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(54) Titre : COMPOSITIONS COMPRENANT DU PARACETAMOL ET DE L'IBUPROFENE
(54) Title: A COMBINATION COMPOSITION COMPRISING PARACETAMOL AND IBUPROFEN

(57) Abrégé/Abstract:
A combination pharmaceutical composition for the treatment of pain including about 125 mg to about 150 mg ibuprofen and about 475 mg to about 500 mg paracetamol.

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(54) Title: A COMBINATION COMPOSITION

(57) Abstract: A combination pharmaceutical composition for the treatment of pain including about 125 mg to about 150 mg ibuprofen and about 475 mg to about 500 mg paracetamol.

A COMBINATION COMPOSITION COMPRISING PARACETAMOL AND IBUPROFEN

Technical Field

The invention relates to a method and combination composition for the treatment of pain. In particular, the invention relates to a composition containing ibuprofen and paracetamol for the treatment of pain.

Background to the Invention

Without a medical practitioner's prescription (ie over the counter ("OTC")), a full therapeutic dose of paracetamol (acetaminophen) is 1000 mg, a full therapeutic dose of ibuprofen is 400 mg to relieve pain. The total daily amount is also limited to 4000 mg of paracetamol and 1200 mg of ibuprofen, per day in divided doses.

Dosing regimes for each of paracetamol and ibuprofen, when given individually to patients, are often maximised to give the full individual therapeutic dose. Care needs to be taken that the maximum daily dose is met but not exceeded for each medication.

Pharmaceutical combinations such as paracetamol and codeine (500 mg/8 mg) and ibuprofen and codeine (200 mg/12.8 mg) in single dose forms are known. Avoiding use of codeine can be an advantage due to constipation difficulties that are a common side effect.

Combinations of paracetamol, ibuprofen and codeine are known in South Africa, with a single tablet including paracetamol 250 mg, ibuprofen 200 mg, codeine 10 mg. Another combination of paracetamol, aspirin and codeine is also known in a single dose form including 325 mg paracetamol, 325 mg aspirin and 10 mg codeine. In both cases, at a dose of two capsules, sub-therapeutic doses of paracetamol are delivered. In the case of the South African combination, while 4 capsules would give a full OTC therapeutic dose of paracetamol, the amount of ibuprofen would then exceed allowed OTC dose limits.

Paracetamol can be taken without prescription in dosages of 500-1000 mg every 4 to 6 hours up to 4 g/day for the treatment of fever/pain. Ibuprofen is taken without prescription in doses of 200-400 mg every 6 hours up to 1200 mg/day for analgesia.

Ibuprofen is generally well tolerated in divided self medicated doses of up to 1.2 g/day, but it is still associated with side effects in some individuals, such as gastro-intestinal damage. (Reference: Scheiman JM et al 2004 - A randomised controlled comparison of ibuprofen at maximal over-the-counter dose compared with prescription-dose celecoxib on upper gastrointestinal mucosal injury. Clin Gastroenterol Hepatol 2(4): 290-5) and a number of other adverse effects (reference: AHFS Drug Information, 2004).

Paracetamol, however, is regarded as "relatively non-toxic in therapeutic doses" (AHFS Drug Information 2004).

The literature has reported that for some drugs the frequency of dosing is more important in determining adverse reactions rather than total dose (IR Edwards, Pharmacological Basis of Adverse Drug Reactions, Chapter 6, page 293 in Avery's Drug Treatment, 1996, 4th edn: Adis International, Auckland). This suggests that giving 2 x 150 mg ibuprofen four times a day rather than 2 x 200 mg three times a day may be better tolerated. This type of principle is also in part behind that of sustained release products where drug is gradually released avoiding such extreme peak and trough effects from immediate release dose forms. It is also conceivable that decreasing the amount of ibuprofen given as a single dose will improve the tolerability of ibuprofen.

However, it is a concern that using a lower dose of ibuprofen would result in less pain relief due to a lower peak drug concentrations with the result that the efficacy of the pain relief is reduced.

