(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2012 (15.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/154563 A1

(51) International Patent Classification:
A61K 9/22 (2006.01) *A61K 31/167* (2006.01)

(21) International Application Number:
PCT/US2012/036528

(22) International Filing Date:
4 May 2012 (04.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/483,320 6 May 2011 (06.05.2011) US

(71) Applicant *(for all designated States except US)*: **GLAXOSMITHKLINE LLC** [US/US]; One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BUAN, Carla, Valenti** [US/US]; 1500 Littleton Road, Parsippany, NJ 07054 (US). **LIU, Dongzhou** [US/US]; 1500 Littleton Road, Parsippany, NJ 07054 (US). **MEGHPARA, Kanji** [US/US]; 1500 Littleton Road, Parsippany, NJ 07054 (US).

(74) Agents: **STEIN, Nora, L.** et al.; GlaxoSmithKline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: SUSTAINED RELEASE PARACETAMOL FORMULATIONS

(57) Abstract: The present invention is directed to twice daily sustained release pharmaceutical composition of paracetamol having an immediate release phase of paracetamol and a sustained release phase of paracetamol, said composition having unique and advantageous pharmacokinetic properties and a pharmaceutical composition comprising only a sustained release phase of paracetamol having unique and advantageous pharmacokinetic properties.

WO 2012/154563 A1

SUSTAINED RELEASE PARACETAMOL FORMULATIONS

FIELD OF THE INVENTION

The present invention is directed to twice daily sustained release pharmaceutical compositions of paracetamol having an immediate release phase and a sustained release phase of paracetamol and having unique and advantageous pharmacokinetic properties.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical compositions containing N-acetyl-p-aminophenol, known by the generic names paracetamol, acetaminophen and APAP (hereinafter referred to as paracetamol). In particular, the invention relates to a sustained release paracetamol formulation having an advantageous pharmacokinetic profile.

Paracetamol is an analgesic and antipyretic agent widely used in prescription and non-prescription medicines, often in combination with other biologically active compounds, such as various opiate derivatives.

The elimination half-life of paracetamol is reported to be in the range of 1.9-2.5 hours. Its absorption following oral doses of conventional immediate release tablets is characterized by passive absorption with high bioavailability (80%) and rapidly occurring maximum plasma concentration (t_{max} 30-90 min). These characteristics determine a conventional dosage regimen of 1000mg paracetamol being administered every 4 to 6 hours. Although this regimen is acceptable for the short-term treatment of acute pain, it becomes inconvenient for long-term treatment of sub-chronic or chronic pain. Osteoarthritis (OA) and musculoskeletal disorders prevalence is widely associated with ageing. Globally data is available which demonstrates that while 25% of all pain occasions are headache, joint pain represents 14% of all pain occasions. This percentage will likely increase proportionally with increasing age and changes dramatically in people over 60 to be 55% of all pain occasions.

In joint pain, generally a chronic condition, medication compliance is an essential component for achieving optimal efficacy. Issues of compliance are particularly important for elderly patients who can have a range of co-morbidities requiring pharmacological treatment. Sustained release paracetamol formulations can improve a patient's quality of life by reducing the number of doses to be taken, and providing steadier levels of the drug in the blood as determined by plasma or serum drug concentrations.

Paracetamol is recommended as first-line treatment because it effectively relieves the mild to moderate pain of OA, while avoiding non-steroidal anti-inflammatory drug (NSAID)-associated risks, such as gastrointestinal (GI), cardiovascular and renal complications and has few drug interactions. Even at OTC doses, NSAIDs such as ibuprofen and aspirin have the potential to produce significant adverse GI effects when used regularly. Elderly patients are also at a greater risk from serious GI events.

A paracetamol product designed for three times daily dosing (tid) will contain enough paracetamol to give close to the maximum daily dose when two tablets are taken three times daily, i.e., about 600 mg to 667 mg per tablet. Such a product is sold as Panadol® Extend around the world and is described in US 7,943,170. The product described in US 7,943,170 is a sustained release bilayer tablet containing 665 mg of paracetamol. These tablets contain 70% of paracetamol in a sustained release layer and 30% in an immediate release layer. The sustained release layer in these tablets is provided by a matrix comprising a mixture of hydroxypropylmethylcellulose and polyvinyl-pyrrolidone.

The product described in EP-A-305051 (McNeil, Inc) is a sustained release bilayer tablet containing either 650 or 667 mg of paracetamol. These tablets contain equal amounts of paracetamol in an immediate release layer and a sustained release layer. The sustained release layer in these tablets is provided by a matrix comprising a mixture of hydroxyethylcellulose and polyvinyl-pyrrolidone. McNeil, Inc. markets such a bilayer tablet as Tylenol® Extended Relief in the US.

The product described in US 5,773,031, Shah et al. is a mixture of polymeric coated, sustained release acetaminophen particles and uncoated, quick release acetaminophen particles pressed together in a tablet. The coating is water permeable, but not soluble or pH dependent, e.g., a water-insoluble, pH independent coating. The patent does not describe a release rate profile for the acetaminophen.

There are many additional publications on sustained release formulations of paracetamol; however none of them appear to have addressed the issue of twice daily dosing of the active agent. While three times daily dosing has significant advantages over every 4 hours or every 6 hours, twice daily dosing is preferred for not only patient compliance, but to be able to maintain a therapeutic effectiveness over longer periods of time for analgesic control. Attaining suitable pharmacokinetic profiles at twice daily dosing has

been found to be extremely difficult. Many years of experimentation has failed to achieve the desired concentration levels over the necessary time periods.
Thus, there still exists a need in the art for a formulation for twice daily administration, e.g., a 12 hour dosing regimen of paracetamol, which can achieve and maintain a therapeutic effectiveness for up to 12 hours, suitably at steady state.

Brief Description of the Drawings

Figure 1a shows the biorelevant dissolution profiles for the product of Example 1, a conventional immediate release paracetamol formulation, and an 8-hour extended release formulation, Panadol Extend®.

Figure 1b shows the biorelevant dissolution profiles for Examples 2 through 6b.

Figure 2a shows single dose pharmacokinetic profiles in the fasted state for a 2000mg dose of the product of Example 1, and a 1000mg dose of a conventional immediate release paracetamol formulation.

Figure 2b shows single dose pharmacokinetic profiles in the fed state for a 2000mg dose of the product of Example 1, and a 1000mg dose of a conventional immediate release paracetamol formulation.

Figure 3a shows single dose pharmacokinetic profiles in the fasted state for a 2000mg dose of the product of Example 1 and for a 1330mg dose of an 8-hour extended release formulation, Panadol Extend®.

Figure 3b shows single dose pharmacokinetic profiles in the fed state for a 2000mg dose of the product of Example 1, and for a 1330mg dose of an 8-hour extended release formulation, Panadol Extend®.

Figure 4 shows multiple dose (Steady-State) pharmacokinetic profiles over a 24 hour period for a 2000mg dose of Example 1 given every 12 hours, and for a 1000mg dose of a conventional immediate release paracetamol formulation given every 6 hours, and for a 1330mg dose of an 8-hour extended release formulation, Panadol Extend® given every 8 hours (*based on low absorption in the colon beyond 6 hours).

Figure 5 shows the predicted therapeutic effective times for Examples 1 through 6 based upon IVMS. TET is the time from when the medicine starts to work and becomes effective, to the time the effect of the medicine is gone.

Figure 6 shows a single dose pharmacokinetic profile in a semi-fed state for the product of Example 2, Example 3 and Example 4.

SUMMARY OF THE INVENTION

The present invention is directed to a unit dose sustained release formulation for oral administration comprising about 2000mg paracetamol present in a sustained release formulation comprising 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, for a single dose pharmacokinetic characteristic in both a fasted and fed state.

In another embodiment, the invention is directed to a unit dose sustained release formulation for oral administration comprising about 2000mg paracetamol present in a sustained release formulation comprising 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.

In yet another embodiment, the invention is directed to a unit dose sustained release formulation for oral administration comprising about 2000mg paracetamol present in a sustained release formulation comprising 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 5ug/ml for a mean duration of about 6 hours, for a single dose pharmacokinetic characteristic in both a fasted and fed state.

In another embodiment of the invention a sustained release formulation of the present invention 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.

In another embodiment, the invention is directed to a method of treating analgesia or pain in a human in need thereof, which comprises administering to said human a unit dosage of a sustained release formulation of paracetamol according to the embodiments described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the term "PK (pharmacokinetics)" refers to the study of the absorption, distribution, metabolism, and excretion of drugs.

As used herein, the term "PD (pharmacodynamics)" refers to the relationship between drug concentration and pharmacological response.

As used herein, the term "steady state" means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose of the formulation.

As used herein, the term "dosage form" refers to at least one dosage unit form of the present invention, that is one tablet or capsule containing 1000mg each of paracetamol (e.g., each single dose of paracetamol can be contained in 2 unit dosage forms of the sustained release formulation herein for twice-a-day administration, for a total daily intake of 4000mg).

As used herein, the terms "single dose"," unit dosage" or "unit dose", used interchangeably, mean that the human patient has received a single dose of the drug formulation and the drug plasma concentration has not achieved a steady state. For the present invention, a single dose, unit dosage or unit dose consists of two dosage unit forms (i.e., which may include, but are not limited to, tablets, capsules and the like), each dosage unit form containing about 1000mg of sustained release paracetamol for a total of about 2000mg per single dose, unit dosage or unit dose.

As used herein, the term "multiple dose" means that the human patient has received at least two doses of the drug formulation in accordance with the dosing interval for that formulation (e.g., on a twice-a-day basis). Patients who have received multiple doses of the sustained release formulation of the invention may or may not have attained steady state drug plasma levels, as the term multiple dose is defined herein.

As used herein, the term "mean", when preceding a pharmacokinetic value represents the arithmetic mean value of the pharmacokinetic value taken from a population of patients unless otherwise specified (e.g., geometric mean).

As used herein, the term "C_{max}" refers to the maximum plasma concentration.

As used herein, the term "C_{min}" refers to the minimum plasma concentration reached after a drug has been dosed and prior to the administration of a second dose.

As used herein, the term "T_{max}" refers to the time to reach maximum plasma concentration.

As used herein the term "K_{el}" (hour) refer to the elimination rate constant. It is the terminal slope (using an ln C versus time plot) of the serum concentration/time curve after absorption and distribution phases are complete. The half-life and elimination rate constant are related to each other by the following equation: $T_{1/2} = 0.693/K_{el}$.
As used herein the term T_{lag} refers to the time delay prior to the start of drug absorption. This may be due to physiologic factors such as stomach emptying time and intestinal mobility.

As used herein "$T_{1/2}$" (hour) refers to the half life or half time elimination. It is the time required for serum concentrations to decrease by one-half after absorption and distribution are complete. See DiPiro JT, Talbert RL, Yee GC, et al: Pharmacotherapy: A Pathophysiologic Approach, 7e.

As used herein, the term "bioavailability" means the rate and extent to which the active drug substance is absorbed from a pharmaceutical dosage form and becomes available at the site of action.

As used herein, the term "bioequivalence" (BE) is the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. In the context of a generic containing the same active ingredient in the same amount, is considered to be bioequivalent to a brand/reference and/or listed drug product if the rate and extent of absorption do not show a significant

difference from the listed drug, or the extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant.

As used herein, the term "generic drug" means a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics and intended use.

The present invention is directed to a sustained release formulation of paracetamol that provides efficacy over a period of at least 10 hours or more, or alternatively at least 12 hours, and can therefore be optionally dosed twice daily. The present invention is also directed to an optionally twice daily administration of a unit dosage sustained release formulation of paracetamol that has a lower C_{max} in the fasted state, and has a slower rate of absorption as compared to a conventional immediate release formulation of paracetamol (of a similar daily dose). The present invention is also directed to an optionally twice daily administration of a sustained release formulation of paracetamol that provides an equivalent time duration of plasma paracetamol concentration at or above therapeutic level, i.e., greater than or equal to 3 – 5μg/ml. Suitably, the duration of action is over a period of at least 10 hours, preferably longer, e.g., up to 11 or 12 hours. The present invention is also directed to an optionally twice daily administration of a unit dosage sustained release formulation of paracetamol which provides for a lower fluctuation index than a conventional immediate release formulation of a similar amount of paracetamol administered over the course of the day.

In one embodiment the present invention is an optionally twice daily administration of a unit dosage sustained release formulation of paracetamol that is well absorbed in both a fed and fasted state. The formulation provides for more than 90% relative bioavailability, as compared to a conventional immediate release formulation and as compared to an 8-hour extended release formulation on a dose adjusted basis.

In one embodiment the present invention is an optionally twice daily administered unit dosage sustained release formulation of paracetamol that provides certain pharmacokinetic parameters, such as a lower K_{el} (elimination rate) and a longer half – time elimination (T ½) that are significantly different when compared to a conventional immediate release formulation and when compared to an 8-hour extended release formulation in a single dose study.

