(12) UK Patent Application (19) GB (11) 2482794 (13) A

(43) Date of A Publication 15.02.2012

(21) Application No: 1113974.8

(22) Date of Filing: 15.08.2011

(30) Priority Data:
(31) 1013680 (32) 14.08.2010 (33) GB

(71) Applicant(s):
Chatfield Pharmaceuticals Ltd
(Incorporated in the United Kingdom)
Chatfield Laboratories, KRAMER MEWS, London, SW5 9JL, United Kingdom

(72) Inventor(s):
Montague Cecil Solomon
Biljana Tocili
David Louis Charles Solomon

(74) Agent and/or Address for Service:
Serjeants
25 The Crescent, King Street, LEICESTER, LE1 6RX, United Kingdom

(51) INT CL:
A61K 8/67 (2006.01) ***A61K 8/34*** (2006.01)
A61Q 19/08 (2006.01)

(56) Documents Cited:
EP 0729745 A1 **WO 2002/019972 A2**
US 6361783 B2 **US 6087393 A1**
US 20070172436 A1 **US 20060263399 A1**

(58) Field of Search:
INT CL **A61K, A61Q**
Other: **CAS ONLINE, EPODOC, WPI**

(54) Title of the Invention: **Stable vitamin c formulations**
Abstract Title: **Formulations comprising vitamin C in glycol carrier**

(57) A method of stabilising L-ascorbic acid from oxidation comprises dissolving the L-ascorbic acid in a glycol carrier in the absence of any other solvent, solubility enhancer or stabilising agent. The glycol carrier is preferably selected from propylene glycol or a mixture of propylene glycol and butylene glycol. The method exemplified involves slowly dissolving dry powdered L-ascorbic acid in constantly stirred propylene glycol, wherein the solution is maintained at room temperature ~20°C until dissolution is complete to provide a solution with 8.0% L-ascorbic acid and 92.0% propylene glycol. The shelf life of such solutions is shown to be over one year. A stabilised solution of L-ascorbic acid in which the L-ascorbic acid is dissolved in a glycol carrier in the absence of any other solvent, solubility enhancer or stabilising agent is also provided.

GB 2482794 A

TITLE

Stable Vitamin C Formulations

DESCRIPTION

Technical Field

The invention relates to formulations containing free ℓ-ascorbic acid (vitamin C) intended to increase the stability and shelf-life of the free vitamin C.

Background of the Invention

Vitamin C is a very valuable health product. It can be taken orally or applied topically to the skin. It is the latter use which is the focus of this invention. Topical application of vitamin C in solution has been found to have a highly beneficial effect on human skin. The generation of collagen and collagenous materials is promoted and the skin is softened. The incidence of wrinkles is reduced, and the overall effect is one which makes the skin appear rejuvenated. Topically applied vitamin C in solution also has the effect of strengthening the skin tissue against UV irradiation, pollution, de-pigmentation and damage by free radicals.

One serious and known problem in the formulation of dermatological compositions containing vitamin C is the basic instability of ℓ-ascorbic acid in solution. Free ℓ-ascorbic acid is very sensitive to light, to heat, to oxygen and to water. Whereas dry powdered ℓ-ascorbic acid can have a stability of up to 3 years, in solution that stability falls to a few weeks at most. Considerable efforts have therefore been made to find a formulation of ℓ-ascorbic acid in solution which has an improved stability. US-B-6087393, for example, discloses a formulation which comprises ℓ-ascorbic acid in solution in a mixed glycol carrier in the presence of other glycols, stabilising agents and solubility

assisting agents. The mixed glycol carrier is said to stabilise the ℓ-ascorbic acid from oxidation, and the preferred carrier is a mixture of propylene glycol and butylene glycol, together with the abovementioned additional stabilisers. US-B-6087393 teaches that using such a mixed glycol carrier, plus other stabilisers, the stability of the solution can be increased so as to provide a shelf life of up to three months. US-B-6087393 provides as a comparison Example a mixture of ℓ-ascorbic acid, propylene glycol and the stabiliser Sepigel 305 (which is a polyacrylamide) but teaches that this comparison Example "did not provide the stability of aesthetics required for a cosmetic product".

The Invention

The invention is based on the surprising discovery that the stability of a solution of ℓ-ascorbic acid in a glycol carrier can be very significantly increased by removing from the composition all other stabilisers. The glycol carrier is preferably a single glycol, such as propylene glycol. Mixed glycol carriers are however included within the scope of the invention. A mixture of propylene glycol and butylene glycol is one such mixed carrier. It is however surprising that the removal from the composition of all of the stabilisers commonly used to prolong the shelf life of vitamin C solutions does have an effect directly opposed to that which would be predicted. The stability of a simple solution in the glycol carrier is in fact significantly improved by the removal of all other stabilisers in the method according to the invention. The useful shelf life can be increased from the mere three months attained as a best scenario case in US-B-6087393 to one year and more.

The glycol used in the formulation of this invention has a function of transporting the ℓ-ascorbic acid to the dermis, where it stimulates the production of collagen. The collagen is combined with elastin in the dermis, and this combination helps to reverse the signs of ageing. The result is reduced fine lines and wrinkles, and an improvement in skin texture.

The following Examples illustrate the invention.

