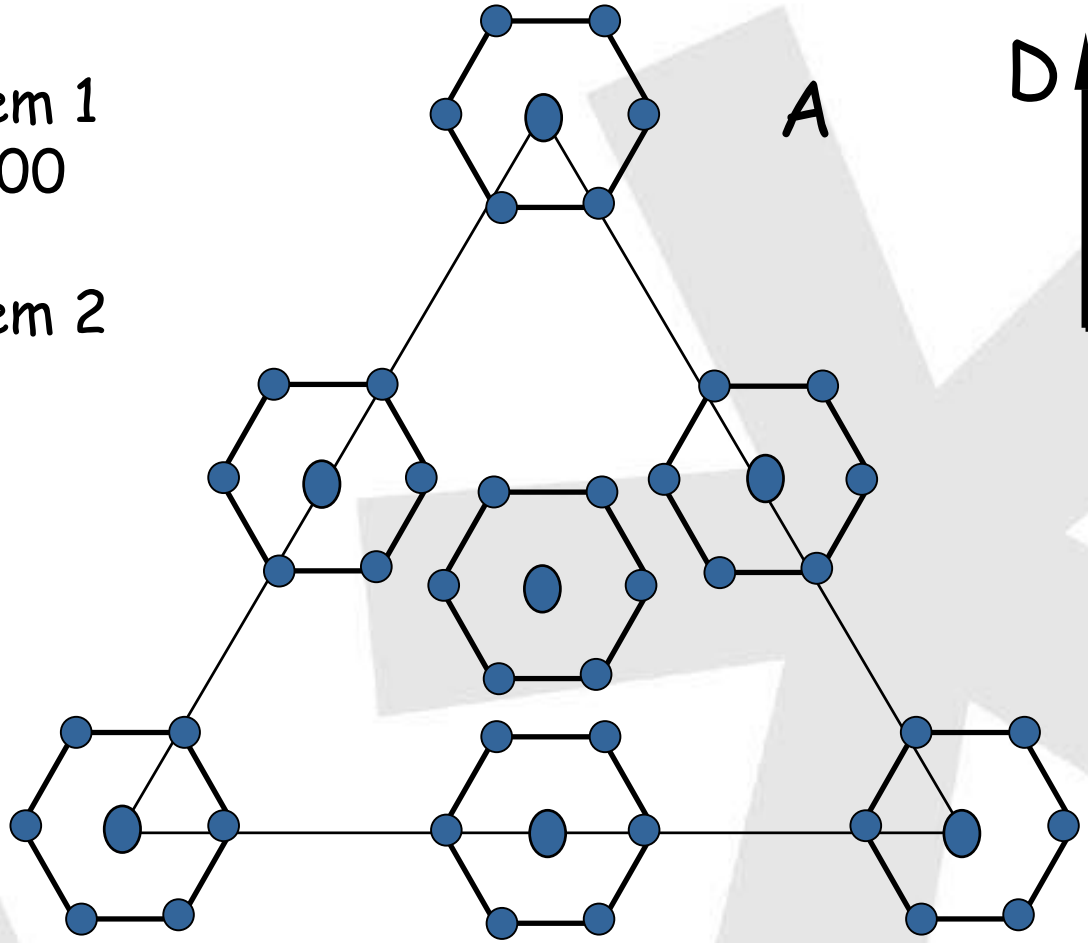
$$X_1 + X_2 + X_3$$

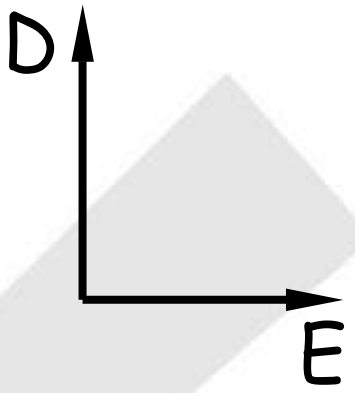


Combined design (5)