In one embodiment the present invention is an optionally twice daily administered unit dosage sustained release formulation of paracetamol that provides a median time to reach a plasma paracetamol concentration of up to 4μg/ml that is similar to a conventional immediate release formulation. The amount of paracetamol in the immediate release layer of the present invention available to the subject in a clinical study was only 1/5th the dose (200mg) available in the conventional formulation (e.g., a 1000mg (2x 500mg tablet dose).

In one embodiment the present invention is an optionally twice daily administered unit dosage of 2000mg paracetamol in a sustained release formulation of paracetamol that delivers 1000mg paracetamol per tablet in a two (2) tablet administration wherein each tablet is an easy to swallow condensed tablet dosage form weighing only about 1110mg thus providing improved patient compliance.

In one embodiment the present invention is an optionally twice daily administered unit dosage sustained release formulation of paracetamol that provides a biorelevant dissolution profile that is significantly longer, e.g., 12 hours as opposed to 5 hours for an 8-hour extended release product, i.e., Panadol Extend®, or 30 minutes for a conventional immediate release dosage form of paracetamol.

In one embodiment the present invention is an optionally twice daily administered unit dosage sustained release formulation of paracetamol that provides the following biorelevant dissolution profile, see Figure 1a.

In one embodiment the present inventive sustained release formulation has been found to be bioequivalent in the fed and fasted state to a 4 times daily conventional immediate release formulation and to a 3 times daily 8-hour extended release formulation Panadol Extend ®. See Figure 4.

It should be recognized herein that all doses of the sustained release formulation administered herein comprise a 2000mg unit dosage of paracetamol, as administered. The sustained release formulations of paracetamol as exemplified herein are comprised of two tablets be it a monolith or bilayer or trilayered tablet, etc., each tablet containing 1000mg of paracetamol each.

Compliance with a twice daily oral dosing regimen is recognized to be better than with a four times daily dosing regimen of an immediate release paracetamol product. Two

systematic reviews, as described below, support this assertion showing good evidence that the number of dosing time points significantly affects compliance.

Greenberg R., *Clinical Therapeutics*, 6(5):592-9 in 1984, included studies that used pill counts, interviews and measurements of drug substances in body fluids to ascertain compliance. The results demonstrate quite clearly that compliance is related to the dosing schedule. Importantly, while the difference between compliance with once- or twice-daily regimens does not greatly differ, reducing the regimen from four- to twice-daily improves compliance by nearly 30%.

Since the Greenberg report, methods of measuring compliance have improved. A second review published by Claxton et al. *Clin. Ther,* 23(8):1296-310) in 2001, included studies that used electronic monitoring. Electronic monitors use microprocessors to record the precise time that a dose is removed from the monitoring unit. They can record both the number of events, especially whether doses are missed, and whether doses are taken at the correct time.

The results obtained in this review demonstrate clear agreement between the newer and older methods of measuring compliance and both give clear evidence that reducing the dosing schedule from four- to twice-daily increases the rate of compliance.

A potential disadvantage concerning a formulation containing more than the standard dose of paracetamol (500 mg) is accidental or intentional overdose. In such circumstances more paracetamol will be ingested from a sustained release formulation compared to a conventional immediate release formulation for any given number of unit doses such as tablets. The large ingestion of paracetamol could have serious consequences for an overdose patient, especially if a large amount of the dose is absorbed before rescue therapy could be initiated. It would therefore be preferable if the unit dose (such as a tablet or capsule) was designed to limit the amount of paracetamol released and therefore absorbed in the first few hours following dosing. An advantageous sustained release formulation should therefore demonstrate a lower C_{max} than a conventional immediate release formulation which would be indicative of a lower initial exposure.

One possible consequence, however, of formulating an orally administered paracetamol product designed to have a lower C_{max} and a slower rate of absorption is that the extent of absorption may also be decreased. The present invention is believed to have overcome the potential issue of decreased absorption.

A further advantage for a product designed to have a lower C_{max} and a slower rate of absorption where the extent of absorption is essentially complete (as demonstrable by an equivalent dose corrected AUC compared to immediate release tablets) is that it should have the advantage of maintaining therapeutic levels of paracetamol in plasma for extended periods following dosing and hence provide analgesia for longer than a conventional immediate release tablet or capsule. Furthermore as a result of the reduced C_{max} in the fasted state, the product of the present invention shows systemic levels of paracetamol remaining at more constant levels, thus benefiting the patient. The fluctuation index of the present invention has been shown to be lower than a conventional immediate release formulation.

While a formulation should have a lower C_{max} compared to conventional immediate release formulations, it is still desirable to also have a fast onset of action. The present invention demonstrated that initial levels of paracetamol in plasma were rapidly attained (preferably within 30 minutes) and were maintained at therapeutic levels for a period of time long enough for the release and absorption of paracetamol from the sustained release phase to start to take effect and maintain therapeutic levels for up to 12 hours.

As used herein a therapeutic level constitutes a level of paracetamol in the plasma of the patient of at least about 3ug/ml. In another embodiment of the invention a therapeutic level of paracetamol constitutes at least about 4ug/ml. In yet another embodiment of the invention a therapeutic level of paracetamol constitutes at least about 5ug/ml.

In one embodiment, the sustained release formulations provide a therapeutic plasma level of paracetamol of at least 3ug/ml for about 10 hours. In another embodiment of the invention the sustained release formulation provides a therapeutic plasma level of paraceatmol of at least 4ug/ml for 8 about hours. In yet another embodiment, the sustained release formulation provides a therapeutic plasma level of paracetamol of at least 5ug/ml for about 6 hours.

In one embodiment, the sustained release formulation provides the time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol which is about double that for a single dose of 1000mg immediate release paracetamol. Suitably, 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.

In one embodiment, the sustained release formulation provides a time duration of plasma paracetamol concentration at or above therapeutic level (≥4μg/ml) for a single dose of 2000mg sustained release paracetamol which is 36 to 46% greater than that for a single dose of an extended release 1330mg dose of paracetamol, formulated for administration three times daily. Suitably, 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 1330mg dose of paracetamol is about 5.9-6.2 hrs.

In one embodiment, the sustained release formulation provides a median time to maximum plasma concentration (T_{max}) of the paracetamol from about 3 hours to about 6.5 hours after administration a single dose of 2000mg sustained release paracetamol.

In one embodiment, the sustained release formulation provides 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 a single dose of 2000mg sustained release paracetamol.

In one embodiment, the sustained release formulation 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.

In one embodiment, the sustained release formulation provides a mean plasma concentration (C_{max}) of the paracetamol of from about 6.3μg/ml to about 17.1μg /ml, based on administration of a single dose of 2000mg sustained release paracetamol. Suitably, the mean plasma concentration (C_{max}) of the paracetamol is from about 8.9μg/ml to about 12.5μg/ml, based on administration of a single dose of 2000mg sustained release paracetamol. Suitably, the mean plasma concentration (C_{max}) of the paracetamol is from about 8μg/ml to about 13μg/ml, based on administration of a single dose of 2000mg sustained release paracetamol.

In one embodiment the sustained release formulation provides a mean plasma concentration (C_{max}) of the paracetamol is from about 9μg/ml to about 17μg /ml, based on administration of a repeat dose (steady state) of 2000mg sustained release paracetamol.

In one embodiment, there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having single dose pharmacokinetic characteristics in fasted and fed states:

a) a plasma level of paracetamol which is at or above at least about 4μg/ml for a mean duration of about 8 hours; and
b) wherein the geometric mean $AUC_{(0-\infty)}$ is about 100 μg*h/ml to 104 μg*h/ml in the fasted state and about 99 μg*h/ml to 103 μg*h/ml in the fed state; and
c) the amount of paracetamol administered is 2000mg, as compared to a single 1000mg dose of immediate release paracetamol formulated for administration every 4-6 hours or as compared to a single 1330 mg dose of an 8-hour extended release paracetamol formulated for administration every 8 hours.

In yet another embodiment, the sustained release formulation according to the formulations described herein has single dose pharmacokinetic characteristics in the fasted and fed state of:

a) a mean $AUC_{(0-\infty)}$ is about 77 μg*h/ml to about 133 μg*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 administered is 2000mg, as compared to a single 1000mg dose of immediate release paracetamol formulated for administration every 4-6 hours or as compared to a single 1330 mg dose of an 8-hour extended release paracetamol formulated for administration every 8 hours.

Suitably, the mean $AUC_{(0-\infty)}$ is about 77 μg*h/ml to 133 μg*h/ml in the fasted state based upon administration of a 2000mg sustained release dose of paracetamol as defined above. Suitably, the mean $AUC_{(0-\infty)}$ is about 85 μg*h/ml to 120 μg*h/ml in the fasted state based upon administration of a 2000mg sustained release dose of paracetamol as defined above. Suitably, the mean $AUC_{(0-\infty)}$ is about 95 μg*h/ml to 115 μg*h/ml in the fasted state based upon administration of a 2000mg sustained release dose of paracetamol as defined above. Suitably, the geometric mean $AUC_{(0-\infty)}$ is about 100 μg*h/ml to 110 μg*h/ml in the fasted state.

In an alternative embodiment there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having single dose pharmacokinetic characteristics in fasted and fed states:

a) a plasma level of paracetamol which is at or above at least 4μg/ml for about a mean duration of about 8 hours; and
b) wherein the K_{el} is about 0.09 hr^{-1} in fasted state and the K_{el} is about 0.13 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.

In another embodiment, there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having single dose pharmacokinetic characteristics in fasted and fed states:

a) a plasma level of paracetamol which is at or above at least 4μg/ml for about a mean duration of about 8 hours; and
b) wherein the mean $AUC_{(0-\infty)}$ is about 100 μg*h/ml to 104 μg*h/ml in the fasted state and about 99 μg*h/ml to 103 μg*h/ml in the fed state; and
c) wherein the K_{el} is about 0.09 hr^{-1} in fasted state and the K_{el} is about 0.13 hr^{-1} in fed state; and
d) the amount of paracetamol administered is 2000mg, as compared to a single 1000mg dose of immediate release paracetamol formulated for administration every 4-6 hours or as compared to a single 1330 mg dose of an 8-hour extended release paracetamol formulated for administration every 8 hours.

In one embodiment, the mean $AUC_{(0-24)}$ of the sustained release formulation described herein at steady state is between about 124 μg*h/ml and about 204 and μg*h/ml; with a mean of about 165 μg*h/ml. In comparison, the mean $AUC_{(0-24)}$of an immediate release formulation of paracetamol is between about 124 μg*h/ml and about 212 μg*h/ml; with a mean of about 168 μg*h/ml.

In one embodiment, the mean $AUC_{(0-24)}$ of the sustained release formulation described herein for a single dose is between about 64 μg*h/ml and about 124 μg*h/ml; with a

mean of about 86-89 μg*h/ml in the fasted state. Suitably, the mean is about 95-97 μg*h/ml in the fed state.

In one embodiment, the mean $AUC_{(0-\infty)}$ of the sustained release formulation described herein at steady state is between about 133 μg*h/ml and about 217 μg*h/ml; with a mean of about 175 μg*h/ml. In comparison, the mean $AUC_{(0-\infty)}$ of an immediate release formulation of paracetamol is between about 129 μg*h/ml and about 225 μg*h/ml; with a mean of about 177 μg*h/ml.

In one embodiment, the mean $AUC_{(0-6)}$ of the sustained release formulation described herein in a fasted state is between about 29 μg*h/ml and about 51 μg*h/ml; with a mean of about 40 μg*h/ml. In comparison, the mean $AUC_{(0-6)}$ of an immediate release formulation of paracetamol is between about 31 μg*h/ml and about 51 μg*h/ml; with a mean of about 41 μg*h/ml.

In one embodiment, the mean $AUC_{(0-6)}$ of the sustained release formulation described herein in a fed state is between about 24 μg*h/ml and about 52 μg*h/ml; with a mean of about 38 μg*h/ml. In comparison, the mean $AUC_{(0-6)}$ of an immediate release formulation of paracetamol is between about 25 μg*h/ml and about 40 μg*h/ml; with a mean of about 33 μg*h/ml.

In another embodiment, a sustained release formulation having the above noted characteristics has an immediate release phase that produces or provides to the patient a therapeutic plasma concentration of paracetamol of 4μg/ml in about 0.5 hours (median time).