Example 1

Dry powdered ℓ-ascorbic acid obtained as a BP grade was dissolved slowly and carefully in constantly stirred propylene glycol. The propylene glycol was obtained from Sigma. The solution was maintained at room temperature, at ~20°C until dissolution was complete, and was then transferred into a clean dry glass container. The quantities used provided a solution with a composition by weight of 8.0% ℓ-ascorbic acid and 92.0% propylene glycol.

The solution was stored at room temperature for a period of 20 months, during which time the solution was periodically tested to determine the % content of ℓ-ascorbic acid. During the course of the testing, the visual appearance of the solution and the chemical composition were monitored for the presence of any degradation products (typically yellow in appearance).

The stability of the ℓ-ascorbic acid was measured using the standard test as outlined in British Pharmacopoeia, with the amount of ℓ-ascorbic acid expressed as a weight percentage shown in Table 1.

Age of sample	Initial formulation	After 10 months	After 18.5 months	After 20 months
% ℓ-ascorbic acid	8.0%	7.59%	7.35%	7.44%

Table 1

After 20 months, it was noted that the solution remained clear and colourless, and that the chemical stability of the ℓ-ascorbic acid was maintained.

Example 2

Example 1 was repeated but using different proportions of the ℓ-ascorbic acid and propylene glycol. The formulations were prepared in an analogous manner to that of Example 1 and stored under the same conditions. The initial compositions by weight of the solutions are shown in Table 2. Formulations B, D and F additionally contain 1 wt % of the stabiliser Sepigel 305 and were made by the method as taught in US-B-6087393. Those formulations are provided for comparison purposes, are not therefore formulations according to this invention, and are therefore highlighted in Tables 2 and 3 to indicate their comparison nature. No other ingredients, either as solutes, solvents or stabilising agents, were added to the solutions.

Ingredients	Formulation (g w/w)					
	A	B	C	D	E	F
ℓ-ascorbic acid	8.0	8.0	6.5	6.5	5.0	5.0
Propylene glycol	92.0	91.0	93.5	92.5	95.0	94.0
Sepigel 305	0.0	1.0	0.0	1.0	0.0	1.0

Table 2

The formulations were tested over a four month period to determine the % content of ℓ-ascorbic acid. The results of these tests are shown in Table 3. Because formulation A is identical to that of Example 1 above, it is reasonable to assume that the ongoing stability of formulations A, C and E for a period of up to 20 months or even longer will match that of Example 1. On the other hand it is known that the comparison formulations B, D and F which are reproductions of formulations according to US-B-6087393 will have the much shorter shelf life reported in that US Patent, and the results shown in Table 3 illustrate that to be true.

	% ℓ-ascorbic acid in formulation	
Age of sample	Initial formulation	4 months
Formulation A	8.0%	7.04%
Formulation B	8.0%	3.10%
Formulation C	6.5%	6.23%
Formulation D	6.5%	3.86%
Formulation E	5.0%	4.81%
Formulation F	5.0%	2.47%

Table 3

The following was noted at the end of the four month storage period. Formulation A contained a small amount of un-dissolved vitamin C; formulations C and E were clear solutions. Comparison formulations B, D and F are dispersions, and each contains a significantly larger proportion of vitamin C that was unable to dissolve into the solution due to the presence of the Sepigel stabiliser. The vitamin C concentration in formulations A, C and E is significantly higher than compared with the corresponding formulations (B, D and F) that contained the Sepigel. The concentration of vitamin C in formulations A, C and E is constant and shows only a slight reduction over time due to natural degradation of the free ℓ-ascorbic acid, as well as to analytical variations due to the nature of the technique.

CLAIMS

1. A method of stabilising ℓ-ascorbic acid from oxidation by dissolving the ℓ-ascorbic acid in a glycol carrier in the absence of any other solvent, solubility enhancer or stabilising agent.

2. A method according to claim 1, wherein the glycol carrier is propylene glycol alone.

3. A method according to claim 1, wherein the glycol carrier is a mixture of propylene glycol and butylene glycol.

4. A stabilised solution of ℓ-ascorbic acid in which the ℓ-ascorbic acid is dissolved in a glycol carrier in the absence of any other solvent, solubility enhancer or stabilising agent.

5. A stabilised solution according to claim 4, wherein the glycol carrier is propylene glycol alone.

6. A stabilised solution according to claim 4, wherein the glycol carrier is a mixture of propylene glycol and butylene glycol.

7. A stabilised solution according to claim 4, which has a shelf life of over one year.

Application No: GB1113974.8 **Examiner:** Dr Natalie Cole

Claims searched: 1-7 **Date of search:** 3 November 2011

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1, 2, 4, 5, 7	US2007/172436 A1 (ZHANG) See comparative example 1 within paragraphs [0102]-[0104] and comparative example 5 within paragraphs [0114]-[0116]
X	1, 2, 4, 5, 7	EP0729745 A1 (UNILEVER PLC) See whole document especially example 6
X	1, 4, 7	US2006/263399 A1 (YASUNO) See comparative example 1 within table 1
X	1, 4 at least	US6361783 B2 (MOADDEL) See example 4
A	-	US6087393 A1 (MATHUR) See whole document especially abstract and examples
A	-	WO02/19972 A2 (VIVIER PHARAMA INC.) See whole document especially abstract and examples

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61K; A61Q

The following online and other databases have been used in the preparation of this search report

CAS ONLINE, EPODOC, WPI

International Classification:

Subclass	Subgroup	Valid From
A61K	0008/67	01/01/2006
A61K	0008/34	01/01/2006
A61Q	0019/08	01/01/2006