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(54) **Title**: INJECTABLE LIQUID FORMULATION OF THE COMBINATION OF TRAMADOL AND PARACETAMOL

(57) **Abstract**: A liquid formulation for intravenous infusion comprising tramadol and paracetamol in a non-deoxygenated aqueous solvent. The formulation has shown to be suitable for intravenous infusion, is stable upon autoclaving with a minimum loss of active principles and a minimum development of undesirable impurities.

INJECTABLE LIQUID FORMULATION OF THE COMBINATION OF TRAMADOL AND PARACETAMOL

BACKGROUND OF THE INVENTION

The treatment of pain is an essential role of the doctors due to the fact that pain is one of the main symptoms of the patients, more particularly in patients after surgery. For the treatment of pain, there is a wide range of analgesics to choose, and the final analgesic elected is normally chosen taking into account its efficacy as well as all the aspects related to its safety and adverse effects. Usually, the treatment is in monotherapy, although in many cases the combination of different drugs that act in different targets facilitates the treatment.

Paracetamol, also known as acetaminophen or N-acetyl-p-aminophenol, is an active ingredient that has been widely used in the last decades in pharmaceutical preparations due to its activity as an analgesic and an antipyretic, which was introduced by Von Mering in 1893. It is further well tolerated by human beings and does not alter the acid-base equilibrium, therefore it is widely used to relive mild to moderate pain both in adults and in children and in the elderly. However, it is poorly soluble in water, and for this reason a number of prior art liquid paracetamol solutions need an additional solubilizing adjuvant such as an alcohol like ethanol. Paracetamol does not become habit-forming when taken for a long time, but may cause other unwanted effects with taken in large doses, including liver damage.

Tramadol ((1R,2R) or (1S, 2S) (dimethylamino)methyl-1-(3-methoxyphenyl) cyclohexanol) belongs to the group of medicines called opioid analgesics (narcotics), acting in the central nervous system to relieve pain. Tramadol is used in the treatment of modere to severe pain. When tramadol is used for a long time, it may become habit-forming, causing mental or physical dependence.

In our experience in the area of pain treatment in hospitals and the information received from the specialists, we have detected the need to develop an intravenous analgesic for the treatment of moderate to severe pain that is not a

morphine derivative due to the risk to use this type of drugs, not only for the addictive action of this component but also because of the long list of adverse reaction this could cause: constipation, nausea, dizziness, vomiting, ...

In the market, combinations of tramadol and paracetamol are present in tablet form. In fact, Mac Neil, the owner of the patent protecting these formulations, granted a licence to Grünenthal, a German pharmaceutical company, that has successfully marketed the tramadol plus paracetamol combinations in tablets (oral administration) but has never marketed so far an intravenous preparation for infusion. However, combinations of tramadol and paracetamol in tablet form usually cannot be used following surgery due to the fact that the patient is not able to swallow oral medicines, and the administration of an analgesic before the effect of the anesthesia vanishes is normally required. Thus, for those cases it is essential to develop an intravenous formulation directed to the combination of tramadol and paracetamol. Although there are presently commercially available intravenous tramadol and intravenous paracetamol as separate solutions, however at this stage there is not available in the market an intravenous solution for infusion containing the combination of both active ingredients.

In the prior art, document WO 93/04675 discloses the combination of tramadol and paracetamol. The experimental tests included in this document have been made in mice, not in humans. Furthermore, the mice are dosed with a combination of paracetamol and tramadol either by oral route or by injection of a solution of the combination of both active substances using distilled water, not water for injection. In addition, the solutions disclosed in this document lack of any of the stabilizing compounds used in the present invention; the only additive used there is Tween 80, a pharmacological dispersant. Thus, it is not apparent from this document whether those formulations could be suitable for intravenous infusion in humans, where these solutions should comply with very strict parameters to be sterile, and moreover is neither apparent whether they could be autoclavable.