Upon multiple dosing of a formulation of the present invention, steady state plasma levels of paracetamol should be more constant than those achieved following multiple dosing of a conventional immediate release formulation. A convenient measure of the fluctuation in plasma concentrations is the fluctuation index (FI) which is defined as $(C_{max}-C_{min})/C_{average}$. A low FI number is considered to be advantageous as it suggests a reduction in the variability of plasma concentrations which is indicative of a safer product. A clinical study has demonstrated that a formulation of the present invention provides a slightly lower mean C_{max} and a smaller FI, showing less fluctuation in paracetamol plasma concentrations, as compared to conventional immediate release formulation (FI mean value of 1.4 as compared to 1.5 for conventional immediate release formulation). This study appears to indicate that the present formulation has less

fluctuation in paracetamol plasma concentrations over a 24 hour period when dosed every 12 hours as compared to a conventional immediate release formulation dosed every 6 hours (2x 1000mg every 12 hours vs. 2 x 500 mg every 6 hours).

The formulation of the present invention showed a greater fluctuation than Panadol® Extend (FI mean value of 1.4 as compared to 1.2) in paracetamol plasma concentrations.

In one embodiment, the sustained release formulations described herein provide 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 $AUC_{(0-\infty)}$ as provided by administration of 1000mg 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.

Suitably, the sustained release formulation described herein 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 $AUC_{(0-\infty)}$ provided by administration of 1000mg of an immediate release reference standard 4 times daily, wherein the 4 times daily dose of the reference standard is substantially equal to a twice daily dose of 2000mg of the sustained release paracetamol formulation.

In another embodiment, the sustained release formulations as described herein provide a mean $AUC_{(0-6)}$ of at least 95% to about 105% of the mean $AUC_{(0-6)}$ provided by administration of 1000mg 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 2000mg of the sustained release paracetamol formulation.

Suitably, the sustained release formulations as described herein provide a mean $AUC_{(0-6)}$ of at least 85% to about 115% of the mean $AUC_{(0-6)}$ provided by administration of 1000mg 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 2000mg of the sustained release paracetamol formulation (in the fed state).

In a clinical study, a single 2000mg dose of a formulation of the present invention demonstrated greater than 90% relative bioavailability as compared to a single 1000mg dose of a conventional immediate release paracetamol formulation based upon a dose corrected adjustment.

In a second clinical study, a single 2000mg dose of the formulation of the present invention demonstrated greater than 90% relative bioavailability as compared a single 1330mg dose of an 8-hour extended release formulation, Panadol Extend®, based upon a dose corrected adjustment.

It has now been found that these advantageous pharmacokinetic profiles can be provided by a two phase (immediate release and sustained release) formulation of paracetamol that satisfies not only a unique *in vitro* dissolution profile, but also has a unique *in vivo* pharmacokinetic profile.

In an alternative embodiment there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having repeat dose pharmacokinetic characteristics:

a) a plasma level of paracetamol which is at or above at least about 4μg/ml for about a mean duration of about 16 hours, suitably 17 hours (during 24 hours at steady state);
b) wherein the mean $AUC_{(0-\infty)}$ is about 173 μg*h/ml at steady state (when administered twice daily);
c) wherein the 90% confidence intervals for the ratios of the formulation versus an 8-hour extended release formulation, and the formulation versus a conventional immediate release formulation, for three pharmacokinetic parameters (AUC0-t, AUC0-inf, and Cmax) all lie within the bioequivalence boundaries (0.8, 1.25);
d) the amount of paracetamol 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 or as compared to 1330 mg of 8 hours paracetamol three times a day for three days.

Suitably, a sustained release formulation as described herein provides a mean $AUC_{(0-\infty)}$ in a patient in a range between about 173 μg*h/ml to 175 μg*h/ml at steady state (when the unit dosage of 2000mg is administered twice daily).

In an alternative embodiment there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having repeat dose pharmacokinetic characteristics:

a) a plasma level of paracetamol which is at or above at least about 4μg/ml for a mean duration of about 16 hours, suitably 17 hours (during 24 hours at steady state);
b) wherein the K_{el} is about 0.26 hr^{-1}; and
c) wherein the fluctuation index FI is about 1.4; and
d) the amount of paracetamol 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 or as compared to a 1330 mg dose of an 8-hour extended release paracetamol formulation three times a day for three days.

In an alternative embodiment there is a sustained release formulation of paracetamol comprising a sustained release phase of paracetamol and an immediate release phase of paracetamol, the formulation having repeat dose pharmacokinetic characteristics:

a) a plasma level of paracetamol which is at or above at least 4μg/ml for about a mean duration of 16 hours, suitably about 17 hours (during 24 hours at steady state);
b) wherein the mean $AUC_{(0-\infty)}$ is about 173μg*h/ml at steady state (when administered twice daily);
c) wherein the 90% confidence intervals for the ratios of the formulation versus an 8-hour extended release formulation, and the formulation versus a conventional immediate release formulation, for three pharmacokinetic parameters (AUC0-t, AUC0-inf, and Cmax) all lie within the bioequivalence boundaries (0.8, 1.25);
d) wherein the K_{el} is about 0.26 hr^{-1}; and
e) wherein the fluctuation index FI is about 1.4; and
f) the amount of paracetamol 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 or as compared to 1330 mg of 8-hours paracetamol three times a day for three days.

Suitably, the formulation described herein provides a mean $AUC_{(0-\infty)}$ in a patient in a range between about 173 μg*h/ml and 175 μg*h/ml at steady state (when administered twice daily).

In one embodiment the invention is directed to 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).

An *in vitro* bio-dissolution profile of the sustained release formulations described herein, having these pharmacokinetic parameters, will also have the following dissolution release range 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.

In an alternative embodiment 15 to 50% is released at 120 minutes.
In an alternative embodiment 28 to 70% is released at 240 minutes.
In an alternative embodiment 81 to 100% is released at 600 minutes.

In another embodiment there is an *in vitro* bio-dissolution profile of the sustained release formulations described herein, having these pharmacokinetic parameters, which will also have the following dissolution release range 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;
- 15 to 50% released at 120 minutes
- 22 to 62% released at 180 minutes;
- 28 to 70% released at 240 minutes;

- 50 to 88% released at 360 minutes;
- 81 to 100% released at 600 minutes; and
- >90% released after 720 minutes.

Many physiological factors influence both the gastrointestinal transit time and the release of a drug from a controlled release dosage form, and thus influence the uptake of the drug into the systemic circulation. A sustained-release dosage form should release the paracetamol at a controlled rate such that the amount of active ingredient available in the body to treat the condition is maintained at a relatively constant level over an extended period of time. That is, it is desirable that paracetamol be released at a reproducible, predictable rate which is substantially independent of physiological factors which can vary considerably among different individuals and even over time for a particular individual.

The release of an active ingredient from a controlled release dosage form is generally controlled either by diffusion through a coating, diffusion of the agent from a monolithic device, or by erosion of a coating by a process which is dependent upon enzymes or pH. Because such factors can vary from time to time for a particular individual, and can also vary from one individual to another, enzymes or pH dependent sustained-release pharmaceutical formulations generally may not provide a reproducible rate of release of the active pharmaceutical ingredient. Thus these types of formulations do not minimize intra-subject and inter-subject variation in bioavailability of the active ingredient.

As can be shown by many failed experiments, previous formulations fail to maintain a median therapeutic plasma level (e.g., 3 - 5μg/ml) in the body for sufficient time (i.e., 10 or more hours). In some formulations, the resulting tablet sizes containing 1000mg APAP were very large and could be highly inconvenient for the patient to swallow. The ability to maintain a therapeutic level of paracetamol (e.g., 3 - 4μg/ml) in the body over a period of at least 10 hours in a 2 tablets per dose formulation and in a tablet size that is readily swallowable has been virtually impossible until the present invention.

Similarity factor (f2) is a recognized method for the determination of the similarity between the dissolution profiles of a reference and a test compound. Similarity factor (f2) is a logarithmic transformation of the sum of squared error. The similarity factor (f2) is 100 when the test and reference profiles are identical and approaches zero as the dissimilarity increases. The similarity factor has also been adapted to apply to the determination of the similarity between the dissolution profiles of a reference and test

compound as they relate to modified release formulations, such as those exemplified herein.

The f2 similarity factor has been adopted in the SUPAC guidelines and by the FDA guidance on dissolution testing of immediate release dosage forms (FDA Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, FDA, (CDER), August 1997 (Dissolution Tech. 4, 15-22, 1997).

The f2 similarity factor has been adopted in the FDA in the SUPAC guidelines for modified release solid oral dosage forms (FDA Guidance for Industry, SUPAC-MR: Modified Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation; CDER; September 1997). The FDA Guidance for Industry on Dissolution Testing of Immediate Release Solid Oral Dosage Forms may be found at http://www.fda.gov/cder/guidance/1713bp1.pdf.

In one embodiment, the sustained release dosage form of the present invention comprises a bi-layer dosage unit having a sustained release (SR) phase layer and an immediate release phase layer. The SR phase contains a therapeutically effective amount of paracetamol, suitably in granulate form. The immediate release phase and the sustained release phase will both contain paracetamol and other pharmaceutically acceptable carriers and functional excipients that are suitably combined together into the separate layers of a bi-layer unit dosage form.

The present invention is also directed to other formulations of sustained release paracetamol that have an *in vitro* dissolution profile generated using the USP Type II apparatus, rotating paddle method as described herein with a similarity factor (f2) between 50 and 100 when calculated using one of the examples of the present invention described herein in Figure 1a and 1b as the reference profile.

In another embodiment, the sustained release dosage form is a single layer unit (a monolith tablet) having a sustained release phase of paracetamol and an immediate release phase of paracetamol. Suitably, in one embodiment the sustained release phase is a separate blend, granules or pellets which form an intragranular component, and the immediate phase can be comprised of separate blends, granules or pellets to form the extragranular component. The immediate release phase and the sustained release phase

can be then be admixed together with any other pharmaceutically acceptable excipients desired before being compressed into a single layer tablet.

In yet another embodiment of this invention, the sustained release dosage form is a single layer unit having a therapeutically effective amount of paracetamol present only as a sustained release intragranular phase. The extragranular phase comprises a non-water soluble matrix forming polymer and other suitable carriers and excipients. This dosage form does not have an immediate release component of paracetamol.

As used herein granulate is a material that has been adapted and preprocessed by suitable means such as slugging, aqueous or non-aqueous wet granulation, fluidized bed granulation, spray drying or roller compaction to form granules. For purposes herein, a component of the granulate is referred to as "intragranular" or an "intragranular component", whereas a component that is admixed with said granulate is referred to as "extragranular" or an "extragranular component".

Suitably, the paracetamol in either the bilayer or monolith dosage form is approximately a 80:20 ratio of sustained release to immediate release amounts of paracetamol. In another embodiment, the paracetamol is in an approximate 90:10 ratio of sustained to immediate release amounts. Explained differently, for a 1000mg containing unit dosage form, such as a tablet, the paracetamol is present in an amount of about 900mg in the sustained release phase and about 100mg in the immediate release phase. For example, in one embodiment, the ratios of sustained release to immediate release phase represent the proportional amount of each layer in a bi-layer dosage form. In another embodiment, the ratios represent the amount of paracetamol in the sustained release intragranular component versus the immediate release extragranular component of a single layer dosage form.

In another embodiment the amount of sustained release intragranular component containing paracetamol is 100%. In this embodiment there is no immediate release phase. See a representative example of this in Table 3, Example 3.

Bi-Layer Dosage Form

When the sustained release phase granulate is in a multiple layer tablet, such as a bi-layer dosage form the sustained release layer of that dosage form will comprise at least one high viscosity hypromellose (HPMC) ingredient. HPMC is a water soluble matrix-forming polymer used to provide a sustained release effect of paracetamol. Suitably the

viscosity of the HPMC used is in the SR phase is in the range of about 3500-6000 centipoise.

It will be understood by the skilled artisan that the high viscosity HPMC can suitably be a blend of multiple high viscosity HPMC's resulting in a total overall range of 3500-6000 centipoise.

The amount of matrix-forming polymer in the sustained release phase and the relative amounts of paracetamol in the sustained release and immediate release phases are selected so as to provide the desired *in vitro* dissolution rate as described herein.

In accordance with one embodiment of the invention, there is a bilayer tablet having a sustained release layer and an immediate release layer. The sustained release layer comprises a therapeutically effective amount of paracetamol, at least one high viscosity hypromellose, at least one binding agent, a low viscosity hypromellose, at least one modified starch, and optionally one or more other pharmaceutically acceptable intragranular components including but not limited to a second pharmaceutically acceptable active ingredient, other pharmaceutically acceptable excipients and/or adjuvants. In one embodiment, the ratio of high-viscosity hypromellose to low viscosity hypromellose is about 3.3 to about 0.85. In another embodiment the ratio of high to low is about 3:1. For representative examples of this range, see Working Examples 1 & 2.

Suitably, the viscosity of the low viscosity hypromellose is in the range of about 10-30 centipoises. In another embodiment the low viscosity is about 15 centipoises.

