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(19)

(54) PHARMACEUTICAL COMPOSITIONS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a pharmaceutical composition comprising aggregates of diameter of at most 20,000 Å, comprising:—
as component a) at least one pharmaceutically acceptable ergot alkaloid, and
as component b) a pharmaceutically acceptable ethoxylated cholesterin emulsifier,
component b) having a mean HLB value of 10 to 30 and present in an amount greater than 10 times by weight of component a).

Component a) is preferably an ergot alkaloid which is difficultly absorbable into the bloodstream on enteral, e.g. oral, administration. Such difficulty absorbable ergot alkaloid are those which are absorbed by the body at a cumulative percentage absorption up to 45% at most, e.g. in amounts below 35% or even below 25% as indicated by standard tests. For example, in one test material is administered p.o. in a ca. 0.008% weight/volume aqueous solution of the test material to the bile fistula rat. The cumulative percentage elimination of material in the bile and in the urine is measured in conventional manner.

The dose of material administered is conveniently chosen such that the cumulative percentage absorption substantially levels out after 48 hours. In the same test the initial rate of elimination of material in e.g. the bile is also determined in conventional manner.

The present composition exhibits enhanced resorption properties as indicated in standard tests, e.g. by a greater cumulative percentage absorption and initial rate of absorption in the above-indicated test than would be expected for such compositions.

The present compositions are therefore indicated for use with ergot alkaloids, when it is desired to obtain high blood level values in the bloodstream as rapidly as possible.

Examples of component a) include lysergic acid derivatives, e.g. ergolene, ergot peptide alkaloids such as ergotamine or hydrogenated ergot peptide alkaloids, e.g. dihydroergotoxine, dihydroergocristine and the 13-bromoderivative thereof, dihydroergonine, dihydroergocryptine, dihydroergotamine and the 13-bromo derivative thereof, dihydroergocornine and dihydroergovaline.

The active agent content may naturally vary considerably and may be adjusted to the desired dose depending on the ergot alkaloid used and the condition to be treated, the amount to be administered per unit dose and the type of composition.

However, in order to obtain a specific therapeutic result, the amount of active agent administered per dose in the composition of the invention may be smaller than the amount of the same active agent in one of the hitherto used formulations required for the obtention of an equal result. In the case of single dosage form, component a), may amount up to 5% e.g. up to 2.5% by weight in the case of solid preparations and in the case of liquid preparations up to 1% by weight of the composition. For example, component a) in drop solutions preferably amounts to between 0.05% and 0.6% and in tablets and capsules preferably between 0.2% and 4.0%, especially 0.2 and 2.5%, e.g. from 0.4 to 2.5%.

H.L.B. value (hydrophilic/lipophilic balance) of component b) is a measure for the relative portion of hydrophilic groups in an emulsifier molecule [see Pharm. Act. Helv. *44*, 9 (1969) and H. P. Fiedler, Lexicon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, page 263, Edicio Cantor KG. 1971].

Component b) may be a cholesterin ethoxylated with e.g. 24 moles of ethylene per mole such as Solulan C24 (Registered Trade Mark) of the American Cholesterol Corporation.

It is preferred to use physiologically tolerable emulsifiers having a mean H.L.B. value of 10 to 20, especially 12 to 16. If desired further emulsifiers of other types may be present, e.g. polyethylene glycol sorbitan fatty acid esters, e.g. polyoxyethylene - 4 - sorbitan monostearate, such as Tween ® 61 [Registered Trade Mark] (Atlas Chemical Industries),

polyethylene glycol fatty acid esters, e.g. polyoxyethylene - 10 - stearate such as Myrj ® 52 [Registered Trade Mark] (Atlas Chemical Industries), polyethylene glycol - 400 - stearate DAB7, polyoxyethylene glycol glycerin fatty acid esters, e.g. polyoxyethylene castor oil, such as Cremophor ® EL [Registered Trade Mark] (Bad. Anilin u. Sodafabrik), polyol ethers of higher fatty alcohols, e.g. polyoxyethylene - 20 - cetylic ether, such as Brij ® 56 [Registered Trade Mark] (Atlas Chemical Industries), ethoxylated wool fat alcohols (e.g. with 16 mols of ethylene oxide, such as Solulan ® 16 (American Cholesterol Comp.), or an oxy - ethylenoxy - propylene polymer containing 40% of polyoxyethylene and having a mean molecular weight of approximately 2900, such as Pluronic ® L 64 [Registered Trade Mark] (Wyandotte Chemicals), an oxy - ethylenoxy - propylene polymer having a mean molecular weight of approximately 3500, such as Pluronic ® P 65 [Registered Trade Mark] (Wyandotte Chemicals) or an oxy - ethylenoxy - propylene polymer containing 80% of polyoxyethylene and having a mean molecular weight of approximately 8700, such as Pluronic ® F 68 [Registered Trade Mark] (Wyandotte Chemicals), or sodium dioctyl sulphosuccinate, such as Aerosol ® OT [Registered Trade Mark] (American Cyanamid Co.).

