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(12) EX PARTE REEXAMINATION CERTIFICATE (9115th)
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(54) **THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY AND DRUG DELIVERY SYSTEMS MADE THEREFROM**

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(51) **Int. Cl.**

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(52) **U.S. Cl.** ..... **264/172.19**; 264/212; 264/217
(58) **Field of Classification Search** ..... None
See application file for complete search history.

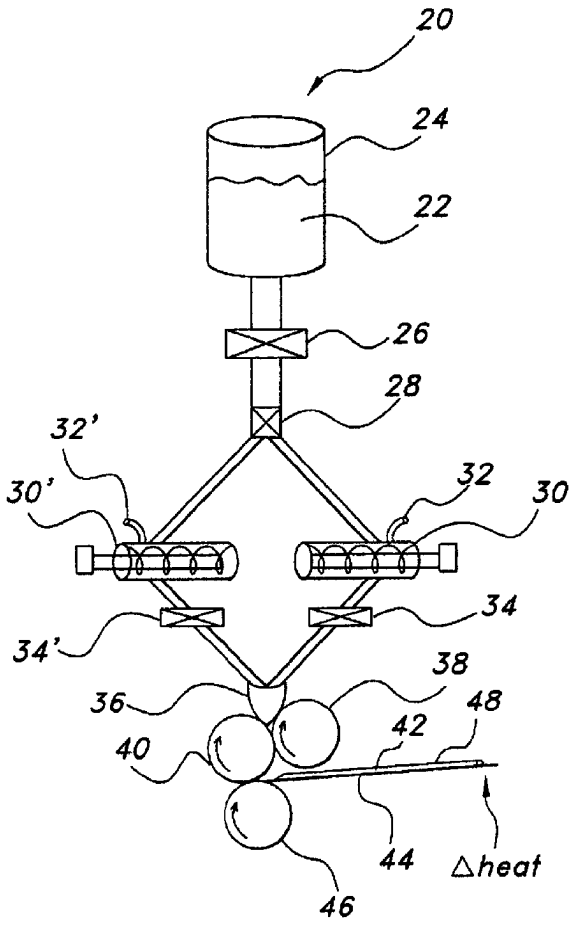
(56) **References Cited**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/012,097, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

*Primary Examiner*—Alan Diamond

(57) **ABSTRACT**

The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film.



# EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

**Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.**

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1**, **10**, **13-15** and **17-22** are determined to be patentable as amended.

Claims **2-9**, **11**, **12** and **16** dependent on an amended claim, are determined to be patentable.

New claims **23-55** are added and determined to be patentable.

**1**. A process for making a self supporting, edible film having a substantially uniform distribution of components comprising:

(a) mixing an edible water-soluble polymer component, water and an active component comprising drug particles to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing; (c) forming a wet film from said deaerated matrix by coating or coating the film; (d) providing a surface having top and bottom sides; (e) feeding said film onto said top side of said surface; and (f) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) **[**rapidiy**]** *rapidly* forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said bottom side of said surface with substantially no top air flow to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**10**. A process for making a self-supporting, edible film dosage unit having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing to prevent cavitation of the matrix in a manner which pulls air into the matrix; (c) forming a wet film from said deaerated wet matrix by coating or casting the film; (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout; and (e) dividing said self-supporting film into dosage forms of substantially equal dimensions, wherein each of said dosage forms is compositionally equal, *whereby said compositional uniform distribution is measured by said substantially equally sized dosage forms which do not vary by more than 10% of active component.*

**13**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing to prevent cavitation of the matrix, thereby reducing formation of air bubbles; (c) forming a wet film from said deaerated wet matrix by coating or casting the film, said film having a top surface, a bottom surface and a depth between said top and bottom surfaces; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout, said dried film having a uniform distribution of said polymer and said solvent components, a uniform weight and a uniform thickness, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**14**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles and water to form an

edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing; (c) forming a wet film from said deaerated wet matrix within a time period before the active degrades by coating or casting the film, said film having a top surface, a bottom surface and a depth between said top and bottom surfaces; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film to initiate drying of the depth of said film prior to forming a polymer skin on said top surface of said film and to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout, said dried film having a uniform distribution of said polymer and said solvent components, a uniform weight and a uniform thickness, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**15**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing to reduce formation of air bubbles; (c) forming a wet edible film from said deaerated wet matrix by coating or casting the film, said film having a top surface and a bottom surface; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film, wherein said air currents are applied to said bottom surface of said film at a velocity greater than to said top surface of said film to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *said active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**17**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, a pharmaceutical active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing; (c) forming a wet edible film from said deaerated wet matrix by coating or casting the film, said film having a top surface, a bottom surface and depth of at least about 500 μm between said top and bottom surfaces; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film, wherein said air currents are less than that which cause surface rippling or skinning prior to drying of the depth of said film, to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**18**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing: (c) forming a wet edible film from said deaerated wet matrix by coating or casting the film, said film having a top surface, a bottom surface and a depth between said top and bottom surfaces; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film to prevent flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film, wherein said dried film is self-supporting and has *active component comprising* drug particles uniformly distributed throughout and said top surface of said dried film is non-rippled, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**19**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) combining and mixing an edible water-soluble polymer component, an active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of said components *including said active component*; (b) deaerating said matrix by mixing to reduce air bubble inclusions and applying a vacuum; (c) forming an edible film from said deaerated matrix by coating or casting the film, said film having a top surface and a bottom surface; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) drying said film from said bottom surface to said top surface *by rapidly increasing the viscosity of said film upon initiation of drying* by applying hot air currents at temperatures of about 60° C. to about 100° C. to said bottom surface of said film unitl a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout is achieved within about the first 4.0 minutes; and (ii) further drying said visco-elastic film to form a self supporting edible film having *active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**20**. A process for making a self supporting, edible film having a substantially uniform distribution of components comprising:

(a) providing a wet matrix having a uniform distribution of edible components, said components comprising a water-soluble polymer component, an active component comprising drug particles water and to form an edible matrix with a compositionally uniform distribution of components *including said active component*; (b) deaerating said matrix by mixing; (c) forming a wet edible film from said deaerated wet matrix by coating or casting the film, said film having a top surface, a bottom surface and a depth between said top and bottom surfaces; and (d) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said film, wherein said air currents are insufficient to cause one or more of the following: (i) surface skinning prior to drying the depth of said film; (ii) surface rippling; (iii) self aggregation of components; (iv) non-uniformity in the thickness of said film; and (v) non-uniformity of mass per unit volume; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *said active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**21**. A process for making a self supporting, edible film having a substantially uniform distribution of components comprising:

(a) combining and mixing an edible water-soluble polymer component, an edible active component comprising drug particles and water to form an edible matrix with a compositionally uniform distribution of components *including said active component*; (b) adding an anti-foaming agent to release oxygen from said mixture of components; (c) further deaerating said matrix by mixing; (d) forming a wet edible film from said deaerated matrix by coating or casting the film; (e) providing a surface having top and bottom sides; (f) feeding said wet film onto said top side of said surface; and (g) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by directing hot air currents at temperatures of about 60° C. to about 100° C. at said bottom side of said surface to prevent air flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self-supporting edible film having *active component comprising* drug particles uniformly distributed throughout, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

**22**. A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a masterbatch premix of an edible water-soluble polymer component and water; (b) deaerating said premix by mixing; (c) feeding a predetermined amount of said deaerated premix via a first metering pump and a control valve to at least one of a first mixer and a second mixer; (d) adding an active component comprising drug particles that degrade with prolonged exposure to water to at least one of said first and second mixers; (e) mixing said active component and said predetermined amount of said premix to form a matrix having a uniform distribution of components *including said active component*; (f) feeding an amount of said matrix to a pan through at least one second metering pump; (g) forming a wet film from said matrix within a time period before the active degrades by coating or casting the film with one or more rollers; (h) providing a surface having top and bottom sides; (i) feeding said film onto said top side of said surface; (j) drying said film within about 10 minutes or fewer, wherein said drying step further comprises: (i) rapidly forming a visco-elastic film having said *active component comprising* drug particles uniformly distributed throughout *by rapidly increasing the viscosity of said film upon initiation of drying* within about the first 4.0 minutes by applying hot air currents at temperatures of about 60° C. to about 100° C. to said bottom side of said surface with substantially no top air flow to prevent air flow migration and intermolecular forces from creating aggregates or conglomerates of said drug particles thereby maintaining the compositional uniform distribution of components *including said active component*; and (ii) further drying said visco-elastic film to form a self supporting edible film having *active component comprising* drug particles uniformly distributed throughout; and (k) removing said self supporting film from said surface, *whereby said compositional uniform distribution is measured by substantially equally sized individual unit doses which do not vary by more than 10% of active component.*

23. The process of claim 1, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

24. The process of claim 10, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

25. The process of claim 13, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

26. The process of claim 14, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

27. The process of claim 15, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

28. The process of claim 17, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

29. The process of claim 18, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

30. The process of claim 19, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

31. The process of claim 20, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

32. The process of claim 21, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

33. The process of claim 22, wherein said step of further drying said visco-elastic film comprises drying to obtain a self-supporting edible film having a water content of no more than 10% by weight.

34. The process of claim 1, wherein said step of feeding said wet film onto the top surface comprises feeding said wet film onto the top surface of an already-formed film layer.

35. The process of claim 10, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

36. The process of claim 13, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

37. The process of claim 14, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

38. The process of claim 15, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

39. The process of claim 17, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

40. The process of claim 18, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

41. The process of claim 19, wherein said step of coating or casting said edible film comprises coating or casting said edible film onto the top surface of an already-formed film layer.

42. The process of claim 20, wherein said step of coating or casting said wet film comprises coating or casting said wet film onto the top surface of an already-formed film layer.

43. The process of claim 21, wherein said step of feeding said wet film onto the top surface comprises feeding said wet film onto the top surface of an already-formed film layer.

44. The process of claim 22, wherein said step (i) of feeding said film comprises feeding said film onto the top surface of an already-formed film layer.

45. The process of claim 1, wherein said active component is in the form of a solution, emulsion, or suspension.

46. The process of claim 10, wherein said active component is in the form of a solution, emulsion, or suspension.

47. The process of claim 13, wherein said active component is in the form of a solution, emulsion, or suspension.

48. The process of claim 14, wherein said active component is in the form of a solution, emulsion, or suspension.

49. The process of claim 15, wherein said active component is in the form of a solution, emulsion, or suspension.

50. The process of claim 17, wherein said active component is in the form of a solution, emulsion, or suspension.

51. The process of claim 18, wherein said active component is in the form of a solution, emulsion, or suspension.

52. The process of claim 19, wherein said active component is in the form of a solution, emulsion, or suspension.

53. The process of claim 20, wherein said active component is in the form of a solution, emulsion, or suspension.

54. The process of claim 21, wherein said active component is in the form of a solution, emulsion, or suspension.

55. The process of claim 22, wherein said active component is in the form of a solution, emulsion, or suspension.

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