There would be an advantage to be able to deliver these medications in combination at a high therapeutic dose in order to minimise the number of doses required throughout the day, while still achieving the maximum daily dose rate per day for more effective pain relief. Reduction of the amount of ibuprofen to reduce the likelihood of side effects occurring while maintaining pain relief effect and minimising doses needed would achieve those advantages. The ability to achieve effective pain relief from such a combination to treat short term, intermittent, type pain would also be an advantage. Such a combination has not been previously provided and the concept would allow a number of advantages to be achieved, such as convenience of administration, increased ease of user compliance, and effective pain relief over time.

Summary of the Invention

According to one aspect of the invention there is provided a combination pharmaceutical composition for the treatment of pain including about 125 mg to about 150 mg ibuprofen and about 475 mg to about 500 mg paracetamol.

Preferably the ratio of paracetamol:ibuprofen is about 50:15.

Preferably the composition has 125-150 mg ibuprofen and 475-500 mg paracetamol.

Preferably the ibuprofen is present as a salt, ester or complexed form in an amount suitable to deliver about 125 mg to about 150 mg ibuprofen.

Preferably the composition has 150 mg ibuprofen and 500 mg paracetamol.

Preferably the composition is suitable to be administered as two unit doses four times a day.

Preferably the composition is in the form of a tablet or capsule.

According to another aspect of the invention there is provided a use of about 475 mg to about 500 mg paracetamol and about 125 mg to about 150 mg ibuprofen in the manufacture of a medicament to be administered in two unit doses four times a day for the treatment of pain.

Preferably the ratio of paracetamol: ibuprofen is about 50:15.

Preferably the ibuprofen is present as a salt, ester or complexed form in an amount suitable to deliver about 125 mg to about 150 mg ibuprofen.

Preferably the composition has 125-150 mg ibuprofen and 475-500 mg paracetamol per unit dose.

According to a further aspect of the invention there is provided a pharmaceutical pack including tablets or capsules, each tablet or capsule including a pharmaceutical composition according to any one of claims 1 to 7, the pack including instructions to a user to take two tablets or capsules no more than 4 times a day.

Preferably the pack includes an even number of tablets or capsules.

Preferably the pack includes at least 8 tablets or capsules.

According to a further aspect of the invention there is provided a pharmaceutical composition for the treatment of pain, the composition including paracetamol and ibuprofen in a ratio range of from 47.5:12.5 to 50:15, the composition formed in discrete dosage units whereby the taking of one or more complete dosage units delivers substantially 250-300 mg ibuprofen and substantially 950-1,000 mg paracetamol to provide synergistic pain relief.

Preferably the pharmaceutical composition is presented with instructions to the effect that a user should take the number of dosage units necessary to deliver the 250-300 mg ibuprofen and 950-1,000 mg paracetamol.

Preferably the ratio is 50:15.

Preferably the composition includes a salt, ester or complexed form of ibuprofen in an amount sufficient to deliver ibuprofen to the user within the stated ratio range or at the stated ratio.

Preferably each dosage unit is a tablet or capsule.

Preferably the composition is suitable for administration four times a day.

According to a further aspect of the invention there is provided a pharmaceutical combination composition suitable for the treatment of pain, the composition including paracetamol and ibuprofen in a ratio range of from 47.5:12.5 to 50:15 suitable for providing synergistic pain relief.

Preferably paracetamol and ibuprofen are the only active ingredients.

Preferably the ratio of paracetamol to ibuprofen is 50:15.

Preferably the composition includes a salt, ester or complexed form of ibuprofen in an amount sufficient to deliver ibuprofen to the user within the stated ratio range or at the stated ratio.

Preferably the composition comprises a tablet or capsule.

Preferably the pharmaceutical composition is suitable to be administered four times a day.

According to a further aspect of the invention there is provided a pharmaceutical composition for the treatment of pain, the composition including paracetamol and ibuprofen formed in discrete dosage units whereby the taking of one or more complete dosage units delivers substantially 250-300 mg ibuprofen and substantially 950-1,000 mg paracetamol to provide synergistic pain relief, presented with instructions to the effect that a user should take the number of dosage units necessary to deliver the 250-300 mg ibuprofen and 950-1,000 mg paracetamol.