In addition, document FR 2 751 875 and its several patent family members such as AU 199739451, disclose methods for obtaining aqueous formulations for paracetamol, optionally including a central nervous system analgesic. However,

the aqueous solvent used in these formulations needs to be bubbled into an inert gas (or, in the case of AU2006203741B2, the solution is alternatively placed under vacuum) in order to substantially eliminate any dissolved oxygen from the solvent. In addition, the formulations disclosed therein require additional components such as anti-radical agents or free radical scavengers. Finally, no experimental examples of solutions comprising both paracetamol and tramadol were included in these documents, and consequently it is not clear how solutions comprising paracetamol and tramadol prepared according to these disclosures could react upon autoclaving.

Also, document CN101147731 discloses formulations containing paracetamol and tramadol. However, all the examples refer to either small-capacity vials (3 mL) or to a freeze-dried (lyophilized) powder, which should be dissolved before administration. Therefore, these compositions are not suitable for infusion but, probably, just for intravenous injection as bolus, because intravenous solution in bolus should have a volume lower than 10 mL to allow the drug to act quickly; therefore these solutions should be administered in 1-2 minutes. On the other hand, intravenous infusion is used when the drug is to be administered in more than 10 min, the volume of these solutions being usually higher than 50 mL (intravenous infusion is the usual administration method for pain control). In addition, no data are provided about any eventual stabilizing compound added to the formulations and, as it is well known, aqueous paracetamol compositions require a stabilizing compound for the paracetamol since otherwise this active ingredient readily degrades in the aqueous medium at the short term. Therefore, the teaching of this document cannot enable the skilled person to prepare stable aqueous formulations of paracetamol plus tramadol that are suitable for infusion.

Finally, EP 2377514 discloses a liquid parenterally deliverable pharmaceutical formulation comprising a tramadol material and paracetamol with different excipients including an alcoholic solvent (ethanol) in addition to water for injection, a buffer, an antioxidant and a chelating agent. The formulations therein disclosed are clearly designed for subcutaneous, intramuscular or direct intravenous injection (bolus), this being evidenced by the fact that the examples contained in the cited document always refer to small volume vials (1 mL or 4 mL), ampoules

or soft bags. Also, the formulations therein disclosed can also contain as an optional ingredient lidocaine, a local anesthesic, which also completely discards their use for intravenous administration. Finally, even though in this document nothing is said about the sterilization method to be used in those formulations, however autoclaving is not possible, since the ethanol added as a necessary component to those formulations is totally incompatible with the temperatures needed for autoclaving (110 – 130ºC). This has been demonstrated in experimental tests carried out by the applicant, which have shown that, because of the presence of an alcohol in their composition, these formulations explode when subjected to the autoclaving conditions.

The present invention is thus directed to combinations of tramadol and paracetamol in different proportions, combinations that are suitable to be administered by intravenous infusion and that are stable upon autoclaving, i.e, they can be successfully sterilised by autoclaving with a minimal loss of active principle and development of undesirable impurities.

SUMMARY

Accordingly, the problem to be solved by the present invention is to provide a stable pharmaceutical composition injectable aqueous formulations containing a combination of paracetamol and tramadol hydrochloride that is suitable to be administered by infusion in the treatment of moderate to acute pain, that allows thermal sterilization by autoclaving with minimal loss of content of the active ingredients and minimal production of impurities and with other parameters of pharmaceutical interest remaining within the acceptable limits described in the pharmacopoeia after the autoclaving process. The method used to manufacture this composition does not include deoxygenation by bubbling with inert gas or placing vacuum protecting resorption of oxygen.

The solution is based on the fact that the inventors have found that, through the provision of formulations having the features and compositions described below, stable liquid formulations suitable for intravenous infusion and stable upon autoclaving can be obtained. Without wishing to be bound by theory, the inventors

believe that the benefits of the invention are obtained through the combination of the low concentration levels of both active principles (paracetamol and tramadol) with the addition of a stabilizing compound selected among those herein disclosed. Experimental tests carried out by the inventors have shown that, outside of the preferred concentration ranges of both active principles, the solutions tend not to be autoclavable even in the presence of the stabilizer compounds used in the present invention. Conversely, in the absence of a stabilizing compound selected among those herein disclosed, the addition of both active principles in the preferred concentration ranges does not always produce autoclavable solutions. In other words, apparently the stabilizer compounds are only able to effectively stabilize the paracetamol plus tramadol solutions enough to make them safely autoclavable when they are in the low concentration ranges disclosed. This synergy between both factors is surprising and unexpected, and leads to an advantageous technical effect, not hinted or foreseen up to now.

