What is Claimed Is:

1. A sustained release formulation for oral administration comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an immediate release phase of paracetamol, providing a therapeutic plasma level of paracetamol in a human upon administration, which plasma level is at or above at least 4μg/ml for a mean duration of about 8 hours, for a single dose pharmacokinetic characteristic in both a fasted and fed state.

2. The sustained release formulation according to claim 1 wherein the plasma level is at least 3ug/ml for a mean duration of about 10 hours.

3. The sustained release formulation according to claims 1 or 2 wherein the plasma level is at or above at least 5ug/ml for a mean duration of about 6 hours.

4. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about double that for a single dose of 1000 mg immediate release paracetamol.

5. The sustained release formulation according to claim 4 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about 8.0-8.6 hrs and the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of an immediate release 1000mg dose of paracetamol is about 4.0-4.2 hrs.

6. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is 36 to 46% greater than that for a single dose of an extended release 1330 mg dose of paracetamol, formulated for administration three times daily.

7. The sustained release formulation according to claim 6 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about 8.0-8.6 hrs and the time duration of plasma paracetamol concentration at or above therapeutic level

(≥4μg/ml) for a single dose of an extended release 1330 mg dose of paracetamol is about 5.9-6.2 hrs.

8. The sustained release formulation according to claims 1 or 2 wherein the formulation provides a median time to maximum plasma concentration of paracetamol (T_{max}) from about 3 hours to about 6.5 hours after administration of a single dose of 2000mg sustained release paracetamol.

9. The sustained release formulation according any of the preceding claims which provide a width (time duration) at or above 50% of the height of a mean plasma concentration/time curve of the paracetamol from about 7 hrs to about 9 hrs after administration of a single dose of 2000mg sustained release paracetamol.

10. The sustained release formulation according to any of the preceding claims which provides a maximum mean plasma concentration (C_{max}) of the paracetamol which is more than about 3 to about 4 times the minimum mean plasma level concentration (C_{min}) of paracetamol at about 12 hours after administration of a single dose of 2000mg sustained release paracetamol.

11. The sustained release formulation according to claim 1 which provides a mean plasma concentration (C_{max}) of paracetamol from about 6.3μg/ml to about 17.1μg /ml, based on administration of a single dose of 2000mg sustained release paracetamol.

12. The sustained release formulation according to claim 11 which provides a mean plasma concentration (C_{max}) of paracetamol from about 8.9μg/ml to about 12.5μg/ml, based upon administration of a single 2000 mg dose of paracetamol.

13. The sustained release formulation according to claim 11 which provides a mean plasma concentration (C_{max}) of paracetamol from about 8μg/ml to about 13μg /ml, based on administration of a single 2000mg dose of paracetamol.

14. The sustained release formulation according to any one of claims 1 to 3 which provides a mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ of at least 80% to about 125% of the mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ provided by administration of 1000 mg of an immediate release reference standard 4 times daily, wherein the daily dose of the reference standard is substantially equal to a twice daily dose of the sustained release paracetamol formulation.

15. The sustained release formulation according to claim 14 which provides a mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ of at least about 95 % to about 105% of the mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ wherein the 4 times daily dose of the reference standard is substantially equal to a twice daily dose of sustained release paracetamol.

16. The sustained release formulation according to any one of claims 1 to 3 which provides a mean AUC $_{(0-6)}$ of at least 95% to about 105% of the mean AUC $_{(0-6)}$ provided by administration of a 1000 mg dose of an immediate release reference standard.

17. The sustained release formulation according to any one of claims 1 to 3 which provides a mean AUC $_{(0-6)}$ of at least 85% to about 115% of the mean AUC $_{(0-6)}$ provided by administration of a 1000 mg dose of an immediate release reference standard.

18. The sustained release formulation according to any of the preceding claims wherein the K_{el} is about 0.09 to about 0.17 hr^{-1} in fed state.

19. The sustained release formulation according to claim 18 wherein the K_{el} is about 0.13 hr^{-1} in a fed state.

20. The sustained release formulation according to any of the preceding claims wherein the K_{el} is about 0.05 to about 0.13 hr^{-1} in fasted state.

