EUTECTIC FORMULATIONS OF CYCLOBENZAPRINE HYDROCHLORIDE AND AMITRIPTYLINE HYDROCHLORIDE

Related Application

[0001] This application claims priority and benefit from U.S. Provisional Patent Application 61/792,757, filed March 15, 2013, the contents and disclosures of which are incorporated by reference in their entirety.

Background of the Invention

[0002] Cyclobenzaprine, or 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine, was first approved by the U.S. Food and Drug Administration in 1977 for the treatment of acute muscle spasms of local origin. (Katz, W., et al., Clinical Therapeutics 10:216-228 (1988)). Amitriptyline, or 3-(10,11-dihydro-5H-dibenzo [a,d] cycloheptene-5-ylidene)-*N*,*N*-dimethyl-1-propanamine, was first approved by the U.S. Food and Drug Administration for the treatment of depression.

[0003] Subsequent studies have shown cyclobenzaprine to also be effective in the treatment of fibromyalgia syndrome, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), generalized anxiety disorder and depression. Furthermore, the utility of cyclobenzaprine as an agent for improving the quality of sleep, as a sleep deepener, or for treating sleep disturbances has been investigated. However, while FDA-approved therapeutics address pain and mood, there are currently no FDA-approved treatments that address the disturbed sleep and fatigue

associated with fibromyalgia syndrome. Treatment with cyclobenzaprine may be particularly useful in treating sleep disturbances caused by, exacerbated by, or associated with fibromyalgia syndrome, prolonged fatigue, chronic fatigue, chronic fatigue syndrome, a sleep disorder, a psychogenic pain disorder, chronic pain syndrome (type II), the administration of a drug, autoimmune disease, stress or anxiety, or for treating an illness caused by or exacerbated by sleep disturbances, and symptoms of such illness. See, for example, U.S. Patent Nos. 6,395,788 and 6,358,944, incorporated herein by reference.

[0004] Cyclobenzaprine HCl or Amitriptyline HCl Active Pharmaceutical Ingredients (or APIs) are stable in pill, tablet or capsule formulations for oral administration when combined with certain excipients. However, Cyclobenzaprine HCl or Amitriptyline HCl have slow absorption when ingested by mouth (per oral, or po). To speed absorption, tablets containing Cyclobenzaprine HCl or Amitriptyline HCl have been formulated in various sublingual (SL) preparations. However, both sublingual and oral formulations can have issues with the stability of the APIs and the physical compositions themselves, especially when a basifying agent (a chemical compound that increases the pH of solutions after dissolution of Cyclobenzaprine HCl or Amitriptyline HCl) is present. Therefore, a method or composition that increases stability of Cyclobenzaprine HCl or Amitriptyline HCl (with or without the presence of a basifying agent) in a formulation would be useful.

Summary of the Invention

[0005] Some embodiments of the invention are:

1. A pharmaceutical composition comprising a eutectic of mannitol and Cyclobenzaprine HCl.

2. The pharmaceutical composition of embodiment 1, comprising 60%-90% Cyclobenzaprine HCl and 40%-10% mannitol by weight.

3. The pharmaceutical composition of embodiment 2, comprising amounts of Cyclobenzaprine HCl and mannitol selected from: 60%±2% Cyclobenzaprine HCl

and 40%±2% mannitol, 65%±2% Cyclobenzaprine HCl and 35%±2% mannitol, 70%±2% Cyclobenzaprine HCl and 30%±2% mannitol, 75%±2% Cyclobenzaprine HCl and 25%±2% mannitol, 80%±2% Cyclobenzaprine HCl and 20%±2% mannitol, 85%±2% Cyclobenzaprine HCl and 15%±2% mannitol, and 90%±2% Cyclobenzaprine HCl and 10%±2% mannitol by weight.

4. The pharmaceutical composition of embodiment 3, comprising 75%±2% Cyclobenzaprine HCl and 25%±2% mannitol by weight.

5. The pharmaceutical composition of any one of embodiments 1-4, wherein the Cyclobenzaprine HCl:mannitol molar ratio is 1.76±0.1.

6. The pharmaceutical composition of any one of embodiments 1-5, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.

7. The pharmaceutical composition of any one of embodiments 1-6, further comprising a basifying agent.

8. The pharmaceutical composition of embodiment 7, wherein the basifying agent is K_2HPO_4.

9. The pharmaceutical composition of embodiment 7, wherein the basifying agent is Na_2HPO_4.

10. The pharmaceutical composition of embodiment 7, wherein the basifying agent is trisodium citrate, anhydrous.

11. A method of manufacturing a eutectic composition of any one of embodiments 1-10, comprising mixing Cyclobenzaprine HCl and mannitol or milling Cyclobenzaprine HCl and mannitol.

12. The method of embodiment 11, comprising milling Cyclobenzaprine HCl and mannitol.

13. The method of embodiment 12, wherein, the Cyclobenzaprine HCl and mannitol are milled in a high shear granulator.

14. The method of embodiment 11, comprising mixing Cyclobenzaprine HCl and mannitol.

15. The method of embodiment 14, wherein the Cyclobenzaprine HCl and mannitol are mixed via compression.

16. The method of embodiment 15, wherein the Cyclobenzaprine HCl and mannitol are compressed via roller compaction.

17. A method of manufacturing a eutectic composition of any one of embodiments 1-10, comprising spray drying Cyclobenzaprine HCl and mannitol.

18. The method of any one of embodiments 11-17, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.

19. The method of any one of embodiments 11-18, wherein the pharmaceutical composition comprises a basifying agent.

20. The method of embodiment 19, wherein the basifying agent is K_2HPO_4.

21. The method of embodiment 19, wherein the basifying agent is Na_2HPO_4.

22. The method of embodiment 19, wherein the basifying agent is trisodium citrate, anhydrous.

23. A pharmaceutical composition comprising a eutectic of mannitol and Amitriptyline HCl.

24. The pharmaceutical composition of embodiment 23, wherein the eutectic mixture melts at 133±3°C.

25. The pharmaceutical composition of embodiment 23, comprising 60%-90% Amitriptyline HCl and 40%-10% mannitol by weight.

26. The pharmaceutical composition of embodiment 25, comprising amounts of Amitriptyline HCl and mannitol selected from: 40%±2% Amitriptyline HCl and 60%±2% mannitol, 45%±2% Amitriptyline HCl and 55%±2% mannitol, 50%±2%

Amitriptyline HCl and 50%±2% mannitol, 55%±2% Amitriptyline HCl and 45%±2% mannitol, 60%±2% Amitriptyline HCl and 40%±2% mannitol, 65%±2% Amitriptyline HCl and 35%±2% mannitol, 70%±2% Amitriptyline HCl and 30%±2% mannitol, 75%±2% Amitriptyline HCl and 25%±2% mannitol, 80%±2% Amitriptyline HCl and 20%±2% mannitol, 85%±2% Amitriptyline HCl and 15%±2% mannitol, and 90%±2% Amitriptyline HCl and 10%±2% mannitol by weight.

27. The pharmaceutical composition of embodiment 26, comprising 75%±2% Amitriptyline HCl and 25%±2% mannitol by weight.

28. The pharmaceutical composition of embodiment 26, comprising 50%±2% Amitriptyline HCl and 50%±2% mannitol by weight.

29. The pharmaceutical composition of any one of embodiments 23-28, wherein the Amitriptyline HCl is micronized Amitriptyline HCl.

30. The pharmaceutical composition of any one of embodiments 23-29, further comprising a basifying agent.

31. The pharmaceutical composition of embodiment 30, wherein the basifying agent is K_2HPO_4.

32. The pharmaceutical composition of embodiment 30, wherein the basifying agent is Na_2HPO_4.

33. The pharmaceutical composition of embodiment 30, wherein the basifying agent is trisodium citrate, anhydrous.

34. The pharmaceutical composition of any one of embodiments 1-10 and 23-33, wherein the mannitol is β mannitol.

35. The pharmaceutical composition of embodiment 34, wherein the composition comprises Cyclobenzaprine HCl and the eutectic melts at 143.6±3 °C.

36. The pharmaceutical composition of any one of embodiments 1-10 and 23-33, wherein the mannitol is δ mannitol.

37. The pharmaceutical composition of embodiment 36, wherein the composition comprises Cyclobenzaprine HCl and the eutectic melts at 134 °C±3 °C.

38. A method of manufacturing a eutectic composition of any one of embodiments 23-35, comprising mixing Amitriptyline HCl and mannitol or milling Amitriptyline HCl and mannitol.

39. The method of embodiment 38, comprising milling Amitriptyline HCl and mannitol.

40. The method of embodiment 39, wherein, the Amitriptyline HCl and mannitol are milled in a high shear granulator.

41. The method of embodiment 38, comprising mixing Amitriptyline HCl and mannitol.

42. The method of embodiment 41, wherein the Amitriptyline HCl and mannitol are mixed via compression.

43. The method of embodiment 42, wherein the Amitriptyline HCl and mannitol are compressed via roller compaction.

44. A method of manufacturing a eutectic composition of any one of embodiments 23-34 and 36, comprising spray drying Amitriptyline HCl and mannitol.

45. The method of any one of embodiments 38-44, wherein the Amitriptyline HCl is micronized Amitriptyline HCl.

46. The method of any one of embodiments 38-45, wherein the pharmaceutical composition comprises a basifying agent.

47. The method of embodiment 46, wherein the basifying agent is K_2HPO_4.

48. The method of embodiment 46, wherein the basifying agent is Na_2HPO_4.

49. The method of embodiment 46, wherein the basifying agent is trisodium citrate, anhydrous.

50. The method of any one of embodiments 11-22 and 38-49, wherein the eutectic composition comprises β mannitol.

51. The method of embodiment 50, wherein the composition comprises Cyclobenzaprine HCl and the eutectic melts at 143.6±3 °C.

52. The method of any one of embodiments 11-22 and 38-49, wherein the eutectic composition comprises δ mannitol.

53. The method of embodiment 52, wherein the composition comprises Cyclobenzaprine HCl and the eutectic melts at 134 °C±3 °C.

Brief Description of the Drawings

[0006] Fig. 1: DSC heating curve of Cyclobenzaprine HCl.

[0007] Fig. 2: DSC heating curve of Cyclobenzaprine HCl + Sodium stearyl Fumarate 1:1.

[0008] Fig. 3: DSC heating curve of Cyclobenzaprine HCl + Sodium stearyl Fumarate, formulation ratio.

[0009] Fig. 4: DSC heating curve of Cyclobenzaprine HCl + Potassium Phosphate dibasic 1:1.

[0010] Fig. 5: DSC heating curve of Cyclobenzaprine HCl + Potassium Phosphate dibasic, formulation ratio.

[0011] Fig. 6: DSC heating curve of Cyclobenzaprine HCl + Crospovidone (Kollidon CL) 1:1.

[0012] Fig. 7: DSC heating curve of Cyclobenzaprine HCl + Silicon (colloidal) 1:1.

[0013] Fig. 8: DSC heating curve of Cyclobenzaprine HCl + Pearlitol Flash® 1:1.

[0014] Fig. 9: DSC heating curve of Cyclobenzaprine HCl + Pearlitol Flash®, formulation ratio.

[0015] Fig. 10: DSC heating curve of Cyclobenzaprine HCl +Opadry Clear 1:1.

[0016] Fig. 11: DSC heating curve of Cyclobenzaprine HCl + Opadry II Clear 1:1.

[0017] Fig. 12: DSC heating curve relative to final, formulation mixture.

[0018] Fig. 13: DSC heating curve relative to the tablet at time zero of Cyclobenzaprine HCl.

[0019] Fig. 14: DSC heating curve relative to the tablet of Cyclobenzaprine HCl at 40°C.

[0020] Fig. 15: DSC heating curve relative to tablet Cyclobenzaprine HCl after storage at 50°C.

[0021] Fig. 16: DSC heating curve of Cyclobenzaprine HCl.

[0022] Fig. 17: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate anhydrous 1:1 (mixture A).

[0023] Fig. 18: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate anhydrous 1:1 (mixture B).

[0024] Fig. 19: Comparison of DSC heating curves of Cyclobenzaprine HCl + Sodium phosphate anhydrous 1:1 (mixture A & B).

[0025] Fig. 20: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate dihydrate 1:1 (mixture A).

[0026] Fig. 21: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate dihydrate 1:1 (mixture B).

[0027] Fig. 22: Comparison of DSC heating curves of Cyclobenzaprine HCl + Sodium phosphate dihydrate 1:1 (mixture A & B).

[0028] Fig. 23: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate heptahydrate 1:1 (mixture A).

[0029] Fig. 24: DSC heating curve of Cyclobenzaprine HCl + Sodium phosphate heptahydrate 1:1 (mixture B).

[0030] Fig. 25: Comparison of DSC heating curves of Cyclobenzaprine HCl + Sodium phosphate heptahydrate 1:1 (mixture A & B).

[0031] Fig. 26: DSC heating curve of Cyclobenzaprine HCl + Sodium citrate dihydrate 1:1 (mixture A).

[0032] Fig. 27: DSC heating curve of Cyclobenzaprine HCl + Sodium citrate dihydrate 1:1 (mixture B).

[0033] Fig. 28: Comparison of DSC heating curves of Cyclobenzaprine HCl + Sodium citrate dihydrate 1:1 (mixture A & B).

[0034] Fig. 29: DSC heating curve of Cyclobenzaprine HCl + Effersoda®Effersoda®® 1:1 (mixture A).

[0035] Fig. 30: DSC heating curve of Cyclobenzaprine HCl + Effersoda®Effersoda®® 1:1 (mixture B).

[0036] Fig. 31: Comparison of DSC heating curves of Cyclobenzaprine HCl + Effersoda® 1:1 (mixture A & B).

[0037] Fig. 32: DSC heating curve of Cyclobenzaprine HCl + Sorbitol 1:1 (mixture A).

[0038] Fig. 33: DSC heating curve of Cyclobenzaprine HCl + Sorbitol 1:1 (mixture B).

[0039] Fig. 34: Comparison of DSC heating curves of Cyclobenzaprine HCl + Sorbitol 1:1 (mixture A & B).

[0040] Fig. 35: Stacking of XRPD patterns of Cyclobenzaprine HCl + Sorbitol 1:1 (mixture B).

[0041] Fig. 36: DSC heating curve of Cyclobenzaprine HCl + Mannitol 1:1 (mixture A).

[0042] Fig. 37: DSC heating curve of Cyclobenzaprine HCl + Mannitol 1:1 (mixture B).

[0043] Fig. 38: Comparison of DSC heating curves of Cyclobenzaprine HCl + Mannitol 1:1 (mixture A & B).

[0044] Fig. 39: DSC heating curve of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A).

[0045] Fig. 40: DSC heating curve of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A).

[0046] Fig. 41: Comparison of DSC heating curves of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A & B).

[0047] Fig. 42: DSC heating curve of Cyclobenzaprine HCl + Disodium glycine carbonate 1:1 (mixture A).