It may be convenient to use different types of emulsifiers depending on the chemical and physical properties, molecule size and form of the component a) used and component c), mentioned hereafter.

The amounts of emulsifier to be used may vary depending on the emulsifier used, especially its chemical and physical properties, the type and amount of adjuvants used, the type of active agents used and the desired extent of improvement in resorption. The upper limit of the amount of emulsifier to be used will naturally depend on the physiological tolerability of said emulsifier, taking into consideration the planned duration of treatment and frequency of administration. The components in the composition are preferably present in such amounts that the total amount of component b) does not exceed 50 mg/unit dose. The weight ratio of total amount of component b) to component a) may, for example, be from 10:1 to 50:1, preferably 20:1 to 30:1. In anhydrous administration forms, the total quantity of emulsifier may amount up to 60% by weight, e.g. in unit-dose preparations preferably between 20% and 50% by weight. In water-containing compositions, the concentration of component b) conveniently is between the critical micelle concentration (CMC) and maximal addition concentration (MAC) of the emulsifiers used. The total amount of component b) in water-containing administration forms preferably is between 1% and 5% by weight.

The aggregates may conveniently contain as component c) a pharmaceutical carrier, preferably a lipoid carrier. Component c) is preferably present in an amount 25 times or especially up to 10 times the amount of component a) present.

Lipoid carrier materials which may be used are, for example, monovalent or polyvalent lower alcohols (C_{2-6}) partially or completely esterified with higher aliphatic carboxylic acids (C_{6-20}), preferably alcohols of 2—3 carbon atoms, especially glycerin or propylene glycol, or condensates thereof, e.g. polyglycerins. For the production of solid compositions it is convenient to use lipoid carrier materials which are solid at room temperature, and for the production of liquid medicinal preparations liquid lipoid carrier materials or mixtures of solid and/or liquid lipoid carrier materials which are liquid at room temperature. Especially suitable solid lipoid carrier materials are only partially esterified alcohols, especially saturated monoglycerides and diglycerides. The aliphatic carboxylic acids contained in the solid esters may preferably contain 12 to 20 carbon atoms and may be straight chain or branched and/or hydroxylated. Especially suited for the production of liquid medicinal preparations are completely esterified alcohols, especially triglycerides, e.g. esters of unsaturated carboxylic acids or saturated carboxylic acids, preferably containing 8 to 12 carbon atoms. Examples of suitable esters are *inter alia* monoglycerides, diglycerides or triglycerides of saturated or unsaturated fatty acids, e.g. glycerin monolaurate, monomyristate, monooleate or monoricinoleate, peanut oil, oily triglyceride mixtures of saturated vegetable fatty acids containing 8 to 12 carbon atoms or propylene glycol esters, e.g. propylene glycol monostearate.

The non-aggregate portion of the composition may contain further pharmaceutical carriers or diluents [component d)] which do not hinder the formation of the active agent- and emulsifier-containing aggregates or impair the stability of the resulting aggregates.

For example, it is convenient to add water-soluble solid or liquid physiologically tolerable monovalent or polyvalent alcohols. Examples of suitable alcohols are: ethanol, propylene glycol, glycerin, sugar alcohols and polyethylene glycols having a mean molecular weight of, for example, 300 to 10,000. An addition of polyalcohols, e.g. polyethylene glycol, which will promote the solubilization of the active agents which are difficultly soluble in water, is particularly desirable when the emulsifier mixture used contains no oxyethylenoxy-propylene polymers or only small amounts thereof. For the production of liquid administration forms it is preferred to add liquid alcohols, e.g. lower monovalent or polyvalent alcohols and/or polyethylene glycols with mean molecular weights below 2000, preferably between 300 and 1500. For solid medicinal pre-

parations it is convenient to use alcohols which are solid at room temperature, e.g. sugar alcohols and/or polyethylene glycols having mean molecular weights over 1800, preferably between 2000 and 10,000, especially 5000—7000.

