## CLAIMS

1. Transdermal therapeutic system for the transdermal administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid/buprenorphine mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer.

2. Transdermal therapeutic system in accordance with claim 1, wherein said buprenorphine is present in the form of buprenorphine base.

3. Transdermal therapeutic system in accordance with claim 1, wherein said carboxylic acid is levulinic acid.

4. Transdermal therapeutic system in accordance with claim 1, wherein said buprenorphine is present in the form of buprenorphine base and said carboxylic acid is levulinic acid.

5. Transdermal therapeutic system in accordance with claim 1, wherein said polymer-based pressure-sensitive adhesive is based on polysiloxanes or polyisobutylenes.

6. Transdermal therapeutic system in accordance with claim 1, wherein said polymer-based pressure-sensitive adhesive is based on polysiloxanes.

7. Transdermal therapeutic system in accordance with claim 1, wherein said buprenorphine is present in the form of buprenorphine base, said carboxylic acid is levulinic acid and the polymer-based pressure-sensitive adhesive is based on polysiloxanes.

8. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 1 mg to about 4 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof, or
about 3.5 mg to about 8 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof, or
about 6.5 mg to about 16 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof, or
about 11.5 mg to about 24 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof, or
about 15 mg to about 32 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

9. Transdermal therapeutic system in accordance with any one of claims

1 to 8, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from
about 1 $cm^2$ to about 4.8 $cm^2$, or
about 3 $cm^2$ to about 9.5 $cm^2$, or
about 6 $cm^2$ to about 19 $cm^2$, or
about 12 $cm^2$ to about 28.5 $cm^2$, or
about 16 $cm^2$ to about 38 $cm^2$.

10. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 1 $cm^2$ to about 4.8 $cm^2$ and the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 1 mg to about 4 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

11. Transdermal therapeutic system in accordance with claim 10, said transdermal therapeutic system providing a mean AUCt of more than 7,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

12. Transdermal therapeutic system in accordance with claim 11, said transdermal therapeutic system providing a mean AUCt of more than 8,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

13. Transdermal therapeutic system in accordance with any one of claims 10 to 12, wherein the transdermal therapeutic system provides a nominal mean release rate of about 5 µg/hr over about 168 hours of administration.

14. Transdermal therapeutic system in accordance with any one of claims 10 to 13, wherein buprenorphine is present in the form of buprenorphine base and wherein the transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to the commercial product BuTrans® having an area of release of 6.25 $cm^2$.

15. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 3 $cm^2$ to about 9.5 $cm^2$, and the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 3.5 mg to about 8 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

16. Transdermal therapeutic system in accordance with claim 15, said transdermal therapeutic system providing a mean AUCt of more than 14,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

17. Transdermal therapeutic system in accordance with claim 16, said transdermal therapeutic system providing a mean AUCt of more than 16,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

18. Transdermal therapeutic system in accordance with any one of claims 15 to 17, wherein the transdermal therapeutic system provides a nominal mean release rate of about 10 µg/hr over about 168 hours of administration.

19. Transdermal therapeutic system in accordance with any one of claims 15 to 18, wherein buprenorphine is present in the form of buprenorphine base and wherein the transdermal therapeutic system when tested in a comparative clinical study is

bioequivalent to the commercial product BuTrans® having an area of release of 12.5 $cm^2$.

20. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 6 $cm^2$ to about 19 $cm^2$ and the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 6.5 mg to about 16 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

21. Transdermal therapeutic system in accordance with claim 20, said transdermal therapeutic system providing a mean AUCt of more than 28,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

22. Transdermal therapeutic system in accordance with claim 21, said transdermal therapeutic system providing a mean AUCt of more than 32,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

23. Transdermal therapeutic system in accordance with any one of claims 20 to 22, wherein the transdermal therapeutic system provides a nominal mean release rate of about 20 µg/hr over about 168 hours of administration.

24. Transdermal therapeutic system in accordance with any one of claims 20 to 23, wherein buprenorphine is present in the form of buprenorphine base and wherein the transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to the commercial product BuTrans® having an area of release of 25 $cm^2$.

25. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 12 $cm^2$ to about 28.5 $cm^2$, and the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 11.5 mg to about 24 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

26. Transdermal therapeutic system in accordance with claim 25, said transdermal therapeutic system providing a mean AUCt of more than 42,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

27. Transdermal therapeutic system in accordance with claim 26, said transdermal therapeutic system providing a mean AUCt of more than 48,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

28. Transdermal therapeutic system in accordance with any one of claims 25 to 27, wherein the transdermal therapeutic system provides a nominal mean release rate of about 30 µg/hr over about 168 hours of administration.