Suitably the amount of at least one binding agent in the sustained release phase of the bilayer tablet is from about 0.5% to about 3% w/w. In one embodiment there are at least two binding agents present in the SR phase.

Suitably the amount of at least one modified starch in the sustained release phase of the bilayer tablet is from about 0.5% to about 3% w/w. In one embodiment, the amount of modified starch is about 1% w/w of the SR phase. In one embodiment there are at least two modified starches present in the SR phase. Suitably, the modified starch is pre-gelatinized.

Suitably, the amount of the high viscosity hypromellose present in the sustained release phase is from about 3% to about 7% of the sustained release phase formulation weight.

In another embodiment, the amount of high viscosity hypromellose is from about 4% to about 6% of the sustained release phase formulation weight.

In yet another embodiment the amount of high viscosity HPMC is present in an amount of about 5% w/w sustained release phase formulation weight.

Suitably, the amount of the low viscosity hypromellose present in the sustained release phase is from about 0.5% to about 3% of the sustained release phase formulation weight. In another embodiment, the amount of low viscosity hypromellose is from about 1% to about 2% of the sustained release phase formulation weight. In another embodiment the amount of low viscosity HPMC is present in an amount of about 1.6% w/w sustained release phase formulation weight.

Alternatively, the total amount of cellulosic derivatives of HPMC present in the SR granulate range from about 3% to about 10% by weight of the total amount of sustained release components. This encompasses both the high and the low viscosity HPMC's.

In one embodiment the SR phase comprises paracetamol, povidone, pre-gelatinized corn starch, and a high and low viscosity HPMC.

The immediate release layer may be prepared by combining a directly compressible commercially available grade of paracetamol with a lubricant, and one or more disintegrating agents if necessary or desired. Binders and other excipients and/or adjuvants may be included in the immediate release layer, also if necessary or desired. Paracetamol in the immediate release layer is generally combined with a modified starch such as a pre-gelatinized starch, e.g., corn starch, a disintegrant, or super disintegrant such as croscarmellose sodium or Explotab®, a binder and a lubricant.

Monolith Dosage Form

In one embodiment of the invention, there is only a single layer tablet having a sustained release intragranular phase and an immediate release extragranular phase. The sustained release phase will be comprised of an intragranular component of paracetamol and a high viscosity hypromellose as defined above, at least one binding agent, a low viscosity hypromellose as defined above, at least one modified starch, and optionally one or more other pharmaceutically acceptable intragranular components including but not limited to a second pharmaceutically acceptable active ingredient, and optional excipients and/or

adjuvants. These components form the SR granulate. The SR blend could be made into pellets and compressed accordingly with the extragranular immediate release blend.

A suitable amount of the high viscosity hypromellose present in the sustained release phase granulate is from about 3% to about 7% of the sustained release phase formulation weight. In another embodiment, the amount of high viscosity hypromellose is from about 4% to about 6% of the sustained release phase formulation weight. In another embodiment, the amount of high viscosity HPMC is present in an amount of about 5% w/w sustained release phase formulation weight.

Suitably, the amount of the low viscosity hypromellose present in the sustained release phase granulate is from about 0.5% to about 3% of the sustained release phase formulation weight. In another embodiment, the amount of low viscosity hypromellose is from about 1% to about 2% of the sustained release phase formulation weight. In another embodiment the amount of low viscosity HPMC is present in an amount of about 1.6% w/w sustained release phase formulation weight.

Alternatively, the total amount of cellulosic derivatives of HPMC present in the SR granulate range from about 3% to about 10% by weight of the total amount of sustained release components. This encompasses both the high and the low viscosity HPMC's.

Suitably the amount of at least one binding agent in the sustained release phase granulate is from about 0.5% to about 3% w/w. In one embodiment there are at least two binding agents present in the SR granulate.

Suitably the amount of at least one modified starch in the sustained release phase granulate is from about modified starch is from about 0.5% to about 3% w/w. In one embodiment there are at least two modified starches present in the SR granulate.

A suitable extragranular component or phase, i.e., the immediate release phase, may be prepared by combining a directly compressible commercially available grade of paracetamol with a lubricant, and one or more disintegrating agents if necessary or desired. Binders and other excipients and/or adjuvants may be included in the extragranular phase if necessary or desired. Alternatively, an extragranular component can be prepared by combining paracetamol with a modified starch, such as a pre-gelatinized starch, e.g., corn starch, a disintegrant or super disintegrant, such as

croscarmellose sodium, a binder and a lubricant. Most commercially available blends of immediate release paracetamol will be satisfactory for this component.

Alternative Monolith Dosage Form

In yet another embodiment of the invention, the ratio of high-viscosity hypromellose to low viscosity hypromellose can be altered to be about a 2:1 ratio. A suitable amount of the high viscosity hypromellose present in the sustained release phase is from about 0.5% to about 4% of the sustained release phase formulation weight. A suitable amount of low viscosity hypromellose in the sustained release phase is from about 0.5% to about 3% by weight of the sustained release phase. When the ratio of the HPMC's are altered, the extragranular phase will necessarily be comprised of a second, and different sustained release polymer, such as Kollidon® SR (BASF) suitably, in the amount of 4-8% by weight of the total composition. Kollidon® SR is derived from a polyvinyl acetate-dispersion such as Kollicoat SR 30D) and is a powder consisting of polyvinyl acetate (8 parts w/w) and polyvinyl pyrrolidone (2 parts w/w).

The extragranular phase also includes a suitable lubricant, and optionally a second pharmaceutically acceptable active ingredient, and any other optional excipients and/or adjuvants as needed or desired. A representative example of this type of formulation is shown in Example 3 herein.

Excipients

The present invention includes components that functions as a binder or binding agent. Suitably, the binding agent may comprise a first binding agent and a second binding agent. Suitable binding agents for use herein include conventional binding agents used in the art such as starches, povidone, polymers and cellulose derivatives or combinations thereof. Suitably, the binding agent is povidone.

Suitably, the starch, is of vegetable origin, such as corn (or maize) starch, modified corn starch, wheat starch, modified wheat starch, potato starch, or pre-gelatinized starch e.g., available commercially as Starch 1500 G or Prejel; or a combination of two or more thereof.

If the binding agent includes a cellulosic derivative, suitably it is hydroxypropyl cellulose (HPC) (of low to medium viscosity) e.g., as may be available commercially under the brand name Klucel® from the Aqualon division of Hercules Inc., Dow Chemical Company e.g., Klucel GF, Klucel JF, Klucel LF and Klucel EF; microcrystalline cellulose

(MCC), carboxymethylcellulose (MC), sodium carboxymethylethyl cellulose; or a combination of two or more thereof. Combinations of a cellulosic derivative with other binding agents noted above are also envisaged within the scope of the invention.

The term "low to medium" viscosity as used herein means a viscosity in the range of from about 15 to about 1000 mPas. It is recognized in the art that the determination of the viscosity of cellulosic derivatives is based upon standard techniques and grading in the art e.g., for HPMC, viscosity may be determined at 20°C with a 2% solution using a Ubbelohde viscometer, or for HPC, viscosity may be determined at 25°C with a 2-10% solution using a Brookfield LVF viscometer. Generally the total amount of cellulosic derivatives present in the granulate are in an amount ranging from about 3% to about 10% by weight of the sustained release components. It is recognized in the art that certain cellulosic derivatives, such as hypromellose, will have varying roles in a formulation, depending upon the amount used. For example hypromellose (low or medium viscosity) may function as a binding agent, a coating agent, or as a matrix forming agent.

While a binding agent is present as an intragranular component, it is recognized that a modest amount of binding agent e.g., up to about an additional 3.0%- 10.0% by weight of the intragranular binding agent content of the composition, may also be present extragranularly.

It is recognized that the present invention also requires a modified starch to be present. As modified starches can also be binding agents there will be at least two different components present in the particular phase.

In one embodiment, suitably the starch is pre-gelatinized starch. Pre-gelatinized starch is a starch that has been chemically and/or mechanically processed. Typically pre-gelatinized starch contains 5% of free amylase, 15% of free amylopectin, and 80% unmodified starch. Pre-gelatinized starch may be obtained from corn (or maize), potato or rice starch.

The granulate provides an intimate admixture of a combination of ingredients and may then be mixed with one or more pharmaceutically acceptable extragranular components of the composition i.e., with any pharmaceutically acceptable ingredient e.g., a diluent, flavor, sweetening agent, binder, disintegrant, glidant, lubricant, anti-adherent, anti-static agent, anti-oxidant, desiccant, or a second pharmaceutically acceptable active agent. It is

recognized that these same ingredients may be present both as an intragranular and as an extragranular ingredient.

As noted above there are other inactive ingredients that may optionally be employed in relatively small quantities, and which do not affect the fundamental and essential characteristics of the invention which include lubricants, flow agents, and binders that facilitate compression.

Suitable disintegrating agents include a non-super disintegrant, a super disintegrant or a combination of both. Suitable non-super disintegrants include conventional disintegrants such as starch (corn or maize), pre-gelatinized starch e.g., Starch 1500 G, clays (Veegum or Bentonite), microcrystalline cellulose, cellulose or powdered cellulose. It is recognized in the art, that some excipients may perform more than one role in a given pharmaceutical formulation. For example certain excipients, e.g., starches including pre-gelatinized starch, and microcrystalline cellulose (hereinbefore identified as binding agents) function as both binders and disintegrants.

A "super disintegrant" represents a class of disintegrating agent which may generally be used in lower amounts in pharmaceutical preparations, as compared to conventional disintegrants. Examples of super disintegrants include sodium starch glycolate, the sodium salt of carboxymethyl starch, modified cellulose and cross-linked polyvinyl pyrrolidone. Sodium starch glycolate is available commercially under the trade names Explotab® (Edward Mendell Co.), Primojel® (Generichem Corp) and Tablo® (Blanver, Brazil). An example of modified cellulose includes croscarmellose, the sodium salt of carboxymethyl cellulose. Croscarmellose is available commercially under the trade names AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Netherlands), Primellose® (Avebe, Netherlands), Solutab® (Blanver, Brazil). An example of a cross-linked polyvinyl pyrrolidone includes crospovidone, and is commercially available under the trade names Kollidon CL® or Kollidon CL-M (Basf Corp.), and Polyplasdone XL® (ISP Corp). A suitable super disintegrants includes croscarmellose sodium or sodium starch glycolate (Explotab) or a combination thereof. A super disintegrant may be used extragranularly, in an amount ranging from about 0.5% to about 5.0% by weight of the composition.

Suitable preservative or antimicrobial agents for use include potassium sorbate or a paraben, i.e., one or more hydroxy benzoic acid esters e.g., methyl, ethyl, propyl or butyl,

suitably singularly or as mixtures. Parabens are commercially available under the Nipa® brand name, e.g., Nipasept® sodium.

Suitable lubricants include magnesium, calcium or sodium stearate, stearic acid or talc that may be added in suitable amounts. In one embodiment the lubricant is magnesium stearate.

Suitable flow agents include silicon dioxide (Cab-O-Sil, Syloid™), that may be added in an amount from about 0.5% to about 1% by weight.

The compressed tablet may further comprise a film coat e.g., hypromellose. Suitably the film coat is a transparent film coat e.g., a dye, although an opaque film coat e.g., as obtained when using a film coat in combination with an opacifier or a pigment such as titanium dioxide or a lake may also be used. For example one commercially available film coat is an Opadry coating system from Colorcon.

If the dosage form is a bilayer tablet, the immediate release layer may be compressed directly on a previously compressed sustained release layer, or alternatively, the sustained release layer may be compressed onto a previously compressed immediate release layer.

In addition to paracetamol, compositions of the invention may also contain other pharmaceutically active agents. The term "pharmaceutically active agent" includes, but is not limited to, drugs, nutritional agents, as described herein. This term includes bioactive agents, active agents, therapeutic agents, or drug(s) as defined herein, and follows the guidelines from the European Union Guide to Good Manufacturing Practice. Such substances are intended to furnish pharmacological activity or other direct effect in the cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. The pharmacological activity may be prophylactic, or for treatment of a disease state.

Drug substances include those intended for oral administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989. The drug substances are commercially available and/or can be prepared by techniques known in the art.

Suitable pharmaceutically active agents include but are not limited to other analgesics such as codeine, hydrocodone, oxycodone, tramadol and propoxyphene; anti-inflammatory analgesics such as NSAIDs e.g., aspirin and ibuprofen; decongestants such as pseudoephedrine and phenylephrine; antitussives such as pholcodine and dextromethorphan; expectorants such as guaifenesin and bromhexine; diuretics such as pamabrom; non-sedating and sedating antihistamines such as diphenydramine, doxylamine and mepyramine; gastrointestinal agents such as metoclopramide; triptans such as sumatriptan; muscle relaxants such as methocarbamol. Compositions may also contain a pharmaceutically acceptable adjuvant, for example caffeine. Pharmaceutically active agents and adjuvants e.g., may be present intragranularly, extragranularly or both intragranularly and extragranularly.