Water-containing compositions of the invention may contain between 20% and 95 e.g. up to 90%, preferably between 30% and 70%, e.g. between 30 and 50% by weight of water and optionally further adjuvants. The alcoholic (including polyol) content of the aqueous liquid may, for example, be between 0% and 50%, preferably between 20% and 40% by weight of the formulation.

Anhydrous liquid preparations may contain the active agent- and emulsifier-containing aggregates finely distributed in a water-soluble and/or water-dispersible liquid carrier material consisting of one or several liquid carriers and optionally further adjuvants. Suitable liquid carrier materials are especially physiologically tolerable lower monovalent or polyvalent alcohols and/or liquid polyethylene glycols, e.g. polyethylene glycols having mean molecular weights below 2000.

Liquid compositions may contain as further components additional pharmaceutical adjuvants, e.g. preserving and flavouring agents and buffer materials. The liquid preparations may contain further physiologically tolerable water-soluble and/or water-dispersible solid materials, especially when they are to be worked up into solid dosage forms.

The solid medicinal preparations of the invention contain the active agent and emulsifier-containing aggregates finely distributed in a carrier material which is formed from one or several water-soluble and/or water-dispersible solid materials and optionally further pharmaceutical adjuvants.

Suitable physiologically tolerable, water-soluble solid materials are, for example, polyethylene glycols which are solid at room temperature, preferably polyethylene glycols having a mean molecular weight between about 2000 and 10,000, preferably between 6000 and 10,000, polyvinyl pyrrolidones, solid oxyethylenoxy-propylene polymers, sugars, e.g. lactose, sugar alcohols, e.g. mannitol or sorbitol, and carboxymethyl cellulose.

The solid materials dispersible in water are preferably used in the form of finely dispersed powders which owing to their large surface are capable of absorbing the finely distributed active agent- and emulsifier-containing aggregates.

Suitable solid materials are, for example, physiologically tolerable, water dispersible, non-swelling inorganic and/or organic carrier materials, insofar as they do not irreversibly bind the active agents used. Suitable inorganic carrier materials are, for example, dicalcium phosphates or highly dispersed silicic acids having a tapped volume preferably between 250 and 1000 cc/100 g, especially wet precipitated silicic acid.

Depending on the desired formulation, the solid medicinal preparations may contain as further components additional physiologically tolerable pharmaceutical adjuvants, e.g. preserving and flavouring agents and any desired tabletting adjuvants generally used in the production of tablets or any desired suppository masses used in the production of suppositories.

The active agent-containing aggregates present have a diameter up to 20,000 Å, preferably between 100 and 10,000 Å, especially below 2000 Å and above 400 Å.

In aqueous medicinal preparations the distribution of the emulsifier- and ergot alkaloid-containing aggregates in the aqueous liquid preferably is so fine that transparent or slightly opalescent liquids are obtained. The diameter of the active agent- and emulsifier-containing aggregates preferably is less than 2000, especially less than 1000 Å.

The anhydrous solid or liquid compositions of the invention are dried preparations or liquid preparations which contain the ergot alkaloid-containing aggregates preferably so finely distributed that when brought into an aqueous medium they rapidly give a transparent or slightly opalescent liquid, wherein the difficultly absorbable active agent or agents are solubilized in the form of finely distributed ergot-alkaloid- and emulsifier-containing aggregates.

The new compositions of the invention may be liquid or solid and are preferably administered orally. The liquid compositions of the invention may, for example, be administered as a drop solution or syrup. Anhydrous liquid compositions may also be filled into soft gelatin capsules for the production of unit-dose administration forms. The preferred water-containing compositions are drop solutions. Suitable solid administration forms are, for example, powders, granulates, capsules, tablets or film tablets for oral administration, or suppositories for rectal administration.

A preferred form of the compositions of the invention are liquid or preferably solid preparations of ergot alkaloids wherein the total amount of polyalcohols and emulsifiers in the case of water-containing preparations preferably is between 15% and 80 e.g. up to 70% by weight of the total formulation and in the case of anhydrous preparations between 40% and 99% by weight of the total formulation.

The compositions may be obtained by a process including the step of formulating aggregates having at most a diameter of 20,000 Å of components a) and b) as defined above.

The production of the liquid compositions may be effected in accordance with the invention by dispersing components a) and b) if desired with the addition of further pharmaceutical adjuvants, in the liquid carrier

material, e.g. in an anhydrous medium or in water or in a water-containing medium, preferably using ultrasonic waves and/or high speed stirrers.