29. Transdermal therapeutic system in accordance with any one of claims 1 to 7, the size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 16 $cm^2$ to about 38 $cm^2$, and the amount of said buprenorphine contained in the transdermal therapeutic system ranging from
about 15 mg to about 32 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

30. Transdermal therapeutic system in accordance with claim 29, said transdermal therapeutic system providing a mean AUCt of more than 62,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

31. Transdermal therapeutic system in accordance with claim 30, said transdermal therapeutic system providing a mean AUCt of more than 64,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

32. Transdermal therapeutic system in accordance with any one of claims 29 to 31, wherein the transdermal therapeutic system provides a nominal mean release rate of about 40 μg/hr over about 168 hours of administration.

33. Transdermal therapeutic system in accordance with any one of claims 1 to 32, said transdermal therapeutic system providing an arithmetic mean tmax of from about 60 hr to about 120 hr after a single-dose administration to a subject population.

34. Transdermal therapeutic system in accordance with claim 33, said transdermal therapeutic system providing an arithmetic mean tmax of from about 66 hr to less than 108 hr after a single-dose administration to a subject population.

35. Transdermal therapeutic system in accordance with any one of claims 1 to 34, said transdermal therapeutic system providing a mean AUCt per area of release of more than 1,700 pg.hr/ml-$cm^2$ over about 168 hours of administration after a single-dose administration to a subject population.

36. Transdermal therapeutic system in accordance with any one of claims 1 to 35, said buprenorphine-containing pressure-sensitive adhesive layer containing more than 0.55 mg/$cm^2$ of buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

37. Transdermal therapeutic system in accordance with claim 36, said buprenorphine-containing pressure-sensitive adhesive layer containing more than 0.6 mg/cm$^2$ of buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

38. Transdermal therapeutic system in accordance with any one of claims 1 to 37, the buprenorphine-containing pressure-sensitive adhesive layer being coated at a dry weight of more than 6 mg/cm$^2$.

39. Transdermal therapeutic system in accordance with claim 38, the buprenorphine-containing pressure-sensitive adhesive layer being coated at a dry weight of more than 8 mg/cm$^2$.

40. Transdermal therapeutic system in accordance with any one of claims 1 to 39, wherein the carboxylic acid is levulinic acid, said buprenorphine-containing pressure-sensitive adhesive layer containing the same % amounts of levulinic acid and buprenorphine, based on the % amount of buprenorphine base.

41. Transdermal therapeutic system in accordance with any one of claims 1 to 39, wherein the carboxylic acid is levulinic acid, said buprenorphine-containing pressure-sensitive adhesive layer containing less % amounts of levulinic acid than % amounts of buprenorphine, based on the % amount of buprenorphine base.

42. Transdermal therapeutic system in accordance with any one of claims 1 to 41, said buprenorphine-containing self-adhesive layer structure being attached to a second larger active agent-free self-adhesive layer structure for enhancing the adhesive properties of the overall transdermal therapeutic system.

43. Transdermal therapeutic system in accordance with claim 42, said second active-free self-adhesive layer structure comprising a backing layer and an active

agent-free pressure-sensitive adhesive layer of pressure-sensitive adhesive based on polyacrylates.

44. Transdermal therapeutic system in accordance with claim 42, said second active-free self-adhesive layer structure comprising a backing layer and an active agent-free pressure-sensitive adhesive layer of pressure-sensitive adhesive based on polysiloxane.

45. Transdermal therapeutic system in accordance with any one of claims 1 to 44, wherein buprenorphine is present in the form of buprenorphine base and providing a mean cumulative skin permeation rate measured in a Franz diffusion cell with dermatomed human skin of more than 1.3 $\mu g/cm^2$-hr over a 168 hours test.

46. Transdermal therapeutic system in accordance with any one of claims 1 to 45, wherein buprenorphine is present in the form of buprenorphine base and providing a cumulative release of buprenorphine base as measured in a Franz diffusion cell with dermatomed human skin of 220 $\mu g/cm^2$ to 640 $\mu g/cm^2$ over a time period of 168 hours.