Therefore a first aspect of the invention is related to a liquid formulation for intravenous infusion stable and autoclavable liquid formulation for intravenous infusion comprising tramadol hydrochloride and paracetamol in an aqueous solvent having a pH between 4.0 and 6.0, characterised in that the concentration of tramadol hydrochloride is between 0.075 and 10 mg/mL, the concentration of paracetamol is between 0.65 and 10 mg/mL, and the formulation further comprises a stabilizing compound selected from the group consisting of cyclic and aliphatic glucitols, organic compounds having a thiol group, sodium edetate (EDTA) and povidone.

DETAILED DESCRIPTION

Thus, the problem to be solved by the present invention is to provide an stable liquid formulation based on the combination of tramadol and paracetamol in a aqueous solvent that is suitable to be administered by infusion in the treatment of moderate to acute pain, that allows thermal sterilization by autoclaving with minimal loss of content of the active ingredients and minimal production of impurities. These solutions, during their manufacturing process, have not been de-oxigenated or bubbled out with an inert gas.

Stability of mentioned above aqueous solution depends of the choice of the different components of the formulation, such as the pH and the sterilization process, among others variables. Stability of this aqueous solution is achieved by adding different stabilizing agents that provide different protection of paracetamol against oxidation; such agents are selected from the group of reducing sugars such us glucose, manitol or hydroxyl ethyl starch; thiol derivatives or other stabilizing agents such as EDTA or povidone. Moreover, the formulations prepared according to the invention do not need the presence of sodium metabisulfite or other sulfite derivatives as antioxidants, as in EP 2377514 A2, which additives, as it is well known, can induce undesirable bronchospams in patients.

Parenteral solutions to be administered in humans should have a pH compatible with blood. The buffer used in the compositions according to the invention is preferably a buffer able to adjust the pH of the compositions to a value between 4 and 6. Preferred buffers are based on citrates, acetates or phosphates salts, and the final pH adjustment is made with hydrochloric acid or sodium hydroxide as required. Isotonicity of the preparation is achieved by adding an appropriate quantity of an isotonizing agent where the most preferred are sodium chloride or glucose.

The liquid pharmaceutical compositions described in this invention are intended for injection, thus have to be sterile. The sterility on the composition described here is achieved by heat treatment such as sterilization and the resulting solution containing the different components is thermally stable.

Throughout the present specification, "autoclaving" means any thermal method that makes sterilization of the formulation possible, and in particular a procedure during which the formulations are submitted to a temperature between 110 and 130°C for a time of 2 to 190 minutes, and more particularly to a temperature between 120 and 125°C for a time of 15 to 20 minutes.

Also throughout the present specification, it will be understood that a solution for injection is sterilizable by heat or "autoclavable" when, after undergoing an autoclaving procedure according to the preceding paragraph, its content in tramadol and paracetamol is at least 95% of the initial respective tramadol and paracetamol contents added to the solution.

On the other hand, the liquid pharmaceutical compositions according to the invention are preferably compositions with combination of tramadol hydrochloride and paracetamol where the paracetamol content of the solution may range from 0.65 mg/mL to 10 mg/mL and the preferred tramadol concentration may range from 0.075 mg/mL to 10 mg/mL. More preferably, the paracetamol content may range from 3.25 mg/mL to 8 mg/mL, even more preferably from 5 to 7 mg/mL, and most preferably about 6.5 mg/mL. In the case of tramadol hydrochloride, its concentration may range from 0.075 to 10 mg/mL; more preferably its content may range from 0.375 mg/mL to 1 mg/mL; even more preferably from 0.5 to 0.85 mg/mL, and most preferably around 0.75 mg/mL.