The compositions of the present invention can be formulated by conventional methods of admixture such as granulating, blending, filling and compressing. For example, tablets can be produced by a wet granulation process, where the immediate release phase and sustained release phase are separately prepared. Suitably, for either the immediate release or sustained release phase, the active drug substance and excipients are screened and mixed in a high shear mixer granulator or fluid bed dryer. The blend is granulated by the addition of a granulating solution (typically purified water, disintegration agent dissolved/dispersed in purified water, or drug dissolved/dispersed in purified water or a suitable solvent) sprayed into the high shear mixer granulator or fluid bed dryer. If desired wetting agents e.g., surfactants can be added. The resulting granules (optionally pelletized) are dried usually with residual moisture of 1-5% by tray, fluid bed or microwave drying techniques. The dried granules are milled to produce a uniform particle size, the granules are blended with extragranular excipients as necessary, typically a lubricant and glidant (e.g., magnesium stearate, silicon dioxide). The separately prepared immediate release and sustained release granules can then be compressed together using a rotary tablet press (such as a bilayer tablet press) if desired. If the dosage form is a single layer tablet, then the sustained release granules are admixed with the immediate release extragranular components and compressed together using a rotary tablet press, etc. These resulting tablets can all be coated in a pan coater typically with a 1-5% aqueous film coat, followed by a wax polishing.

Alternatively tablets can be produced by a direct compression process. Suitably the active drug substance and excipients for the immediate release and sustained release phases are separately screened and mixed in a suitable blender e.g., a cone, cube or V-blender. Other excipients are added as necessary, and further blended. The separately

prepared immediate release and sustained release phases can be combined and compressed together using a rotary tablet press as hereinbefore described. The resulting tablets can be coated in a pan coater.

Tablets can also be prepared by using both methods of wet granulation and direct compression. For example the sustained release phase can be prepared by wet granulation as described herein, while the immediate release phase can be prepared by blending the excipients for direct compression. Furthermore commercially available blends of immediate release paracetamol are also available for direct compression such as the DC90 paracetamol supplied by Rhodia. The two phases can then be combined and compressed together as hereinbefore described.

A suitable dissolution rate profile for the product of the present invention described herein is wherein at least 10-30% of the paracetamol is released from the composition at 30 minutes and wherein at least 80% of the paracetamol is released from the composition at 600 minutes as determined by a dissolution method that utilizes a USP paddle apparatus rotating at 75 rpm, employing 900ml of phosphate buffer at pH7.4.

Accordingly, the present invention provides a pharmaceutical composition, having an immediate release phase and a sustained release phase of paracetamol in a bilayer tablet, said composition comprising about 1000mg of paracetamol per unit dose and a pharmaceutically acceptable carrier, characterized in having an *in vitro* paracetamol dissolution profile (as determined by the USP type II apparatus, rotating paddle, with 900ml of Phosphate buffer at pH7.4, 37C set at rotating speed of 75 rpm) with the following constraints:

- 10 to 30% released after 30 minutes
- 20 to 40% released after 90 minutes
- 35 to 55% released after 180 minutes
- >80% released after 600 minutes.

In another embodiment the present invention provides a pharmaceutical composition, having an immediate release phase and a sustained release phase of paracetamol in a monolith tablet, said composition comprising about 1000mg of paracetamol per unit dose and a pharmaceutically acceptable carrier, characterized in having an *in vitro* paracetamol dissolution profile (as determined by the USP type II apparatus, rotating paddle, with 900ml of Phosphate buffer at pH7.4, 37C set at rotating speed of 75 rpm) with the following constraints:

- 5 to 25% released after 30 minutes
- 15 to 35% released after 90 minutes
- 35 to 55% released after 180 minutes
- >80% released after 600 minutes.

In yet another embodiment, the *in vitro* dissolution profile has the following constraints:

- 5 to 25% released after 30 minutes
- 15 to 35% released after 90 minutes
- 30 to 50% released after 180 minutes
- >80% released after 600 minutes.

In yet a further embodiment, the *in vitro* dissolution profile has the following constraints:

- 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.

It was expected that an insufficient amount of paracetamol would be released from the immediate release layers of two tablets to rapidly reach 4μg/ml paracetamol in the plasma. Surprisingly, it has been discovered that this was not the case. A clinical study demonstrated that the median time to reach 4μg/ml in the plasma for the formulation of Example 1 was similar to 1000mg standard paracetamol in the fasted state.

The following non-limiting Examples illustrate the advantageous properties of the compositions of the present invention.

EXAMPLE 1

In a first example, a bilayer extended release paracetamol tablet is prepared using the following ingredients:

EXAMPLE - 1 (Bi-Layer Tablet)

No.	INGREDIENT	mg per tablet
A	**Sustained Release Layer (SR Layer)**	
	Intragranular components:	
1	Paracetamol fine	900.0
2	Hypromellose (HPMC) 2208 4000 cP	50.0
3	Povidone K25	20.0
4	Pregel starch fine	10.0
5	Hypromellose (HPMC) 2910 15 cP	16.0
	Extragranular components:	
6	Magnesium Stearate	3.0
B	**Immediate Release Layer (IR Layer)**	
7	Paracetamol (DC90)	111.2
	Bi-Layer Tablet	
A	Sustained Release Layer (SR Layer)	999.0
B	Immediate Release Layer (IR Layer)	111.2
	Final Tablet weight (mg)	1110.2

The total tablet weight is about 1100mg, with about 1000mg of paracetamol per tablet. Layer 1 has a total weight of about 1000mg (approx 900.0mg paracetamol), and Layer 2 has a total weight of about 110mg (about 100 mg paracetamol). The mixtures for each of the layers are prepared and the layers are compressed on a suitable type rotary bi-layer tablet press.

Manufacturing Instructions for Sustained Release Layer:

1. Mix Paracetamol, HPMC 2208, PVP, HPMC 2910 and Pregel Starch in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen

6. Add lubricant, magnesium stearate, and mix.
7. Blend is now ready for compression.

Manufacturing Instructions for Immediate release Layer:

1. DC 90 paracetamol is used as an immediate release layer.

EXAMPLE 2

In another example, a single layer extended release paracetamol tablet is prepared using the following ingredients:

EXAMPLE - 2 (Single Layer Tablet)

No.	INGREDIENT	mg per tablet
	Intragranular Components:	
1	Paracetamol fine	900.0
2	Hypromellose (HPMC) 2208 4000 cP	50.0
3	Povidone K25	20.0
4	Pregel starch fine	10.0
5	Hypromellose (HPMC) 2910 15 cP	16.0
	Extragranular Components:	
6	Paracetamol (DC90)	111.2
7	Magnesium Stearate	3.0
	Final Tablet weight (mg)	1110.2

The total tablet weight is about 1100mg, with about 1000mg of paracetamol per tablet.

Manufacturing Instructions for Intragranular components:

1. Mix Paracetamol fine, HPMC 2208, povidone, HPMC 2910 and Pregel Starch in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen

Manufacturing instructions for final mix:

1. Add intragranular blend and paracetamol DC 90 to a suitable low shear blender and mix.
2. Add the lubricant, magnesium stearate, to the blender and mix.

The final mix is now ready for compression. Compress the tablets on a suitable size rotary tablet press.

EXAMPLE 3

In another example, a single layer extended release paracetamol tablet is prepared using the following ingredients:

EXAMPLE - 3 (Single Layer Tablet with 6% Kollidon SR)

No.	INGREDIENT	mg per tablet
	Intragranular Components:	
1	Paracetamol fine	1000.0
2	Hypromellose (HPMC) 2208 4000 cP	32.6
3	Povidone K25	21.7
4	Pregel starch fine	10.9
5	Hypromellose (HPMC) 2910 15 cP	17.4
	Extragranular Components:	
6	Kollidon SR	69.3
7	Magnesium Stearate	3.0
	Final Tablet weight (mg)	1154.9

Manufacturing Instructions for Sustained Release Granulation:

1. Mix Paracetamol, HPMC 2208, PVP, HPMC 2910 and Pregel Starch in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen

Manufacturing Instructions for Final Blend:

1. Add sustained release blend to a suitable low shear blender.
2. Add Kollidon-SR and mix.
3. Add lubricant, magnesium stearate and mix.

Blend is now ready for compression on a suitable size rotary tablet press.

EXAMPLE 4

In another example, a single layer sustained release acetaminophen tablet is prepared using the following ingredients:

EXAMPLE - 4 (Single Layer Enteric Coated Tablet)

No.	INGREDIENT	mg per tablet
	Intragranular Components:	
1	Paracetamol fine	900.0
2	Hypromellose (HPMC) 2208 4000 cP	50.0
3	Povidone K25	20.0
4	Pregel starch fine	10.0
5	Hypromellose (HPMC) 2910 15 cP	16.0
	Extragranular Components:	
6	Paracetamol (DC90)	111.2
7	Magnesium Stearate	3.0
	Enteric Coat	
8	Acryl-EZ	44.4
9	Triethyl Citrate	4.4
	Final Tablet weight (mg)	1159.0

Manufacturing Instructions for Sustained Release Granulation:

1. Mix Paracetamol, HPMC 2208, PVP, HPMC 2910 and Pregel Starch in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen
6. Add DC 90 (paracetamol) and mix for 5 minutes
7. Add lubricant, magnesium stearate and mix.
8. Blend is now ready for compression
9. Compressed single layer tablets on a suitable size rotary tablet press.
10. Tablets are then coated in a suitable size coating pan using Acryl-EZ as an enteric coat.

EXAMPLE 5

In this example, three different Bilayer sustained release paracetamol tablets are prepared using the following ingredients:

EXAMPLE - 5 (Bi-Layer Tablet)

No.	INGREDIENT	5A	5B	5C
A	**Sustained Release Layer (SR Layer)**	**mg per tablet**		
1	Paracetamol fine	800.0	900.0	800.0
2	Hypromellose (HPMC) 2208 4000 cP	48.0	27.0	24.0
3	Povidone K25	--	--	--
4	Pregel starch fine	--	--	--
5	Hypromellose (HPMC) 2910 15 cP	--	--	--
6	Magnesium Stearate	3.0	3.0	3.0
B	**Immediate Release Layer (IR Layer)**			
7	Paracetamol (DC90)	222.4	111.2	222.4
	Bi-Layer Tablet			
A	Sustained Release Layer (SR Layer)	851.0	930.0	827.0
B	Immediate Release Layer (IR Layer)	222.4	111.2	222.4
	Final Tablet weight (mg)	1073.4	1041.2	1049.4

Manufacturing Instructions for Sustained Release Layer:

1. Mix Paracetamol and HPMC 2208, in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen
6. Add lubricant, magnesium stearate and mix.
7. Blend is now ready for compression

Manufacturing Instructions for Immediate release Layer:

DC 90 paracetamol, a commercially available blend (paracetamol is 90% w/w) is used in the immediate release layer, and the tablets are compressed on a suitable size bi-layer rotary tablet press.

The biorelevant dissolution profile of the formulations listed in the Example 5 above, are shown in Figure 1b. It is recognized that these formulations are outside the scope of the present invention. They are provided as a demonstration of the principles of the IVMS formulation selection and prediction process.

5

EXAMPLE 6

In this example, two different Bi-layer Sustained Release paracetamol tablets are prepared using the following ingredients:

EXAMPLE - 6

No.	INGREDIENT	6A	6B
A	**Sustained Release Layer (SR Layer)**	**mg per tablet**	
1	Paracetamol fine	800.0	900.0
2	Hypromellose (HPMC) 2208 4000 cP	32.0	36.0
3	Povidone K25	20.0	22.5
4	Pregel starch fine	10.0	11.3
5	Hypromellose (HPMC) 2910 15 cP	16.0	18
6	Magnesium Stearate	3.0	3.4
B	**Immediate Release Layer (IR Layer)**		
7	Paracetamol (DC90)	222.4	111.2
	Bi-Layer Tablet		
A	Sustained Release Layer (SR Layer)	881.0	991.1
B	Immediate Release Layer (IR Layer)	222.4	111.2
	Final Tablet weight (mg)	1103.4	1102.3

10 Manufacturing Instructions for Sustained Release Layer:

1. Mix Paracetamol, HPMC 2208, PVP, HPMC 2910 and Pregel Starch in a high shear granulator.
2. Add purified water while mixing.
3. Continue mixing until suitable granulation end point is attained.
15 4. Dry the granulation to the target % LOD.
5. Milled dry granulation using Co-mill equipped with suitable size screen
6. Add lubricant, magnesium stearate and mix.
7. Blend is now ready for compression

20 Manufacturing Instructions for Immediate release Layer:

1. DC 90 paracetamol is used as an immediate release layer

The biorelevant dissolution profile of the formulations listed in the Example 6 above, are shown in Figure 1b.