The inventors have therefore recognised that an adjustment of the ratio of paracetamol to ibuprofen would maximise the efficiency with which a combination composition could be given to ensure that the individual therapeutic doses are of a concentration strong enough to deliver effective pain relief, while resulting in the maximum daily allowance. By reducing the amount of ibuprofen in the composition to an amount less than the recommended maximum single therapeutic dose, it can be given more frequently throughout the day to result in the maximum daily amount being given. This allows a combination composition containing about 1000 mg of paracetamol and about 300 mg of ibuprofen (about 500 mg paracetamol + about 150 mg ibuprofen in 2 pills/capsules) to be given four times daily, resulting in the maximum daily amount given for each medication. The expected detriment is that the amount of ibuprofen administered per dose is lower thus it would be expected that pain relief will not be sufficient or at least lower. As stated earlier, it has been surprisingly found that this is not the case. Pain relief is consistently of at least equivalent efficacy.

It has also been surprisingly found that the composition (paracetamol:ibuprofen ratio between about 47.5:12.5 and about 50:15; preferably 50:15) provides enhanced pain relief during the first dose interval in comparison to the individual actives when taken alone. This effect of itself provides options for pain management in situations where continued administration may be unnecessary. The user obtains effective pain relief being able to ingest reduced levels of ibuprofen. To achieve this effect it is very much preferred that the lowest individual adult dose of ibuprofen will be about 250 mg taken with about 950 mg paracetamol (eg in 2 tablets/pills with 125 mg ibuprofen and 475 mg paracetamol in each pill). The largest amount of actives will be dependent on practical aspects such as safety aspects relating to the maximum OTC amount per day and the size of the resultant pill/capsule. Preferably the amount of actives in a single pill/capsule will be about 150 mg ibuprofen and 500 mg paracetamol. Two such pills/capsules would be taken to provide a single dose of 300 mg ibuprofen and 1000 mg paracetamol. While pills/capsules containing more than 500 mg paracetamol and 150 mg ibuprofen could be made, such options are not preferred due to the size of the pill/capsule and resultant ingestion and compliance difficulties.

As would be known to the skilled person, pharmaceutically acceptable salts or esters of the two actives could also be used. For example, ibuprofen is usually given as the acid but various salts, esters and other complexes are also used. These include lysine and sodium salts, guaiacol and pyridoxine esters, and aminoethanol, isobutanolammonium,

and meglumine derivatives. Ibuprofen is usually administered as a racemic mixture but preparations containing only the S(+)-isomer (dexibuprofen) are available in some countries.

As will be apparent, when a salt form is used in the formulation sufficient will need to be included to meet the desired amount of acid (eg 342 mg ibuprofen lysinate = 200 mg ibuprofen).

In a preferred form the active ingredients (paracetamol: ibuprofen) are formulated in the ratio of about 50:15 in a single tablet or capsule in amounts by weight which are suitable to be administered four times a day to meet the recommended maximum dose (without medical practitioner's prescription) without excessive tablet or capsule administration. Given the weight amounts of the components that can be used, it is preferable that the pharmaceutical preparation is given in two tablets or capsules for ease of ingestion by the user. It has been found that it is possible to formulate a preparation that includes paracetamol (500 mg) and ibuprofen (150 mg) in a single tablet or capsule. Thus two tablets/capsules four times a day (ie in a 24 hour period; preferably qid) will deliver the maximum allowed daily dose.

While effective pain management can be achieved within the first dose interval, it is preferred to couple this with a quarterly administration regime. This new combination of component amounts and dosing regime allows for a simple, effective, and achievable self-medication for pain relief thus overcoming problems that can occur with self medication requirements. Such problems will include ease of compliance with the required dosing regime. Two tablet or capsules four times a day is a relatively easy regime to be met by a user. Increasing from this amount can result in dosage and administration problems. This is an additional advantage to that of the potential for reduction in occurrence of adverse side effects. The amount of ibuprofen and paracetamol could be adjusted to slightly lower levels if desired, in order to maintain a safety margin from a daily dose perspective. The amount of ibuprofen (as the acid) in a single dose would therefore be between about 125 mg and about 150 mg; and the amount of paracetamol between about 475 mg and about 500 mg. Acceptable pharmaceutical variations are intended to be covered.