47. Transdermal therapeutic system in accordance with any one of claims 1 to 46, wherein buprenorphine is present in the form of buprenorphine base and providing a non-cumulative release of buprenorphine base as measured in a Franz diffusion cell with dermatomed human skin of
2 $\mu g/cm^2$ to 10 $\mu g/cm^2$ in the first 8 hours,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 8 to hour 24,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 24 to hour 32,
30 $\mu g/cm^2$ to 120 $\mu g/cm^2$ from hour 32 to hour 48,
40 $\mu g/cm^2$ to 150 $\mu g/cm^2$ from hour 48 to hour 72,
100 $\mu g/cm^2$ to 300 $\mu g/cm^2$ from hour 72 to hour 144, and
30 $\mu g/cm^2$ to 100 $\mu g/cm^2$ from hour 144 to hour 168.

48. A set of two to five different transdermal therapeutic systems each in accordance with any one of claims 1 to 47, wherein

the first transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 1 $cm^2$ to about 4.8 $cm^2$ and contains an amount of said buprenorphine from about 1 mg to about 4 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof;

the second transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 3 $cm^2$ to about 9.5 $cm^2$ and contains an amount of said buprenorphine from about 3.5 mg to about 8 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof; and

the third transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 6 $cm^2$ to about 19 $cm^2$ and contains an amount of said buprenorphine from about 6.5 mg to about 16 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof; and

the fourth transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 12 $cm^2$ to about 28.5 $cm^2$ and contains an amount of said buprenorphine from about 11.5 mg to about 24 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof; and

the fifth transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 16 $cm^2$ to about 38 $cm^2$ and contains an amount of said buprenorphine from about 15 mg to about 32 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

49. Transdermal therapeutic system selected from a set in accordance with claim 48, wherein buprenorphine is present in the form of buprenorphine base and wherein the first transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to a reference product having an area of release of about 6.25 $cm^2$ and providing a nominal mean release rate of about 5 µg/hr over about 168 hours of administration,

the second transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to a reference product having an area of release of about 12.5 $cm^2$ and providing a nominal mean release rate of about 10 µg/hr over about 168 hours of administration,

the third transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to a reference product having an area of release of about 25 $cm^2$ and providing a nominal mean release rate of about 20 µg/hr over about 168 hours of administration,

the fourth transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to a reference product having an area of release of about 37.5 $cm^2$ and providing a nominal mean release rate of about 30 µg/hr over about 168 hours of administration,

the fifth transdermal therapeutic system when tested in a comparative clinical study is bioequivalent to a reference product having an area of release of about 50 $cm^2$ and providing a nominal mean release rate of about 40 µg/hr over about 168 hours of administration,

wherein the reference product is prepared by the following steps:

1. homogenizing of 1,139 g of a 47.83 % polyacrylate solution of a self-crosslinked acrylate copolymer of 2-ethylhexyl acrylate, vinyl acetate, acrylic acid (solvent: ethyl acetate:heptanes:isopropanol:toluene:acetylacetonate in the ratio of 37:26:26:4:1), 100 g of levulinic acid, 150 g of oleyl oleate, 100 g of polyvinylpyrrolidone, 150 g of ethanol, 200 g of ethyl acetate, and 100 g of buprenorphine base to provide a mixture;

2. stirring the mixture of step 1 for about 2 hours and controlling the dissolution of all solids visually whereas controlling the evaporation loss by reweighing and replenishing the possible solvent loss by ethyl acetate;
3. subsequently applying the mixture on a transparent polyester film in such a manner that the mass per unit area of the dry adhesive layer amounts to about 80 g/m$^2$ wherein the polyester film is rendered removable by means of siliconization and serves as protective layer;
4. removing the solvents of the mixture applied on a transparent polyester film in step 3 by drying with heated air which is led over a moist lane resulting in evaporation of the solvents, but also in melting of the levulinic acid and covering the adhesive film with a polyester foil;
5. punching the area of release of 6.25 cm$^2$, 12.5 cm$^2$, 25 cm$^2$, 37.5 cm$^2$ and 50 cm$^2$, respectively, by means of suitable cutting tools and removing the edges left between the individual systems.