[0048] Fig. 43: DSC heating curve of Cyclobenzaprine HCl + Disodium glycine carbonate 1:1 (mixture B).

[0049] Fig. 44: Comparison of DSC heating curve of Cyclobenzaprine HCl + Disodium glycine carbonate 1:1 (mixture A & B).

[0050] Fig. 45: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A).

[0051] Fig. 46: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A).

[0052] Fig. 47: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A).

[0053] Fig. 48: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Trisodium citrate anhydrous 1:1 (mixture A & B).

[0054] Fig. 49: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Disodium Glycine carbonate 1:1 (mixture A).

[0055] Fig. 50: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Disodium Glycine carbonate 1:1 (mixture A).

[0056] Fig. 51: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Disodium Glycine carbonate 1:1 (mixture A).

[0057] Fig. 52: FT-IR/ATR spectra stacking of Cyclobenzaprine HCl + Disodium Glycine carbonate 1:1 (mixture A & B).

[0058] Fig. 53: DSC heating curve of Cyclobenzaprine HCl.

[0059] Fig. 54: DSC heating curve of Mannitol, beta form.

[0060] Fig. 55: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 15% of API.

[0061] Fig. 56: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 30% of API.

[0062] Fig. 57: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 40% of API.44

[0063] Fig. 58: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 45% of API.

[0064] Fig. 59: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 50% of API.

[0065] Fig. 60: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 65% of API.

[0066] Fig. 61: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 75% of API.

[0067] Fig 62: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 80% of API.

[0068] Fig. 63: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 90% of API.

[0069] Fig. 64: DSC heating curve of a mixture of Cyclobenzaprine HCl and Mannitol at 95% of API.

[0070] Fig. 65: Phase diagram of binary mixtures between Cyclobenzaprine HCl and Mannitol.

[0071] Fig. 66: Plot of melting enthalpy as function of API percentage.

[0072] Fig. 67: XRPD pattern of Cyclobenzaprine HCl.

[0073] Fig. 68: XRPD peaks of Cyclobenzaprine HCl (table).

[0074] Fig. 69: XRPD pattern of Mannitol, beta form.

[0075] Fig. 70: XRPD peaks of Mannitol, beta form (table).

[0076] Fig. 71: Stacking of XRPD patterns of pure compounds and eutectic mixture.

[0077] Fig. 72: Stacking of XRPD patterns of pure compounds and mixtures.

[0078] Fig. 73: Linearity of Mannitol peaks in the range of 14.1-15° 2θ.

[0079] Fig. 74: Linearity of API peaks in the range of 12.5-13.3° 2θ.

[0080] Fig. 75: DSC heating curve of Amitriptyline HCl.

[0081] Fig. 76: DSC heating curve of Amitriptyline HCl + Sodium stearyl Fumarate 1:1.

[0082] Fig. 77: DSC heating curve of Amitriptyline HCl + Stearic acid 1:1.

[0083] Fig. 78: DSC heating curve of Amitriptyline HCl + Glycerol dibehenate 1:1.

[0084] Fig. 79: DSC heating curve of Amitriptyline HCl + Magnesium stearate 1:1.

[0085] Fig. 80: DSC heating curve of Amitriptyline HCl + Pearlitol flash 1:1.

[0086] Fig. 81: Eutectic evaluation of DSC heating curve of API + Pearlitol 1:1.

[0087] Fig. 82: DSC heating curve of Amitriptyline HCl + Pearlitol 200 SD/Mannitol 1:1.

[0088] Fig. 83: Eutectic evaluation of DSC heating curve of API + Pearlitol/mannitol 1:1.

[0089] Fig. 84: DSC heating curve of Amitriptyline HCl + Unipure DW/Corn starch partially pregelatinized 1:1.

[0090] Fig. 85: DSC heating curve of Amitriptyline HCl + Crospovidone – Kollidon CL 1:1.

[0091] Fig. 86: DSC heating curve of Amitriptyline HCl + Silicon Colloidal/Aerosil 200 1:1.

[0092] Fig. 87: DSC heating curve of Amitriptyline HCl + Sodium phosphate dibasic 1:1.

[0093] Fig. 88: DSC heating curve of Amitriptyline HCl + Sodium bicarbonate 1:1.

[0094] Fig. 89: DSC heating curve of Amitriptyline HCl + Sodium carbonate 1:1.

[0095] Fig. 90: DSC heating curve of Amitriptyline HCl + Sodium phosphate dodecahydrate 1:1.

[0096] Fig. 91: DSC heating curve of Amitriptyline HCl + Sodium phosphate anhydrous 1:1.

[0097] Fig. 92: SEM of particles formed by wet granulation.

[0098] Fig. 93: SEM of pure Cyclobenzaprine HCl.

[0099] Fig. 94: SEM of pure mannitol.

[0100] Fig. 95: wet granulated eutectic particle size distribution.

[0101] Fig. 96: wet granulated eutectic pore volume over diameter.

[0102] Fig. 97: DSC heating curve of the Cyclobenzaprine HCl/mannitol eutectic.

[0103] Fig. 98: XRPD pattern of the Cyclobenzaprine HCl/mannitol eutectic.

[0104] Fig. 99: SEM of spray dried mannitol.

[0105] Fig. 100: SEM of spray dried mannitol.

[0106] Fig. 101: DSC heating curve of spray dried mannitol.

[0107] Fig. 102: DSC heating curve of 25% Cyclobenzaprine HCl by weight ±75% mannitol by weight, spray dried.

[0108] Fig. 103: DSC heating curve of 50% Cyclobenzaprine HCl by weight ±50% mannitol by weight, spray dried.

[0109] Fig. 104: DSC heating curve of 75% Cyclobenzaprine HCl by weight ±25% mannitol by weight, spray dried.

[0110] Fig. 105: DSC heating curve of 90% Cyclobenzaprine HCl by weight ±10% mannitol by weight, spray dried.

[0111] Fig. 106: Phase diagram of the eutectic formed between Cyclobenzaprine HCl and δ mannitol after spray drying.

[0112] Fig. 107: XRPD pattern of Cyclobenzaprine HCl and spray dried mannitol.

[0113] Fig. 108: Overlaid XRPD patterns from 25% Cyclobenzaprine HCl by weight ±75% mannitol by weight, spray dried; 50% Cyclobenzaprine HCl by weight ±50% mannitol by weight, spray dried; 75% Cyclobenzaprine HCl by weight ±25% mannitol by weight, spray dried; and 90% Cyclobenzaprine HCl by weight ±10% mannitol by weight, spray dried.

[0114] Fig. 109: SEM of the Cyclobenzaprine HCl/δ mannitol eutectic.

[0115] Fig. 110: SEM of the Cyclobenzaprine HCl/δ mannitol eutectic.

[0116] Fig. 111: Spray dried eutectic particle size distribution.

[0117] Fig. 112: Spray dried eutectic pore volume over diameter.

[0118] Fig. 113: XRPD patterns of 25% mannitol + 75% Cyclobenzaprine HCl, spray dried; and Cyclobenzaprine HCl.

[0119] Fig. 114: XRPD patterns of 25% mannitol + 75% Cyclobenzaprine HCl, spray dried; and Cyclobenzaprine HCl.

[0120] Fig. 115: XRPD patterns of 25% mannitol + 75% Cyclobenzaprine HCl, spray dried; Cyclobenzaprine HCl; and spray dried mannitol.

[0121] Fig. 116: XRPD patterns of 25% mannitol + 75% Cyclobenzaprine HCl, spray dried; Cyclobenzaprine HCl; and spray dried mannitol.

[0122] Fig. 117: Theoretical Ionization of Cyclobenzaprine HCl at different pHs.

[0123] Fig. 118: Dissolution test of the wet granulated (WG) Cyclobenzaprine eutectic in 1) sodium acetate and sodium chloride; 2) potassium phosphate monobasic; 3) sodium pyrophosphate, and 4) sodium acetate at pH 4.5 over 60 minutes.

[0124] Fig. 119: Dissolution test of the Cyclobenzaprine HCl (API); the Cyclobenzaprine HCl/mannitol eutectic formed from wet granulation (WG); the Cyclobenzaprine HCl/mannitol eutectic formed from dry mixing (MIX); and the Cyclobenzaprine HCl/mannitol eutectic formed from spray drying (SD) in sodium pyrophosphate and methocel at pH 4.5 over 6 hours.

[0125] Fig. 120: Closeup of the dissolution test of Fig. 119 over the first 60 minutes.

Detailed Description of the Invention

[0126] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, pharmacology, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

[0127] The methods and techniques of the present invention are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification.

[0128] Chemistry terms used herein are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

[0129] All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by

reference herein. In case of conflict, the present specification, including its specific definitions, will control.

[0130] Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

[0131] The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

[0132] The term "including" is used to mean "including but not limited to." "Including" and "including but not limited to" are used interchangeably.

[0133] A "patient", "subject", or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

[0134] "Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms associated with a disease or condition as described herein.

[0135] "Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered sublingually or intranasally, by inhalation into the lung or rectally. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods. In some aspects, the administration includes both direct administration, including self-administration, and indirect administration, including the act of prescribing a drug. For example, as used herein, a physician who instructs a patient to self-administer a drug, or to have the drug administered by

another and/or who provides a patient with a prescription for a drug is administering the drug to the patient.

[0136] In solid drug product formulation, the knowledge of possible interactions between the drug substance and the excipients is a crucial point for the prediction of chemical and physical stability.

[0137] Very often the excipients can modify the biological activity and chemical stability of the API because the dissolution or chemical structures are changed. In some cases, the excipient can improve the chemical stability profile over time and avoid undesirable physical behavior of the final dosage form.

[0138] A eutectic system is a mixture of chemical compounds or elements that has a single chemical composition that melts at a lower temperature than any other composition made up of the same ingredients. A composition comprising a eutectic is known as the eutectic composition and its melting temperature is known as the eutectic temperature. To define a eutectic composition, a binary phase diagram should be built by analyzing different compounds ratios.

[0139] The effect of a eutectic on tablet properties shows that compaction provides the intimate contact and mutual solubility sufficient for eutectic formation. Eutectic compositions often have higher stability and/or dissolution rates than their non-eutectic counterparts. Because eutectics enhance dissolution, they can be employed to increase permeability in solid dispersions and dispersion systems. However, in the development of certain tableted dosage forms, undesired eutectic formation (during manufacturing operation such as wet granulation), can lead to unwanted changes in physical or chemical characteristics of the tablet, such as low eutectic melting temperature, sticking, unpredictable hardness, instability or difficulties in accelerated assessment of stability.

[0140] Mannitol and Sorbitol are excipients commonly used in solid drug products. Mannitol and Sorbitol are 6-carbon sugar alcohols isomers. Sugar alcohols are hydrogenated carbohydrates whose carbonyl group has been reduced

to a primary or secondary hydroxyl group. Other 6-carbon sugar alcohols include Inositol, Galactitol, Fucitol, and Iditol.

[0141] Although Mannitol and Sorbitol can be included in pharmaceutical compositions, it is typically because they provide qualitative benefits such as sweet taste or a cooling effect in the mouth, but are physically inert. Thus, it was surprising to discover that mannitol formed a eutectic composition with Cyclobenzaprine HCl and with Amitriptyline HCl. By contrast, sorbitol dissolved Cyclobenzaprine HCl and did not form a eutectic, underscoring the unpredictability of eutectic formation and the protective effect of the eutectic formed with mannitol. Without wishing to be bound by theory, it is possible that the two co-penetrating crystal lattices of mannitol and Cyclobenzaprine HCl provide protection of the Cyclobenzaprine HCl from hydration and other chemical interactions.

Compounds

[0142] The compounds useful in embodiments of the present invention include Cyclobenzaprine HCl and Amitriptyline HCl. In some embodiments, the compounds are micronized. In alternative embodiments, the compounds are not micronized. In some embodiments, the compounds may be present in one or more crystal isoforms.

[0143] As used herein, "Cyclobenzaprine HCl" refers to the pharmaceutically acceptable cyclobenzaprine hydrochloride salt of cyclobenzaprine.

[0144] As used herein, "Amitriptyline HCl" refers to the pharmaceutically acceptable amitriptyline hydrochloride salt of amitriptyline.

Eutectic compositions

[0145] In some embodiments, the invention provides a pharmaceutical composition comprising a eutectic mixture of mannitol and an active pharmaceutical ingredient. In certain embodiments, the active pharmaceutical ingredient is Cyclobenzaprine HCl or Amitriptyline HCl.

[0146] In some embodiments, the invention provides a pharmaceutical composition comprising a eutectic mixture of mannitol and Cyclobenzaprine HCl. In certain embodiments (for example, when the composition comprises a β mannitol eutectic), the eutectic has a melting temperature of 143.6±3 °C. In certain embodiments, a melting temperature of the eutectic is approximately 135.6 °C, 136.6 °C, 137.6 °C, 138.6 °C, 139.6 °C, 140.6 °C, 141.6 °C, 142.6 °C, 143.6 °C, 144.6 °C, 145.6 °C, 146.6 °C, 147.6 °C, 148.6 °C, 149.6 °C, 150.6 °C, 151.6 °C, 152.6 °C, or 153.6 °C. In certain embodiments (for example, when the composition comprises a δ mannitol eutectic), the eutectic has a melting temperature of 134±3 °C. In certain embodiments (for example, when the composition comprises a δ mannitol eutectic), a melting temperature of the eutectic is approximately 124 °C, 125 °C, 126 °C, 127 °C, 128 °C, 129 °C, 130 °C, 131 °C, 132 °C, 133 °C, 134 °C, 135 °C, 136 °C, 137 °C, 138 °C, 139 °C, 140 °C, 141 °C, 142 °C, 143 °C, or 144 °C. In particular embodiments, the melting temperature of the eutectic is the temperature at which melting begins. In alternative embodiments, the melting temperature of the eutectic is the temperature at which maximum melting is observed. In certain embodiments, the composition comprises greater than 5% Cyclobenzaprine HCl and less than 95% mannitol by weight. In certain embodiments, the composition comprises 1%-5% Cyclobenzaprine HCl and 99%-95% mannitol by weight. In certain embodiments, the composition comprises 5%-10% Cyclobenzaprine HCl and 95%-90% mannitol by weight. In certain embodiments, the composition comprises 10%-20% Cyclobenzaprine HCl and 90%-80% mannitol by weight. In certain embodiments, the composition comprises 10%-90% Cyclobenzaprine HCl and 90%-10% mannitol by weight, for example, 60%-90% Cyclobenzaprine HCl and 40%-10% mannitol or 70%-80% Cyclobenzaprine HCl and 30%-20% mannitol by weight. Exemplary compositions comprise 60%±2% Cyclobenzaprine HCl and 40%±2% mannitol, 65%±2% Cyclobenzaprine HCl and 35%±2% mannitol, 70%±2% Cyclobenzaprine HCl and 30%±2% mannitol, 75%±2% Cyclobenzaprine HCl and 25%±2% mannitol, 80%±2% Cyclobenzaprine HCl and 20%±2% mannitol, 85%±2% Cyclobenzaprine HCl and 15%±2% mannitol, and 90%±2% Cyclobenzaprine HCl and 10%±2% mannitol by weight. In certain embodiments,

a composition comprises 75%±10% Cyclobenzaprine HCl and 25%±10% mannitol by weight. In certain embodiments, a composition comprises 75%±2% Cyclobenzaprine HCl and 25%±2% mannitol by weight. In certain embodiments, a composition comprises 75% Cyclobenzaprine HCl and 25% mannitol by weight. In certain embodiments, the composition comprises Cyclobenzaprine HCl and mannitol in a Cyclobenzaprine HCl:mannitol molar ratio of 1.70±0.1 to 1.80±0.1. In certain embodiments, the molar ratio is about 1.6 to 2.0. In particular embodiments, the molar ration is 1.70±0.1, 1.71±0.1, 1.72±0.1, 1.73±0.1, 1.74±0.1, 1.75±0.1, 1.76±0.1, 1.77±0.1, 1.78±0.1, 1.79±0.1, or 1.80±0.1. In certain embodiments, the molar ratio is 1.60±0.5, 1.65±0.5, 1.70±0.5, 1.75±0.5, 1.80±0.5, 1.85±0.5, 1.90±0.5, 1.95±0.5, or 2.0±0.5. In certain embodiments the molar ratio is 1.76±0.1. In certain embodiments the molar ratio is 1.76±0.5.