The ingredients will be formulated into a tablet or capsule using known pharmaceutical carriers and excipients. Preferably they will be formulated into a film-coated tablet of a size capable of containing the amounts of ingredient preferred. Preferably this will be

oval for ease of swallowing and film coated. The composition can also be administered in, for example, two 00 size capsules. In a less preferred aspect, the actives could be administered as separate unit doses. The result would for example be the administration of two 500 mg paracetamol pills/capsules and two 150 mg ibuprofen pills/capsules. This is less preferred as the administration of four pills/capsules is not conducive to compliance.

Essentially, by using a ratio of about 50:15 (eg 500 mg paracetamol:150 mg ibuprofen) a full OTC daily therapeutic dose (non-prescription) can be conveniently provided to the user in two tablets/capsules for ingestion 4 times a day (ie 6 hourly). The ingestion of higher numbers of pills in a single dose is impractical and tends to meet consumer resistance.

In a preferred form, the tablet containing the active ingredients would be created using pharmaceutically acceptable ingredients including maize starch, colloidal silicon dioxide, disodium EDTA, polyvinyl pyrrolidine, sodium benzoate, colloidal silicon dioxide, magnesium stearate, sodium starch glycollate. Other pharmaceutically acceptable ingredients as would be known to the skilled person could also be used.

The paracetamol may be provided in either powder or crystalline form.

The ibuprofen may be provided in any suitable particle size such as either 25 micron or 50 micron particle size.

Purified water will preferably be used when preparing the formulation.

The tablets/capsules ("pills") will preferably be presented to the consumer as part of a pharmaceutical pack, such as a blister pack, as will be well known. The pack should have an even number of pills, preferably at least 8 pills, contained within it and have instructions to take 2 pills no more than 4 times per day (ie in a 24 hour period). Preferably the instructions will be to take the pills at 6 hourly intervals (ie qid). It is of course possible that the pills could be sold contained in a bottle, the pills held loosely within that bottle.

Examples

Example 1: Tablets for oral use

Core	
Paracetamol	500.0 mg
Ibuprofen	150.0 mg
Maize Starch (dry mix)	14.83 mg
Colloidal Silicon Dioxide	1.70 mg
Maize Starch (for paste)	22.5 mg
Disodium EDTA	0.50 mg
Polyvinyl Pyrrolidone	7.54 mg
Sodium Benzoate	1.00 mg
Maize Starch (Lubrication)	12.50 mg
Colloidal Silicon Dioxide	12.00 mg
Magnesium Stearate	2.45 mg
Sodium Starch Glycollate	25.00 mg
Purified Water	q.s.
Coating	
Hydroxypropylmethyl cellulose	7.20 mg
Polyethylene Glycol 6000	0.80 mg
Titanium Dioxide (Colourant)	0.21 mg
Methylhydroxybenzoate	0.20 mg
Propylhydroxybenzoate	0.02 mg
Purified Water	q.s.
Total	**758.45 mg**

Example 2: Preparation of tablets

A. Preparation of a Granulation Mixture

1. Weigh paracetamol and ibuprofen and sift using a suitable vibrosifter and transfer to mixer. Discard any material not passing through #12 sieve.
2. Weigh and sift maize starch using a suitable vibrosifter (#40 sieve) and transfer to mixer.
3. Weigh and sift colloidal silicon dioxide using a suitable vibrosifter (#100 sieve) and transfer to mixer.
4. Mix for 10-11 minutes at slow speed.

B. Wet Granulation and Drying

1. Add purified water (0.03 ml/tablet) to stainless steel container
2. Sift maize starch (for paste) using suitable sieve (for example #60) and stir until slurry is formed.
3. Add purified water (0.18 ml/tablet) to a suitable jacketed planetary mixer and heat to boiling.
4. Add disodium EDTA, polyvinyl pyrrolidine and sodium benzoate. Dissolve and stir for 5-6 minutes until a clear solution is obtained.
5. Add starch slurry under continuous stirring until a translucent paste is obtained.
6. Cool paste to 50-55°C by circulating cool water in the jacket of the planetary mixer.
7. Slowly add the paste to a high speed granulator, mix at slow speed, then high speed until consistency is achieved.
8. Unload wet granules into the Fluid Bed Dryer, keeping mixer and chopper at slow speed followed by fast speed. Dry until Loss on Drying value is not more than 1% w/w