EXAMPLE 7

The present invention is an extended release paracetamol tablet wherein the dissolution rate is controlled by the Hypromellose component. A current available supplier of HPMC is Shin-Etsu with the grade being identified as 90SH-4000SR having an average viscosity of 4000cps. In order to identify the critical parameters of HPMC that control dissolution and compaction behavior, four different grades of HPMCs from two suppliers were evaluated – 90SH-4000 & 90SH-4000SR (Shin-Etsu Chemical Co., Ltd.) and K4M & K4MCR (Colorcon). All four grades had the same HPMC viscosity range, 3600-5200cps as specified in the USP. The main difference amongst the two grades within the same supplier was in the particle size with the SR and CR grade generally being the preferred ones for controlled release formulation due to their small and narrow particle size distribution. In addition, lots of K4M and K4MCR at the higher end of the viscosity specification range were also used to determine the effect of viscosity on dissolution.

An Ishikawa diagram was used to identify the HPMC characteristics that can potentially impact dissolution and compaction. Pre-formulation studies were done to study these properties. Tablets were made with the various HPMC grades using the formulation of EXAMPLE 2 and processes thereof. Both a FBRM profile and power curve were recorded during the granulation process. Tablets were compressed to the same target hardness and tableting parameters recorded. Dissolution studies were conducted using the method described herein in a USP Apparatus II in pH 7.4 buffer.

All the formulations made with the various HPMCs met the required dissolution specification. Based on the f_1/f_2 criteria, however, differences were noted among the HPMC grades depending on the Tg, viscosity and specific surface area, which were confirmed to be the critical quality attributes for HPMC. 90SH-4000 with the highest Tg and largest surface area gave a higher dissolution compared to other grades. All grades/lots of HPMC showed similar compaction and flow behavior compared to the 90SH-4000SR grade.

EXAMPLE 8

IVMS method:

In vivo modeling and simulation (IVMS) is a physiologically-based drug ADME, PK/PD modeling and simulation tool. IVMS provides a platform for drug absorption, distribution, metabolism and excretion (ADME) in virtual populations. IVMS can effectively guide and assemble the development of new target formulations and optimum line extensions of drug products including OTC medicines.

In the present sustained release formulations, as the bio-dissolution method was developed and formulations were tested, the dissolution data was linked to the IVMS work and processed according to the IVMS model. IVMS methods and principles were published in 2002-2008. With use of these methods and principles it was unexpectedly discovered that with the bi-layered formulation of Example 1 and the single layer formulation of Example 2, that a 4μg/ml paracetamol plasma level could be reached and sustained for the necessary therapeutic duration.

Table 1

Predicted (IVMS) vs. Observed Therapeutic Effective Time (TET) Values

	Single Dose	**Clinical Study**
Formulation Candidates (Recommended Rank before Study Start)	**Predicted Time ≥ 4μg/ml**	**Observed Time ≥ 4μg/ml (M ± SD)**
Example 1	8.8	8.1 (6.1 ~10.1)
Example 2	8.7	7.3 (6.3 ~ 9.0)
Example 3	8.2	7.5 (5.0 ~ 10.0)
Example 4	N/A	7.1 (3.5 ~10.6)

Pharmacokinetic (PK) Variables:

The PK characteristics of Example Formulations 1 to 4 herein were assessed by a single dose clinical study in semi-fed state. Surprisingly, it was found that the formulation of Example 1 gave plasma concentrations above 4μg/ml for the longest period of time (8.1 hours). This was similar to the time-period of two doses of a standard paracetamol formulation (8.3 hours). Example 1 Formulation maintained plasma paracetamol concentrations higher than 3μg/ml up to the 11th hour post-dose. The Example 1 Formulation also had the highest mean value of $AUC_{(0\text{-}12\ hours)}$ (75.2 μg*h/ml). The T_{max}

value for the Example 1 Formulation (4.5 hours) was among the highest of the formulations. This is surprising as it was expected that a bi-layer tablet containing 100 mg APAP in the immediate layer portion would have a lower T_{max} than the single layer formulation of Example 3 which contained no immediate release paracetamol (T_{max} =4.0 hours). The formulation of Example 1 also demonstrated the highest T ≥ 5µg/ml among the 4 formulations as shown below. The T ≥ 3µg/ml for the formulation of Example 1 (10.3 hours) was similar to the other 3 candidates.

Table 3

Summary statistics for time of plasma paracetamol concentration equal or greater than 5, 4, 3 and 2 µg/mL

Time - T (hours)	Statistics	Example 1 1 g x 2 at 0 hr	Example 2 1 g x 2 at 0 hr	Example 3 1 g x 2 at 0 hr	Example 4 1 g x 2 at 0 hr	Conventional IR Tablet (0.5g x 2 at 0 and 6 hrs
T ≥ 5µg/mL	**Mean (hours)**	**6.3**	**5.5**	**5.4**	**5.2**	**6.6**
	Min (hours)	4.0	3.0	2.0	1.0	4.5
	Max (hours)	10.0	9.0	11.0	10.0	11.0
	CV (%)	31	32	43	50	26
T ≥ 4µg/mL	**Mean (hours)**	**8.1**	**7.3**	**7.5**	**7.1**	**8.3**
	Min (hours)	5.0	5.0	3.0	3.0	5.5
	Max (hours)	12.0	10.5	14.0	17.5	12.0
	CV (%)	25	23	34	50	22
T ≥ 3µg/mL	**Mean (hours)**	**10.3**	**10.3**	**10.6**	**10.1**	**10.1**
	Min (hours)	7.0	7.0	6.0	5.5	7.0
	Max (hours)	14.0	16.0	17.0	17.5	13.0
	CV (%)	20	25	26	40	18

PK Data from Steady State Clinical Study

The formulation of Example 1was evaluated to determine bioequivalence at steady state (final 24 hours of dosing) between 2000mg paracetamol of Example 1 given twice a day, 1330mg dose of an 8-hour extended release paracetamol formulation, Panadol® Extend given 3 times a day and 1000mg of a conventional immediate release paracetamol formulation, Panadol®, given 4 times a day for 3 days. At steady state, 2000mg of Example 1 Formulation (2000mg paracetamol twice a day) was bioequivalent to both an 8-hour extended release paracetamol formulation, Panadol® Extend (1330mg paracetamol 3 times a day) and a conventional immediate release paracetamol formulation, Panadol® (1000mg paracetamol 4 times a day) with regards to paracetamol C_{max}, AUC $_{0\text{-}t}$ and $AUC_{0\text{-}inf.}$ Over a 24 hr period at steady state the mean time period where the plasma paracetamol was greater than or equal to 4μg/ml for Example 1 was significantly longer (1.5 hours) than the conventional immediate release formulation, Panadol® dosed four times a day. This is clinically relevant as well as statistically significant (P=0.0046).

PK Data from Pivotal PK Studies (Fasted & Fed) Vs Conventional Immediate Release Formulation

The PK characteristics of the bi-layer formulation of Example 1 were assessed in a single dose study in order to determine absorption and food effect characteristics of the formulation in a fed and fasted state. The formulation of example 1 was given as a single 2000mg paracetamol dose (1000mg x 2 tablets). The conventional immediate release formulation Pandaol ® was given as a single 1000mg dose (500mg x 2 tablets). 2000mg of the Example 1 Formulation was well absorbed in both fasted and fed states with more than 90% relative bioavailability as compared to a conventional immediate release formulation, Panadol®. Time at or above the therapeutic level (≥ 4μg/ml) from 2000mg of Example 1 formulation was approximately double that of one dose (1000mg) of standard Panadol®. Surprisingly food had a significant effect on the peak exposure of paracetamol by increasing the C_{max} of 2000mg Example 1 formulation and decreasing the C_{max} of Panadol®. Food caused a significant decrease in overall extent of paracetamol absorption ($AUC_{0\text{-}inf}$) for Panadol® but had less impact for the Example 1 Formulation.

Pharmacodynamics

There is no well established PK-PD link for paracetamol. Conventional thinking suggests that in order for paracetamol to be effective, paracetamol must be present in the blood plasma at a concentration of at least 3μg/ml-4μg/ml. It is believed that time above at

least 3μg/ml, and more importantly time above 4μg/ml, may be clinically significant. Time above 5μg may also be clinically significant.
Thus, one aspect of the present invention is the time that paracetamol must be present in the blood at a concentration of at least 3μg/ml, such as for about a 10 hour window. Another aspect of the present invention is the time that paracetamol must be present in the blood at a concentration of at least 4μg/ml, such as for about an 8 hour window. Another aspect of the present invention is the time that paracetamol must be present in the blood at a concentration of at least 5μg/ml, such as for about a 6 hour window, when dosed at 2000mg paracetamol twice daily, and as compared to the conventional immediate release formulation when taken as a 1000mg dose four times per day.

Another aspect of the invention is the plasma C_{max} value obtained by the formulations of the present invention. Even though the formulations of the present invention were given at a higher dose of paracetamol (2000mg) than other conventional formulations, the C_{max} in the fasted state is lower than a conventional immediate release formulation dosed at half that amount (1000mg). As a result of a lower C_{max}, additional adverse effects would not be expected to be observed with the formulations of the present invention as compared to a conventional immediate release formulation.

The minimum time that a formulation should be at or above the desired plasma levels is also an aspect of this invention. As shown in Table 3 above, one aspect of the invention is a mean plasma concentration of at least 5μg/ml which should be maintained for at least about 6 hours; or a mean plasma concentration of at least 4ug/ml which should be maintained for at least about 8.0 hours; or mean plasma concentration of at least about 3ug/ml for at least about 10 hours. The mean plasma concentration should be maintained for these time periods longer than a standard immediate release formulation.

In another embodiment of the invention, the extent of absorption of the paracetamol should be equivalent to a conventional immediate release paracetamol. It is also desired that the therapeutically active drug plasma concentration of paracetamol should be attained rapidly by the immediate release phase of the paracetamol.

Another aspect of the invention is the slope of the decline in plasma level of APAP. In a repeat dose clinical study, the elimination rate constant (K_{el}) for the formulation of the present invention was 25% lower than that for the conventional immediate release formulation. This is related to a slower controlled release rate of paracetamol from the tablets of the formulation, such as those exemplified by Example 1, as compared to a

conventional immediate release formulation. The elimination rate constants of Example 1 tablets and the tablets of an 8-hr extended release formulation, Panadol® Extend, were also found to be comparable (0.26 hr^{-1} and 0.27 hr^{-1}, respectively).

A biorelevant dissolution process was developed to reflect in vivo drug release or absorption. Dissolution of various commercially available sustained release products was assessed in different dissolution media, at different pH and different rotations per minute. The data was correlated with known in vivo data for the same formulation. The best correlation was obtained with a USP Apparatus II in 900 ml of 40mM phosphate buffer, at pH 7.4 and at 75 RPM. This fluid was used for all the tested formulations.

Using a biorelevant dissolution model such as that described herein, Figures 1a & 1b demonstrate the dissolution characteristics of the example formulations and commercially available immediate release paracetamol formulation, Panadol®, and an 8 hour extended release formulation, Panadol® Extend.

Figure 5 demonstrates the Therapeutic Effect Time (TET) of the various example formulations.

The above description is considered that of the preferred embodiments only. Modifications of the invention will occur to those skilled in the art and to those who make or use the invention. Therefore, it is understood that the embodiments shown in the drawings and described above are merely for illustrative purposes and not intended to limit the scope of the invention, which is defined by the following claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

References

1. J.T. DiPiro, R.L. Talbert, G.C. Yee, et al., Pharmacotherapy: A Pathophysiologic Approach, 7e.

2. C. Dollery. Therapeutic drugs, vol 1; 2nd ed. Churchill Livingston Publications: 1999. p A19-21.

3. M Hossain, J.W. Ayres, Pharmacokinetics and pharmacodynamics in the design of controlled-release beads with acetaminophen as model drug. J Pharm Sci 1992; 81: 444–448.

4. D.J. Liu, et al., Simulating/predicting in vivo absorption profile. AAPS Workshop on Computer Simulation and Its Role in Drug Development Research. 2002

5. D.J. Liu, Profiling Drug Absorption and Metabolism by In Situ Gastrointestinal Perfusion Studies to Predict in vivo Performance of Oral Drugs. American Association of Pharmaceutical Scientists (AAPS) Annul Meeting, 2008

6. D.J. Liu, G. Davies, et al., New IVMS approach to develop novel oral drug formulation, American Association of Pharmaceutical Scientists (AAPS) Annul Meeting, 2010

7. J.C. Nielsen, P. Bjerring, L. Arendt-Nielsen. A comparison of the hypoalgesic effect of paracetamol in slow-release and plain tablets on laser-induced pain. Br J Clin Pharmacol 1991;31: 267–270.