In accordance with an embodiment of the process the ergot alkaloid active agent may first be dissolved with slight heating in the emulsifier optionally with the addition of lipoid carrier materials, this mixture may subsequently be diluted with the liquid carrier materials and homogenized while treating with ultrasonic wave or high-speed stirrers.

The production of the solid compositions may also be effected in accordance with the invention by carefully removing the liquid carrier materials, e.g. water and/or lower alcohols, from primarily produced liquid preparations and converting the resulting powdery or spongy-porous dry preparation in known manner into the desired administration form.

The careful drying of the liquid preparations may be effected in known manner, e.g. by freeze-drying or spray-drying. For example, the liquid preparations may be freezed at temperatures between −80° and −50°C and then lyophilized in a high vacuum, or the liquid preparations may be atomized in a drying chamber and dried by a warm air stream, e.g. at temperatures from 120° to 180°C.

If desired, the resulting dry preparations may subsequently be worked up in known manner, optionally with the addition of further suitable pharmaceutical adjuvants such as tabletting adjuvants and suppository mass, e.g. filled into capsules, granulated, tabletted or moulded into suppositories.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade, and all aggregates formed are below 20,000 Å in diameter.

Polytron is a trade mark.

EXAMPLES 1—10.

Water-containing drop solutions of difficultly absorbable active agents

The formulations of Examples 1—10 having the composition indicated in the following Table 1, are produced as follows:

The difficultly absorbable ergot alkaloids are dissolved with slight heating (at temperatures between 30 and 50°) in the emulsifiers and any lipoid carrier materials which may be present, optionally with the addition of part of the polyalcohols.

The water or an aqueous solution of any further adjuvants or a mixture of water and any polyalcohols used is added to the above solution while stirring vigorously with a polytron homogenizer, and the resulting mixture is homogenized for 5 to 6 minutes by treatment with ultrasonic wave and/or a polytron homogenizer.

The resulting homogenous liquids are filled into bottles fitted with droppers.

TABLE 1

Water-containing drop solutions

Example No.	1	2	3	4	5	6	7	8	9	10
mg of active agents:										
Dihydroergocristine Dihydroergonine Dihydroergotamine 13-bromo-dihydroergotamine	400	400	400	200	200	800	200	120	600	300
g of emulsifiers:										
Cholesterin ethoxylated with approx. 24 mols of ethylene oxide[a)]	10	6	6	3	3	8	2.5	5.8	6	3
Oxy-ethylenoxy-propylene polymer, mean molecular weight 8700[d)]										1
g of lipoid carrier materials:										
Glycerin monolaurate Glycerin monostearate palmitate k) Glycerin monoricinoleate Glycerin monooleate Propylene glycol monostearate Glycerin monomyristate Glycerin monoisostearate		2	2	1	1	1	0.5			
g of polyalcohols:										
Polyethylene glycol 300 Polyethylene glycol 400 Polyethylene glycol 600						40		47	30	25
g of further adjuvants:										
Water	89.6	91.6	91.6	95.8	95.8	53.2	96.8	47+	50+	40+

+Buffered to pH value 4.3 with a buffer mixture of sodium acetate/acetic acid.

a) Solulan C 24® of American Cholesterol Comp.

d) Pluronic F 68® of Wyandotte Chemicals

g) Brij 56® of Atlas Chemical Industries

k) Tegomuls 70® of Goldschmidt AG

(all Registered Trade Marks)

EXAMPLE 11.

Dihydroergotamine-containing drop solution

60 mg of dihydroergotamine mesylate are added together with 1.5 g of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] to 60 cc of water adjusted to pH 4.1 with a buffer mixture of sodium acetate/acetic acid, and homogenized with a polytron homogenizer. The clear liquid is filled into bottles fitted with droppers.

EXAMPLE 12.

Dihydroergotamine-containing anhydrous drop solutions

a) 2 g of dihydroergotamine are added together with 50 g of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] to 500 g of polyethylene glycol 400 while heating to 50° in a water bath, treatment is effected with ultrasonic waves for 5 minutes, and the resulting clear liquid is filled into bottles fitted with droppers.

b) The process is effected as described in section a) above, except that a mixture of 250 g of polyethylene glycol 400 and 250 g of glycerin is used in place of 50 g of polyethylene glycol 400.

EXAMPLE 13.