21. The sustained release formulation according to claim 20 wherein the K_{el} is about 0.09 hr^{-1} in a fasted state.

22. The sustained release formulation according to any of the preceding claims wherein the formulation has a single dose pharmacokinetic characteristics in the fasted and fed state of:
    a) a mean AUC (0-∞) is about 77 µg*h/ml to about 133µg*h/ml (or more); and
    b) a K_{el} is about 0.5 to about 0.13 hr^{-1} in fasted state or a K_{el} of about 0.09 to about 0.17 hr^{-1} in fed state; and
    c) the amount of paracetamol 2000mg is administered as compared to a single 1000mg dose of immediate release paracetamol, formulated for administration

every 4-6 hours, or compared to a single 1330 mg dose of an extended release formulation of paracetamol, formulated for administration every 8 hours.

23. The sustained release formulation according to any of the preceding claims which provides a mean AUC $_{(0-\infty)}$ from about 95 μg*h/ml to about 115 μg*h/ml in the fasted state based upon administration of a 2000mg dose of paracetamol.

24. The sustained release formulation according to claim 23 which provides a geometric mean AUC (0-∞) from about 100 μg*h/ml to 110 μg*h/ml in the fasted state based upon administration of a 2000mg dose of paracetamol.

25. The sustained release formulation according to any of the preceding claims wherein the sustained release formulation is a bilayer tablet having a sustained release phase in the one layer and an immediate release phase in the other layer.

26. The sustained release formulation according to claim 25 in which the sustained release phase comprises a matrix forming polymer of hydroxypropylmethyl cellulose to provide sustained release of paracetamol.

27. The sustained release formulation according to claim 26 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose.

28. The sustained release formulation according to claim 27 in which the high viscosity hydroxypropylmethylcellulose has a viscosity of about 3500 to about 6000 centipoise.

29. The sustained release formulation according to claim 25 to 28 in which the high viscosity hypromellose is present in an amount from about 3% to about 7% by weight of the sustained release phase.

30. The sustained release formulation according to claim 27 to 29 in which the high viscosity hypromellose is present in an amount from about 4% to about 6% by weight of the sustained release phase.

31. The sustained release formulation according to claims 27 in which the low viscosity hypromellose is present in an amount from about 0.5% to about 3% by weight of the sustained release phase.

32. The sustained release formulation according to claim 31 in which the low viscosity hypromellose is present in an amount from about 1% to about 2% by weight of the sustained release phase.

33. The sustained release formulation according to any of claims 25 to 32 wherein the sustained release phase comprises a modified starch present in an amount of about 0.5% to about 3% w/w.

34. The sustained release formulation according to claim 33 wherein the modified starch is a pre-gelatinized starch.

35. The sustained release formulation according to claim 26 or claim 27 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose present in an amount of about 3% to about 10% by weight of the total amount of sustained release components.

36. The sustained release formulation according to any of claims 25 to 35 in which ratio of paracetamol in the sustained release phase to the immediate release phase is about 80:20.

37. The sustained release formulation according to claim 36 in which ratio of paracetamol in the sustained release phase to the immediate release phase is about 90:10.

38. The sustained release formulation according to any of claims 1 to 25 wherein the sustained release formulation is a monolith tablet having a sustained release phase and an immediate release phase in one layer.

39. The sustained release formulation according to claim 38 in which the sustained release phase comprises a matrix forming polymer of hydroxypropylmethyl cellulose to provide sustained release of paracetamol.

40. The sustained release formulation according to claim 39 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose.

41. The sustained release formulation according to claim 40 in which the high viscosity hydroxypropylmethylcellulose has a viscosity of about 3500 to about 6000 centipoise.

42. The sustained release formulation according to claim 40 or 41 in which the high viscosity hypromellose is present in an amount from about 0.5% to about 4% by weight of the sustained release formulation weight.

43. The sustained release formulation according to claim 40 in which the ratio of high-viscosity hypromellose to low viscosity hypromellose is present in about a 2:1 ratio.

44. The sustained release formulation according to any of claims 40 to 43 in which the low viscosity hypromellose is present in an amount from about 0.5 to about 3% by weight of the sustained release formulation weight.

45. The sustained release formulation according to any of the preceding claims wherein the formulation is administered to said human as two tablets, optionally twice daily.