[0147] In some embodiments, the invention provides a pharmaceutical composition comprising a eutectic mixture of mannitol and Amitriptyline HCl. In certain embodiments, the composition has a melting temperature of 133±3 °C. In certain embodiments, a melting temperature of the composition is approximately 125 °C, 126 °C, 127 °C, 128 °C, 129 °C, 130 °C, 131 °C, 132 °C, 133 °C, 134 °C, 135 °C, 136 °C, 137 °C, 138 °C, 139 °C, 140 °C, 141 °C, 142 °C, or 143 °C. In particular embodiments, the melting temperature of the eutectic is the temperature at which melting begins. In alternative embodiments, the melting temperature of the eutectic is the temperature at which maximum melting is observed. In certain embodiments, the composition comprises greater than 5% Amitriptyline HCl and less than 95% mannitol by weight. In certain embodiments, the composition comprises 1%-5% Amitriptyline HCl and 99%-95% mannitol by weight. In certain embodiments, the composition comprises 5%-10% Amitriptyline HCl and 95%-90% mannitol by weight. In certain embodiments, the composition comprises 10%-20% Amitriptyline HCl and 90%-80% mannitol by weight. In certain embodiments, the composition comprises 10%-90% Amitriptyline HCl and 90%-10% mannitol by weight, for example, 60%-90% Amitriptyline HCl and 40%-10% mannitol or 70%-80% Amitriptyline HCl and 30%-20% mannitol by weight. Exemplary compositions comprise 60%±2% Amitriptyline HCl and 40%±2% mannitol, 65%±2% Amitriptyline HCl and 35%±2% mannitol, 70%±2%

Amitriptyline HCl and 30%±2% mannitol, 75%±2% Amitriptyline HCl and 25%±2% mannitol, 80%±2% Amitriptyline HCl and 20%±2% mannitol, 85%±2% Amitriptyline HCl and 15%±2% mannitol, and 90%±2% Amitriptyline HCl and 10%±2% mannitol by weight. In certain embodiments, a composition comprises 75%±10% Amitriptyline HCl and 25%±10% mannitol by weight. In certain embodiments, a composition comprises 75%±2% Amitriptyline HCl and 25%±2% mannitol by weight. In certain embodiments, a composition comprises 75% Amitriptyline HCl and 25% mannitol by weight. In certain embodiments, the composition comprises Amitriptyline HCl and mannitol in an Amitriptyline HCl:mannitol molar ratio 1.70±0.1 to 1.80±0.1. In certain embodiments, the molar ratio is of 1.70±0.1, 1.71±0.1, 1.72±0.1, 1.73±0.1, 1.74±0.1, 1.75±0.1, 1.76±0.1, 1.77±0.1, 1.78±0.1, 1.79±0.1, or 1.80±0.1. In certain embodiments the molar ratio is 1.76±0.1.

[0148] Another benefit of the eutectic compositions of the invention is increased stability of a tablet containing Cyclobenzaprine HCl. In some embodiments, the invention provides a pharmaceutical composition comprising Cyclobenzaprine HCl and mannitol or Amitriptyline HCl and mannitol, wherein the composition has an increased stability in tablet form as compared to the same tablet without mannitol, e.g., to a tablet comprising sorbitol but not mannitol. Indeed, a tablet containing Cyclobenzaprine HCl, K_2HPO_4, and mannitol was stable for three months at 40 °C and 75% relative humidity. By contrast, a tablet containing Cyclobenzaprine HCl, K_2HPO_4, and sorbitol stored at the same conditions disintegrated before reaching even reaching one week.

[0149] In some embodiments, the invention provides a pharmaceutical composition comprising Cyclobenzaprine HCl and mannitol or Amitriptyline HCl and mannitol, wherein the composition has an increased dissolution rate of a stable tablet compared to Cyclobenzaprine HCl or Amitriptyline HCl alone or in a formulation containing one or more excipients that are not basifying agents. For example, the composition at 5 minutes can exhibit greater than 55%, greater than 50%, greater than 45%, greater than 40%, greater than 35%, greater than 30%, or greater than 25% dissolution when mixed with 100 mL of 50 mM Citrate pH 4 at

37.0 ± 0.5 °C. For example, the composition at 10 minutes can exhibit greater than 80%, greater than 75%, greater than 65%, greater than 60%, greater than 55%, greater than 50%, dissolution when mixed with 100 mL of 50 mM Citrate pH 4 at 37.0 ± 0.5 °C. For example, the composition at 240 minutes can exhibit greater than 80%, greater than 75%, greater than 65%, greater than 60%, greater than 55%, greater than 50%, dissolution when mixed with 100 mL of 50 mM Citrate pH 4 at 37.0 ± 0.5 °C.

[0150] Mannitol is capable of crystallizing in three polymorphic states: α, β, and δ. These three forms can be distinguished by X-ray powder diffraction, and each polymorph has a different melting point. See, e.g., Sharma and Kalonia, AAPS PharmaSciTech 5(1):E10 (2004). Even more surprising than the observation of a first eutectic with Cyclobenzaprine HCl and mannitol (β polymorph) was the observation of a second eutectic with a different polymorphic form of mannitol (δ polymorph). The eutectic comprising δ mannitol and Cyclobenzaprine HCl or Amitriptyline HCl (also referred to herein as the "δ mannitol eutectic") has several advantages over the eutectic comprising β mannitol and Cyclobenzaprine HCl or Amitriptyline HCl (also referred to herein as the "β mannitol eutectic"). Prime among these are a lower melting point than the β mannitol eutectic and enhanced dissolution over the β mannitol eutectic.

[0151] In some embodiments, the invention provides a eutectic pharmaceutical composition comprising Cyclobenzaprine HCl and mannitol or Amitriptyline HCl and mannitol, wherein the mannitol is in its β polymorphic state. In some embodiments, the invention provides a eutectic pharmaceutical composition comprising Cyclobenzaprine HCl and mannitol or Amitriptyline HCl and mannitol, wherein the mannitol is in its δ polymorphic state. In certain embodiments, the pharmaceutical composition comprising the mannitol in its β polymorphic state is a sublingual composition. In certain embodiments, the pharmaceutical composition comprising the mannitol in its β polymorphic state is an oral composition. In certain embodiments, the pharmaceutical composition comprising the mannitol in its δ polymorphic state is a sublingual composition. In certain embodiments, the pharmaceutical composition comprising the mannitol in its δ polymorphic state is

an oral composition. In particular embodiments wherein the composition is an oral composition, the oral composition is bioequivalent to 5mg Cyclobenzaprine HCl oral tablets (e.g., Flexeril 5mg). In particular embodiments wherein the composition is an oral composition, the oral composition is bioequivalent to 10mg Cyclobenzaprine HCl oral tablets (e.g., Flexeril 10mg). Flexeril tablets are composed of hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide. Dosing 10 mg t.i.d. in normal healthy volunteers, the AUC at steady state (after 4 days of dosing) was 177 ng.hr/mL (range, 80-319 ng.hr/mL) and the Cmax was 25.9 ng/mL (range, 12.8-46.1 ng/mL). Additional pharmacokinetic properties of orally administered Cyclobenzaprine can be found, for example, in Winchell et al., J Clin Pharmacol. 42(1):61-9 (2002) and Hucker et al., J Clin Pharmacol. 17(11-12):719-27 (1977).

[0152] In some embodiments, the invention provides a composition comprising eutectic of mannitol and Cyclobenzaprine HCl. In some embodiments, the invention provides a composition comprising eutectic of mannitol and Amitriptyline HCl. The skilled worker will understand that these compositions may be suitable for administration in a variety of ways, such as those described herein. For example, a composition may be suitable for administration orally (administration wherein the Cyclobenzaprine or Amitriptyline is absorbed in the gastrointestinal tract), or for transmucosal absorption (e.g., sublingual, buccal, or intranasal absorption, or by inhalation).

Methods of manufacturing eutectic compositions

[0153] The skilled worker will appreciate that a eutectic composition of the invention can be manufactured according to any of a number of known methods. In some embodiments, the invention provides methods for producing a eutectic composition of the invention comprising milling an API (Cyclobenzaprine HCl or Amitriptyline HCl) with mannitol, mixing an API (Cyclobenzaprine HCl or Amitriptyline HCl) with mannitol, or a combination thereof. For example, the API and mannitol can be milled in an agate mortar or mixed in a high shear granulator. High shear mixing combines dry powders using a high speed impellor and chopper blades to uniformly mix the ingredients. Some particle size reduction is possible

due to the shear force and the high speed of the mixing blades. The API and mannitol also can be milled and mixed in a Turbula® Shaker-Mixer. In certain embodiments, the API and mannitol can be mixed via compression, for example, via roller compaction. Roller compaction forces fine powders between two counter-rotating rolls and presses the raw materials into a solid compact or sheet (referred to as flakes). The flakes are reduced in size until they reach a desired grain size. In certain embodiments, mannitol can be melted and mixed with Cyclobenzaprine HCl or Amitriptyline HCl to form a eutectic composition. In certain embodiments, the API is a micronized API (e.g., micronized Cyclobenzaprine HCl or micronized Amitriptyline HCl).

[0154] In some embodiments, the invention provides methods for producing a eutectic composition of the invention comprising spray drying a solution of an API (Cyclobenzaprine HCl or Amitriptyline HCl) with mannitol. The skilled worker will appreciate that spray drying is routine, and parameters for spray drying can be determined without undue experimentation. For example, spray drying can be performed under any of the following conditions:

T Inlet (°C): 120

T Outlet (°C): 73-76

Feed rate (ml/min): 4

Flow Rate (L/h): 600

Aspiration (100%): 100

delta Pressure (mbar): 2-10

These conditions also may be scaled up to provide higher throughput manufacturing.

Methods of detecting eutectic compositions

[0155] Methods of detecting eutectic compositions are well known. The skilled worker will appreciate that eutectic compositions can be detected by any of these

methods. For example, rapid differential scanning calorimetry ("DSC") can be used to detect a eutectic melting point by evaluating the amount of heat recorded from eutectic melting and comparing it with the melting heat of the eutectic composition. During a slow scan of DSC, the increased temperature in the crucible facilitates the formation of the eutectic even when the two components (such as Mannitol and cyclobenzaprine HCl may not have been mixed before the start of the experiment.) In contrast, a rapid DSC scan reduces the time during which eutectic compositions can form in the crucible because the temperature inside the crucible rapidly increases during the analysis and rapidly reaches the values at which the mannitol melts. Another useful method is measuring compaction force vs. DSC eutectic melting point. In this method, mixtures are prepared with known ratios and then submitted to well-defined compaction forces. DSC analyses are then performed and the heat of the eutectic melting versus the forces is then recorded and plotted. These values are compared with those obtained with the eutectic ratio, providing the percentage of eutectic in the formulation.

[0156] An additional method that can be used to detect the amount of eutectic in a composition is to compare tensile strength and compression force. In this method, tablets are prepared with only mannitol and API at different compression forces. For each tablet prepared, the percentage of eutectic formed versus tensile strength of the tablets is correlated. There is a proportionally linear correlation between the tensile strength and the intimate contact area. The slope of this correlation provides the percentage of the eutectic formed.

[0157] There is a linear correlation between the percentage of eutectic composition in a preparation and the porosity of powders in a composition. In this method, a standard curve can be generated by preparing samples with different ratios of components in which at least one of the components has a variety of different particle sizes, measuring the specific surface area and the porosity of the powders and plotting porosity against the percentage of eutectic. Because there is a linear correlation between the two parameters, the slope of this correlation with what is recorded for the eutectic mixture provides the percentage of the eutectic formed

[0158] Dissolution rate also can be used to detect the percent of eutectic because a eutectic may have higher dissolution and higher bioavailability. In this method, the intrinsic dissolution rate (using disk sample holder in a defined and appropriate medium) of the single components is calculated, followed by the dissolution rate of the eutectic mixture. Based on the thermodynamic parameters (entropy), the eutectic should have a more rapid dissolution rate than the other mixtures. By these analyses, it is also possible to obtain information on the performance of a tablet in terms of bioavailability. This approach also can evaluate the higher bioavailability of a eutectic versus mixtures of the individual components.

[0159] Scanning Electron Microscopy (SEM) can be used by performing a scanning EM of each pure component, on the eutectic, and on the mixtures, and observing the different crystal morphology by pointing out the differently shaped particles.

Methods of administering eutectic compositions

[0160] Appropriate methods of administering a pharmaceutical composition of the invention to a subject will depend, for example, on the age of the subject, whether the subject is active or inactive at the time of administering, whether the subject is experiencing symptoms of a disease or condition at the time of administering, the extent of the symptoms, and the chemical and biological properties of the API (e.g. solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, the pharmaceutical composition is administered for oral or transmucosal absorption.

[0161] Methods of administering compositions for oral absorption are well known in the art. For example, a composition may be administered orally through tablets, capsules, pills, or powders. In these embodiments, the compositions are absorbed by the gastrointestinal tract after swallowing. In certain embodiments, the composition lacks a film or membrane (e.g., a semipermeable membrane).