Dihydroergonine-containing soft gelatin capsules

3 g of dihydroergonine are added together with 75 g of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] to 150 cc of polyethylene glycol 300 while heating in a water bath of 50° and subjecting to ultrasonic waves. The clear liquid is subsequently filled into soft gelatin capsules in quantities of 100 mg/capsule.

EXAMPLE 14.

Dihydroergocristine-containing capsules

300 mg of dihydroergocristine are dissolved together with 1.7 g of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] and 1.2 g of glycerin monolaurate while heating to 40°, and homogenized with the addition of 30 g of a 22% solution of oxy-ethylenoxy-propylene polymers having a mean molecular weight of 8700 [d] in water. After diluting with 50 cc of water, freezing is rapidly effected in a rotating flask at −80° and lyophilization is effected in a high vacuum. As lyophilization progresses the dry material is gradually heated to 25—30°. The resulting dry preparation is subsequently filled into capsules in quantities of 50 mg/capsule.

EXAMPLE 15.

Dihydroergotamine-containing capsules

30 mg of dihydroergotamine are dissolved together with 750 mg of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] in 50 cc of absolute ethanol, and the solution is evaporated to dryness in a vacuum at 30°. The residue is homogenized with a polytron homogenizer for about 5 minutes while gradually adding 100 cc of distilled water. 225 mg of highly dispersed silicic acid [n] are suspended in the resulting clear liquid, and the suspension is homogenized by treatment with ultrasonic waves at 30° for 3 minutes. The suspension is freezed at −80° and subsequently lyophilized. The lyophilized product is filled into gelatin capsules in quantities of 100 mg/capsule.

EXAMPLE 16.

Dihydroergovaline-containing lyophilized product in freeze-dried ampoules

400 mg of dihydroergovaline are dissolved together with 10 g of cholesterin ethoxylated with approx. 24 mols of ethylene oxide [a] and 40 g of polyethylene glycol 2000 in 300 cc of absolute ethanol. The solution is evaporated to dryness in a rotary evaporator at 30°. 200 cc of distilled water are slowly added to the residue while homogenized continually with the polytron homogenizer. The clear micellar solution of the active agent is filled into ampoules (2 mg of dihydroergovaline per ampoule) and the ampoules are rapidly freezed at −80°, lyophilized and sealed in a vacuum.

The dry preparations having the composition indicated in Table 2 may also be produced in a manner analogous to that described in Examples 14—16, and filled into capsules or dry ampoules or granulated and/or tabletted with the addition of suitable galenic adjuvants:

TABLE 2

Example No.	17	18	19	20	21	22	23	24	25	26	27	28	29
g of active agents:													
Dihydroergovaline	0.8	0.4											
Dihydroergotamine			3	2	3	2	2	3	3	3	3	3	3
g of emulsifiers:													
Oxy-ethylenoxy-propylene polymer, mean molecular weight 8700[d]													20
Cholesterin ethoxylated with approx. 24 mols of ethylene oxide[a]	20	10	75	42	75	25	25	60	60	75	35	45	20
Cholesterin ethoxylated with approx. 16 mols of ethylene oxide[o]						15							
Polyoxyethylene-10-cetylic ether[g]							10						
g of lipoid carrier materials:													
Glycerin monomyristate											1		
Glycerin monolaurate												2	
g of polyalcohols:													
Polyethylene glycol 2000	78.2					40			90				
Polyethylene glycol 6000		20											
Polyethylene glycol 10000						10							
g of further adjuvants:													
Dispersed silicic acid[n]	20		22	56			20				20	10	20
Dicalcium phosphate					300								
Mannitol								20				10	10
Polyvinyl pyrrolidone, mean molecular weight 40000[p]								10					
Lactose									50				
Carboxymethyl cellulose[q]										300			

n) Silicic acid K320 (tapped volume about 500 cc/100 g) of the firm Degussa

o) Solulan C16® of the firm American Cholesterol Comp.

p) PVP K30® of the firm Badische Anilin- und Sodafabrik

q) Primojel® of the firm Scholten's Chemische Fabrieken N.V.

WHAT WE CLAIM IS:—

1. Pharmaceutical composition comprising aggregates of diameter of at most 20,000 Å, comprising:
as component a) at least one pharmaceutically acceptable ergot alkaloid, and
as component b) a pharmaceutically acceptable ethoxylated cholesterin emulsifier,
component b) having a mean HLB value of 10 to 30 and present in an amount greater than 10 times by weight of component a).

2. A composition according to claim 1, wherein component a) is difficultly absorbable into the bloodstream on enteral administration.