C. Dry Sifting, Milling and Lubrication

1. Screen dried granules through a suitable multimill and with a 2.5 mm screen. Re-mill remaining granules.
2. Check theoretical yield (99-100%)
3. Weigh and sift through 40 mesh sieve on a suitable vibro-sifter, sodium starch glycollate, magnesium stearate, colloidal silicon dioxide and maize starch (for lubrication) through a 100 mesh sieve. Transfer lubricants to dried granules and mix for 5 minutes at 25 rpm in a suitable mixer.
4. Check theoretical yield (99-100%).

E. Tablet Compression, Film Coating and Polishing

1. Compress on a rotary press using specified punches into tablets
2. Add coating ingredients, Hydroxypropylmethyl cellulose, Polyethylene Glycol 6000, Titanium Dioxide (Colourant), Methylhydroxybenzoate, Propylhydroxybenzoate to water to form a slurry (10-12%w/v).
3. Coat tablets in a suitable auto-coater. Set spray guns (3) at a suitable rate e.g. 35 mls/minute i.e. 105 mls/min and coat tablets.
4. Polish final tablets with wax (beeswax 0.1 mg/tablet and carnuba wax 0.3 mg/tablet. Sprinkle mixed waxes over tablets and rotate for about 10 minutes.

The tablets satisfy the disintegration time requirements of the Ph.Eur. and USP.

Example 3: Tablets for oral use

Part 1 (Dry Mixing)	
Paracetamol	500.0 mg
Ibuprofen	150.0 mg
Maize Starch (dry mix)	25.32 mg
Microcrystalline Cellulose	30.00 mg
Pregelatanised starch	32.00 mg
Croscarmellose sodium	2.50 mg
Part II (Granulation)	
Maize starch (paste)	50.00 mg
Methyl parahydoxybenzoate	0.30 mg
Propyl parahydroxybenzoate	0.03 mg
Purified Water	q.s.
Part III (Lubrication)	
Maize starch	10.00 mg
Croscarmellose sodium	10.00 mg
Magnesium stearate	4.85 mg
Talc	10.00 mg
Film Coating	
Opadry™ white OYLS 58900	14.00 mg
Talc	1.00 mg
Purified Water	q.s.

Example 4: Preparation of tablets of Example 3

Part I

1. Transfer, sieve & blend into a suitable stainless steel high speed mixer granulator – Paracetamol. Ibuprofen. maize starch, microcrystalline cellulose, pregelatanised

Part II

1. Transfer into a stainless steel container purified water (amount equivalent to 6.00L/120,000 tablet batch) and maize starch, stir to obtain a uniform slurry.
2. Transfer water (30.00L/120,000 tablet batch) into a stainless steel paste kettle, heat to boiling and dissolve Methyl parahydoxybenzoate and Propyl parahydroxybenzoate.
3. Add starch slurry under constant stirring for gelatinisation.
4. Slowly add starch paste to mixture from Part I in a high speed mixer granulator. Run the mixer blade slowly for 10-20 minutes, then simultaneously run the agitator at slow speed and chopper at fast speed for 5-7 minutes.
5. Granulate the above weight mass by using a multimill equipped with 8mm screen, knives forward, medium speed.
6. Dry the wet granulate in a fluid bed dryer at 52-55^{0}C until the LOD value is obtained in between 2.5-3.5% w/w.
7. Sieve the dried granulate through a sifter equipped with a 20 mesh sieve and oversize through multimill with 1.5mm screen, knife forward, medium speed arrangement.

Part III: Final Mixture

1. Transfer the milled granules to inprocess bin blender
2. Sift the maize starch, croscarmellose sodium and purified talc & transfer to the milled granules.
3. Mix for 4 minutes at slow speed, keeping chopper in off position & record premix time.

Tabletting

1. Compress the final mixture by a tabletting machine, equipped with a capsule shaped punches, to obtain a weight of 825mg per tablet.

