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 $AUC(0-\infty)$, 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.

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 a high viscosity hydroxypropylmethyl cellulose having a viscosity between 3500 and 6000 centipoise present in an amount from 4% to 6% by weight of the sustained release phase of the formulation and a low viscosity hydroxypropylmethyl cellulose having a viscosity between 10 and 30 centipoise present in an amount from 1% to 2% by weight of the sustained release phase of the formulation.

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 a high viscosity

hydroxypropylmethyl cellulose having a viscosity between 3500 and 6000 centipoise present in an amount from 4% to 6% by weight of the sustained release phase of the formulation and a low viscosity hydroxypropylmethyl cellulose having a viscosity between 10 and 30 centipoise present in an amount from 1% to 2% by weight of the sustained release phase of the formulation.

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 ($\geq$4μg/ml) for a 2000mg single dose of sustained release paracetamol which is 8.0-8.6 hrs and which is double the time duration of plasma paracetamol concentration at or above therapeutic level ($\geq$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 ($\geq 4\mu g/ml$) 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. The use of a sustained release formulation comprising about 2000mg paracetamol present in a sustained release phase of paracetamol and an

immediate release phase of paracetamol, in the manufacture of a medicament for the treatment of analgesia or pain, 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.