46. The sustained release formulation according to claim 45 wherein the plasma level of paracetamol is at or above at least 4µg/ml for a mean duration of time of about 16 hours (during 24 hours at steady state).

47. The sustained release formulation according to any of the preceding claims which has the following *in vitro* bio-dissolution profile of the dissolution release

ranges at various time points (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 °C set at rotating speed of 75rpm) of:

- 2 to 15% released at 15 minutes;
- 4 to 22% released at 30 minutes;
- 10 to 40% released at 60 minutes;
- 22 to 62% released at 180 minutes
- 50 to 88% released at 360 minutes;
- >90% released after 720 minutes.

48. The sustained release formulation according to any of claims 1 to 38 which has an *in vitro* dissolution profile of the dissolution release ranges at various time points (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 °C set at rotating speed of 75rpm) of:
    - 10 to 30% released after 30 minutes;
    - 20 to 40% released after 90 minutes;
    - 35 to 55% released after 180 minutes; and
    - >80% released after 600 minutes.

49. The sustained release formulation according to any of claims 1-25 or 39-45 which has an *in vitro* dissolution profile of (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 C set at rotating speed of 75rpm):
    - 5 to 25 % released after 30 minutes;
    - 15 to 35 % released after 90 minutes;
    - 35 to 55 % released after 180 minutes; and
    - >80% released after 600 minutes.

50. The sustained release formulation according to any of the preceding claims which is bioequivalent to a second formulation with respect to AUC indicating that the extent of absorption was the same as for a conventional immediate release paracetamol, or the sustained release formulation is well absorbed in both the fasted and fed states with more than 90% relative bioavailability as compared to a conventional immediate release formulation and an 8 hour extended release formulation, on a dose adjusted basis.

51. The sustained release formulation according to any of the preceding claims which provides a maximum mean plasma concentration (C_{max}) of the paracetamol which is about 5 to about 6 times the minimum mean plasma level concentration (C_{min}) of paracetamol at about 12 hours after administration of a 2000 mg dose at steady state.

52. The sustained release formulation according to claim 1 which provides a mean plasma concentration (C_{max}) of the paracetamol from about 9µg/ml to about 17µg /ml, based on administration of a repeat dose (steady state) of 2000mg sustained release paracetamol.

53. A sustained release formulation of paracetamol having a sustained release phase of paracetamol and an immediate release phase of paracetamol with the following pharmacokinetic characteristics in human upon a repeat dose (steady state) for oral administration in the fasted and fed states:
    a) a plasma level of paracetamol which has a minimum duration time above the mean of at least 4µg/ml for about 16 hours (during 24 hours at steady state);
    b) wherein the mean AUC $_{(0-\infty)}$ is about 173 µg*h/ml at steady state of the present invention formulation (when administered twice daily); and
    c) wherein the 90% confidence intervals for the ratios of the present invention formulation versus 8 hours sustained release formulation, and the present invention formulation versus the conventional immediate release formulation for all three PK parameters (AUC_{0-t}, AUC $_{0-\infty}$, and C_{max}) all lie within the bioequivalence boundaries (0.8, 1.25); and
    d) the amount of acetaminophen administered is 2000mg twice a day for three days, as compared to an 1000mg of immediate release paracetamol four times a day for three days and 1330 mg of 8 hours paracetamol three times a day for three days.

54. The sustained release formulation of claim 53 wherein the plasma level of paracetamol is at or above at least 4µg/ml for a mean duration of about 17 hours (during 24 hours at steady state).

55. The sustained release formulation of claim 53 wherein the K_{el} is about 0.26 hr^{-1}.

56. The sustained release formulation of claim 53 wherein the fluctuation index FI is about 1.4.

57. A sustained release formulation of paracetamol administered in two tablets each tablet having a sustained release phase and an immediate release phase of paracetamol with the following characteristics in a human upon oral administration of one single dose:

    a) a plasma level of paracetamol which has a minimum duration time above the mean of at least 5μg/ml for about 6 hours after a single dose;
    b) a plasma level of paracetamol which has a minimum duration time above the mean of at least 4μg/ml for about 8 hours after a single dose;
    c) a plasma level of paracetamol which has a minimum duration time above the mean of at least 3μg/ml for about 10 hours after a single dose;
    d) wherein the mean AUC $_{(0-\infty)}$ is about 85 μg*h/ml to about 120 μg*h/ml;
    e) wherein the mean AUC $_{(0-24)}$ is about 64 μg*h/ml to about 124 μg*h/ml;
    f) wherein the mean AUC $_{(0-6)}$ is about 38 μg*h/ml to about 40 μg*h/ml; and
    g) wherein the 90% confidence intervals for the ratios of the extend release formulation/conventional immediate release formulation and the extend release formulation/8 hours extend formulation for all three pharmacokinetic parameters AUC(0-∞), AUC(0-t), and C_{max} all lie within the bioequivalence boundaries [0.80, 1.25]; and
    h) the amount of paracetamol administered is 2000mg, as compared to an equivalent amount of immediate release paracetamol.

58. The sustained release formulation according to claim 57 wherein the K_{el} is about 0.5 hr-1 to about 0.13 h^{-1}

59. The sustained release formulation according to claim 57 wherein the T_{max} is about 3 hours to about 6.5 hours.

60. The sustained release formulation according to claim 53 wherein the AUC $_{(0-\infty)}$ is about 173 μg *h/ml.

61. A method of treating of analgesia or pain in a human in need thereof, which comprises administering to said human a sustained release formulation according to any of the preceding claims.

62. A method of treating of analgesia or pain in a human in need thereof, which comprises administering to said human a sustained release formulation comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an immediate release phase of paracetamol, providing a therapeutic plasma level of paracetamol in a human upon administration, which plasma level is at or above at least 3μg/ml for a mean duration of about 10 hours, and a plasma level of at or above at least 4μg/ml for a mean duration of about 8 hours, for a single dose pharmacokinetic characteristic in both a fasted and fed state.

63. A method of treating of analgesia or pain in a human in need thereof, which comprises administering to said human a sustained release formulation comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an immediate release phase of paracetamol, wherein said dosage form has the following *in vitro* bio-dissolution profile of the dissolution release ranges at various time points (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 °C set at rotating speed of 75rpm) of:
    - 2 to 15% released at 15 minutes;
    - 4 to 22% released at 30 minutes;
    - 10 to 40% released at 60 minutes;
    - 22 to 62% released at 180 minutes
    - 50 to 88% released at 360 minutes;
    - >90% released after 720 minutes, and

    wherein said formulation provides a therapeutically effective plasma concentration over a 12 hours period to treat analgesia or pain.

64. The method according to claim 63 wherein the wherein the sustained release formulation is a bilayer tablet having a sustained release phase in one layer and an immediate release phase in the other layer.

65. The method according to claim 64 in which the sustained release phase comprises a matrix forming polymer of hydroxypropylmethyl cellulose to provide sustained release of paracetamol.

66. The method according to claim 65 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose.

67. The method according to claim 66 in which the high viscosity hydroxypropylmethylcellulose has a viscosity of about 3500 to about 6000 centipoise.

68. The method according to any of claims 66 to 67 in which the high viscosity hypromellose is present in an amount from about 3% to about 7% by weight of the sustained release phase.

69. The method according to claim 68 in which the high viscosity hypromellose is present in an amount from about 4% to about 6% by weight of the sustained release phase.

70. The method according to claim 66 in which the low viscosity hypromellose is present in an amount from about 0.5% to about 3% by weight of the sustained release phase.

71. The method according to claim 70 in which the low viscosity hypromellose is present in an amount from about 1% to about 2% by weight of the sustained release phase.

72. The method according to any of claims 64 to 71 wherein the sustained release phase comprises a modified starch present in an amount of about 0.5% to about 3% w/w.

73. The method according to claim 72 wherein the modified starch is a pre-gelatinized starch.

74. The method according to claim 66 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose present in an amount of about 3% to about 10% by weight of the total amount of sustained release components.

75. The method according to any of claims 62 to 74 in which ratio of paracetamol in the sustained release phase to the immediate release phase is about 80:20.

76. The method according to claim 75 in which ratio of paracetamol in the sustained release phase to the immediate release phase is about 90:10.