50. Transdermal therapeutic system comprising buprenorphine for the transdermal administration of buprenorphine selected from:
a first transdermal therapeutic system providing a size of the area of release ranging from about 1 cm$^2$ to about 4.8 cm$^2$ and containing an amount of said buprenorphine from 1 mg to about 4 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a mean AUCt of more than 8,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population;
a second transdermal therapeutic system providing a size of the area of release ranging from about 3 cm$^2$ to about 9.5 cm$^2$ and containing an amount of said buprenorphine from about 3.5 mg to about 8 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a mean AUCt of more than 16,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population; and

a third transdermal therapeutic system providing a size of the area of release ranging from about 6 $cm^2$ to about 19 $cm^2$ and containing an amount of said buprenorphine from about 6.5 mg to about 16 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a mean AUCt of more than 32,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population; and

a fourth transdermal therapeutic system providing a size of the area of release ranging from about 12 $cm^2$ to about 28.5 $cm^2$ and containing an amount of said buprenorphine from about 11.5 mg to about 24 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a mean AUCt of more than 48,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population; and

a fifth transdermal therapeutic system providing a size of the area of release ranging from about 16 $cm^2$ to about 38 $cm^2$ and containing an amount of said buprenorphine from about 15 mg to about 32 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a mean AUCt of more than 64,000 pg.hr/ml over about 168 hours of administration after a single-dose administration to a subject population.

51. Transdermal therapeutic system comprising buprenorphine for the transdermal administration of buprenorphine selected from:

a first transdermal therapeutic system providing a size of the area of release ranging from about 1 $cm^2$ to about 4.8 $cm^2$ and containing an amount of said buprenorphine from 1 mg to about 4 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a nominal mean release rate of about 5 µg/hr over about 168 hours of administration;

a second transdermal therapeutic system providing a size of the area of release ranging from about 3 $cm^2$ to about 9.5 $cm^2$ and containing an amount of said buprenorphine from about 3.5 mg to about 8 mg buprenorphine base or an equimolar

amount of a pharmaceutically acceptable salt thereof and providing a nominal mean release rate of about 10 µg/hr over about 168 hours of administration; and
a third transdermal therapeutic system providing a size of the area of release ranging from about 6 $cm^2$ to about 19 $cm^2$ and containing an amount of said buprenorphine from about 6.5 mg to about 16 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a nominal mean release rate of about 20 µg/hr over about 168 hours of administration; and
a fourth transdermal therapeutic system providing a size of the area of release ranging from about 12 $cm^2$ to about 28.5 $cm^2$ and containing an amount of said buprenorphine from about 11.5 mg to about 24 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a nominal mean release rate of about 30 µg/hr over about 168 hours of administration; and
a fifth transdermal therapeutic system providing a size of the area of release ranging from about 16 $cm^2$ to about 38 $cm^2$ and containing an amount of said buprenorphine from about 15 mg to about 32 mg buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof and providing a nominal mean release rate of about 40 µg/hr over about 168 hours of administration.

52. Transdermal therapeutic system in accordance with claim 50 or 51, wherein buprenorphine is present in the form of buprenorphine base and providing a non-cumulative release of buprenorphine base as measured in a Franz diffusion cell with dermatomed human skin of
2 µg/$cm^2$ to 20 µg/$cm^2$ in the first 8 hours,
20 µg/$cm^2$ to 80 µg/$cm^2$ from hour 8 to hour 24,
20 µg/$cm^2$ to 80 µg/$cm^2$ from hour 24 to hour 32,
30 µg/$cm^2$ to 120 µg/$cm^2$ from hour 32 to hour 48,
40 µg/$cm^2$ to 150 µg/$cm^2$ from hour 48 to hour 72,
100 µg/$cm^2$ to 300 µg/$cm^2$ from hour 72 to hour 144, and
30 µg/$cm^2$ to 100 µg/$cm^2$ from hour 144 to hour 168.

53. A set of transdermal therapeutic systems including at least two transdermal therapeutic systems selected from the first, second, third, fourth and fifth transdermal therapeutic system in accordance with any one of claims 50 to 52.

54. Transdermal therapeutic system comprising buprenorphine for the transdermal administration of buprenorphine, wherein buprenorphine is present in the form of buprenorphine base and providing a non-cumulative release of buprenorphine base as measured in a Franz diffusion cell with dermatomed human skin of

2 $\mu g/cm^2$ to 10 $\mu g/cm^2$ in the first 8 hours,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 8 to hour 24,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 24 to hour 32,
30 $\mu g/cm^2$ to 120 $\mu g/cm^2$ from hour 32 to hour 48,
40 $\mu g/cm^2$ to 150 $\mu g/cm^2$ from hour 48 to hour 72,
100 $\mu g/cm^2$ to 300 $\mu g/cm^2$ from hour 72 to hour 144, and
30 $\mu g/cm^2$ to 100 $\mu g/cm^2$ from hour 144 to hour 168.