3. A composition according to claim 1 or 2, wherein component a) comprises an ergot peptide alkaloid.

4. A composition according to any preceding claim, wherein component a) comprises a hydrogenated ergot peptide alkaloid.

5. A composition according to any preceding claim, wherein component a) comprises dihydroergocristine.

6. A composition according to any preceding claim, wherein component a) comprises dihydroergovaline.

7. A composition according to any preceding claim, wherein component a) comprises dihydroergonine.

8. A composition according to any preceding claim wherein component a) comprises dihydroergotamine.

9. A composition according to any preceding claim wherein component a) comprises dihydroergotoxin.

10. A composition according to any preceding claim in solid form.

11. A composition according to claim 10, wherein component a) is present in an amount of up to 5% by weight of the whole composition.

12. A composition according to one of claims 1 to 9 in liquid form.

13. A composition according to claim 12, wherein component a) is present in an amount of up to 1% by weight of the whole composition.

14. A composition according to any preceding claim, wherein component b) has a mean HLB value of 10 to 20.

15. A composition according to any preceding claim, wherein component b) has a mean HLB value of 12 to 16.

16. A composition according to any preceding claim, wherein component b) comprises cholesterin ethoxylated with 24 moles of ethylene per mole.

17. A composition according to any preceding claim, wherein the aggregates contain as component c) a pharmaceutical carrier material.

18. A composition according to claim 18, wherein component c) is a lipoid carrier material.

19. A composition according to claim 17 or 18, wherein component c) is present in an amount of up to 25 times the weight of component a).

20. A composition according to claim 19, wherein component c) is present in an amount of up to 10 times the weight of component a).

21. A composition according to any preceding claim, wherein the non-aggregate portion contains as component d) at least one pharmaceutical carrier.

22. A composition according to claim 21, wherein component d) contains a water soluble solid or liquid physiologically tolerable monovalent or polyvalent alcohol.

23. A composition according to claim 21 or 22, wherein component d) is a water containing liquid.

24. A composition according to claim 21 or 22, wherein component d) is a water soluble material.

25. A composition according to claim 21 or 22, wherein component d) is a water dispersible material.

26. A composition according to claim 21 or 22, wherein the aggregate is dispersed throughout the component d).

27. A composition according to any one of claims 21 to 26, wherein components b) and d) are present in an amount of between 15% and 80% of the weight of the whole composition.

28. A composition according to any one of claims 21 to 27, wherein component d) comprises water.

29. A composition according to claim 28, wherein component d) contains an alcoholic portion between 0 and 50% by weight of the composition.

30. A composition according to claim 28, wherein component d) contains an alcoholic portion of between 20 and 40% by weight of the composition.

31. A composition according to any one of claims 1 to 27 in anhydrous form.

32. A composition according to claim 29, wherein component b) is present in an amount of up to 60% by weight of the total composition.

33. A composition according to claim 31 or 32, wherein the amount of components b) and d) is between 40 and 99% by weight of the weight of the whole composition.

34. A composition according to claim 31, 32 or 33, wherein the amount of components b) and d) is above 40% of the weight of the whole composition.

35. A composition according to claim 31, 32, or 33, wherein component d) comprises a dicalcium phosphate.

36. A composition according to any one of claims 31, 35, wherein component d) comprises a highly dispersible silicic acid.

37. A composition according to any one of

claims 31 to 36, wherein component d) has a tapped volume between 250 and 1000 cc/100 g.

38. A composition according to any preceding claim in unit dosage form.

39. A composition according to claim 38, wherein component b) is present in an amount of up to 50 mg/unit dose.

40. A composition according to any preceding claim, wherein the aggregates have a diameter of between 100 Å and 10,000 Å.

41. A composition according to any preceding claim, wherein the aggregates have a diameter of between 400 and 2000 Å.

42. A composition according to any preceding claim, wherein the weight ratio of component b) to component a) is between 10:1 and 50:1.

43. A composition according to any preceding claim, wherein the weight ratio of component b) to component a) is between 20:1 and 30:1.

44. A pharmaceutical composition according to claim 1 substantially as hereinbefore described.

45. Process for preparation of a composition as set forth in any one of the preceding claims which includes the step of formulating aggregates of components a) and b) having at most a diameter of 20,000 Å.

46. Process for the production of a composition as set forth in claim 1 substantially as hereinbefore described.

47. A composition whenever prepared by a process according to claim 45 or 46.

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