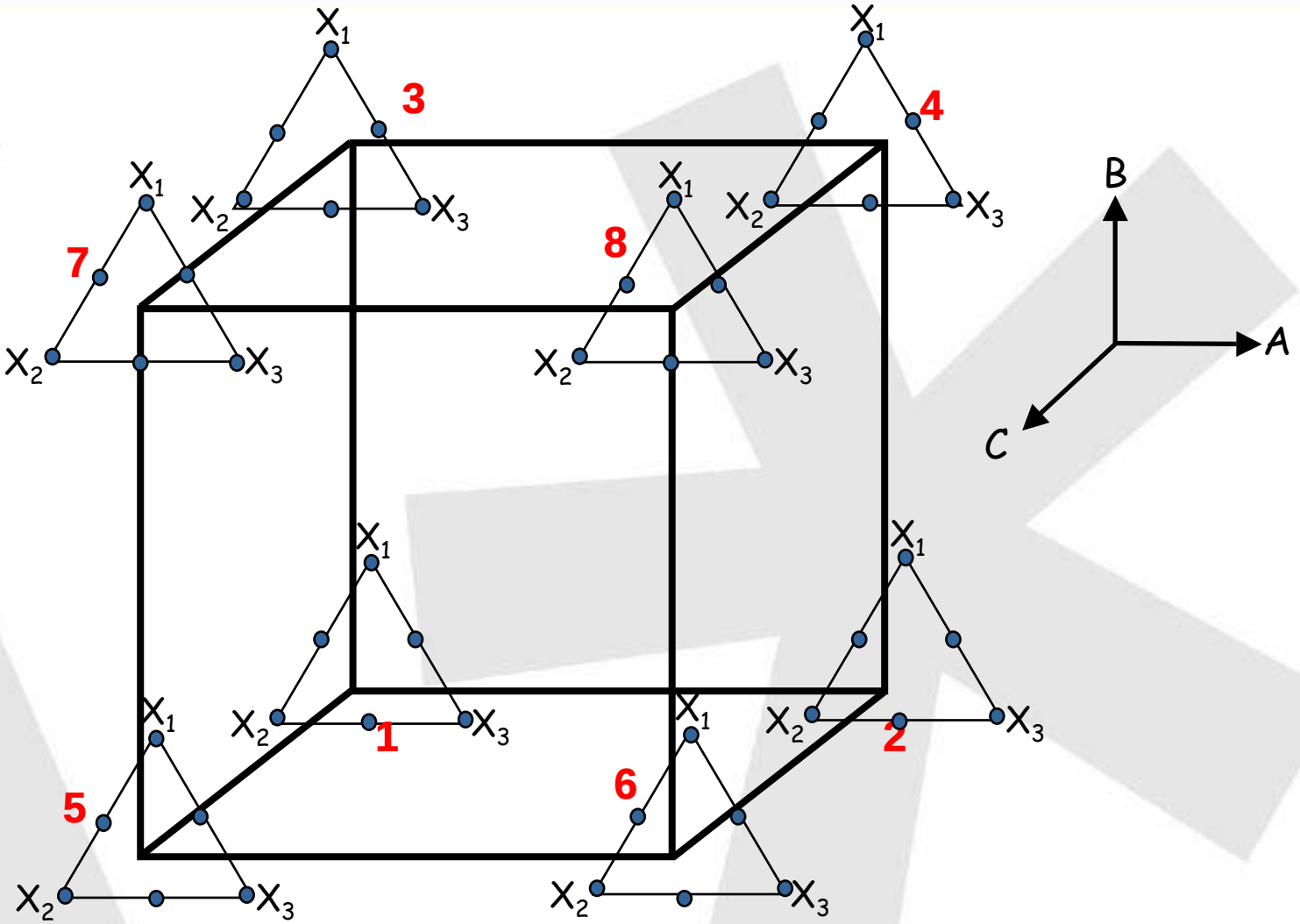
Sub-system 1
A+B+C = 100

Sub-system 2
D, E





Combined design (6)



Conclusions (1)

- Experimental design provides simple and multipurpose designs to face both screening work and optimization efficiently and saving resources.

Conclusions (2)

- Experimental design can help to define better the scope of the invention:
  - concentration ranges
  - pH ranges
  - temperature ranges
  - delimiting good performance regions
  - solvents
  - excipients
  - process conditions

Conclusions (3)

- Experimental design can help:

  - showing clearly sinergistic effects to support inventive step,

  - providing coherent experimental data to support the claims

  - providing technical arguments to objections raised during examination and opposition procedure

Thank you very much for your attention.