Preferred tramadol salts are all its pharmaceutical acceptable salts, more preferably its hydrocloride salt. The stabilizing agent is preferably selected from aliphatic or cyclic glucitols, more preferably glucose or manitol; organic compounds having a thiol group, more preferably cysteine; or others like povidone, hydroxyethylstarch or sodium edetate.

Further embodiments are contained in the dependent claims.

EXAMPLES

In order to investigate the stability of different compositions of the liquid pharmaceutical formulation according to the invention, we have run different experiments with variable compositions. All the experiments have been carried out without any previous deoxygenation of the solvent media and therefore the solvent contains the naturally dissolved oxygen. Then, the compositions were subjected to wet heat sterilization by autoclaving, which is the safest currently admitted process to sterilize solutions for injection. Thus, in the present

experiments the solutions were autoclaved at 121°C for 15 minutes, as specified in the European Pharmacopoeia for this process. In parallel, a comparative study was done with all the solutions before and after autoclaving. In those studies the content of both active ingredients, the content of degradation-related substances of both active ingredients, subvisible particles, visual appearance of the solution and pH both before and after the autoclaving process were investigated.

The following formulations were prepared. In each case, the osmolality was adjusted to 300 mOsmol/kg with an isotonizing agent, if required.

1. Formulation A containing tramadol and paracetamol using glucose as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), 3.3 g glucose monohydrate were added and the solution was buffered with citrate-acetate buffer. Then, 75 mg of tramadol hydrochloride were added, and the final pH was adjusted using hydrochloric acid or sodium hydroxide as required to a final pH= 4.90-5.30, adjusting the volume to 100 mL using water for injection. The composition of formula A is described in the table below.

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg
Tramadol HCl anhydrous	75 mg
Excipients	
Glucose monohydrate	3.3 g
Acetic acid glacial	0.095 mL
Sodium acetate trihydrate	53.5 mg
Sodium citrate dihydrate	0.3 g
HCl or NaOH q.s.	pH = 4.90 - 5.30
Water for injection in bulk q.s.	100 mL

2. Formulation B containing tramadol and paracetamol using manitol and cysteine as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), cysteine HCl 16.2 mg, and manitol 2.5 g (or q.s. for isotonicity) buffered with phosphate buffer, 75 mg of tramadol hydrochloride were added and the volume was completed to 100 mL using water for injection, the final pH being adjusted to a value between 4.90-5.30 using hydrochloric acid or sodium hydroxide as required. The composition of formula B is described in the table below:

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg
Tramadol HCl anhydrous	75 mg
Excipients	
Manitol	2.5 g or q.s. for isotonicity
Dibasic sodium phosphate	6.7 mg
Cysteine HCl	16.2 mg
HCl or NaOH q.s.	pH = 4.90 - 5.30
Water for injection in bulk q.s.	100 mL

3. Formulation C containing tramadol and paracetamol using manitol and povidone as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), cysteine HCl 16.2 mg, povidone 65 mg and manitol 868 mg or q.s. for isotonicity, buffered with phosphate buffer, 75 mg of tramadol hydrochloride were added and the volume was completed to 100 mL using water for injection, the final pH being adjusted to a value between 4.90-5.30 using hydrochloric acid

or sodium hydroxide as required. The composition of formula C is described in the table below

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg
Tramadol HCl anhydrous	75 mg
Excipients	
Manitol	868 mg or q.s. for isotonicity
Cysteine HCl	16.2 mg
Sodium dihydrogenphosphate monohydrate	8.5 mg
Povidone	65 mg
Sodium bicarbonate q.s.	pH = 4.90 - 5.30
Citric acid q.s.	pH = 4.90 - 5.30
Water for injection in bulk q.s.	100 mL

4. Formulation D containing tramadol and paracetamol using sodium chloride and EDTA as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), EDTA 6.5 mg and sodium chloride (q.s. for isotonicity) buffered with acetate buffer, 75 mg of tramadol hydrochloride were added and the volume was completed to 100 mL using water for injection, the final pH being adjusted to a value between 5.40 – 5.80 using hydrochloric acid or sodium hydroxide as required. The composition of formula D is described in the table below:

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg

Tramadol HCl anhydrous	75 mg
Excipients	
Sodium chloride	400 mg or q.s. for isotonicity
Sodium acetate trihydrate	53.5 mg
EDTA	6.5 mg
HCl or NaOH q.s.	pH = 5.40 – 5.80
Water for injection in bulk q.s.	100 mL

5. Formulation E containing tramadol and paracetamol using manitol and sodium metabisulfite as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), sodium metabisulfite 6.5 mg and manitol 2.1 g or q.s for isotonicity, buffered with citrate-acetate buffer, 75 mg of tramadol hydrochloride were added and the volume was completed to 100 mL using water for injection, the final pH being adjusted to a value between 5.40 – 5.80 using hydrochloric acid or sodium hydroxide as required. The composition of formula E is described in the table below:

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg
Tramadol HCl anhydrous	75 mg
Excipients	
Manitol	2.1 g or q.s. for isotonicity
Sodium metabisulfite	6.5 mg
Sodium acetate trihydrate	34.8 mg
Sodium citrate dihydrate	195 mg

HCl or NaOH q.s.	pH = 5.40 – 5.80
Water for injection in bulk q.s.	100 mL

6. Formulation F containing tramadol and paracetamol using manitol and hydroxyethylstarch as stabilizing agent:

To a 65 mL aqueous solution containing paracetamol (650 mg, 10 mg/mL paracetamol), hydroxyethylstarch 325 mg and manitol 2.0 g or q.s. for isotonicity buffered with citrate-acetate buffer, 75 mg of tramadol hydrochloride were added and the volume was completed to 100 mL using water for injection, the final pH being adjusted to a value between 5.30 – 5.80 using acetic acid as required. The composition of formula F is described in the table below:

Name	**Calculated content (100 mL)**
Active substance	
Paracetamol anhydrous	650 mg
Tramadol HCl anhydrous	75 mg
Excipients	
Manitol	2.0 g or q.s. for isotonicity
Hydroxyethylstarch	325 mg
Sodium acetate trihydrate	195 mg
Sodium citrate dihydrate	195 mg
Acetic acid q.s.	pH = 5.30 – 5.80
Water for injection in bulk q.s.	100 mL

FORMULATION STUDIES

A comparative study was done in parallel involving all the above solutions and stabilizing agents before autoclaving, after autoclaving and after accelerated degradation tests for 1 and 2 months at 40ºC and 20% relative humidity. In those

studies the content of the active ingredients, the content of related substances of the active ingredients, subvisible particles, visual appearance of the solution and pH were investigated before and after autoclaving.

1) Investigation of the content of active substances in the tested formulations before and after autoclaving:

As can be easily understood, for a pharmaceutical composition for injection the content of active substances after autoclaving is an essential parameter. For the present purposes, the minimum acceptable content of tramadol and paracetamol after autoclaving has been considered to be at least 95% of the initial active substance content added to the solution.

		Formulation A (glucose)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	99.2 %	100.0%	102.7%	101.4%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 mL	100.5 %	98.7 %	100.2 %	102.5 %

		Formulation B (manitol and cysteine)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	99.1 %	100.0 %	101.6%	99.7%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 mL	100.2 %	100.4 %	100.2%	101.7%

		Formulation C (manitol and povidone)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	98.8 %	98.8 %	102.2%	100.7%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 Ml	99.4%	97.6 %	99.5%	101.1%

		Formulation D (EDTA)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	99.8%	98.5%	103.0%	101.0%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 mL	101.3%	98.1%	100.7%	102.4%

		Formulation E (manitol and sodium metabisulfite)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	99.8%	99.1%	103.1%	101.1%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 mL	100.8%	97.0 %	98.9%	98.3%

		Formulation F (manitol and hydroxyethylstarch)			
Active ingredient	**Specifications**	Before autoclaving	After autoclaving	After 1 month at 40ºC	After 2 months at 40ºC
Paracetamol content	95.0 – 105.0 % of 650 mg/100 mL	99.6%	99.7%	101.9%	101.6%
Tramadol·HCl content	95.0 – 105.0 % of 75 mg/ 100 mL	99.9%	97.4%	98.4%	101.5%

After autoclaving, the content of tramadol and paracetamol remaining in the formulations was determined. In all cases the content of both active substances is higher than the limit (>95%) established for the purpose.