77. The method according to any of claims 62 wherein the sustained release formulation is a monolith tablet having a sustained release phase and an immediate release phase in one layer.

78. The method according to claim 77 in which the sustained release phase comprises a matrix forming polymer of hydroxypropylmethyl cellulose to provide sustained release of paracetamol.

79. The method according to claim 78 in which the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose.

80. The method according to claim 79 in which the high viscosity hydroxypropylmethylcellulose has a viscosity of about 3500 to about 6000 centipoise.

81. The method according to claim 79 or 80 in which the high viscosity hypromellose is present in an amount from about 0.5% to about 4% by weight of the sustained release formulation weight.

82. The method according to claim 79 in which the ratio of high-viscosity hypromellose to low viscosity hypromellose is present in about a 2:1 ratio.

83. The method according to any of claims 79 in which the low viscosity hypromellose is present in an amount from about 0.5% to about 3% by weight of the sustained release formulation weight.

84. The method according to any of to any of claims 62 to 83 wherein the formulation is administered to said human as two tablets, optionally twice daily.

85. A sustained release formulation containing 1000mg paracetamol present in a sustained release phase and an immediate release phase in which the ratio of the paracetamol in the sustained release phase to the immediate release phase is about 80-90% to 10-20% and wherein the sustained release phase comprises a matrix forming polymer of at least one hydroxypropylmethyl cellulose and a starch , and which when ingested by a human reduces maximum attained plasma-paracetamol concentration (C_{max}) by at least about 4.5% at steady state

(relative to rapid-release paracetamol formulations), and increases time to reach maximum paracetamol-plasma concentration (T_{max}) by at least about 140% at steady state (relative to rapid-release paracetamol formulations), while having an insignificant effect on area under the plasma-paracetamol concentration time curve $AUC_{(0-24)}$; mean $AUC_{(0-24)}$ of about 165 μg*h/ml for sustained release paracetamol at steady state (2000mg dosed every 12 hours) versus a mean $AUC_{(0-24)}$ of about 168 μg*h/ml for 1000mg immediate release at steady state (dosed every 6 hours) and wherein the formulation is repeatedly administered (steady state).

What is claimed is:

1. A sustained release formulation for oral administration comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an immediate release phase of paracetamol, providing a therapeutic plasma level of paracetamol in a human upon administration, which plasma level is at or above at least 4μg/ml for a mean duration of about 8 hours, for a single dose pharmacokinetic characteristic in both a fasted and fed state.

2. The sustained release formulation according to claim 1 wherein the plasma level is at least 3μg/ml for a mean duration of about 10 hours.

3. The sustained release formulation according to claims 1 or 2 wherein the plasma level is at or above at least 5μg/ml for a mean duration of about 6 hours.

4. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about double that for a single dose of 1000 mg immediate release paracetamol.

5. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about 8.0-8.6 hrs and the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of an immediate release 1000mg dose of paracetamol is about 4.0-4.2 hrs.

6. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is about 8.0-8.6 hrs and the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of an extended release 1330 mg dose of paracetamol is about 5.9-6.2 hrs.

7. The sustained release formulation according to claim 1 wherein the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol is 36 to 46% greater than that for a single dose of an extended release 1330 mg dose of paracetamol, formulated for administration three times daily.

8. The sustained release formulation according to claims 1 or 2 wherein the formulation provides a median time to maximum plasma concentration of paracetamol

(T_{max}) from about 3 hours to about 6.5 hours after administration of a single dose of 2000mg sustained release paracetamol.

9. The sustained release formulation according to claims 1 or 2 which provide a width (time duration) at or above 50% of the height of a mean plasma concentration/time curve of the paracetamol from about 7 hrs to about 9 hrs after administration of a single dose of 2000mg sustained release paracetamol.

10. The sustained release formulation according to claims 1 or 2 which provides a maximum mean plasma concentration (C_{max}) of the paracetamol which is more than about 3 to about 4 times the minimum mean plasma level concentration (C_{min}) of paracetamol at about 12 hours after administration of a single dose of 2000mg sustained release paracetamol.