55. Transdermal therapeutic system in accordance with claim 54, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive, and

b) an analgesically effective amount of buprenorphine base,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer.

56. Transdermal therapeutic system comprising buprenorphine for the transdermal administration of buprenorphine, wherein buprenorphine is present in the form of buprenorphine base and providing a non-cumulative release of buprenorphine base as measured in a Franz diffusion cell with dermatomed human skin of

2 $\mu g/cm^2$ to 10 $\mu g/cm^2$ in the first 8 hours,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 8 to hour 24,
20 $\mu g/cm^2$ to 80 $\mu g/cm^2$ from hour 24 to hour 32,
30 $\mu g/cm^2$ to 120 $\mu g/cm^2$ from hour 32 to hour 48,
40 $\mu g/cm^2$ to 150 $\mu g/cm^2$ from hour 48 to hour 72,
100 $\mu g/cm^2$ to 300 $\mu g/cm^2$ from hour 72 to hour 144, and
30 $\mu g/cm^2$ to 100 $\mu g/cm^2$ from hour 144 to hour 168, and

comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the carboxylic acid buprenorphine base solution forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer.

57. Transdermal therapeutic system in accordance with any one of claims 1 to 56 for use in a method of treating pain.

58. Transdermal therapeutic system in accordance with any one of claims 1 to 56 for use in a method of treating pain by applying a transdermal therapeutic system for more than 96 hours on the skin of a patient.

59. Transdermal therapeutic system in accordance with any one of claims 1 to 56 for use in a method of treating pain by applying a transdermal therapeutic system for about 120 hours on the skin of a patient.

60. Transdermal therapeutic system in accordance with any one of claims 1 to 56 for use in a method of treating pain by applying a transdermal therapeutic system for about 144 hours on the skin of a patient.

61. Transdermal therapeutic system in accordance with any one of claims 1 to 56 for use in a method of treating pain by applying a transdermal therapeutic system for about 168 hours on the skin of a patient.

62. Method of treating pain in a patient by applying a transdermal therapeutic system in accordance with any one of claims 1 to 56 for more than 96 hours on the skin of a patient.

63. Method of treating pain in a patient by applying a transdermal therapeutic system in accordance with any one of claims 1 to 56 for about 120 hours on the skin of a patient.

64. Method of treating pain in a patient by applying a transdermal therapeutic system in accordance with any one of claims 1 to 56 for about 144 hours on the skin of a patient.

65. Method of treating pain in a patient by applying a transdermal therapeutic system in accordance with any one of claims 1 to 56 for about 168 hours on the skin of a patient.

66. Method of manufacture of a transdermal therapeutic system for the transdermal administration of buprenorphine in accordance with any one of claims 1 to 61, comprising the steps of

1. providing a buprenorphine-containing adhesive mixture or solution comprising
   a) buprenorphine base or a pharmaceutically acceptable salt thereof
   b) a carboxylic acid,
   c) a polymer-based pressure-sensitive adhesive, and
   d) solvent
2. coating said buprenorphine-containing adhesive mixture or solution on a film in an amount to provide the desired coating dry weight,
3. drying said coated buprenorphine-containing adhesive mixture or solution to provide a buprenorphine-containing adhesive layer with the desired coating dry weight,
4. laminating said buprenorphine-containing adhesive layer to a backing layer to provide an buprenorphine-containing self-adhesive layer structure,
5. punching the individual systems from the buprenorphine-containing self-adhesive layer structure with the desired area of release, and
6. optionally adhering to the individual systems an active-free self-adhesive layer structure comprising also a backing layer and an active agent-free pressure-sensitive adhesive layer and which is larger than the individual systems of buprenorphine-containing self-adhesive layer structure.

67. Method in accordance with claim 66, wherein in step 1 buprenorphine is present in the form of buprenorphine base and the carboxylic acid is levulinic acid

and are suspended in ethanol and subsequently combined with a polymer-based pressure-sensitive adhesive based on polysiloxane in heptane to provide the buprenorphine-containing adhesive mixture or solution.

68. Method of treating pain in a patient by applying for about 168 hours on the skin of a patient a transdermal therapeutic system for the transdermal administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid and linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid buprenorphine mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer.