Preparation of Film Coating

Mix Opadry™ white, purified talc and water (13.20 L/120,000 tablet batch), stir for 10 minutes, check weight, add more water if necessary to get required weight, filter suspension through 100# nylon cloth.

Film Coating

1. Coat the compressed tablets in a coating pan with coating suspension.
2. Polish the coated tablets in a coating pan with purified talc

The tablets satisfy the disintegration time requirements of the Ph.Eur. and USP.

Example 5

The combination of Example 3 was tested in a pilot study using a dental pain model i.e. patients were given either 2 Paracetamol 500mg + Ibuprofen 150mg tablets four times a day or 2 150mg tablets containing ibuprofen alone four times a day for analgesia following wisdom tooth extraction under local anaesthesia. Pain scores at rest and on activity were measured by visual analogue scales which were used to derive an area-under-the curve (AUC) pain score. A lower AUC represents better pain relief.

The results shown in Table 1 are surprising in that despite limited patient numbers the combination of Paracetamol 500mg + ibuprofen 150mg demonstrated a very clear superiority in pain relief over ibuprofen alone in all parameters.

TABLE 1

Treatment	AUC Pain Score (mm x mins)	
	Rest	Activity
Ibuprofen (N=2)		
Mean	34,105	40,015
Median	34,105	40,015
Minimum	11,335	12,368
Maximum	56,876	67,662
Maxigesic (N=3)		
Mean	9,970	10,053
Median	3,780	3,510
Minimum	0	0
Maximum	26,130	26,650

The present invention allows effective pain relief to be achieved using reduced ibuprofen amounts in combination with paracetamol. Minimisation of potential adverse reactions from high peak amounts of ibuprofen is achieved as a result. The composition allows a pain management regime to be set up that is achievable and effective for an individual,

and which can be provided without prescription.

Example 6

Table 2 below provides a comparison of mean visual analogue pain scores (VAS scores) for ibuprofen only, paracetamol only and ibuprofen + paracetamol compositions in a dental pain model. A lower VAS score is consistent with less pain due to better pain relief. The VAS scores for the ibuprofen only, and the ibuprofen + paracetamol (Maxigesic), compositions have been calculated from the AUC trials as reported in Example 5. Pain scores were calculated as means over the first dose interval rather than AUC values to allow comparison with literature values for paracetamol in the dental pain model.

TABLE 2

Treatment Group	**Mean Pain Score at Rest (over first dose interval)**
Ibuprofen 300 mg qid	28 mm
Maxigesic qid (Paracetamol 1000 mg + Ibuprofen 300 mg)	8 mm
Paracetamol 1000 mg (RA Seymour *et al* 2003)	42 mm (over 4 hours) 46-48 mm (0-30 minutes)

Paracetamol reference: RA Seymour *et al*. An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery. Br Dental J (2003) 194(3), 153-7. Compares pain after dental surgery for 240 minutes after dosing. Patients took paracetamol 1000 mg or aspirin soluble 900 mg.

The effectiveness of the ibuprofen + paracetamol combination (Maxigesic) in comparison to the actives alone, as reflected in VAS score comparison, is clearly seen. This enhanced pain relief effect over the first dose interval is unexpected and offers advantages in pain relief management to the user. The observed increase in effective pain relief of the combination over the first pain interval, at reduced ibuprofen amounts, offers pain management options for users when treating intermittent pain with a single dose administration. The enhanced effect reinforces the results observed for the daily administration (4 times a day for maximum OTC administration) and shows that, at the ratios of actives used in the treatment (ie between about 47.5:12.5 to about 50:15;

preferably about 50:15; paracetamol:ibuprofen), a synergistic pain relief effect is occurring.

Although this invention has been described by way of example only and with reference to possible embodiments thereof it is to be understood that modifications or improvements may be made without departing from the scope or spirit of the invention as defined in the attached claims.

CLAIMS:

1. A combination pharmaceutical composition for the treatment of pain including about 125 mg to about 150 mg ibuprofen and about 475 mg to about 500 mg paracetamol.

2. The combination composition according to claim 1 wherein the ratio of paracetamol:ibuprofen is about 50:15.

3. The combination composition according to claim 1 wherein the composition has 125-150 mg ibuprofen and 475-500 mg paracetamol.