11. The sustained release formulation according to claim 1 which provides a mean plasma concentration (C_{max}) of paracetamol from about 6.3µg/ml to about 17.1µg /ml, based on administration of a single 2000mg dose of paracetamol.

12. The sustained release formulation according to claim 11 which provides a mean plasma concentration (C_{max}) of paracetamol from about 8.9µg/ml to about 12.5µg/ml, based upon administration of a single 2000 mg dose of paracetamol.

13. The sustained release formulation according to claim 11 which provides a mean plasma concentration (C_{max}) of paracetamol from about 8µg/ml to about 13µg /ml, based on administration of a single 2000mg dose of paracetamol.

14. The sustained release formulation according to any one of claims 1 to 3 which provides a mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ of at least 80% to about 125% of the mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ provided by administration of 1000 mg of an immediate release reference standard 4 times daily, wherein the daily dose of the reference standard is substantially equal to a twice daily dose of the sustained release paracetamol formulation.

15. The sustained release formulation according to claim 14 which provides a mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ of at least about 95 % to about 105% of the mean AUC $_{(0-24)}$ or mean AUC $_{(0-\infty)}$ wherein the 4 times daily dose of the reference standard is substantially equal to a twice daily dose of sustained release paracetamol.

16. The sustained release formulation according to any one of claims 1 to 3 which provides a mean AUC $_{(0-6)}$ of at least 85% to about 115% of the mean AUC $_{(0-6)}$ provided by administration of a 1000 mg dose of an immediate release reference standard.

17. The sustained release formulation according to claim 16 which provides a mean AUC $_{(0-6)}$ of at least 95% to about 105% of the mean AUC $_{(0-6)}$ provided by administration of a 1000 mg dose of an immediate release reference standard.

18. The sustained release formulation according to claims 1 or 2 wherein the K_{el} is about 0.09 to about 0.17 hr^{-1} in fed state.

19. The sustained release formulation according to claim 18 wherein the K_{el} is about 0.13 hr^{-1} in a fed state.

20. The sustained release formulation according to claims 1 or 2 wherein the K_{el} is about 0.05 to about 0.13 hr^{-1} in fasted state.

21. The sustained release formulation according to claim 20 wherein the K_{el} is about 0.09 hr^{-1} in a fasted state.

22. The sustained release formulation according to any of the preceding claims wherein the formulation has a single dose pharmacokinetic characteristics in the fasted and fed state of:

a) a mean AUC (0-∞) is about 77 µg*h/ml to about 133µg*h/ml (or more); and

b) a K_{el} is about 0.5 to about 0.13 hr^{-1} in fasted state or a K_{el} of about 0.09 to about 0.17 hr^{-1} in fed state; and

c) the amount of paracetamol 2000mg is administered as compared to a single 1000mg dose of immediate release paracetamol, formulated for administration every 4-6 hours, or compared to a single 1330 mg dose of an extended release formulation of paracetamol, formulated for administration every 8 hours.

23. The sustained release formulation according to claim 1 which provides a mean AUC $_{(0-\infty)}$ from about 95 µg*h/ml to about 115 µg*h/ml in the fasted state based upon administration of a 2000mg dose of paracetamol.

24. The sustained release formulation according to claims 1 or 2 wherein the sustained release formulation is a bilayer tablet having a sustained release phase in the one layer and an immediate release phase in the other layer.

25. The sustained release formulation according to claim 24 in which the sustained release phase comprises a matrix forming polymer of hydroxypropylmethyl cellulose to provide sustained release of paracetamol, wherein the hydroxypropylmethyl cellulose comprises a high viscosity hypromellose and a low viscosity hypromellose.

26. The sustained release formulation according to any of claims 1 to 23 wherein the sustained release formulation is a monolith tablet having a sustained release phase and an immediate release phase in one layer.

27. The sustained release formulation according to claims 1 to 26 wherein the formulation is administered to said human as two tablets, optionally twice daily.