[0162] Methods of administering compositions for transmucosal absorption are well known in the art. For example, a composition may be administered for buccal

absorption through buccal tablets, lozenges, buccal powders, and buccal spray solutions. A composition may be administered for sublingual absorption through sublingual tablets, sublingual films, liquids, sublingual powders, and sublingual spray solutions. In certain embodiments, the composition lacks a film or membrane (e.g., a semipermeable membrane). A composition may be administered for intranasal absorption through nasal sprays. A composition may be administered for pulmonary absorption through aerosolized compositions and inhalable dried powders. Because mannitol powder is an inhalation product in the U.S. (trade name: Aridol®; Pharmaxis Ltd.), inhalation may be an especially beneficial form of administration. When administered via sprays or aerosolized compositions, a composition may be prepared with saline as a solution, employ benzyl alcohol or other suitable preservatives, or include absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents.

[0163] Doses and dosing regimens can be determined by one of skill in the art according to the needs of a subject to be treated. The skilled worker may take into consideration factors such as the age or weight of the subject, the severity of the disease or condition being treated, and the response of the subject to treatment. A composition of the invention can be administered, for example, as needed or on a daily basis. In some embodiments, a composition can be administered immediately prior to sleep or several hours before sleep. Administration prior to sleep may be beneficial by providing the therapeutic effect before the onset of the symptoms of the disease or condition being treated. Dosing may take place over varying time periods. For example, a dosing regimen may last for 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, or longer. In some embodiments, a dosing regimen will last 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or longer.

Therapeutic uses

[0164] The pharmaceutical compositions of the invention may be employed for treating or preventing the development of fibromyalgia syndrome, also known as

fibrositis (see, e.g., Moldofsky et al,. J Rheumatol 38(12):2653-2663 (2011) and Thomas, J Rheumatol 38(12):2499-2500 (2011)). Fibromyalgia is a chronic, non-inflammatory rheumatic disorder. The American College of Rheumatology (ACR) published classification criteria for fibromyalgia in 1990 (Wolfe, F., et al., Arthritis and Rheumatism 33:160-172 (1990)). Subsequently, a modification to the ACR criteria been published (Wolfe et al., J Rheumatol 38(6):1113-22 (2011)). Diagnostic criteria have also been published by an international network of working groups called, "Outcome Measures in Rheumatology" clinical trials or OMERACT (Mease P, et al. J Rheumatol. 2009;36(10):2318-29.). Fibromyalgia is traditionally characterized by stiffness or diffuse pain, aches, muscle soreness, sleep disturbances or fatigue. The pain is generally widespread and generally localized at specific "tender points," which may bring on widespread pain and muscle spasm when touched. Other symptoms include mental and emotional disturbances such as poor concentration and irritability, neuropsychiatric symptoms such as depression and anxiety, joint swelling, headache, numbness. Fibromyalgia is associated with nonrefreshing sleep, tiredness, sleepiness, reflux, mental fog and cognitive impairments including difficulty multi-tasking. Fibromyalgia also is often comorbid with sleep disorders, fatigue, non-restorative sleep, anxiety, and depression. The compositions and methods of the invention can be used to treat any one of the above-identified conditions, and any combination thereof.

[0165] Some practitioners further classify fibromyalgia into two categories--primary or secondary-concomitant fibromyalgia. Generally, primary fibromyalgia syndrome can be considered fibromyalgia occurring in the absence of another significant condition whereas secondary-concomitant fibromyalgia can be considered fibromyalgia occurring in the presence of another significant medical disorder, which may have been caused by or is merely associated with the patient's fibromyalgia. Secondary or concomitant fibromyalgia can include fibromyalgia in patients with classical or definite rheumatoid arthritis, osteoarthritis of the knee or hand, low back pain syndromes, cervical pain syndromes, cancer pain syndromes, temporomandibular joint disorders, migraine headaches, menopause, post-

traumatic stress disorder and interstitial cystitis or painful bladder syndrome (or combinations thereof).

[0166] The compositions of the invention also may be employed for treating or preventing the development (either the initiation, consolidation or perpetuation) of a PTSD symptom following a traumatic event. A traumatic event is defined as a direct personal experience that involves actual or threatened death or serious injury, or other threat to one's physical integrity, or witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate. Traumatic events that are experienced directly include, but are not limited to, military combat, violent personal assault (sexual assault, physical attack, robbery, mugging), being kidnapped, being taken hostage, terrorist attack, torture, incarceration as a prisoner of war or in a concentration camp, natural or manmade disasters, severe automobile accidents, or being diagnosed with a life-threatening illness. For children, sexually traumatic events may include developmentally inappropriate sexual experiences without threatened or actual violence or injury. Witnessed events include, but are not limited to, observing the serious injury or unnatural death of another person due to violent assault, accident, war, or disaster or unexpectedly witnessing a dead body or body parts. Events experienced by others that are learned about may include, but are not limited to, violent personal assault, serious accident, or serious injury experienced by a family member or a close friend, learning about the sudden, unexpected death of a family member or a close friend, or learning that one's child has a life-threatening disease. The disorder may be especially severe or long lasting when the stressor is of human design (e.g., torture or rape). The initiation of a PTSD symptom typically occurs immediately following the traumatic event, during which the symptoms of PTSD appear and become increasingly severe. One theory of how PTSD develops is that there is a type of "learning" or reinforcement process during which the memories of the trauma are engrained in the mind. As these memories become more fixed (a process called consolidation), symptoms such as flashbacks and nightmares grow in severity and frequency. Interventions during this critical time may prevent some

patients from developing full-blown PTSD. The consolidation of a PTSD symptom typically occurs during the weeks and months following a traumatic event. A person's memories of that event become consolidated into highly vivid and concrete memories that are re-experienced with increasing frequency either as flashbacks or nightmares. During this time, hyperarousal symptoms and avoidant behavior can become increasingly severe and disabling. The perpetuation of a PTSD symptom occurs once traumatic memories are consolidated, and the re-experienced symptoms (flashbacks and nightmares) and hyperarousal symptoms become persistent and remain at a level that is functionally disabling to the patient.

[0167] The compositions of the invention may be used to treat different phases of PTSD development at various time intervals after a traumatic event. For example, treating the initiation phase of PTSD may require the administration of a composition of the invention soon after the traumatic event, for example within the first week, within the second week, within the third week, or within the fourth week or later. By contrast, when treating the consolidation phase of PTSD, the skilled worker may be able to administer a composition of the invention later after the traumatic event and later during the development of the symptoms, for example, within the first month, within the second month, or within the third month or later. The perpetuation phase of PTSD may be treated with a composition of the invention administered 3 months or longer after the traumatic event, for example within the third month, within the fourth month, within the fifth month, or later. As a result of treatment at the initiation, consolidation, or perpetuation phase, PTSD symptoms will be ameliorated or be eliminated.

[0168] The compositions of the invention also can be used to treat traumatic brain injury (TBI). TBI is associated with sleep disorders, sleep disturbances, fatigue, non-restorative sleep, anxiety, and depression. The compositions and methods of the invention also can be used to treat any of the above conditions, in combination with or independently of treating TBI.

[0169] The compositions of the invention also can be used to chronic traumatic encephalopathy (CTE). CTE is associated with sleep disorders, sleep disturbances, fatigue, non-restorative sleep, anxiety, and depression. The compositions and

methods of the invention also can be used to treat any of the above conditions, in combination with or independently of treating CTE.

[0170] The compositions and methods of the invention may be used to treat sleep disorders or sleep disturbances. A "sleep disorder" may be any one of four major categories of sleep dysfunction (DSM-IV, pp. 551-607; *see also* The International Classification of Sleep Disorders: (ICSD) Diagnostic and Coding Manual, 1990, American Sleep Disorders Association). One category, primary sleep disorders, comprises sleep disorders that do not result from another mental disorder, a substance, or a general medical condition. They include without limitation primary insomnia, primary hypersomnia, narcolepsy, circadian rhythm sleep disorder, nightmare disorder, sleep terror disorder, sleepwalking disorder, REM sleep behavior disorder, sleep paralysis, day/night reversal and other related disorders; substance-induced sleep disorders; and sleep disorders due to a general medical condition. Primary insomnia non-restorative sleep is described by the DSM-IV-TR as a type of primary insomnia wherein the predominant problem is waking up feeling unrefreshed or nonrefreshed. A second category comprises those sleep disorders attributable to substances, including medications and drugs of abuse. A third category comprises sleep disturbances arising from the effects of a general medical condition on the sleep/wake system. A fourth category of sleep disorders comprises those resulting from an identifiable mental disorder such as a mood or anxiety disorder. A fifth category of sleep disorders comprises those described as non-restorative sleep. One definition of non-restorative sleep is in the DSM-IV-TR as a type of primary insomnia (A1.3) wherein the predominant problem is waking up feeling unrefreshed or nonrefreshed. Symptoms of each category of sleep disorder are known in the art. A "sleep disturbance" may be an impairment in refreshing sleep. Such a clinical diagnosis may be made based on a patient's self described feeling of fatigue upon waking or the patient's report of poor quality sleep. Such impediments to good quality sleep may be described as shallow sleep or frequent awakenings which may be associated with an increase in the Cyclic Alternating Pattern (CAP) A2 or A3 rate or cycle duration or an increase in the normalized CAP A2 + A3 which is determined by CAP (A2+A3)/CAP (A1+A2+A3) in non-REM sleep (see, e.g., Moldofsky et al,. J Rheumatol

38(12):2653-2663 (2011) and Thomas, J Rheumatol 38(12):2499-2500 (2011)), alpha rhythm contamination in non-REM sleep, or absence of delta waves during deeper physically restorative sleep. Such "sleep disturbances" may or may not rise to the level of a "sleep disorder" as defined in the DSM-IV, although they may share one or more symptom in common. Symptoms of sleep disturbances are known in the art. Among the known symptoms are groggy or spacey feelings, tiredness, feelings of being run down, and having difficulty concentrating during waking hours. Among the sleep-related conditions that may be treated with the methods and compositions of the invention are dyssomnias (e.g., intrinsic sleep disorders such as sleep state misperception, psychophysiological insomnia, idiopathic insomnia, obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome, restless leg syndrome, and periodic limb movement disorder; extrinsic sleep disorders such as environmental sleep disorder, adjustment sleep disorder, limit-setting sleep disorder, stimulant-dependent sleep disorder, alcohol-dependent sleep disorder, toxin-induced sleep disorder, sleep onset association disorder, hypnotic dependent sleep disorder, inadequate sleep hygiene, altitude insomnia, insufficient sleep syndrome, nocturnal eating syndrome, and nocturnal drinking syndrome; and circadian rhythm sleep disorders such as jet lag syndrome, delayed sleep phase syndrome, advanced sleep phase syndrome, shift work sleep disorder, non-24 hour sleep-wake disorder, and irregular sleep-wake patterns), parasomnias (e.g., arousal disorders such as sleepwalking, confusional arousals, and sleep terrors and sleep-wake transition disorders such as rhythmic movement disorder, sleep talking and sleep starts, and nocturnal leg cramps), and sleep disorders associated with medical or psychiatric conditions or disorders. The compositions of the invention also can be used to treat muscle spasms. Muscle spasms can be associated with muscle pain, e.g., back pain. The compositions and methods of the invention also can be used to treat any of the above conditions, in combination with or independently of treating muscle spasms.

Basifying agents

[0171] The compositions of the invention may include a basifying agent. As used herein, a "basifying agent" refers to an agent (e.g., a substance that increases

the local pH of a liquid comprising Cyclobenzaprine HCl or Amitriptyline HCl, including potassium dihydrogen phosphate (monopotassium phosphate, monobasic potassium phosphate, KH_2PO_4), dipotassium hydrogen phosphate (dipotassium phosphate, dibasic potassium phosphate, K_2HPO_4), tripotassium phosphate (K_3PO_4), sodium dihydrogen phosphate (monosodium phosphate, monobasic sodium phosphate, NaH_2PO_4), disodium hydrogen phosphate (disodium phosphate, dibasic sodium phosphate, Na_2HPO_4), trisodium phosphate (Na_3PO_4), trisodium citrate anhydrous, bicarbonate or carbonate salts, borate, hydroxide, silicate, nitrate, dissolved ammonia, the conjugate bases of some organic acids (including bicarbonate), and sulfide) that raises the pH of a solution containing Cyclobenzaprine HCl or Amitriptyline HCl. Without wishing to be bound by theory, a basifying agent, while providing beneficial pharmacokinetic attributes to pharmaceutical compositions comprising Cyclobenzaprine HCl or Amitriptyline HCl, also may destabilize the Cyclobenzaprine HCl or Amitriptyline HCl due to interactions between the HCl and basifying agent. Thus, a eutectic composition as described herein may be especially useful in compositions comprising a basifying agent.

Excipients

[0172] In some embodiments, a composition of the invention is useful as a medicament. In some embodiments, the invention provides for the use of a composition of the invention in the manufacture of a medicament. In some embodiments, it may be beneficial to include one or more excipients in the compositions of the invention. One of skill in the art would appreciate that the choice of any one excipient may influence the choice of any other excipient. For example, the choice of a particular excipient may preclude the use of one or more additional excipient because the combination of excipients would produce undesirable effects. One of skill in the art would be able to empirically determine which additional excipients, if any, to include in the formulations of the invention. For example, Cyclobenzaprine HCl or Amitriptyline HCl can be combined with at least one pharmaceutically acceptable carrier such as a solvent, bulking agents, binder, humectant, disintegrating agent, solution retarder, disintegrant, glidant,

absorption accelerator, wetting agent, solubilizing agent, lubricant, sweetening agent, or flavorant agent. A "pharmaceutically acceptable carrier" refers to any diluent or excipient that is compatible with the other ingredients of the formulation, and which is not deleterious to the recipient. A pharmaceutically acceptable carrier can be selected on the basis of the desired route of administration, in accordance with standard pharmaceutical practices.

Bulking agents

[0173] In some embodiments, it may be beneficial to include a bulking agent in the compositions of the invention. Bulking agents are commonly used in pharmaceutical compositions to provide added volume to the composition. Bulking agents are well known in the art. Accordingly, the bulking agents described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary bulking agents that may be used in the compositions and methods of the invention.

[0174] Exemplary bulking agents may include carbohydrates, sugar alcohols, amino acids, and sugar acids. Bulking agents include, but are not limited to, mono-, di-, or poly-, carbohydrates, starches, aldoses, ketoses, amino sugars, glyceraldehyde, arabinose, lyxose, pentose, ribose, xylose, galactose, glucose, hexose, idose, mannose, talose, heptose, glucose, fructose, methyl a-D-glucopyranoside, maltose, lactone, sorbose, erythrose, threose, arabinose, allose, altrose, gulose, idose, talose, erythrulose, ribulose, xylulose, psicose, tagatose, glucosamine, galactosamine, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans, inulin, levan, fucoidan, carrageenan, galactocarolose, pectins, amylose, pullulan, glycogen, amylopectin, cellulose, microcrystalline cellulose, pustulan, chitin, agarose, keratin, chondroitin, dermatan, hyaluronic acid, xanthin gum, sucrose, trehalose, dextran, lactose, alditols, inositols, sorbitol, mannitol, glycine, aldonic acids, uronic acids, aldaric acids, gluconic acid, isoascorbic acid, ascorbic acid, glucaric acid, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, neuraminic acid, pectic acids, maize starch, and alginic acid.

