"Pharmaceutical composition for injection based on paracetamol"

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The present invention relates to a pharmaceutical composition for injection based on paracetamol.

In particular, in a first aspect, the present invention relates to a pharmaceutical composition for injection comprising paracetamol, a low molecular weight alcohol and a polyethylene glycol.

It has been known practice for a long time to use paracetamol as an analgesic and an antipyretic.

By virtue of its very satisfactory tolerability, paracetamol is, in some cases, even preferred to NSAIDs (non-steroidal anti-inflammatory drugs) and, in particular, to aspirin.

Indeed paracetamol, like aspirin, exhibits its activity by inhibiting the synthesis of the prostaglandins produced by cyclooxygenase. However, unlike most NSAIDs, its inhibition is exerted almost exclusively on the brain and, to a much smaller level, on the peripheral tissues (stomach, kidneys and blood platelets). For this reason its use does not produce the side effects typical of NSAIDs such as, for example, heartburn and gastric lesions with possible loss of blood.

The only possible complication associated with its use is liver cytolysis, although this occurs only in the case of an overdose (Flower R.J., Vane J.R., "Nature", 240, 410-411, 1972; Lanz R., Poster P., "J. Pharmacol", 130, 105-109, 1986,; Black M., "Annual Reviews of Medicine", 35, 577-593, 1984).

It is also known that paracetamol is very slightly soluble in water ("The Merck Index", 12th edition, page 9, No. 45, 1996).

This characteristic represents a major obstacle to its administration by injection. Moreover, in the presence of water, paracetamol undergoes degradations which also give rise to pink- to brown-coloured derivatives. The most common types of degradation are hydrolysis to p-

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aminophenol and/or oxidation by, for example, oxygen dissolved in water. This second reaction appears to be responsible for the formation of the said derivatives.

Patent application WO 98/05314 attempts to overcome the above-mentioned drawbacks by means of a composition containing a solution of paracetamol in an aqueous solvent in combination with a buffer having a pH of from 4 to 8 and an agent capable of capturing free radicals. In addition, the above-mentioned document recommends removing any oxygen which may be present in the said solvent by means of flushing with a water-insoluble inert gas.

Among the pharmaceutical compositions given as examples in the above-mentioned patent application, those capable of dissolving the majority of paracetamol contain, besides water, PEG-400 and propylene glycol.

In particular, according to the above-mentioned document, a solution consisting of 30% propylene glycol, 40% PEG-400 and 30% water is able to dissolve up to about 200 mg/ml of paracetamol at 20°C (WO 98/05314, page 9, lines 7-12).

However, this solvent mixture is very viscous (see Comparative Example 1) and is thus unsuitable for administration by injection.

There is thus still a great need for a paracetamol-based pharmaceutical composition which, besides containing therapeutic levels of paracetamol, can be injected easily and does not give rise to weals.

It has now been found, surprisingly, that low molecular weight alcohols promote the dissolution of paracetamol in a polyethylene glycol.

As can be seen in the examples, the amount of paracetamol dissolved by a mixture of a low molecular weight alcohol and of a polyethylene glycol (Example 1) is greater than that dissolved, for an

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equal volume, by the low molecular weight alcohol and polyethylene glycol alone (Comparative Examples 2 and 3).

This is all the more surprising if one considers that, according to the above-mentioned patent application WO 98/05314, the addition of ethanol does not increase the solubility of paracetamol in a polyethylene glycol (page 11, last line).

In a first aspect, the present invention provides a pharmaceutical composition, characterized in that

a) it comprises

i) paracetamol,

ii) from 1 to 4 parts by volume of a low molecular weight alcohol for each part by weight of paracetamol, and

iii) from 1 to 5 parts by volume of a polyethylene glycol for each part by weight of paracetamol,

b) it is substantially anhydrous, and

c) it forms a clear solution for injection with 4-10 parts by volume of water for each part by weight of paracetamol.

In a second aspect, the present invention relates to a pharmaceutical composition consisting of a clear solution for injection, characterized in that it comprises paracetamol and, for each part by weight of paracetamol,

i) from 1 to 4 parts by volume of a low molecular weight alcohol,

ii) from 1 to 5 parts by volume of a polyethylene glycol, and

iii) from 4 to 10 parts by volume of water.

In the description and in the claims which follow, the term "substantially anhydrous" is understood to mean a composition containing less than 0.1% by weight of water.

Preferably, for each part by weight of paracetamol, the parts by volume of low molecular weight alcohol are between 1.5 and 3, and even more preferably between 2 and 2.5.

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In turn, for each part by weight of paracetamol, the parts by volume of polyethylene glycol are preferably between 1.5 and 4, and even more preferably between 2 and 3.

Lastly, the parts by volume of water for each part by weight of paracetamol are preferably between 5 and 8.

Preferably, the low molecular weight alcohol contains from 1 to 4 carbon atoms. A typical example of a preferred low molecular weight alcohol is absolute ethanol.