8. D.J. Liu, Apply In Vivo Modeling and Simulation to Identify the Minimum Therapeutic/Effective Doses (MTD/MED) of Paracetamol for Pain Relief. 8th World Congress World Institute of Pain Management Annual Meeting, 2012

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).

Figure 1a

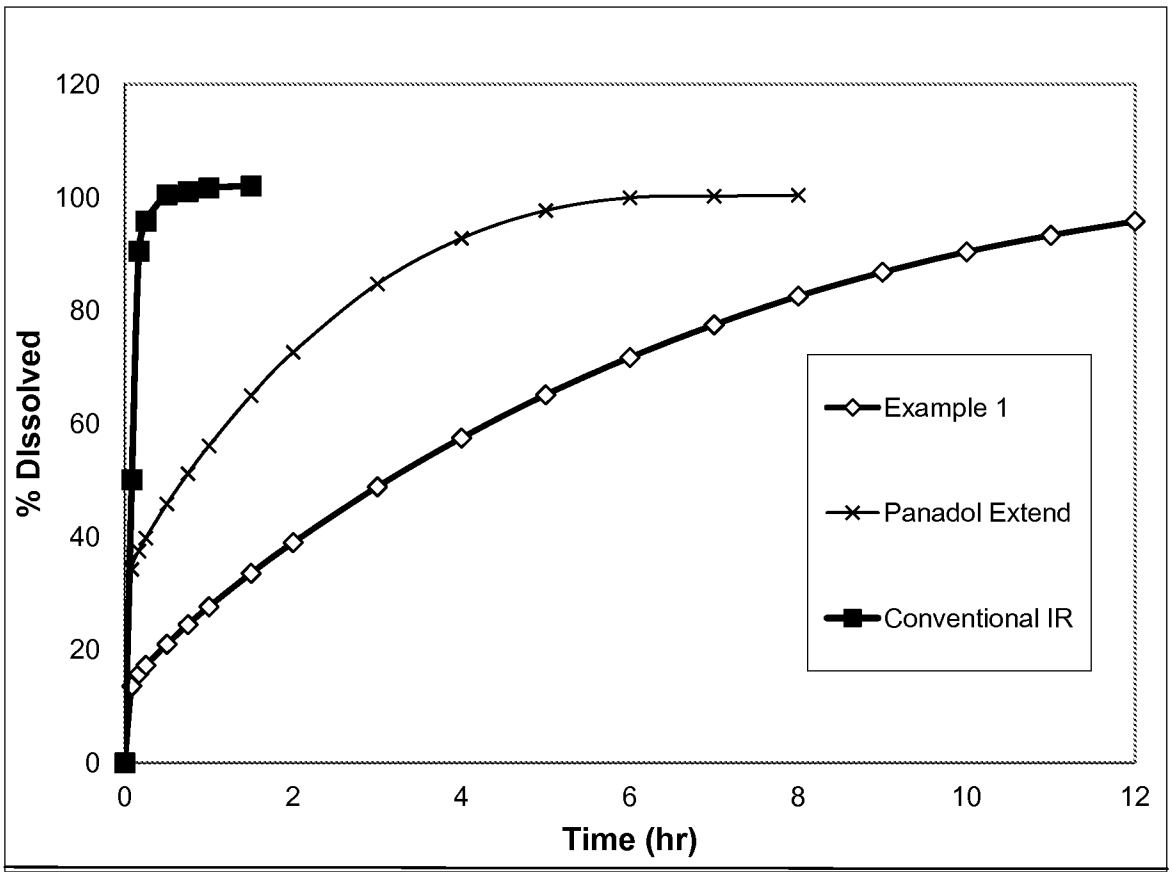

120
100
80
60
40
20
0
% Dissolved
0
2
4
6
8
10
12
Time (hr)
Example 1
Panadol Extend
Conventional IR

Figure 1b

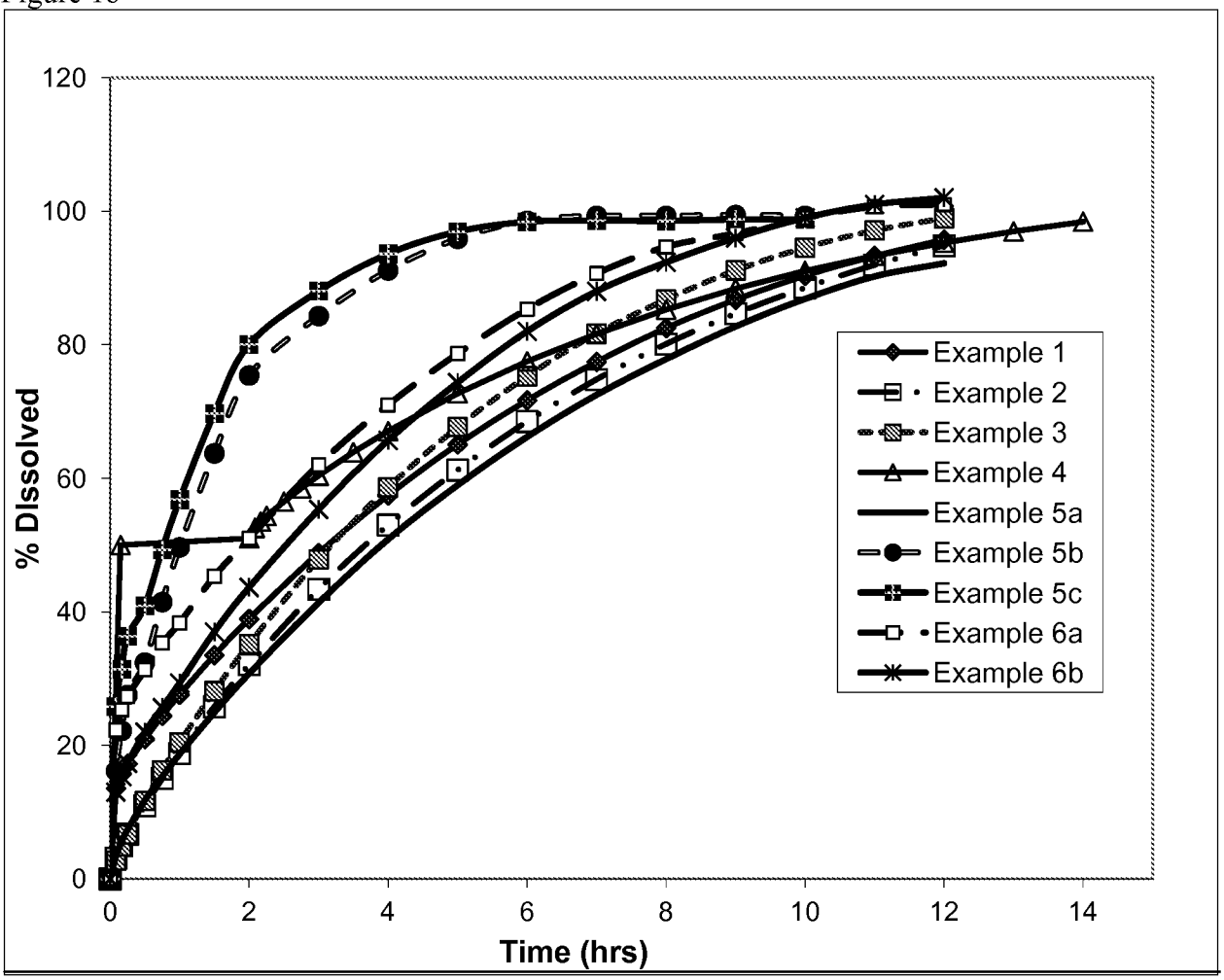

120
100
80
60
40
20
0
% Dissolved
0
2
4
6
8
10
12
14
Time (hrs)
Example 1
Example 2
Example 3
Example 4
Example 5a
Example 5b
Example 5c
Example 6a
Example 6b