2) Investigation of the content of degradation related substances in the test formulations before and after autoclaving:

The results obtained from the various formulations are shown in the following table. In this table, the degradation-related substances of both active principles has been indicated in those cases when said impurity has been identified according to European Pharmacopoeia, or alternatively they have been referred to as unknown impurities in those cases where they have not been identified.

		Formulation A		**Formulation B**		**Formulation C**	
Related substances:	**Specification**	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
5-HMF	< 0.05%	N.D.	0.001 %	N.D.	N.D.	N.D.	N.D.
Impurity K (4-AP)	< 0.01%	N.D.	< 0.001 %	<0.001 %	0.01 %	N.D.	N.D.
Impurity A of Tramadol	< 0.2%	0.04 %	0.04 %	0.04 %	0.04 %	0.05 %	< 0.03 %
Impurity B of Tramadol	< 0.2%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Impurity C of Tramadol	< 0.2%	0.007 %	0.006 %	0.007 %	0.006 %	< 0.005 %	< 0.005 %
Impurity D of Tramadol	< 0.2%	< 0.02 %	< 0.02 %	< 0.02 %	< 0.02 %	N.D.	< 0.02 %
Unknown impurities from Paracetamol	< 0.1%	< 0.02 %	< 0.02 %	< 0.02 %	< 0.02 %	< 0.02 %	< 0.02 %
Unknown impurities from Tramadol	< 0.2%	N.D.	N.D.	N.D.	< 0.04 %	N.D.	< 0.04 %

Total impurities from Paracetamol	< 0.5%	< 0.02 %	< 0.02 %	< 0.02 %	0.01 %	< 0.02 %	< 0.02 %
Total impurities from Tramadol	< 0.8%	0.05 %	0.05 %	0.05 %	0.05 %	0.05 %	< 0.04 %

		Formulation D		**Formulation E**		**Formulation F**	
Related substances:	**Specifi-cation**	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
5-HMF	< 0.05%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Impurity K (4-AP)	< 0.01%	N.D.	0.002 %	N.D.	N.D.	N.D.	< 0.001 %
Impurity A of Tramadol	< 0.2%	0.03 %	0.04 %	0.04 %	0.04 %	0.04 %	0.04 %
Impurity B of Tramadol	< 0.2%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Impurity C of Tramadol	< 0.2%	0.005 %	0.01 %	< 0.005 %	< 0.005 %	< 0.004 %	0.005 %
Impurity D of Tramadol	< 0.2%	< 0.02 %	N.D.	N.D.	< 0.02 %	< 0.02 %	N.D.
Unknown impurities from Paracetamol	< 0.1%	< 0.02 %	0.03 %	< 0.02 %	< 0.02 %	< 0.02 %	0.04 %
Unknown impurities from Tramadol	< 0.2%	N.D.	N.D.	N.D.	< 0.04 %	N.D.	N.D.
Total impurities from Paracetamol	< 0.5%	< 0.02 %	0.03 %	< 0.02 %	< 0.02 %	< 0.02 %	0.04 %
Total impurities from Tramadol	< 0.8%	0.04 %	0.05 %	0.04 %	0.04 %	0.04 %	0.05 %

The data shown in the table demonstrate that the content of individual known and

unknown substances resulting from the degradation of any of the active substances tested are maintained below the limits established by the European Pharmacopoeia after the solutions have been sterilized by heating.