Preferably, the polyethylene glycol is chosen from the group comprising PEG-200, PEG-300, PEG-400, PEG-1,000, PEG-1,540, PEG-4,000 and PEG-8,000.

Typically, the polyethylene glycol is PEG-400.

The organic paracetamol solution according to the first aspect of the present invention is very stable, since the paracetamol does not precipitate out or undergo degradations, even after sterilization at 121°C for 30 minutes followed by storage at 30°C under constant illumination at 11,000 lux for at least one month. This stability is found even in the absence of preserving agents, stabilizers, surfactants, buffers, agents for capturing free radicals and/or antioxidants.

By addition of water and simple beating by hand, it then readily forms a clear aqueous solution, in accordance with the second aspect of the present invention.

Typically, the clear aqueous solution for injection thus obtained has a viscosity of between 2 and 10 cp. Preferably, the amount of low molecular weight alcohol, polyethylene glycol and water is adjusted such that the said viscosity is between 4 and 7 cp.

According to another aspect, the present invention thus relates to a clear pharmaceutical solution for injection, characterized in that it comprises ethanol, PEG-400, water and from 10 to 25% (w/v) of paracetamol and in that the amounts of ethanol, of PEG-400 and of

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water are adjusted such that the viscosity of the said solution is between 4 and 7 cp.

This solution also has the further advantage of not containing any preserving agents, stabilizers, surfactants, buffers, agents for capturing free radicals and/or antioxidants.

The pharmaceutical composition of the present invention can be prepared according to techniques that are well known in pharmaceutical chemistry, comprising mixing, dissolution, sterilization and the like.

The present invention will be further described by the following examples, which are given for purely illustrative purposes and should not be interpreted in a limiting sense.

EXAMPLE 1

Organic paracetamol solutions

Solution A

Component	Amount
Paracetamol	50 g
Absolute ethanol	100 ml
PEG-400	100 ml

The absolute ethanol and the PEG-400 were added to the paracetamol at room temperature. This mixture was then stirred until the paracetamol had completely dissolved (about 30 minutes).

Some of the solution thus obtained was divided between 60 5-ml bottles in a proportion of 3 ml per bottle.

On some samples, freshly prepared (time 0), the following controls were carried out:

- paracetamol titre: HPLC (mg/gl)
- p-aminophenol titre: HPLC (mg/ml) and
- check for any coloured degradation products: spectrophotometry at 475 nm

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and the following results were obtained:

- average paracetamol titre: 214.1
- p-aminophenol: absent
- average absorption:0.0075

The above-mentioned samples were then stored for one month under the following conditions:

- at 4°C (Samples A),
- at room temperature (Samples B)
- at 30°C in a room under an illumination of 11,000 lux (Samples C).

The results obtained are given in Table 1 below.

Table 1

Sample	Paracetamol titre (mg/ml)	p-aminophenol titre (mg/ml)	Absorption 475 nm
A	213.0	absent	0.0083
B	218.0	absent	0.0082
C	217.0	absent	0.0250

Other samples (Samples D), freshly prepared (time 0), showed the following characteristics:

- paracetamol titre: 204.0
- p-aminophenol: absent
- absorption: 0.0062

They were stored for one month at 30°C in a room under an illumination of 11,000 lux and showed the following characteristics:

- paracetamol titre: 203.0
- p-aminophenol: absent
- absorption: 0.0162

Lastly, another group of samples (Samples E), freshly prepared (time 0) and after sterilization (121°C for 30 minutes), showed the following characteristics:

- paracetamol titre: 202.8

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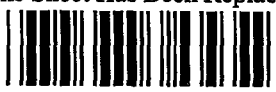

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- p-aminophenol: absent
- absorption: 0.0100

They were stored for one month at 30°C in a room under an illumination of 11,000 lux and showed the following characteristics:

- paracetamol titre: 202.0
- p-aminophenol: absent
- absorption: 0.0104

Solutions B and C

Similar results were obtained with samples having the following compositions:

Solution B

Component	Amount
Paracetamol	50 g
Absolute ethanol	100 ml
PEG-400	150 ml

Solution C

Component	Amount
Paracetamol	80 g
Absolute ethanol	200 ml
PEG-400	200 ml

EXAMPLE 2

Aqueous solution for injection

Solution A (8 ml), prepared as described in Example 1 above, was introduced into a bottle (20 ml). Distilled water for injection (12 ml) was added. The bottle was then shaken manually until a clear solution was obtained (about 10-40 seconds).