Figure 2a

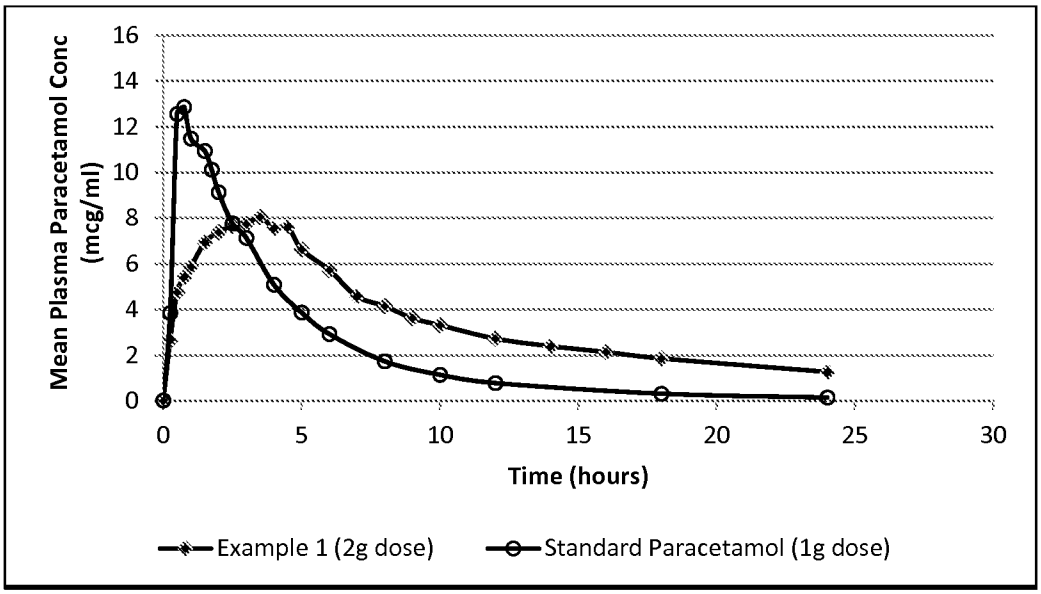


Figure 2b

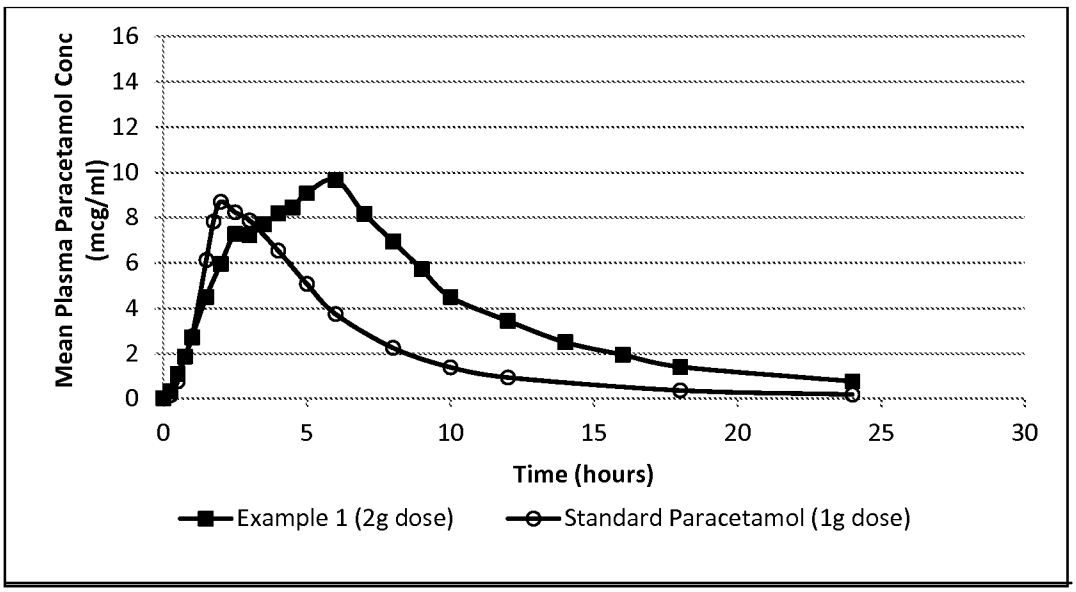


Figure 3a

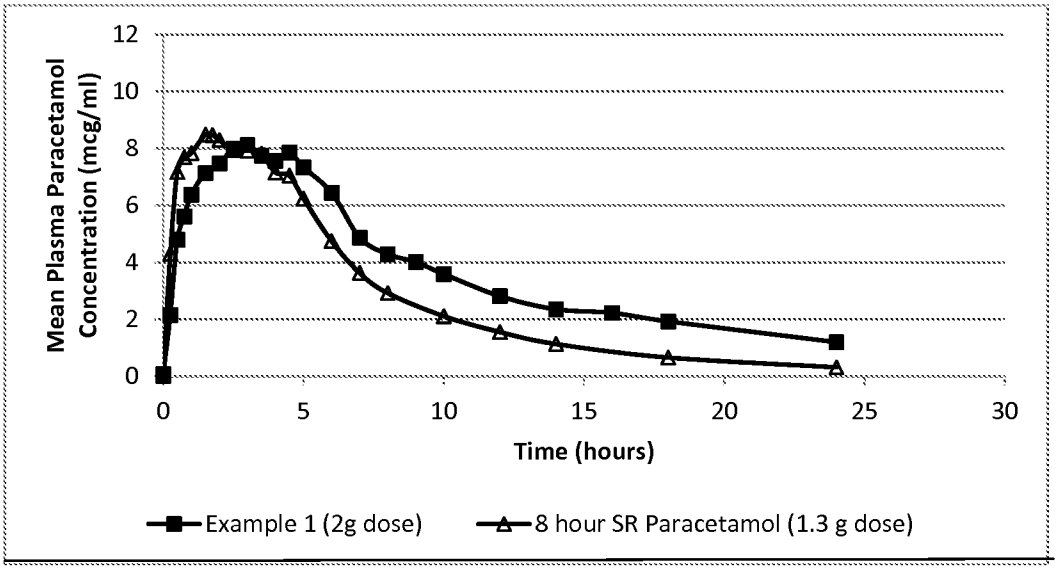


Figure 3b

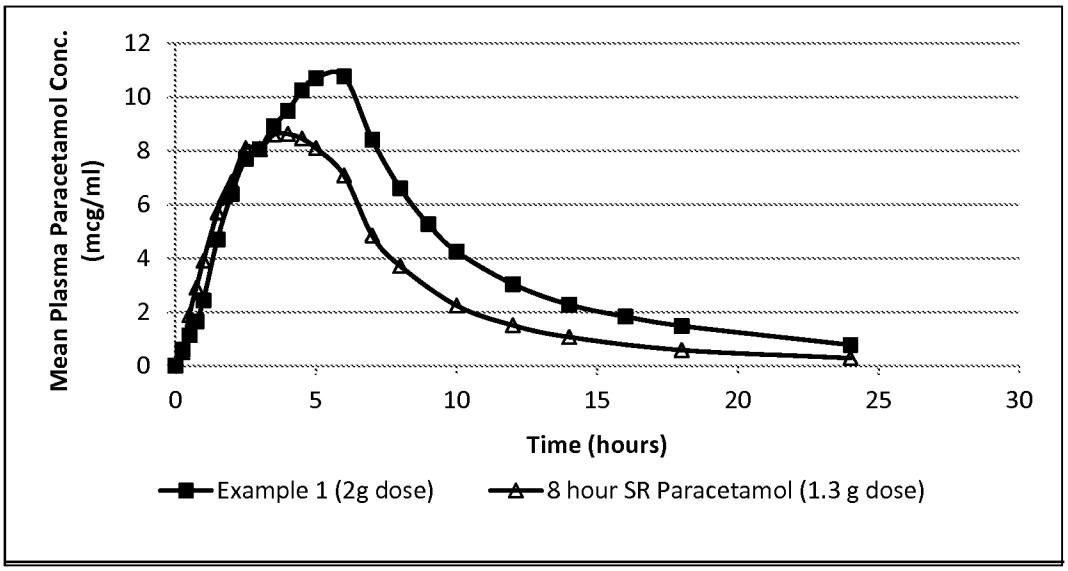


Figure 4

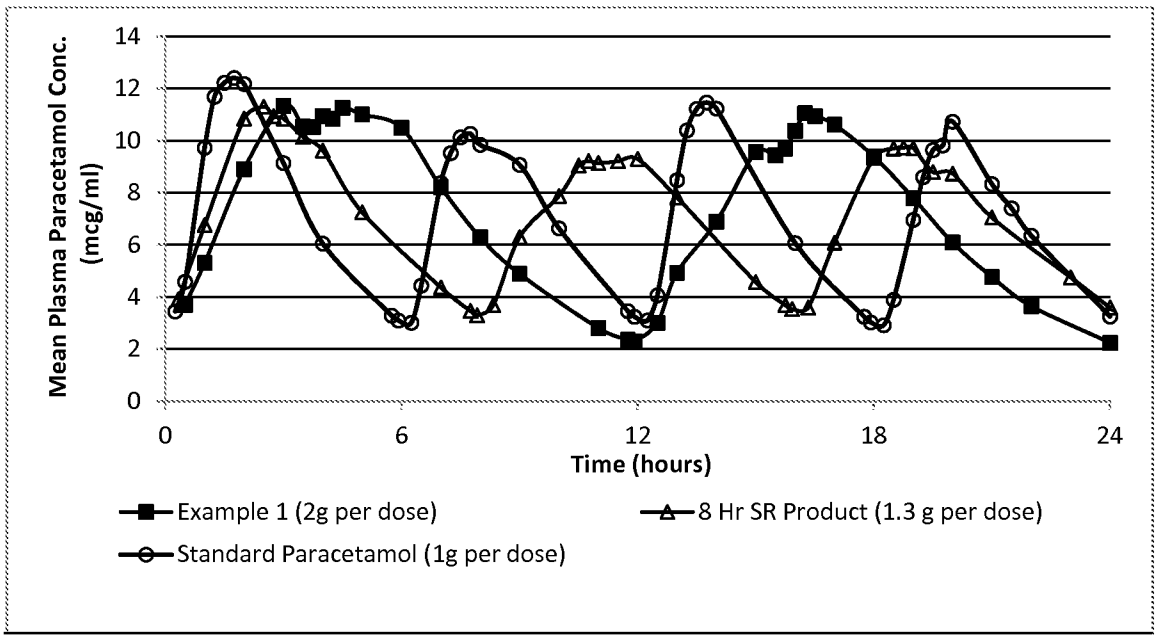

Mean Plasma Paracetamol Conc. (mcg/ml)
14
12
10
8
6
4
2
0
0
6
12
18
24
Time (hours)
Example 1 (2g per dose)
8 Hr SR Product (1.3 g per dose)
Standard Paracetamol (1g per dose)

Figure 5

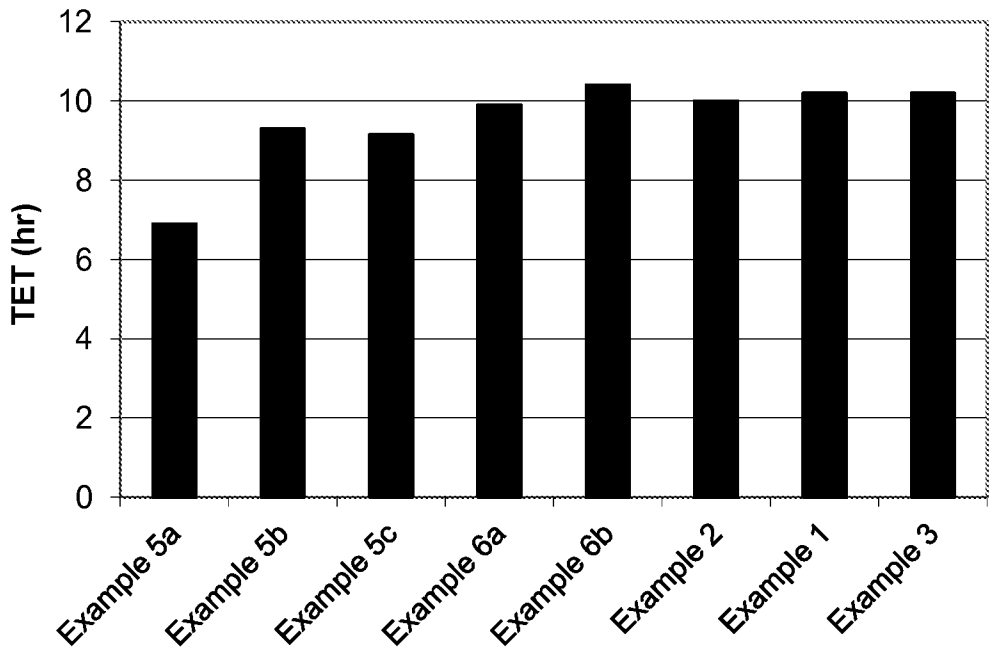
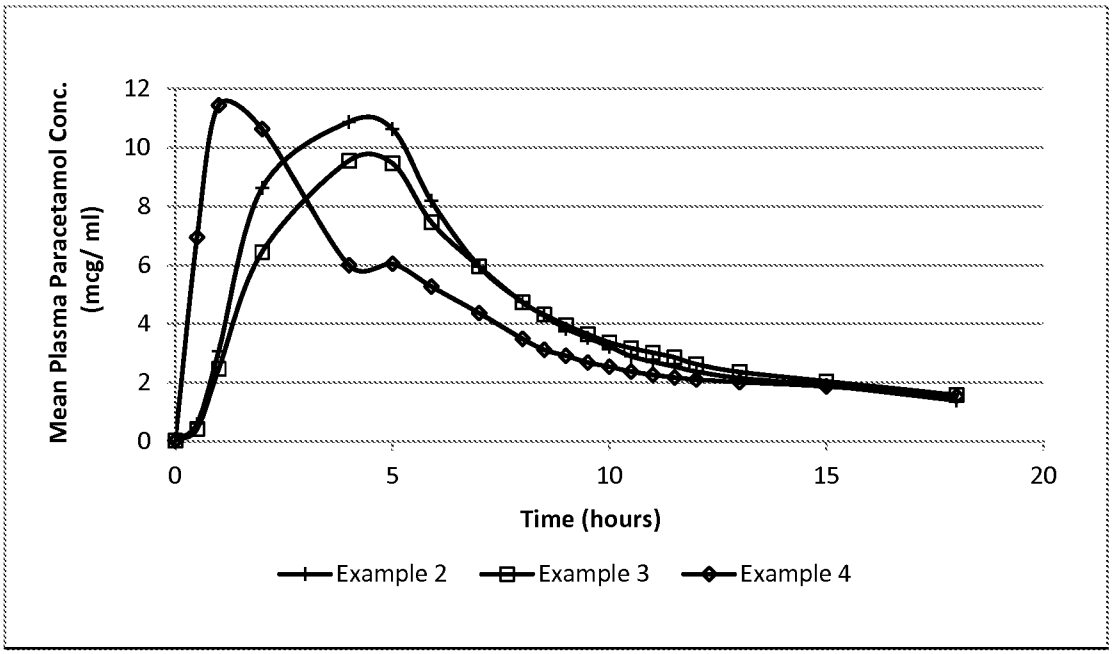

12
10
8
6
4
2
0
TET (hr)
Example 5a
Example 5b
Example 5c
Example 6a
Example 6b
Example 2
Example 1
Example 3

Figure 6


Mean Plasma Paracetamol Conc. (mcg/ ml)
12
10
8
6
4
2
0
0
5
10
15
20
Time (hours)
Example 2
Example 3
Example 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/36528

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/22, A61K 31/167 (2012.01)
USPC - 424/468; 514/620
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-424/468; 514/620

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-424/468; 514/620

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL), GoogleScholar (PL, NPL); search terms: paracetamol acetaminophen sustained immediate release hydroxypropylmethyl cellulose centipoises hypromellose AUC Cmax tmax

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0202716 A1 (Chan et al.) 14 October 2004 (14.10.2004) para [0057] - [0077]	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
Y	WO 2011/026125 A2 (Hou et al.) 03 March 2011 (03.03.2011) para [0153], [0182]	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
Y	US 2003/0064108 A1 (Lukas et al.) 03 April 2003 (03.04.2003) Table 2	55, 58
Y	US 6,599,529 B1 (Skinhoj et al.) 29 July 2003 (29.07.2003) col 8, ln 28-32, col 17, ln 51-59, col 2	63-71, 74
A	US 5,055,306 A (Barry et al.) 08 October 1991 (08.10.1991) Abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	US 5,849,240 A (Miller et al.) 15 December 1998 (15.12.1998) Abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	US 2005/0175706 A1 (Ogorka et al.) 11 August 2005 (11.08.2005) Abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	US 2004/0170681 A1 (Grattan) 2 September 2004 (02.09.2004) Abstract	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85

☒ Further documents are listed in the continuation of Box C. ☒

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2012 (18.07.2012)	02 OCT 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/36528

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/0127484 A1 (Speirs et al.) 15 June 2006 (15.06.2006) Abstract	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	WO 2008/131056 A2 (Qiu et al.) 30 October 2008 (30.10.2008) abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	US 2008/0200549 A1 (Atkinson) 21 August 2008 (21.08.2008) Abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85
A	WO/1997/039747 A1 (Lukas et al.) 30 October 1997 (30.10.1997) Abstract, entire document	1-8, 11-17, 52-60, 62-71, 74, 77-83, 85

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/36528

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9, 10, 18-51, 61, 72, 73, 75, 76, 84
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.