3) Investigation of pH in the test formulations before and after autoclaving

The pH of the test formulations was measured after packaging, either before autoclaving or after autoclaving, to evaluate the change in this parameter caused by said process. The results were as follows:

		Formulation A		**Formulation B**		**Formulation C**	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
pH	4.0 – 6.0	5.3	5.3	5.3	4.3	6.0	5.7

		Formulation D		**Formulation E**		**Formulation F**	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
pH	4.0 – 6.0	5.5	5.5	5.6	5.6	5.5	5.5

On comparing the formulations before autoclaving and autoclaved, it is concluded that there are differences between the samples before and after the autoclaving depending on the formula used: formulation A almost maintain this parameter without modification, however there is a small change in formulations B and C. In all the cases the pH is maintained within the defined limits.

4) Investigation of visual appearance in the test formulations before and after autoclaving

The visual appearance of the solution is a parameter somehow indicative of the degradation of the components of the solution in the sterilization process. Thus, we have decided to include visual appearance as one of the variable in our test.

		Formulation A		Formulation B		Formulation C	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
Appearance	Clear / Colourless	complies	complies	complies	complies	complies	complies

		Formulation D		Formulation E		Formulation F	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
Appearance	Clear / Colourless	complies	complies	complies	complies	complies	complies

As it is shown in the table above, the visual appearance of the samples is maintained in all cases as clear and colourless after autoclaving.

5) Investigation of subvisible particles in the test formulations before and after autoclaving

The sub-visible particles in the formulations studied were also measured before and after autoclaving. This investigation was performed by direct measurement of this parameter in the sub-visible particle counter. The specification according to the European Pharmacopoeia is as shown in the table below.

The results obtained in the formulations tested were as follows:

		Formulation A		Formulation B		Formulation C	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
Subvisible particles	< 6000 part./ bag ≥ 10μm	120 part./ bag	187 part./ bag	3153 part./ bag	93 part./ bag	627 part./ bag	93 part./ bag
	< 600 part./ bag ≥ 25μm	13 part./ bag	27 part./ bag	60 part./ bag	13 part./ bag	80 part./ bag	27 part./ bag

		Formulation D		Formulation E		Formulation F	
	Specifications	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving	Before autoclaving	After autoclaving
Subvisible particles	< 6000 part./ bag ≥ 10μm	67 part./ bag	100 part./ bag	160 part./ bag	140 part./ bag	67part./ bag	253part./ bag
	< 600 part./ bag ≥ 25μm	13 part./ bag	27 part./ bag	7 part./ bag	40 part./ bag	13 part./ bag	13 part./ bag

In this table it can be observed that the level of sub-visible particles is within the specifications in all the formulations tested, although showing slight differences before and after autoclaving depending on the formulation: in the case of formulation A, the level of subvisible particles is slightly higher after sterilization process. However, in formulations B and C, the effect of the heat sterilization is the opposite, the number of subvisible particles after the process being lower after autoclaving than before the sterilizing process. This probably means that the heat of the process helps to the solubilization of some components of the formulation.

6) Investigation of the concentration range of paracetamol and tramadol according to formulation A after autoclaving

The range of concentrations of both active substances using the excipient composition of formula A was studied. The table below shows the content of tramadol hydrochloride and paracetamol remaining after the autoclaving process, expressed as the percentage of the final content with respect to the initial content ((final concentration/initial concentration) x 100). For the present purposes, the minimum acceptable content of tramadol and paracetamol after autoclaving has been considered to be at least 95% of the initial active substance content added to the solution.

		TRAMADOL·HCl (mg/mL)							
	%Paracetamol / % tramadol	**0.075**	**0.375**	**0.50**	**0.75**	**0.85**	**1.0**	**5**	**10**
PARACETAMOL (mg/mL)	**0.65**	101.5 / 98.5	101.6 / 98.4	–	100.9 / 98.1	–	–	–	100.1 / 97.5
	3.25	100.1 / 97.6	–	–	100.1 / 97.6	–	–	–	100.1 / 97.6
	6.5	100.1 / 97.4	100.1 / 97.3	100.0 / 98.1	100.2 / 98.1	101.0 / 98.1	97.1 / 99.5	101.0 / 98.7	101.1 / 101.1
	10	103.0 / 104.0	100.3 / 97.7	–	100.1 / 100.0	–	–	–	100.8 / 99.8

As it is shown in the table, the content of tramadol hydrochloride and paracetamol are within the set limits after autoclaving for all the concentrations within the tramadol hydrochloride range from 0.075 to 10 mg/mL and the paracetamol range from 0.65 to 10 mg/mL.