The solution thus obtained showed the following physicochemical characteristics:

Appearance:	clear, colourless
Viscosity*:	5.068 cp

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Osmolarity calculated:	529.2 mOsmol/litre
Density**:	1.02600 g/cm^3

* measured with a Carri-Med CSL 50 Rheometer viscosimeter;

** measured with a Mettler Toledo DA-310 M densitometer.

COMPARATIVE EXAMPLE 1

Aqueous solution for injection according to patent application WO 98/05314

Component	Amount
Paracetamol	1,600 mg
Propylene glycol	2.7 ml
PEG-400	3.6 ml
Sodium acetate	20 mg
Reduced glutathione	20 mg
Hydrochloric acid	qs pH 6

The above-mentioned composition, prepared as described in patent application WO 98/05314, was introduced into a 15-ml bottle. Distilled water for injections (3.7 ml) was added thereto and the mixture was left stirring until a clear solution was obtained (30 minutes).

The solution thus obtained showed the following physicochemical characteristics:

Appearance:	clear, colourless
Viscosity*:	37.40 cp
Osmolarity calculated:	1,088.8 mOsmol/litre
Density**:	1.09685 g/cm^3

By working in a similar manner to that described above, a second composition was prepared containing 800 mg of paracetamol instead of 1,600 mg.

This solution showed the following physicochemical characteristics:

Appearance:	clear, colourless
Viscosity*:	26.34 cp

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Osmolarity calculated:	560 mOsmol/litre
Density**:	1.09433 g/cm^3

COMPARATIVE EXAMPLE 2

Alcohol-free organic paracetamol solution

Component	Amount
Paracetamol	5 g
PEG-400	10 ml

The PEG-400 was added to the paracetamol at room temperature. This mixture was then kept stirring at room temperature for 2 hours.

4 ml of the above-mentioned suspension were centrifuged in an Eppendorf tube at 25°C for 30 minutes at a speed of 7,000 rpm.

HPLC analysis of the supernatant thus obtained showed that the solubility of the paracetamol was 18-19%.

COMPARATIVE EXAMPLE 3

PEG-free organic paracetamol solution

Component	Amount
Paracetamol	5 g
Absolute ethanol	10 ml

The absolute ethanol was added to the paracetamol at room temperature. This mixture was then kept stirring at room temperature for 2 hours.

4 ml of the above-mentioned suspension were centrifuged in an Eppendorf tube at 4°C for 40 minutes at a speed of 7,000 rpm.

HPLC analysis of the supernatant thus obtained showed that the solubility of the paracetamol was 9-10%.

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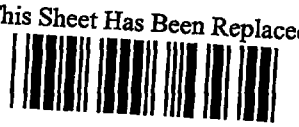

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CLAIMS

1. Pharmaceutical composition, characterized in that
   a) it comprises
      i) paracetamol,
      ii) from 1 to 4 parts by volume of a low molecular weight alcohol for each part by weight of paracetamol, and
      iii) from 1 to 5 parts by volume of a polyethylene glycol for each part by weight of paracetamol,
   b) it is substantially anhydrous, and
   c) it forms a clear solution for injection with 4-10 parts by volume of water for each part by weight of paracetamol.
2. Pharmaceutical composition consisting of a clear solution for injection, characterized in that it comprises paracetamol and, for each part by weight of paracetamol,
   i) from 1 to 4 parts by volume of a low molecular weight alcohol,
   ii) from 1 to 5 parts by volume of a polyethylene glycol, and
   iii) from 4 to 10 parts by volume of water.
3. Pharmaceutical composition according to claim 1 or 2, characterized in that for each part by weight of paracetamol, the parts by volume of low molecular weight alcohol are between 1.5 and 3.
4. Pharmaceutical composition according to claim 3, characterized in that for each part by weight of paracetamol, the parts by volume of low molecular weight alcohol are between 2 and 2.5.
5. Pharmaceutical composition according to claim 1 or 2, characterized in that for each part by weight of paracetamol, the parts by volume of polyethylene glycol are between 1.5 and 4.
6. Pharmaceutical composition according to claim 5, characterized in that for each part by weight of paracetamol, the parts by volume of polyethylene glycol are between 2 and 3.

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7. Pharmaceutical composition according to claim 1 or 2, characterized in that the parts by volume of water for each part by weight of paracetamol are between 5 and 8.
8. Pharmaceutical composition according to claim 1 or 2, characterized in that the low molecular weight alcohol contains from 1 to 4 carbon atoms.
9. Pharmaceutical composition according to claim 8, characterized in that the low molecular weight alcohol is absolute ethanol.
10. Pharmaceutical composition according to claim 1 or 2, characterized in that the polyethylene glycol is chosen from the group comprising PEG-200, PEG-300, PEG-400, PEG-1,000, PEG-1,540, PEG-4,000 and PEG-8,000.
11. Pharmaceutical composition according to claim 10, characterized in that the polyethylene glycol is PEG-400.
12. Clear pharmaceutical solution for injection, characterized in that it comprises ethanol, PEG-400, water and from 10 to 25% (w/v) of paracetamol and in that the amounts of ethanol, of PEG-400 and of water are adjusted such that the viscosity of the said solution is between 4 and 7 cp.

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