28. A sustained release formulation containing 1000mg paracetamol present in a sustained release phase and an immediate release phase in which the ratio of the paracetamol in the sustained release phase to the immediate release phase is about 80-90% to 10-20% and wherein the sustained release phase comprises a matrix forming polymer of at least one hydroxypropylmethyl cellulose and a starch , and which when ingested by a human reduces maximum attained plasma-paracetamol concentration (C_{max}) by at least about 4.5% at steady state (relative to rapid-release paracetamol formulations), and increases time to reach maximum paracetamol-plasma concentration (T_{max}) by at least about 140% at steady state (relative to rapid-release paracetamol formulations), while having an insignificant effect on area under the plasma-paracetamol concentration time curve $AUC_{(0-24)}$; mean $AUC_{(0-24)}$ of about 164 µg*h/ml for sustained release paracetamol at steady state (2000mg dosed every 12 hours) versus a mean $AUC_{(0-24)}$ of about 164 µg*h/ml for 1000mg immediate release at steady state (dosed every 6 hours) and wherein the formulation is repeatedly administered (steady state).

29. The sustained release formulation according to claims 1 or 2 which has the following *in vitro* bio-dissolution profile of the dissolution release ranges at various time points (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 °C set at rotating speed of 75rpm) of:

- 2 to 15% released at 15 minutes;
- 4 to 22% released at 30 minutes;
- 10 to 40% released at 60 minutes;
- 22 to 62% released at 180 minutes
- 50 to 88% released at 360 minutes;
- >90% released after 720 minutes.

30. A sustained release formulation of paracetamol having a sustained release phase of paracetamol and an immediate release phase of paracetamol with the following pharmacokinetic characteristics in human upon a repeat dose (steady state) for oral administration in the fasted and fed states:

- a plasma level of paracetamol which has a minimum duration time above the mean of at least 4µg/ml for about 16 (during 24 hours at steady state);
- wherein the mean $AUC_{(0-\infty)}$ is about 173 µg*h/ml at steady state of the present invention formulation (when administered twice daily); and
- wherein the 90% confidence intervals for the ratios of the present inventive formulation versus 8 hours sustained release formulation, and the present inventive formulation versus the conventional immediate release formulation for all three PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) all lie within the bioequivalence boundaries (0.8, 1.25); and

- the amount of acetaminophen administered is 2000mg twice a day for three days, as compared to a 1000mg of immediate release paracetamol four times a day for three days and 1330 mg of 8 hours paracetamol three times a day for three days.

31. A sustained release formulation of paracetamol administered in two tablets each tablet having a sustained release phase and an immediate release phase of paracetamol with the following characteristics in a human upon oral administration of one single dose:

- a plasma level of paracetamol which has a minimum duration time above the mean of at least 5µg/ml for about 6 hours after a single dose;
- a plasma level of paracetamol which has a minimum duration time above the mean of at least 4µg/ml for about 8 hours after a single dose;
- a plasma level of paracetamol which has a minimum duration time above the mean of at least 3µg/ml for about 10 hours after a single dose;
- wherein the mean AUC $_{(0-\infty)}$ is about 85 µg*h/ml to about 120 µg*h/ml;
- wherein the mean AUC $_{(0-24)}$ is about 64 µg*h/ml to about 124 µg*h/ml;
- wherein the mean AUC $_{(0-6)}$ is about 38 µg*h/ml to about 40 µg*h/ml; and
- wherein the 90% confidence intervals for the ratios of the extend release formulation/conventional immediate release formulation and the extend release formulation/8 hours extend formulation for all three pharmacokinetic parameters AUC(0-∞), AUC(0-t), and C_{max} all lie within the bioequivalence boundaries [0.80, 1.25]; and
- the amount of paracetamol administered is 2000mg, as compared to an equivalent amount of immediate release paracetamol.

32. A sustained release formulation comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an immediate release phase of paracetamol, wherein said dosage form has the following *in vitro* bio-dissolution profile of the dissolution release ranges at various time points (as determined by USP Type II apparatus, rotating paddle, with 900 ml of Phosphate buffer at pH 7.4, 37 °C set at rotating speed of 75rpm) of:

- 2 to 15% released at 15 minutes;
- 4 to 22% released at 30 minutes;
- 10 to 40% released at 60 minutes;
- 22 to 62% released at 180 minutes
- 50 to 88% released at 360 minutes;
- >90% released after 720 minutes, and

wherein said formulation provides a therapeutically effective plasma concentration over a 12 hours period, for use in the treatment of analgesia or pain.