Disintegrants

[0175] In some embodiments, it may be beneficial to include a disintegrant in the compositions of the invention. Disintegrants aid in the breakup of solid compositions, facilitating delivery of an active pharmaceutical composition. Disintegrants are well known in the art. Some disintegrants have been referred to as superdisintegrants because they have fast properties, and may be used as disintegrants in the context of the invention. Accordingly, the disintegrants described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary disintegrants that may be used in the compositions and methods of the invention. Exemplary disintegrants include crospovidone, microcrystalline cellulose, sodium carboxymethyl cellulose, methyl cellulose, sodium starch glycolate, calcium carboxymethyl croscarmellose sodium, polyvinylpyrrolidone, lower alkyl-substituted hydroxypropyl cellulose, Indion 414, starch, pre-gelatinized starch, calcium carbonate, gums, sodium alginate, and Pearlitol Flash®. Pearlitol Flash® (Roquette) is a mannitol-maize starch disintegrant that is specifically designed for orally dispersible tablets (ODT). Certain disintegrants have an effervescent quality.

Glidants

[0176] In some embodiments, it may be beneficial to include a glidant in the compositions of the invention. Glidants aid in the ability of a powder to flow freely. Glidants are well known in the art. Accordingly, the glidants described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary glidants that may be used in the compositions and methods of the invention. Exemplary glidants include colloidal silica (silicon dioxide), magnesium stearate, starch, talc, glycerol behenate, DL-leucine, sodium lauryl sulfate, calcium stearate, and sodium stearate.

Lubricants

[0177] In some embodiments, it may be beneficial to include a lubricant in the compositions of the invention. Lubricants help keep the components of a

composition from clumping. Lubricants are well known in the art. Accordingly, the lubricants described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary lubricants that may be used in the compositions and methods of the invention. Exemplary lubricants include calcium stearate, magnesium stearate, stearic acid, sodium stearyl fumarate, vegetable based fatty acids, talc, mineral oil, light mineral oil, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, safflower oil, canola oil, coconut oil and soybean oil), silica, zinc stearate, ethyl oleate, ethyl laurate.

Sweeteners

[0178] In some embodiments, it may be beneficial to include a sweetener in the compositions of the invention. Sweeteners help improve the palatability of the composition by conferring a sweet taste to the composition. Sweeteners are well known in the art. Accordingly, the sweeteners described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary sweeteners that may be used in the compositions and methods of the invention. Exemplary sweeteners include, without limitation, compounds selected from the saccharide family such as the mono-, di-, tri-, poly-, and oligosaccharides; sugars such as sucrose, glucose (corn syrup), dextrose, invert sugar, fructose, maltodextrin and polydextrose; saccharin and salts thereof such as sodium and calcium salts; cyclamic acid and salts thereof; dipeptide sweeteners; chlorinated sugar derivatives such as sucralose and dihydrochalcone; sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, hexa-resorcinol, and the like, and combinations thereof. Hydrogenated starch hydrolysate, and the potassium, calcium, and sodium salts of 3,6-dihydro-6-methyl-1-1,2,3-oxathiazin-4-one-2,2-dioxide many also be used.

Flavorants

[0179] In some embodiments, it may be beneficial to include a flavorant in the compositions of the invention. Flavorants help improve the palatability of the composition by conferring a more desirable taste to the composition. Flavorants are well known in the art. Accordingly, the flavorants described herein are not

intended to constitute an exhaustive list, but are provided merely as exemplary flavorants that may be used in the compositions and methods of the invention. Exemplary flavorants include, without limitation, natural and/or synthetic (i.e., artificial) compounds such as mint, peppermint, spearmint, wintergreen, menthol, anise, cherry, strawberry, watermelon, grape, banana, peach, pineapple, apricot, pear, raspberry, lemon, grapefruit, orange, plum, apple, lime, fruit punch, passion fruit, pomegranate, chocolate (e.g., white, milk, dark), vanilla, caramel, coffee, hazelnut, cinnamon, combinations thereof, and the like.

Coloring Agents

[0180] Coloring agents can be used to color code the composition, for example, to indicate the type and dosage of the therapeutic agent therein. Coloring Agents are well known in the art. Accordingly, the coloring agents described herein are not intended to constitute an exhaustive list, but are provided merely as exemplary coloring agents that may be used in the compositions and methods of the invention. Exemplary coloring agents include, without limitation, natural and/or artificial compounds such as FD & C coloring agents, natural juice concentrates, pigments such as titanium oxide, silicon dioxide, and zinc oxide, combinations thereof, and the like.

Combination therapy

[0181] As described above, the compositions and methods of the invention may be used to treat PTSD, depression, fibromyalgia, traumatic brain injury, sleep disorder, non-restorative sleep, chronic pain, and anxiety disorder. Any of the methods of treatment described also may be combined with a psychotherapeutic intervention to improve the outcome of the treatment. Exemplary psychotherapeutic interventions directed at either modifying traumatic memories or reducing emotional responses to traumatic memories, including psychological debriefing, cognitive behavior therapy and eye movement desensitization and reprocessing, systematic desensitization, relaxation training, biofeedback, cognitive processing therapy, stress inoculation training, assertiveness training, exposure therapy, combined stress inoculation training and exposure therapy,

combined exposure therapy, and relaxation training and cognitive therapy. In each case, the goal of the intervention involves either modifying traumatic memories or reducing emotional responses to traumatic memories. The intended result is generally an improvement in the symptoms of PTSD or the reduction of occurrences of symptoms, as evidenced in terms of physiological responding, anxiety, depression, and feelings of alienation.

[0182] In some embodiments of the invention, a composition is combined with a drug which may further alleviate the symptoms of PTSD, depression, fibromyalgia, traumatic brain injury, sleep disorder, non-restorative sleep, chronic pain, or anxiety disorder. The drugs include an alpha-1-adrenergic receptor antagonist, a beta-adrenergic antagonist, an anticonvulsant, a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, and an analgesic. Exemplary anticonvulsants include carbamazepine, gabapentin, lamotrigine, oxcarbazepine, pregabalin, tiagabine, topiramate, and valproate. An exemplary alpha-1-adrenergic receptor antagonist is prazosin. Exemplary selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors include, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, escitalopram, fluvoxamine, milnacipran, paroxetine, sertraline, trazodone, and venlafaxine. Exemplary analgesics include pregabalin, gabapentin, acetaminophen, tramadol, and non-steroidal anti-inflammatory drugs (e.g., ibuprofen and naproxen sodium). Additional drugs that can be used in combination with the compositions of the invention include sodium oxybate, zolpidem, pramipexole, modafinil, temazepam, zaleplon, and armodafinil.

[0183] It is to be understood that the embodiments of the present invention which have been described are merely illustrative of some of the applications of the principles of the present invention. Numerous modifications may be made by those skilled in the art based upon the teachings presented herein without departing from the true spirit and scope of the invention.

[0184] The following examples are set forth as being representative of the present invention. These examples are not to be construed as limiting the scope of

the invention as these and other equivalent embodiments will be apparent in view of the present disclosure, figures, and accompanying claims.

Examples

Example 1

[0185] Thermal analytical techniques were used to assess the compatibility of a drug product (tablet) containing Cyclobenzaprine HCl (API). The compatibility assessment was carried out between the API and a number of possible excipients in a 1:1 ratio. Based on the thermal events recorded for each component and for the mixtures, the analyses were carried out by investigating the peaks recorded by differential scanning calorimetry (DSC) in mixture between API and the excipients. Differences in thermal profiles between the single compound and the related mixture obtained after milling the products in an agate mortar were evaluated. Stability and compatibility also were also assessed on the final drug product after stress conditions at 40 °C and 50 °C for one month.

[0186] The following raw materials were used:

Cyclobenzaprine HCl

Sodium stearyl fumarate

Potassium Phosphate Bibasic

Crospovidone (Kollidon CL)

Silicon Colloidal

Pearlitol flash

Opadry 03F190003 Clear

Opadryll 85F19000 Clear

[0187] A "formulation ratio" mixture was made with the following composition: 2.40 mg Cyclobenzaprine HCl, 31.55 mg Mannitol and Maize starch, 2.00

Crospovidone, 0.50 mg colloidal silica, 0.050 mg Sodium Stearyl Fumarate, and 1.05 Potassium hydrogen phosphate.

[0188] Aliquots of API and each excipient were weighed in a ratio of 1:1 (unless specified otherwise) and ground in an agate mortar. The homogeneous mixtures then were analyzed.

Differential Scanning Calorimetry (DSC)

[0189] The DSC heating curves were obtained with a TA 821 DSC Mettler instrument under the following conditions:

Heating rate: l0 °C/min

Ambient: Nitrogen 30 mL/min

Sample holder: normal open aluminum pan

Temperature range: from 25 °C to 250 °C

Instrument calibration: Indium sample purity 99.999 %

[0190] With Cyclobenzaprine HCl alone, melting with decomposition was detected between 210 °C and 223 °C (onset at 215.2 °C, ΔH = -96.5 J/g) (Fig. 1).

[0191] In a 1:1 mixture of Cyclobenzaprine HCl and Sodium Stearyl fumarate, the endothermic transitions of sodium stearyl fumarate were recorded in the range of 100 °C to 120°C (Fig. 2). No API transition peak was detected, but a physical interaction was observed.

[0192] In a 1:1 mixture of Cyclobenzaprine HCl and Sodium Stearyl fumarate, the endothermic transitions of sodium stearyl fumarate were recorded in the range of 90 °C to 120°C (Fig. 3). The API transition peak was detected between 192 °C and 216 °C (onset at 202.31 °C, ΔH = -50.5J/g). A small physical interaction was observed. This interaction likely occurred during tablet compression when a possible rise in temperature can induce changes in the API.

[0193] In a 1:1 mixture of Cyclobenzaprine HCl and Potassium phosphate bibasic, a chemical interaction (acid-base) was observed between API and excipient. A transition between 40 °C and 60 °C was observed (Fig. 4), while, at high temperatures, the API melting peak was slightly visible.

[0194] In the formulation ratio, a peak was observed at 47 °C, likely due to water absorption by K_2HPO_4 while the API melting peak was detected between 182 °C and 210 °C (onset at 195.6 °C, ΔH =-31.4/g) (Fig. 5). A small interaction was observed at higher temperatures.

[0195] In a 1:1 mixture of Cyclobenzaprine HCl and Crospovidone (Kollidon CL), the release of imbibition water was recorded between 30 °C and 110 °C, followed by the melting/decomposition of API between 210 °C and 223 °C (onset at 214.4 °C, ΔH = -37.4 J/g) (Fig. 6). No interaction was detected.

[0196] In a 1:1 mixture of Cyclobenzaprine HCl and Silicon (colloidal), the API melting/decomposition peak was recorded between 186 °C and 221 °C (onset at 207.2 °C, ΔH = -41.4 J/g) (Fig. 7). No interaction was detected, only a lowering of the degree of crystallinity.

[0197] In a 1:1 mixture of Cyclobenzaprine HCl and Pearlitol Flash®, a physical complex interaction peak (eutectic) was surprisingly observed in the range of 130 °C to 168 °C (onset at 143.2 °C, ΔH = -151.8 J/g) (Fig. 8). No API transition melting was detected, only a physical complex fusion at lower temperatures.

[0198] In the formulation mixture, because the ratio is about 13: 1 Pearlitol®:API, the melting peak of Pearlitol® was detected between 150 °C and 173 °C (onset at 162.0 °C, ΔH = -172.2 J/g) (Fig. 9), preceded by a small peak at 137 °C to 151 °C (onset at 142.2 °C, ΔH = -12.2 J/g) due to the eutectic between the two components. The same behavior was observed in the 1:1 mixture.

[0199] In a 1:1 mixture of Cyclobenzaprine HCl and Opadry Clear, the PEG transitions were easily visible between 46 °C and 64°C, followed by an API melting/decomposition peak between 180 °C and 218 °C (onset at 199.0 °C, ΔH = -45.5 J/g) (Fig. 10). The interaction is due to the melted Opadry.

[0200] In a 1:1 mixture of Cyclobenzaprine HCl and Opadry II Clear, the PEG transitions were easily visible between 44 °C and 65 °C, followed by the interaction peak between PVA (Polyvinyl Alcohol) and API, in the range of 44 °C to 213 °C (onset at 154.9 °C, ΔH = -32.5 Jig) (Fig. 11) that could be due to the partial solubilization of the API by the excipients.

[0201] In the formulation mixture, only one thermal event was recorded between 124 °C and 170 °C (onset at 157.0 °C, ΔH = -164.1 Jig) (Fig. 12). The event was cause by Pearlitol Flash® which, due to its amount, covered all the other transitions. Moreover, the API with Pearlitol gave a eutectic (physical interaction at the solid state) that was detected at 142 °C. This physical interaction can stabilize the formula and prevent other interactions with excipients (e.g., Opadry I, Opadray II, and K_2HPO_4).

[0202] To evaluate the interaction between the API and the excipient, thermal investigations were conducted on a tablet stored for 1 month at 40° °C and 50 °C. The data recorded were compared with the thermal profile of the same batch analyzed at time zero. Two thermal events for Cyclobenzaprine HCl were recorded: a first of a small entity at 146.0 °C, and a second between 136 °C and 170 °C (onset at 158.3 °C, ΔH = -143.2 J/g) (Fig. 13), mainly due to melting of Pearlitol flash.

[0203] Two thermal events were recorded for Cyclobenzaprine HCl at 40 °C: the first one of small entity at 145.8 °C, and the second between 134 °C and 171 °C (onset at156.7 °C, ΔH = -169.7 J/g) (Fig. 14), mainly due to melting of Pearlitol Flash®. Two thermal events also were recorded for Cyclobenzaprine HCl at 50 °C: the first one of small entity at 146.5 °C, and the second between 137 °C and 179 °C (onset at 158.4 °C, ΔH = -163.3 J/g) (Fig. 15), mainly due to melting of Pearlitol Flash®. The thermal behaviors recorded were similar, and no interactions were observed in the tablet after storage at 40 °C and 50 °C. The interaction recorded for the binary mixtures was no longer observed, likely due to the dilution of the API by the Pearlitol Flash® excipient and reduced contact between API and the lubricant sodium stearyl fumarate.

[0204] In summary, different types of interaction were observed among the excipients and the API. A physical interaction was observed with Sodium Stearyl fumarate, especially in the 1:1 ratio, likely due to partial API solubilization or reactions at the particles' surfaces between the Cl^- and Na^+ counter ions. In the formulation ratio, this incompatibility disappears. Even in a formulation tested for stability at 40 °C and 50 °C for one month, this interaction was not seen. A chemical (acid-base) interaction was observed with Potassium phosphate bibasic, both in 1:1 and in formulation ratios. No interaction was observed with Silicon (colloidal) and Kollidon. A eutectic interaction was observed with Pearlitol Flash®, due to the presence of mannitol. In the formulation ratio (about 13:1 excipient:API), the thermal transition of the API was completely shifted by excipient complex formation (eutectic). The interaction with Opadry Clear is small and is due to PEG contributions that preceded the API Transition. The interaction with Opadry II Clear is evident and could be due to the presence of PVA (Polyvinyl Alcohol) that partially solubilizes the API. Table 1 summarizes the observations of the various excipients with Cyclobenzaprine HCl API.