69. Transdermal therapeutic system for administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid buprenorphine mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer for use in a method of treating pain by applying said transdermal therapeutic system for about 168 hours on the skin of a patient.

70. Transdermal therapeutic system for the transdermal administration of buprenorphine base, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxane,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer.

71. Method of treating pain in a patient by applying to the skin of said patient for about 168 hours a transdermal therapeutic system, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxane,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer.

72. Transdermal therapeutic system for the transdermal administration of buprenorphine base, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxane,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer for use in a method of treating pain by applying said transdermal therapeutic system for about 168 hours on the skin of a patient.

73. Transdermal therapeutic system for the transdermal administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid buprenorphine solution forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of

buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

74. Method of treating pain in a patient by applying to the skin of said patient for about 168 hours a transdermal therapeutic system for the transdermal administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid buprenorphine solution forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof.

75. Transdermal therapeutic system for the transdermal administration of buprenorphine, comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine-impermeable backing layer, and

B) a buprenorphine-containing pressure-sensitive adhesive layer on said buprenorphine-impermeable backing layer, the adhesive layer comprising

a) at least one polymer-based pressure-sensitive adhesive,

b) an analgesically effective amount of buprenorphine base or a pharmaceutically acceptable salt thereof, and

c) a carboxylic acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, levulinic acid and mixtures thereof, in an amount sufficient so that said analgesically effective amount of buprenorphine is solubilized therein to form a mixture, and the carboxylic acid buprenorphine solution forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of buprenorphine base or an equimolar amount of a pharmaceutically acceptable salt thereof for use in a method of treating pain by applying said transdermal therapeutic system for about 168 hours on the skin of a patient.

76. Transdermal therapeutic system for the transdermal administration of buprenorphine base, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxanes,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of buprenorphine base.

77. Method of treating pain in a patient by applying to the skin of said patient for about 168 hours a transdermal therapeutic system for the transdermal administration of buprenorphine base, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxanes,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of buprenorphine base.

78. Transdermal therapeutic system for the transdermal administration of buprenorphine base, comprising a buprenorphine base-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxanes,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein said buprenorphine base-containing pressure-sensitive adhesive layer is the skin contact layer and contains more than about 0.55 mg/cm$^2$ or more than 0.6 mg/cm$^2$ of buprenorphine base for use in a method of treating pain by applying said transdermal therapeutic system for about 168 hours on the skin of a patient.

79. A set of two to five different transdermal therapeutic systems for the transdermal administration of buprenorphine base selected from five different transdermal therapeutic systems, a first, a second, a third, a forth and a fifth transdermal therapeutic system, each of the five different transdermal therapeutic systems comprising a buprenorphine-containing self-adhesive layer structure comprising

A) a buprenorphine base-impermeable backing layer, and

B) a buprenorphine base-containing pressure-sensitive adhesive layer on said buprenorphine base-impermeable backing layer, the adhesive layer comprising

a) at least one pressure-sensitive adhesive based on polysiloxanes,

b) an analgesically effective amount of buprenorphine base, and

c) levulinic acid, in an amount sufficient so that said analgesically effective amount of buprenorphine base is solubilized therein to form a mixture, and the levulinic acid buprenorphine base mixture forms dispersed deposits in the said pressure-sensitive adhesive,

wherein,

the first transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 1 $cm^2$ to about 4.8 $cm^2$ and contains from about 1 mg to about 4 mg buprenorphine base;

the second transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 3 $cm^2$ to about 9.5 $cm^2$ and contains from about 3.5 mg to about 8 mg buprenorphine base; and

the third transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 6 $cm^2$ to about 19 $cm^2$ and contains from about 6.5 mg to about 16 mg buprenorphine base; and

the fourth transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 12 $cm^2$ to about 28.5 $cm^2$ and contains from about 11.5 mg to about 24 mg buprenorphine base; and

the fifth transdermal therapeutic system provides a size of said buprenorphine-containing pressure-sensitive adhesive layer providing the area of release ranging from about 16 $cm^2$ to about 38 $cm^2$ and contains from about 15 mg to about 32 mg buprenorphine base,

wherein the five different transdermal therapeutic systems have increasing areas of release and amounts of buprenorphine from the first to the fifth transdermal

therapeutic system for use in method of treating pain by applying one of said transdermal therapeutic systems for about 168 hours on the skin of a patient.

**Claims:**

1. An invention not claimed in any divisional application.