Conclusions

The above experimental tests have demonstrated that stable aqueous formulations of paracetamol and tramadol that are suitable for infusion and that can be autoclaved without any noticeable loss in either of both active ingredients can be prepared when the concentration of tramadol hydrochloride is between 0.075 and 10 mg/mL, the concentration of paracetamol is between 0.65 and 10 mg/mL, and the formulation further comprises a stabilizing compound selected from the group consisting of cyclic or aliphatic glucitols, organic compounds having a thiol group, EDTA or povidone. Even though several of the stabilizing compounds tested have previously been used to allegedly stabilize aqueous paracetamol-only formulations, however the presently demonstrated stability of the formulations of the invention in aqueous medium both in relation to paracetamol and to tramadol, as well as their capacity to withstand the autoclaving conditions, could not have been foreseen from the prior art.

CLAIMS

1. A stable and autoclavable liquid formulation for intravenous infusion comprising tramadol hydrochloride and paracetamol in an aqueous solvent having a pH between 4.0 and 6.0, characterised in that the concentration of tramadol hydrochloride is between 0.075 and 10 mg/mL, the concentration of paracetamol is between 0.65 and 10 mg/mL, and the formulation further comprises a stabilizing compound selected from the group consisting of cyclic or aliphatic glucitols, organic compounds having a thiol group, sodium edetate and povidone.

2. Liquid formulation according to claim 1, wherein the cyclic or aliphatic glucitol is glucose.

3. Liquid formulation according to claim 1 wherein the cyclic or aliphatic glucitol is manitol.

4. Liquid formulation according to claim 1 wherein the cyclic or aliphatic glucitol is hydroxyethyl starch.

5. Liquid formulation according to claim 1, wherein the organic compound having a thiol group is cysteine.

6. Liquid formulation according to claim 1, wherein the stabilizing compound is povidone.

7. Liquid formulation according to claim 1, wherein the stabilizing compound is sodium edetate.

8. Liquid formulation according to claim 2 wherein the stabilizing compound is glucose in a concentration between 0.4 m/v and 3.3% m/v.

9. Liquid formulation according to any of the previous claims wherein the concentration of paracetamol is between 3.25 and 8 mg/mL

10. Liquid formulation according to claim 9 wherein the concentration of paracetamol is 6.5 mg/mL.

11. Liquid formulation according to any one of previous claims wherein the concentration of tramadol hydrochloride is between 0.375 and 1 mg/mL.

12. Liquid formulation according to claim 9 wherein the concentration of tramadol hydrochloride is 0.75 mg/mL.

13. Liquid formulation according to any one of the previous claims wherein the formulation is buffered with a buffer composition selected from at least one of the acid form and the ionized form of citric, acetic, phosphoric acids or a mixture of them.

14. Liquid formulation according to claim 11 wherein the solution is buffered with sodium citrate-acetate buffer or phosphate buffer.

15. Liquid formulation according to any one of the preceding claims, further comprising an isotonizing agent in the necessary amount for achieving an osmolality of about 300 mOsm/kg.

16. Liquid formulation according to any one of the previous claims wherein the aqueous solvent is non-deoxygenated.

17. Liquid formulation according to any one of the previous claims wherein the formulation is sterilizable by autoclaving at a temperature between 110ºC and 130ºC for a time between 2 and 190 minutes so that the loss of paracetamol or tramadol after the autoclaving process is less than 5% of each.

18. Liquid formulation according to any one of the previous claims for use in the treatment of moderate to severe pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/074896

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/26 A61K47/48 A61K31/135 A61K31/167
A61P25/04 A61P29/02
ADD.
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)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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1

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