Table 1: Excipient reactions with API

Excipient	Mixture 1:1	Mixture in formulation ratio
Sodium stearyl fumarate	Physical interaction	No interaction
Potassium phosphate dibasic	Acid - base interaction	Low chemical interaction
Crospovidone (Kollidon CL)	No	ND
Silicon (colloidal)	No	ND
Pearlitol Flash®	Eutectic	Eutectic
Opadry Clear	Chemical (small)	ND
Opadry II Clear	Chemical	ND

ND: Not determined

Example 2

[0205] As described above, thermal analytical techniques were further used to assess the compatibility of a drug product (tablet) containing Cyclobenzaprine HCl (API). The compatibility assessment was carried out between the API and additional excipients in a 1:1 ratio. The 1:1 API-excipient mixtures were formed in two different ways: first, by mixing only, and second, by strong milling in an agate mortar. The thermal behavior recorded in the two different mixtures were compared with those of the single components. On the basis of thermal events recorded for each component and for the mixtures, the analyses were carried out by investigating the meanings of the peaks recorded by differential scanning calorimetry (DSC) in mixtures between the API and the excipients. Furthermore, in order to define the nature of the interaction, the Fourier Transform Infra Red Spectroscopy with Total Attenuated Reflectance (FT-IR/ATR) and X-ray powder diffraction (XRPD) of some samples (API, excipient, and mixed and milled mixtures) was carried out and compared.

[0206] The following raw materials were used:

Cyclobenzaprine HCl

Di Sodium phosphate anhydrous

Di Sodium phosphate dihydrate

Di Sodium phosphate heptahydrate

Trisodium citrate dihydrate

Effersoda®

Sorbitol

Mannitol

Mix API + Di Sodium phosphate anhydrous

Mix API + Di Sodium phosphate dihydrate

Mix API + Di Sodium phosphate heptahydrate

Mix API + Trisodium citrate dihydrate

Mix API + Effersoda®

Mix API + Sorbitol

Mix API + Mannitol

Trisodium citrate anhydrous

Disodium Glycine Carbonate

Mix API + Trisodium citrate anhydrous

Mix API + Disodium Glycine Carbonate

[0207] Aliquots of API and each excipient were weighed in a ratio of 1:1 and ground in an agate mortar. Then, the homogeneous mixtures were analyzed. These sample mixtures were labeled "B", while the mechanical-only mixtures were labeled "A."

Differential Scanning Calorimetry (DSC)

[0208] The DSC heating curves were obtained by TA 821 DSC Mettler instrument under the following conditions:

Heating rate: 10°C/min

Ambient: Nitrogen 30 mL/min

Sample holder: normal open aluminum pan

Temperature range: from 25 °C to 250 °C

Instrument calibration: Indium sample purity 99.999 %

Fourier Transform Infra Red Spectroscopy with Total Attenuated Reflectance (FT-IR/ATR)

[0209] The FT-IR spectra were collected with a Perkin Elmer spectrum Two instrument with air as background and 4 cm^{-1} resolution.

X-ray powder diffraction (XRPD)

[0210] X-ray powder diffraction (XRPD) tests were performed with the ULTIMA IV instrument (Rigaku), laying the sample on a static sample holder. The X-ray focusing slit has a variable width, interlocked with the q value. The X-ray tube has a Copper target, with a current intensity of 40 mA and a voltage of 40 kV. Radiation was generated by the Cockcroft-Walton method, and was constituted by $K_{\alpha 1}$ (1.540562 Å) and $K_{\alpha 2}$ (1.544398 Å). The analytical conditions were:

Fixed Time; sampling width 0.02 deg, scanning rate 1.3 s/step, 2 q range 3.35 deg and sample holder; amorphous glass equiangular 9200/2G, 0.2 mm deep. The sample was pressed with a glass plate.

[0211] Decomposition of Cyclobenzaprine HCl with melting was detected between 210 °C and 225 °C (onset at 215.6 °C, ΔH = -105.0 J/g) (Fig. 16). The DSC heating curves of the mixtures in comparison with the API

and excipients (mixtures A and B) were then analyzed. The interaction peak for a 1:1 Cyclobenzaprine HCl – sodium phosphate anhydrous mixture (mixture A) was recorded in the range of 167 °C to 220 °C (onset at 197.0 °C, ΔH = -109.6 J/g). A physical interaction was observed and characterized by the lowering of API melting (Fig. 17). The interaction peak for a 1:1 Cyclobenzaprine HCl – sodium phosphate anhydrous mixture (mixture B) was recorded in the range of 172 °C to 201 °C (onset at 180.9 °C, ΔH = -31.1 J/g). A physical interaction was observed (Fig. 18). By comparing the mixtures A and B, it is evident that the interaction is presented more in the milled mixture (Fig. 19).

[0212] The release of crystallization water from sodium phosphate in a 1:1 mixture of Cyclobenzaprine HCl and sodium phosphate dihydrate (mixture A) was

observed between 57 °C and 108 °C (onset at 73.4 °C, ΔH = -227.8 J/g), followed by the interaction peak in the range of 174 °C to 220 °C (Fig. 20). This effect was composed by two small effects: a physical interaction and partial solubilization. Few peaks on the plot were observed, likely due to release of small amount of water in a melted matrix. The release of crystallization water in a 1:1 mixture of Cyclobenzaprine HCl and sodium phosphate dihydrate (mixture B) was recorded between 61 °C and 100°C (onset at 71.8°C, ΔH = -239.8 J/g), followed by the interaction peak in the range of 160 °C to 221°C (onset at 178.7°C, ΔH = -116.5 J/g) (Fig. 21). A physical interaction was observed. Fig. 22 shows a comparison between mixtures A and B. The interaction is more evident in the milled

mixture. The water present in the excipient can modify the mixture and reduce the API stability.

[0213] The release of crystallization water in a 1:1 mixture of Cyclobenzaprine HCl and sodium phosphate heptahydrate (mixture A) (in two different steps) was recorded between 39 °C and 68 °C (onset at 47.2°C, ΔH = -77.6 J/g) and between 67 °C and 96°C (onset at 73.8°C, H=-68.9 J/g), followed by the interaction peak in the range of 176 °C to 220°C (onset at 199.5 °C, ΔH = -83.4 J/g) (Fig. 23). With mixture B, crystallization water was released (in two different steps) between 43 °C to 54 °C (onset at 45.9 °C, ΔH = -49.6J/g) and between 73 °C and 98 °C (onset at 77.8°C, ΔH = -151.7 J/g), followed by the interaction peak in the range of 174 °C to 215 °C (onset at 174.5 °C, ΔH = -55.4 J/g) (Fig. 24). Fig. 25 shows a comparison between mixtures A and B. The interaction was anticipated in the milled mixture and showed two events, relating to the interaction peak and to a residual of API. The water present in the excipient induced physical changes of the API, even at low temperatures.

[0214] Crystallization water was released and decomposition (complex peak) of a 1:1 mixture of Cyclobenzaprine HCl and trisodium citrate dihydrate (mixture A). was recorded between 154 °C and 183 °C (onset at 167.1 °C, ΔH = -127.6J/g), followed by the interaction peak in the range of 186 °C to 227 °C (onset at 197.2 °C, ΔH = -102.6 J/g) (Fig. 26). A physico-chemical interaction was observed. The

release of crystallization water and excipient decomposition (complex peak) in mixture B were recorded between 146 °C and 181 °C (onset at 157.9 °C, ΔH = -179.4J/g), followed by the interaction peak in the range of 180 °C to 216 °C (onset at 190.5 °C, ΔH = -88.7 J/g). A physico-chemical interaction was observed (Fig. 27). The decomposition of trisodium citrate was similar in mixtures A and B (Fig. 28).

[0215] A release of CO_2 was recorded in a 1:1 Cyclobenzaprine HCl – Effersoda® mixture (mixture A) between 99 °C and 187°C (onset at 109.5 °C, ΔH = -308.0 J/g), followed by the melting of API in the range of 193 °C to 218 °C (onset at 203.2 °C, ΔH = -46.8 J/g) (Fig. 29). The physical interaction observed was small, but due to excipient instability; the API melting peak was anticipated and interaction occurred. Mixture B resulted in a release of CO_2 between 104 °C and 210 °C (onset at 132.9 °C, ΔH = -399.6 J/g) and disappearance of the API peak (Fig. 30). A physico-chemical interaction was observed. In comparing mixtures A and B, the interaction of mechanical mixture was lower, while the milled mixture was higher. Also, the release of CO_2 by Effersoda® covered the API behavior, due to possible interactions (Fig. 31).

[0216] In a 1:1 mixture of Cyclobenzaprine HCl and sorbitol (mixture A), the melting of sorbitol covered the API melting peak. The event was recorded between 81 °C and 108°C (onset at 96.7 °C, ΔH = -88.2 J/g) (Fig. 32). An interaction was observed, due to the solubilization of API by sorbitol. With mixture B, the melting of sorbitol also covered the API melting peak. The event was recorded between 82 °C and 107 °C (onset at 95.3 °C, ΔH = -87.3 J/g) (Fig. 33). An interaction was observed, due to the solubilization of API by sorbitol. The interaction was comparable in both mixtures A and B (Fig. 34). To confirm that sorbitol, during the mixture, solubilized the API, an XRPD investigation was carried out (Fig. 35). The mixture presented several peaks of sorbitol and very few of Cyclobenzaprine HCl. The broadening of the baseline was indicative of amorphous phases, due to the matrix melting.

[0217] Surprisingly, a physical complex interaction peak (eutectic) was observed in the range of 137 °C to 170 °C (onset at 147.3 °C, ΔH= -164.6 J/g) in a 1:1

Cyclobenzaprine HCl – mannitol mixture (mixture A) (Fig. 36). No API transition melting was detected, only the melting of a eutectic at a lower temperature. With mixture B, a physical complex interaction peak (eutectic) also was observed in the range of 132 °C to 167 °C (onset at 141.5 °C, H= -153.4 J/g) (Fig. 37). No API transition melting was detected, only the melting of eutectic at a lower temperature. The interaction was comparable in both the mixtures (Fig. 38).

[0218] In a 1:1 mixture of Cyclobenzaprine HCl and Trisodium Citrate anhydrous (mixture A), the interaction peak was observed in the range of 168 °C to 215°C (onset at 188.8 °C, ΔH= -102.4 J/g) (Fig. 39). No API transition melting was detected, only a physical complex melting at a lower temperature. The interaction peak was observed in the range of 158 °C to 211°C (onset at 167.7 °C, H= -110.1 J/g) in mixture B (Fig. 40). No API transition melting was detected, only a physical complex melting at lower temperature. In comparing the milled and mixed mixtures, the interaction was more evident in the milled mixture (Fig. 41).

[0219] In a 1:1 mixture of Cyclobenzaprine HCl and Disodium Glycine carbonate (Mixture A), a broad interaction peak was observed in the range of 155 °C to 231 °C (onset at 180.7 °C, H= -79.3 J/g) (Fig. 42). No API transition melting was detected, only a physical complex melting at a lower temperature. Mixture B produced an interaction peak in the range of 155 °C to 231°C (onset at 184.0 °C, H= -77.0 J/g) (Fig. 43). No API transition melting was detected, only a physical complex melting at a lower temperature. The interaction was comparable in both the mixtures (Fig. 44)

FT-IR/ATR

[0220] To define the nature of the interactions observed by DSC and understand if the thermal treatment, during the temperature rise, was the root cause of the different DSC profiles, FT-IR/ATR spectroscopy investigation was carried out. In Figs. 45-47, the FT-IR/ATR spectra of Cyclobenzaprine HCl and Trisodium Citrate anhydrous (mixture A) are shown in superimposition, in different regions. In the mixture, the presence of all the bands of both API and excipient were

observed. In particular, in the 3000-2000 cm^{-1} region (Fig. 45), the band of chlorohydrate was still well visible, as a sign that no chemical acid-base reaction had occurred. In Fig. 48, the superimposition of mixtures A and B shows that no substantial modifications were observed.

[0221] Figs. 49-51 show the FT-IR/ATR spectra of Cyclobenzaprine HCl and Disodium Glycine Carbonate (mixture A) in superimposition, in different regions. In the mixture, all bands of both API and excipient were observed. In particular, in the 3000-2000 cm^{-1} region (Fig. 49), the band of chlorohydrate was still visible, as a sign that no chemical acid-basis reaction occurred. Fig. 52 depicts the superimposition of mixtures A and B. No substantial modifications were observed. From the FT-IR/ATR spectra, the thermal transitions recorded originated from the heating of the mixtures, but, at room temperature, the two components were stable and did not interact.

[0222] In summary, different types of interaction were observed among the excipients and the API. With all the basic excipients investigated (especially the hydrates), interactions were observed. The interactions seemed to be acid/base type reactions, possibly between the cation Na and the HCl of the drug substance. The interaction was more evident in milled mixtures, because the contact between API and excipient particles was deeper and closer. With sorbitol, a physical interaction was observed, due to the solubilization of the API in the melted excipient, while with mannitol, the formation of a eutectic was surprisingly observed. The interaction with trisodium citrate anhydrous and disodium glycine carbonate was only physical and occurred at high temperatures as shown by FT-IR/ATR spectroscopy. Table 2 shows a summary of the interactions between the API and excipients for the mixed and milled mixtures.

Table 2: Interactions between Cyclobenzaprine HCl and excipients

Excipient	Mixture 1:1 (mixed)	Mixture 1:1 (milled)
Di Sodium phosphate anhydrous	Low chemical	Low chemical
Di Sodium phosphate di hydrate	Chemical	Chemical
Di Sodium phosphate heptahydrate	Chemical	Chemical
Trisodium citrate dihydrate	Chemical	Chemical
Effersoda®	Low chemical	Chemical
Sorbitol	Chemical	Chemical
Mannitol	Eutectic	Eutectic
Tri Sodium Citrate anhydrous	Physical	Physical
Di Sodium Glycine carbonate	Physical	Physical

Example 3

[0223] The compatibility of mannitol with Cyclobenzaprine HCl was investigated by differential scanning calorimetry (DSC), and the resulting interactions were assessed. In particular, the formation of a eutectic between the mannitol and the Cyclobenzaprine HCl during mixing improved the cohesion between the particles and provided better physical bonding between the Cyclobenzaprine HCl active pharmaceutical ingredient (API) and the mannitol excipient. Additionally, the physical state prevents the erosion of a dosage form for Cyclobenzaprine administration.