4. The combination composition according to any one of claims 1 and 3 wherein the ibuprofen is present as a salt, ester or complexed form in an amount suitable to deliver about 125 mg to about 150 mg ibuprofen.

5. The combination composition according to any one of claims 1 to 4, wherein the composition has 150 mg ibuprofen and 500 mg paracetamol.

6. The combination composition according to any one of claims 1 to 5 wherein the composition is suitable to be administered as two unit doses four times a day.

7. The combination composition according to any one of claims 1 to 6 in the form of a tablet or capsule.

8. The use of about 475 mg to about 500 mg paracetamol and about 125 mg to about 150 mg ibuprofen in the manufacture of a medicament to be administered in two unit doses four times a day for the treatment of pain.

9. The use according to claim 8 wherein the ratio of paracetamol: ibuprofen is about 50:15.

10. The use according to claim 8 wherein the ibuprofen is present as a salt, ester or complexed form in an amount suitable to deliver about 125 mg to about 150 mg ibuprofen.

11. The use according to claim 8 or 10, wherein the composition has 125-150 mg ibuprofen and 475-500 mg paracetamol per unit dose.

12. The use according to any one of claims 8 to 11, wherein 150 mg ibuprofen and 500 mg paracetamol is used per unit dose.

13. A pharmaceutical pack including tablets or capsules, each tablet or capsule including a pharmaceutical composition according to any one of claims 1 to 7, the pack including instructions to a user to take two tablets or capsules no more than 4 times a day.

14. The pharmaceutical pack according to claim 13, wherein the pack includes an even number of tablets or capsules.

15. The pharmaceutical pack according to claim 13 or 14 wherein the pack includes at least 8 tablets or capsules.

16. A pharmaceutical composition for the treatment of pain, the composition including paracetamol and ibuprofen in a ratio range of from 47.5:12.5 to 50:15, the composition formed in discrete dosage units whereby the taking of one or more complete dosage units delivers substantially 250-300 mg ibuprofen and substantially 950-1,000 mg paracetamol to provide synergistic pain relief.

17. A pharmaceutical composition according to claim 16, presented with instructions to the effect that a user should take the number of dosage units necessary to deliver the 250-300 mg ibuprofen and 950-1,000 mg paracetamol.

18. The pharmaceutical composition according to claim 16 or 17 wherein the ratio is 50:15.

19. The pharmaceutical composition according to claim 16, 17 or 18, wherein the composition includes a salt, ester or complexed form of ibuprofen in an amount sufficient to deliver ibuprofen to the user within the stated ratio range or at the stated ratio.

20. The pharmaceutical composition according to any one of claims 16 to 19 wherein each dosage unit is a tablet or capsule.

21. The pharmaceutical composition according to any one of claims 16 to 20 wherein the composition is suitable for administration four times a day.

22. A pharmaceutical combination composition suitable for the treatment of pain, the composition including paracetamol and ibuprofen in a ratio range of from 47.5:12.5 to 50:15 suitable for providing synergistic pain relief.

23. A pharmaceutical composition according to claim 22, wherein paracetamol and ibuprofen are the only active ingredients.

24. A pharmaceutical composition according to claim 22 or 23, wherein the ratio of paracetamol to ibuprofen is 50:15.

25. A pharmaceutical composition according to claim 22, 23 or 24, wherein the composition includes a salt, ester or complexed form of ibuprofen in an amount sufficient to deliver ibuprofen to the user within the stated ratio range or at the stated ratio.

26. A pharmaceutical composition according to any one of claims 22 to 25, wherein the composition comprises a tablet or capsule.

27. A pharmaceutical composition according to any one of claims 22 to 26 suitable to be administered four times a day.

28. A pharmaceutical composition for the treatment of pain, the composition including paracetamol and ibuprofen formed in discrete dosage units whereby the taking of one or more complete dosage units delivers substantially 250-300 mg ibuprofen and substantially 950-1,000 mg paracetamol to provide synergistic pain relief, presented with instructions to the effect that a user should take the number of dosage units necessary to deliver the 250-300 mg ibuprofen and 950-1,000 mg paracetamol.