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 93 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.

CLAIMS

1. A sustained release formulation for oral administration containing 2000mg of paracetamol administered in two tablets, each tablet having 1000mg of 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 from 0.5% to 3% w/w of a pre-gelatinized starch and a matrix forming polymer of hydroxypropylmethyl cellulose, wherein the hydroxypropylmethyl cellulose contains from 4% to 6% by weight of a high viscosity hydroxypropylmethyl cellulose having a viscosity between 3500 and 6000 centipoise and from 1% to 2% by weight of a low viscosity hydroxypropylmethyl cellulose having a viscosity between 10 and 30 centipoise.

2. The sustained release formulation according to claim 1, in which ratio of paracetamol in the sustained release phase to the immediate release phase is about 90:10.

3. The sustained release formulation according to claims 1 or 2 wherein, the formulation provides 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.

4. The sustained release formulation according to claims 1 or 2 wherein, the formulation provides 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.

5. The sustained release formulation according to claims 1 or 2 wherein, the formulation provides a therapeutic plasma level of paracetamol in a human upon administration, which plasma level is at or above at least 5μg/ml for a mean duration of about 6 hours.

6. The sustained release formulation according to claims 1 or 2 wherein, the formulation provides a time duration of plasma paracetamol concentration at or above therapeutic level ($\geq 4\mu g/ml$) for a 2000mg single dose of sustained release paracetamol which is

8.0-8.6 hrs and which is double the time duration of plasma paracetamol concentration at or above therapeutic level ($\geq 4\mu g/ml$) for a conventional 1000mg single dose of an immediate release paracetamol formulation which is about 4.0-4.2 hrs.

7. The sustained release formulation according to claims 1 or 2, wherein the formulation provides a time duration of plasma paracetamol concentration at or above therapeutic level ($\geq 4\mu g/ml$) of 8.0-8.6 hours after a single dose administration of 2000mg of sustained release paracetamol.

8. The sustained release formulation according to any one of the preceding claims, further characterized wherein the formulation provides a mean time for maximum plasma concentration of paracetamol (T_{max}) of 3 to 6.5 hours after a single dose administration of 2000mg of sustained release paracetamol.

9. The sustained release formulation according to any one of the preceding claims, further characterized wherein the formulation provides a maximum plasma concentration (C_{max}) of paracetamol which is 3 or 4 times the minimum mean plasma concentration (C_{min}) of paracetamol at 12 hours after a single dose administration of 2000mg of sustained release paracetamol.

10. The sustained release formulation according to any one of the preceding claims, further characterized wherein the formulation provides a mean $AUC_{(0-24)}$ or a mean $AUC_{(0-\infty)}$ of at least 80% to 125% of the mean $AUC_{(0-24)}$ or mean $AUC_{(0-\infty)}$ as provided by administration of 1000mg of an immediate release reference standard of paracetamol 4 times per day.

11. The sustained release formulation according to any one of the preceding claims, further characterized wherein the formulation provides a mean $AUC_{(0-6)}$ at least 85% to 115% of the mean $AUC_{(0-6)}$ provided by administration of 1000mg of an immediate release reference standard 4 times per day.

12. The sustained release formulation according to any one of the preceding claims, further characterized wherein the formulation has the following dissolution profile *in vitro* from dissolution's release ranges in different times (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 in 15 minutes; 4 to 22% released in 30 minutes; 10 to 40% released in 60 minutes; 22 to 62% released in 180 minutes, 50 to 88% released in 360 minutes; and >90% released after 720 minutes.

13. 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 one layer and an immediate release phase in one layer.

14. The sustained release formulation according to any of the preceding claims, wherein the sustained release formulation is a monolayer tablet.

15. The sustained release formulation according to any of the preceding claims, wherein the ratio of high viscosity hypromellose to low viscosity hypromellose is 3:1.

16. A sustained release formulation for oral administration containing 2000mg of paracetamol administered in two tablets, each tablet having 1000mg of 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 90% to 10%, and wherein the sustained release phase comprises from 0.5% to 3% w/w of a pre-gelatinized starch and a matrix forming polymer of hydroxypropylmethyl cellulose, wherein the hydroxypropylmethyl cellulose contains from 4% to 6% by weight of a high viscosity hydroxypropylmethyl cellulose having a viscosity between 3500 and 6000 centipoise and from 1% to 2% by weight of a low viscosity hydroxypropylmethyl cellulose having a viscosity between 10 and 30 centipoise.

17. The sustained release formulation according to claim 16 wherein, the formulation provides 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.

18. The sustained release formulation according to claim 16 wherein, the formulation provides 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.

19. The sustained release formulation according to claim 16 wherein, the formulation provides a therapeutic plasma level of paracetamol in a human upon administration, which plasma level is at or above at least 5μg/ml for a mean duration of about 6 hours.

20. The sustained release formulation according to claim 16 wherein, the formulation provides a time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a 2000mg single dose of sustained release paracetamol which is 8.0-8.6 hrs and which is double the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a conventional 1000mg single dose of an immediate release paracetamol formulation which is about 4.0-4.2 hrs.

21. The sustained release formulation according to claim 16, wherein the formulation provides a time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) of 8.0-8.6 hours after a single dose administration of 2000mg of sustained release paracetamol.

22. The sustained release formulation according to claim 16, further characterized wherein the formulation provides a mean time for maximum plasma concentration of paracetamol (T_{max}) of 3 to 6.5 hours after a single dose administration of 2000mg of sustained release paracetamol.

23. The sustained release formulation according to claim 16, further characterized wherein the formulation provides a maximum plasma concentration (C_{max}) of paracetamol which is 3 or 4 times the minimum mean plasma concentration (C_{min}) of paracetamol at 12 hours after a single dose administration of 2000mg of sustained release paracetamol.

24. The sustained release formulation according to claim 16, further characterized wherein the formulation provides a mean $AUC_{(0-24)}$ or a mean $AUC_{(0-\infty)}$ of at least 80% to 125% of the mean $AUC_{(0-24)}$ or mean $AUC_{(0-\infty)}$ as provided by administration of 1000mg of an immediate release reference standard of paracetamol 4 times per day.

25. The sustained release formulation according to claim 16, further characterized wherein the formulation provides a mean $AUC_{(0-6)}$ at least 85% to 115% of the mean $AUC_{(0-6)}$ provided by administration of 1000mg of an immediate release reference standard 4 times per day.

26. The sustained release formulation according to claim 16, further characterized wherein the formulation has the following dissolution profile *in vitro* from dissolution's release ranges in different times (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 in 15 minutes; 4 to 22% released in 30 minutes; 10 to 40% released in 60 minutes; 22 to 62% released in 180 minutes, 50 to 88% released in 360 minutes; and >90% released after 720 minutes.

27. The sustained release formulation according to claim 16, wherein the sustained release formulation is a bilayer tablet having a sustained release phase in one layer and an immediate release phase in one layer.

28. The sustained release formulation according to claim 16, wherein the sustained release formulation is a monolayer tablet.

29. The sustained release formulation according to claim 16, wherein the ratio of high viscosity hypromellose to low viscosity hypromellose is 3:1.

30. 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 from 0.5% to 3% w/w of a pre-gelatinized starch and a matrix forming polymer of hydroxypropylmethyl cellulose, wherein the hydroxypropylmethyl cellulose contains from 4% to 6% by weight of a high viscosity hydroxypropylmethyl cellulose having a viscosity between 3500 and 6000 centipoise and from 1% to 2% by weight of a low viscosity hydroxypropylmethyl cellulose having a viscosity between 10 and 30 centipoise , 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).

31. 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.

32. 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.

33. 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.