[0224] The interaction between Cyclobenzaprine HCl and Pearlitol Flash® (an excipient containing mannitol) is an invariant physical interaction because it is in thermal equilibrium in which the two components are well mixed and stabilized.

Physically, this means that the melted eutectic, solid eutectic, and solid mannitol all coexist at the same time and are in chemical equilibrium. The resulting solid macrostructure from the eutectic reaction depends on a few factors, including that the two solid solutions nucleate and grow together during a mechanical mixture.

[0225] Because mannitol is a common excipient in solid drug formulations, it was examined for compatibility with Cyclobenzaprine HCl was investigated using DSC and interactions occurring were assessed. Surprisingly, the formation of a eutectic during mechanical mixing was discovered. To confirm the formation of a eutectic and to characterize its physical properties, several binary mixtures at different ratios of API and excipient were prepared and analyzed by DSC and by XRPD. The eutectic formation improved the cohesion between the API and excipient particles and assured better physical linking between the two.

[0226] In order to confirm the eutectic formation and to characterize its physical properties, several binary mixtures at different ratios of API-excipient were prepared and analyzed by DSC and by X-ray powder diffraction (XRPD). The mixtures were obtained by gently milling in agate mortar of micronized Cyclobenzaprine HCl and mannitol, in order to obtain homogeneous distribution of the particles. For each DSC heating curve, the onset temperature and the enthalpy were evaluated both for the eutectic contribute and for the excess of component. The recorded values were plotted and a phase diagram between the two components was obtained with a characteristic profile of phase diagrams of eutectic mixtures.

[0227] Mixtures also were investigated by XRPD and compared with the patterns of pure components. These analyses were carried out to confirm that the eutectic compound is only a physical interaction between the two products and not a formation of a new entity with different chemical properties. The XRPD patterns obtained in the mixtures, compared with pure components, were plotted in order to confirm the linearity of the peak intensities (cpf) of mannitol and Cyclobenzaprine HCl, and a proportional peak height at characteristic 2θangles.

[0228] Aliquots of Cyclobenzaprine HCl API and Mannitol were weighed in the ratios described below and ground in an agate mortar, and the homogeneous mixtures subsequently analyzed.

Mixture	API amount (%)
1	15
2	30
3	40
4	45
5	50
6	65
7	75
8	80
9	90
10	95

Differential Scanning Calorimetry (DSC)

[0229] DSC heating curves were obtained using a TA 821 DSC Mettler instrument under the following conditions:

Heating rate	10°C/min
Ambient	Nitrogen 30 mL/min
Sample order	Normal open aluminum pan
Temperature range	From 25 °C to 250 °C
Instrument calibration	Indium sample purity 99.999 %

X-ray powder diffraction (XRPD)

[0230] X-ray powder diffraction (XRPD) tests were performed with a ULTIMA IV (Rigaku) instrument, laying the sample on a static sample holder. The X-ray focusing slit had a variable width, interlocked with the θ value. The X-ray tube had a Copper target, with a current intensity of 40 mA and a voltage of 50 kV. The

radiation generated by the Cockcroft-Walton method is constituted by $K_{\alpha 1}$ (1.540562 Å) and $K_{\alpha 2}$ (1.544398 Å). The analytical conditions were as follows:

Fixed Time: Sampling width, 0.02 deg; Scanning rate, 1.0 s/step

2 θ range: 3/50 deg.

Sample holder: amorphous glass - equiangular 9200/2G, 0.2 mm deep. The sample was pressed with a glass plate.

[0231] Pure components of Cyclobenzaprine HCl and mannitol, as well as mixtures of the two, were analyzed with DSC (Table 1). Fig. 53 depicts the melting curve with 100% Cyclobenzaprine HCl. Melting with decomposition was detected between 210 °C and 221 °C (onset at 215.5 °C, ΔH = -100.6 J/g). Fig. 54 depicts the melting curve with 100% mannitol. Melting was detected between 151 °C and 173 °C (onset at 164.4 °C, ΔH = -256.8 J/g). Figs. C-L depict the various mixtures. Table 3 summarizes the data.

Table 3: Summary of DSC data

% API	% Mannitol	T onset eutectic (°C)	T onset 2nd effect (°C)	ΔH eutectic (J/g)	ΔH 2nd effect (J/g)	ΔH global (J/g)	Plot
100	0	-	215.5	-	100.57	-	Fig. 53
0	100	-	164.37	-	-	256.81	Fig. 54
15	85	141.38	161.21	28.78	190.27	219.77	Fig. 55
30	70	142.63	157.57	68.4	134.01	202.88	Fig. 56
40	60	142.69	154.86	88.09	102.08	190.55	Fig. 57
45	55	143.43	156.47	99.55	56.41	157.25	Fig. 58
50	50	142.94	155.41	109.8	44.06	174.12	Fig. 59
65	35	143.61	151.21	130.53	4.6	134.58	Fig. 60
75	25	143.64	143.64	92.7	-	-	Fig. 61
80	20	143.36	177.69	87.8	0.73	-	Fig. 62
90	10	143.57	197.69	46.05	3.14	-	Fig. 63
95	5	142.1	204.9	15.23	45.14	-	Fig. 64

[0232] The above results demonstrated that the eutectic composition formed at approximately 75% Cyclobenzaprine HCl (API) and 25% mannitol. Under 75%, two distinct melting peaks were observed from the melting of the eutectic fraction and the excess of the individual components. Fig. 65 shows a phase diagram depicting the onset melting temperatures of the eutectic fraction and the excess components, plotted as function of API percentage. Five distinct zones are present in the diagram:

Zone A: Excess of Mannitol (liquid eutectic + solid mannitol)

Zone B: Excess of Cyclobenzaprine HCl (liquid eutectic + solid Cyclobenzaprine HCl)

Zone C: Solid eutectic with mannitol

Zone D: Solid eutectic with Cyclobenzaprine HCl

Zone E: Liquid phase with mannitol and Cyclobenzaprine HCl

[0233] In Zone A, when the percentage of API increased, the onset temperature of the excess of mannitol decreased while the temperature of eutectic fraction remained constant around 143 °C. Above the eutectic composition, the excess of API led to an increase in the temperature (Zone B). In addition, there was a good correlation between mixtures and temperature. A few small deviations from the trend curve were due to an incompletely homogeneous powder mixture.

[0234] Fig. 66 shows eutectic melting enthalpy as function of the API percentage. The eutectic melting enthalpy increases until the eutectic composition is attained. At the eutectic composition, the maximum value should be reached, but, due to partial decomposition of the product, it was not possible to correctly evaluate the melting heat. Instead, the plot shows the theoretical value, obtained on the basis of the melting enthalpy of the pure compounds. The eutectic composition corresponds to 75% API, 25 Mannitol, by weight. The theoretical ratio between the molecular weights (311.38 mw/182.17mw) was 1.71, while the ratio from the weight percentage [(0.75/311.38mw) / (0.25/182.17mw)] gives a molar ratio for the eutectic of 1.76 (i.e., 1.76 moles of Cyclobenzaprine HCl to 1 mole of Mannitol in the eutectic).

XRPD

[0235] To confirm that the eutectic composition was only a physical mixture and that a new entity or adduct was not formed, the mixtures were analyzed by X-ray Powder Diffraction, where no thermal treatments were applied (pure Cyclobenzaprine HCl, Figs. O-P; pure mannitol, Figs. Q-R). Fig S depicts the stacking of pure mannitol, API, and the eutectic mixture at 75%, showing different diffraction zones where no peaks of the pure components were distinguishable and no interferences were detected. Fig. 72 shows the stacking of pure mannitol and API and mixtures thereof, where it was possible to point out three distinct diffraction ranges: Mannitol 14.1-15.0° 2θ, API 12.5-13.3° 2θ and 17.5-18.2° 2θ.

[0236] Within these ranges, an evaluation was carried out for each mixture analyzed (30, 50, 65, 75 and 90%). Each peak height was plotted as function of

API % and linearity coefficient was obtained (Figs. U-V). Good correlations between concentration and peak heights were obtained. API and mannitol, when mixed, resulted in no adduct formation, only a physical eutectic formation.

[0237] In summary, the data show that thermal behavior of the mixtures presents two endotherms, relating to the eutectic and to the melting of the excess of the main component. Thermal entities recorded for the mixtures agreed with the percentage of API/Mannitol ratio present in the eutectic mixture. At the eutectic composition, only one melting peak was visible. The eutectic composition was reached at about 75% API and 25% Mannitol. The eutectic composition confirmed the molar stoichiometry (ratio between the two components: 1.76). The melting temperature of the eutectic was about 143.6°C and was recorded for all the investigated mixtures. By XRPD, no adduct interaction occurred between API and mannitol, only a physical eutectic formation.

Example 4

[0238] Thermal analytical techniques were used to assess the compatibility of the drug product Amitriptyline HCI. The compatibility assessment was carried out between the API and the excipients in a 1:1 ratio. On the basis of thermal events recorded for each component and for the mixtures, the analyses were carried out by investigating the peaks recorded by DSC in mixtures between API and the excipients. Differences in thermal profiles between the single compound and the related mixtures were obtained after milling the products in an agate mortar.

[0239] DSC was performed substantially as described in Examples 1 and 2. The following raw materials were used:

Amitriptyline HCl

Sodium stearyl fumarate

Stearic acid

Glycerol dibehenate

Magnesium stearate

Pearlitol flash

Pearlitol 200 SO/Mannitol

Unipure DW /Com starch pregelatinized

Crospovidone - Kollidon CL

Silicon Colloidal/ Aerosil 200

Sodium phosphate dibasic

Sodium bicarbonate

Sodium carbonate

Sodium Phosphate dodecahydrate

Sodium Phosphate anhydrous.

[0240] The melting and decomposition of 100% Amitriptyline HCl was detected between 192 °C and 202 °C (onset at 195.1 °C, ΔH = -93.9J/g) (Fig. 75).

[0241] In a 1:1 mixture of Amitriptyline HCI and Sodium Stearyl fumarate, the endothermic transitions of sodium stearyl fumarate were recorded in the range of 90 °C to l20°C (Fig. 76). No API transition peak was detected, and a physical interaction was observed.

[0242] The endothermic transitions of stearic acid in a 1:1 mixture of Amitriptyline HCl and Stearic acid were recorded in the range of 47 °C to 64°C. The API transition peak was detected between 179 °C and 195°C (onset at 181.1 °C, ΔH =-5.15 J/g) (Fig. 77). A small physical interaction was observed.

[0243] In a 1:1 mixture of Amitriptyline HCl and glycerol dibehenate (or glycerol behenate), the endothermic transitions of glycerol dibehenate were recorded in the range of 63 °C to 74°C. The API transition peak was detected

between 186 °C and 199 °C (onset at 189.0 °C, ΔH =-31.0 J/g) (Fig. 78). A small physical interaction was observed.

[0244] In a 1:1 mixture of Amitriptyline HCl and Magnesium stearate, the endothermic transitions of magnesium stearate were recorded in the range of 100 °C to 120 °C. The API transition peak was detected between 169 °C and 187°C (onset at 174.0 °C, ΔH = -10.6 J/g) (Fig. 79). A small physical interaction was observed.

[0245] In a 1:1 mixture of Amitriptyline HCl and Pearlitol Flash®, a mannitol-containing excipient, a physical complex interaction peak (eutectic) was observed in the range of 130 °C to 170 °C (Fig. 80). No API transition melting was detected, only a physical complex fusion at lower temperature. The eutectic melting point corresponds to 135.1 °C (the onset value) (Fig. 81).

[0246] In a 1:1 mixture of Amitriptyline HCl and Pearlitol 200 SD/Mannitol, a physical complex interaction peak (eutectic) was observed in the range of 130 °C to 170 °C (Fig. 82). No API transition melting was detected, only a physical complex fusion at lower temperature. The eutectic melting point corresponds to 132.8 °C (the onset value) (Fig. 83). The difference in melting temperatures of about 2 °C, as compared to the mixture with only Pearlitol flash, is due to the presence of additional mannitol in this mixture.

[0247] The release of imbibition water in a 1:1 mixture of Amitriptyline HCl and Unipure DW/Com starch (partially pregelatinized) was recorded between 30 °C and 110 °C, followed by the melting of API between 178 °C and 199 °C (onset at 181.9 °C, ΔH =-28.2 J/g) (Fig.84). No interaction was detected

[0248] In a 1:1 mixture of Amitriptyline HCI and Crospovidone (Kollidon CL), the release of imbibition water was recorded between 30 °C and 100 °C, followed by the melting/decomposition of API between 192 °C and 200 °C (onset at 194.4 °C, ΔH = -41.3 J/g) (Fig. 85). No interaction was detected.

[0249] In a 1:1 mixture of Amitriptyline HCl and Silicon (colloidal), the API melting peak was recorded between 188 °C and 200c°C (onset at 193.7c°C, ΔH = -

17.2 J/g) (Fig. 86). No interaction was detected, only a lowering of the degree of crystalline Amitriptyline HCl.

[0250] The endothermic transitions of sodium phosphate dibasic in a 1:1 mixture of Amitriptyline HCl and Sodium phosphate dibasic were recorded in the range of 60 °C and 80°C. API transition peaks were detected at 180 °C and 193 °C (Fig. 87).

[0251] In a 1:1 mixture of Amitriptyline HCI and Sodium bicarbonate, the endothermic transitions of sodium bicarbonate were recorded in the range of 150 °C to 180 °C (Fig. 88). No API transition peak was detected. A physical interaction was observed.

[0252] In a 1:1 mixture of Amitriptyline HCl and Sodium carbonate, the endothermic transitions of sodium carbonate were recorded in the range of 70 °C to 90 °C (Fig. 89). The API transition peak was detected between 180 °C and 197 °C (onset at 182.8 °C, ΔH = -33.8 J/g). A small physical interaction was observed.

[0253] In a 1:1 mixture of Amitriptyline HCl and Sodium phosphate dodecahydrate, the endothermic transitions were recorded in the range of 40 °C to 112 °C (Fig. 90). No API transition peak was detected. A physical/chemical interaction was observed.

[0254] The endothermic transition of sodium phosphate in a 1:1 mixture of Amitriptyline HCl and Sodium phosphate anhydrous was recorded in the range of 40 °C to 90 °C. The API transition peak was detected between 174 °C and 192 °C (onset at 179.8 °C, ΔH = -222.8 J/g) (Fig. 91). No physical interaction was observed.

[0255] In summary, different types of interaction were observed among the excipients and the API. A physical interaction was observed with Magnesium stearate and Sodium phosphate dibasic, probably because of partial API solubilization. A eutectic interaction was observed with Pearlitol flash and Pearlitol 200 SO/Mannitol, due to the presence of mannitol. The thermal transition of the API is completely shifted by excipient complex formation of a eutectic. A

physical interaction was observed with Sodium Stearyl fumarate, likely because of partial API solubilization or reactions at the particles' surfaces between the HCl and Na counter ions. A physical interaction was observed with Sodium Phosphate dodecahydrate, also likely because of partial API solubilization. No interaction was observed with Stearic acid, Glycerol dibehenate, Unipure DW/Cornstarch partially pregelatinized, Silicon (colloidal), Crospovidone/Kollidon CL, Sodium carbonate, Sodium bicarbonate, or Sodium Phosphate anhydrous. Table 4 summarizes the data observed.

Table 4: Interactions between API and excipients

Excipient	Mixture in formulation (1:1 ratio)
Sodium stearyl fumarate	Physical interaction
Stearic acid	No interaction
Glycerol dibehenate	No interaction
Magnesium stearate	Physical interaction
Pearlitol flash	Eutectic interaction
Pearlitol 200 SO/Mannitol	Eutectic interaction
Unipure DW /Corn starch	Partially no interaction
Pregelatinized Crospovidone - Kollidon CL	No interaction
Silicon Colloidal/ Aerosil 200	No interaction
Sodium phosphate dibasic	Physical interaction
Sodium bicarbonate	No interaction
Sodium carbonate	No interaction
Sodium phosphate dodecahydrate	Physical interaction
Sodium phosphate anhydrous	No interaction

Example 4

[0256] To test whether wet mixing of Cyclobenzaprine and mannitol changes the eutectic, 10 g of the eutectic mixture (75% API and 25% Mannitol) were put in a mortar with 1 mL of water and mixed until reaching a paste consistency. This paste was left to dry at room temperature while being ground in the mortar. The ground

powder was sieved in 500 μm sieve. Sample morphology was assessed by a Scanning Electron Microscope (SEM) FEI S50 instrument with an electron beam accelerated by a voltage of 25 kV, supported on an adhesive graphite plate and coated with a gold layer. The Specific Surface Area (SSA) and Powder Porosity was assessed by the BET method (nitrogen), by degassing the samples at 40°C under nitrogen for 2 hours in a Micromeritics Tristar II 3020 instrument. DSC heating curves were obtained by TA 821 DSC Mettler instrument under the following conditions:

Heating rate: *10°C/min*

Ambient: *Nitrogen 30 mL/min*

Sample older: *normal open aluminium pan*

Temperature range: *from 25 to 250°C*

Instrument calibration*:* *Indium sample purity 99.999 %*

X-ray powder diffraction (XRPD) tests were performed with an ULTIMA IV instrument (Rigaku), laying the sample on a static sample holder. The X-ray focusing slit had a variable width, interlocked with the θ value. The X-ray tube had a Copper target, with a current intensity of 40 mA and a voltage of 50 kV, and the radiation generated by the Cockcroft-Walton method is constituted by $K_{\alpha 1}$ (1.540562 Å) and $K_{\alpha 2}$ (1.544398 Å). The analytical conditions were the following:

Fixed Time

Sampling width: 0.02 deg

Scanning rate: 1.0 s/step

2 θ range: 3÷50 deg.

Sample holder: amorphous glass - equiangular 9200/2G, 0.2 mm deep. The sample was pressed with a glass plate.

[0257] SEM shows that the eutectic formed by wet granulation has particles with hard surfaces as seen in Fig. 92. These particles can be compared to particles observed by SEM of pure Cyclobenzaprine HCl (Fig. 93) and pure mannitol (Fig. 94). The physical characteristics were measured and are summarized in Table 5 (SSA: specific surface area; D10: 10% of the particles are smaller than this measurement; D50: 50% of the particles are smaller than this measurement; D90: 90% of the particles are smaller than this measurement). Fig. 95 depicts wet granulated eutectic particle size distribution and Fig. 96 depicts wet granulated eutectic pore volume over diameter. Moreover, both DSC and X-ray powder diffraction show complete incorporation of mannitol into the eutectic composition (Fig. 97 and Fig. 98, respectively).

Table 5: Physical characteristics of eutectic formed by wet granulation

SSA (m^2/g)	0.9148
Pore Volume (cm^3/g)	0.001599
Pore size (Å)	69.91
D10 (um)	4.629
D50 (um)	22.046
D90 (um)	82.096

Example 5

[0258] In addition to wet mixing, spray drying also can be used to mix ingredients to make pharmaceutical compositions. Five mixtures (10 g) of mannitol and Cyclobenzaprine HCl, in different ratios, were dissolved in 500ml of water for spray drying. The total solid concentration was 2% w/v, although 15% w/v also worked in earlier tests (data not shown). The solutions were spray-dried using a Büchi Spray Dryer B-290 (Büchi Labortechnik, Flawil, Switzerland) under the conditions reported in Table 6. Soft micro-particles were obtained in case of the first two batches created, while the other batches had slightly yellow scales and crystals. The yield obtained decreased with the increase of the Cyclobenzaprine HCl percentage in the solution to be spray dried.

Table 6: Spray Drying Process Parameters

Batch	T Inlet (°C)	T Outlet (°C)	Feed rate (ml/min)	Flow Rate (L/h)	Aspiration (100%)	delta Pressure (mbar)
1) 100% Mannitol, 0% API	120	74	4	600	100	10
2) 75% Mannitol, 25% API	120	74	4	600	100	5
3) 50% Mannitol, 50% API	120	76	4	600	100	5
4) 25% Mannitol, 75% API	120	73	4	600	100	5
5) 10% Mannitol, 90% API	120	74	4	600	100	2

[0259] DSC shows that spray drying the Cyclobenzaprine HCl-mannitol mixture unexpectedly converts the mannitol in the eutectic from its β form to its δ form. Mannitol is capable of crystallizing in three polymorphic states: α, β, and δ. These three forms can be distinguished by X-ray powder diffraction and based on different melting points for each polymorph. See, e.g., Sharma and Kalonia, AAPS PharmaSciTech 5(1):E10 (2004). In the above Examples, the mannitol used was β polymorphic mannitol. To test whether the spray drying process itself was sufficient to convert the mannitol from β mannitol to δ mannitol, SEM and DSC were performed on spray dried β mannitol. Fig. 99 and Fig. 100 show that spray dried mannitol appears different than the pure mannitol, but DSC revealed that that spray drying alone was not able to convert β mannitol to δ mannitol (Fig. 101). This is consistent with earlier studies of spray dried mannitol. See, e.g., Hulse et al., Drug Development and Industrial Pharmacy 35(6):712-718 (2009). Without wishing to be bound by theory, the change in mannitol's polymorphic state seems to be due to the combination of spray drying and the addition of Cyclobenzaprine. This may be because spray drying, unlike wet or dry mixing, involves dissolving the components and then allowing them to co-crystallize together. The mixtures tested by DSC were 25% Cyclobenzaprine:75% mannitol (by weight) (Fig. 102), 50% Cyclobenzaprine:50%

mannitol (by weight) (Fig. 103), 75% Cyclobenzaprine:25% mannitol (by weight) (Fig. 104), and 90% Cyclobenzaprine:10% mannitol (by weight) (Fig. 105). These measurements were used to calculate a melting point of 134 °C and to generate a phase diagram for the eutectic composition (Fig. 106). When the phase diagram obtained after spray drying (δ polymorph) is compared to the phase diagram after mixing (β polymorph, Fig. 65), the differences between the melting points can clearly be observed. The melting point for the β polymorph is 143 °C, while the melting point for the δ polymorph is 134 °C. This lower melting point is beneficial because it aids in dissolution, as described below. XRPD of the pure mannitol and Cyclobenzaprine HCl (Fig. 107) as compared to XRPD of the eutectics formed by spray drying (Fig. 108) also confirm that spray drying results in the formation of δ mannitol. Indeed, the XRPD pattern shows that even at 10% mannitol, all of the mannitol is present in the δ polymorph.

[0260] The physical properties of the δ mannitol eutectic also were measured, and are described in Table 7 (SSA: specific surface area; D10: 10% of the particles are smaller than this measurement; D50: 50% of the particles are smaller than this measurement; D90: 90% of the particles are smaller than this measurement). SEM reveals that the particles formed by spray drying are much more porous than those formed from wet granulation (Fig. 109 and Fig. 110). Fig. 111 depicts spray dried eutectic particle size distribution and Fig. 112 depicts spray dried eutectic pore volume over diameter. Figs. 113-116 depict X-ray powder diffraction data. In particular, Figure 113 depicts X-ray powder diffraction (2θ from 8 – 18 degrees) on a 25%:75% solution of mannitol:Cyclobenzaprine HCl (by weight) from the spray dry experiment and from cyclobenzaprine HCl. The locations of expected peaks from the mannitol β polymorph ("form beta") and δ polymorph ("form delta") are marked. Figure 114 depicts X-ray powder diffraction (2θ from 22 – 30 degrees) on the 25%:75% solution of mannitol:Cyclobenzaprine HCl (by weight) from the spray dry experiment and from cyclobenzaprine HCl. The locations of expected peaks from the mannitol β polymorph ("form beta") and δ polymorph ("form delta") are marked. Figure 115 depicts X-ray powder diffraction (2θ from 8 – 19 degrees) on 25%:75% solution of mannitol:Cyclobenzaprine HCl (by weight) from the spray dry experiment, Cyclobenzaprine HCl, and the mannitol β polymorph ("form beta"). Figure 116 depicts X-ray powder diffraction (2θ from 22 – 30 degrees) on the 25%:75% solution of mannitol-Cyclobenzaprine HCl (by weight) from the spray dry experiment, cyclobenzaprine HCl, and the mannitol β polymorph ("form beta").

Table 7: Physical properties of δ mannitol eutectic

SSA (m^2/g)	0.5398
Pore Volume (cm^3/g)	0.000654
Pore size (Å)	48.46
D10 (um)	6.653
D50 (um)	28.834
D90 (um)	143.74

[0261] To test the dissolution properties of the δ mannitol eutectic, dissolution tests were carried out with a Copley DIS 6000 instrument under the following conditions:

Apparatus: USP Paddle

RPM: 50

Medium: Pyrophosphate buffer 0.5% pH = 4.5 ± 0.05

Additive: Methocel 0.3 %

Vessel volume: 300 mL

Temperature: 37 ± 0.5°C

Sampling time: 1, 2, 5, 10, 20, 30, and 60 min, then each hour until 6 hours.

The sampling solutions were diluted 1 to 50 mL and then 1 to 50 mL with medium and submitted to UV analysis with UV (GBC Cintral 10e) under the following conditions:

λmax: 224 nm

Cuvette: Quartz 1 cm

Blank: medium

Fig. 117 shows the ionization of Cyclobenzaprine at different pHs. Notably, at pH 4.5, there still is free base present. The free base does not go into solution, so the Cyclobenzaprine dissolution does not reach 100%. Dissolution tests were

performed on the wet granulated mixture (Fig. 118) and the spray dried mixture (Fig. 119 and 120) to test whether the δ mannitol eutectic had different dissolution properties than the β mannitol dissolution product. Fig. 119 depicts comparisons between the wet granulated (WG), dry mixed (MIX), and spray dried (SD) mixtures, as well as Cyclobenzaprine HCl alone (API), over 6 hours. These experiments show that, especially during the first hour (Fig. 120), the spray dried composition dissolves faster than both the wet granulated and dry mixed compositions, demonstrating the benefits of the δ mannitol eutectic. This enhanced dissolution is beneficial because it will increase the rate of absorption of Cyclobenzaprine in both oral and sublingual formulations. The δ mannitol eutectic also is stable even after three weeks of accelerating stability tests when stored at 50 °C in an oven. In these tests, the δ form remained unchanged and no transformation into the β form was observed (data not shown).

[0262] Based on the surprising observation of δ mannitol in the Cyclobenzaprine eutectic, spray drying also may be used to create a δ mannitol eutectic with Amitriptyline.

Claims

1. A pharmaceutical composition comprising a eutectic of β-mannitol and Cyclobenzaprine HCl, wherein the eutectic comprises 75%±2% Cyclobenzaprine HCl and 25%±2% β-mannitol by weight.

2. The pharmaceutical composition of claim 1, wherein the Cyclobenzaprine HCl:β-mannitol eutectic molar ratio is 1.76±0.1.

3. The pharmaceutical composition of claim 1 or claim 2, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.

4. The pharmaceutical composition of any one of claims 1 to 3, further comprising a basifying agent.

5. The pharmaceutical composition of claim 4, wherein the basifying agent is K_2HPO_4, Na_2HPO_4 or anhydrous trisodium citrate.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the eutectic melts at 143.6±3 °C.

7. A method of manufacturing a pharmaceutical composition comprising a eutectic of β-mannitol and Cyclobenzaprine HCl as claimed in any one of claims 1 to 6, said method comprising mixing Cyclobenzaprine HCl and β-mannitol or milling Cyclobenzaprine HCl and β-mannitol.

8. The method of claim 7, comprising milling Cyclobenzaprine HCl and β-mannitol.

9. The method of claim 8, wherein, the Cyclobenzaprine HCl and β-mannitol are milled in a high shear granulator.

10. The method of claim 7, comprising mixing Cyclobenzaprine HCl and β-mannitol.

11. The method of claim 10, wherein the Cyclobenzaprine HCl and β-mannitol are mixed via compression.

12. The method of claim 11, wherein the Cyclobenzaprine HCl and β-mannitol are compressed via roller compaction.

13. The method of any one of claims 7 to 12, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.

14. The method of any one of claims 7 to 13, wherein the pharmaceutical composition further comprises a basifying agent.

15. The method of claim 14, wherein the basifying agent is K_2HPO_4, Na_2HPO_4 or anhydrous trisodium citrate.

16. The method of any one of claims 7 to 15, wherein the eutectic melts at 143.6±3 °C.

17. A eutectic composition of β-mannitol and Cyclobenzaprine HCl, wherein the eutectic comprises 75%±2% Cyclobenzaprine HCl and 25%±2% β-mannitol by weight.

18. The eutectic composition of claim 17, wherein the Cyclobenzaprine HCl:β-mannitol molar ratio is 1.76±0.1.

19. The eutectic composition of claim 17 or claim 18, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.

20. The eutectic composition of any one of claims 17 to 19, wherein the eutectic composition melts at 143.6±3 °C.

21. A method of manufacturing a eutectic composition comprising β-mannitol and Cyclobenzaprine HCl as claimed in any one of claims 17 to 20, said method comprising mixing Cyclobenzaprine HCl and β-mannitol or milling Cyclobenzaprine HCl and β-mannitol.

22. The method of claim 21, comprising milling Cyclobenzaprine HCl and β-mannitol.

23. The method of claim 22, wherein the Cyclobenzaprine HCl and β-mannitol are milled in a high shear granulator.

24. The method of claim 21, comprising mixing Cyclobenzaprine HCl and β-mannitol.

25. The method of claim 24, wherein the Cyclobenzaprine HCl and β-mannitol are mixed via compression.

26. The method of claim 25, wherein the Cyclobenzaprine HCl and β-mannitol are compressed via roller compaction.

27. The method of any one of claims 21 to 26, wherein the Cyclobenzaprine HCl is micronized Cyclobenzaprine HCl.