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(51) Int.Cl.⁵ A61K 31/375, A61K 7/42
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(54) **COMPOSITIONS STABLES D'ACIDE ASCORBIQUE**
(54) **STABLE ASCORBIC ACID COMPOSITIONS**

(57) Une composition stable localisée est constituée essentiellement d'au moins environ 1 % du poids d'acide ascorbique L, et de préférence d'environ 3 à 20 % en poids d'acide ascorbique, et avantageusement de 5 à 10 % d'acide ascorbique L dans l'eau et d'un véhicule pour une application localisée. Une telle composition semble permettre une pénétration rapide dans la peau et retarde les dommages causés par la lumière ultraviolette. Toute composition comprenant au moins environ 1 % d'acide ascorbique est supposée avoir des effets bénéfiques, la concentration d'acide ascorbique L étant tout d'abord limitée par sa solubilité dans le système eau/véhicule. Le rapport eau/véhicule est au moins 1:1, et de préférence de 2:1 à 10:1, le pH de la composition ne dépasse pas 3,0 à 3,5, se situant préféablement au maximum aux environs de 2,5.

(57) A stable topical composition consists essentially of at least about 1 wt.% L-ascorbic acid, preferably from about 3 to 20 wt. % L-ascorbic acid, and more preferably about 5 to 10 wt% L-ascorbic acid in water and a carrier for topical application is disclosed. Such a composition appears to allow ready penetration into the skin and retards the damage caused by ultraviolet light. Any composition containing at least about 1 wt. % L-ascorbic acid is expected to have beneficial effects, with the concentration of L-ascorbic acid being primarily limited by its solubility in the water/carrier system. The ratio of water to carrier is at least 1:1, and more preferably from 2:1 to 10:1, and the pH of the composition is no more than 3.0 to 3.5, preferably no more than about 2.5.



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(21) International Application Number: PCT/US90/01968 (22) International Filing Date: 16 April 1990 (16.04.90) (30) Priority data: 339,488 17 April 1989 (17.04.89) US (71) Applicant: DUKE UNIVERSITY [US/US]; 3024 Pickett Street, Durham, NC 27706 (US). (72) Inventors: DARR, Douglas ; Box 632, Helena Moriah Road, Timberlake, NC 27583 (US). PINNELL, Sheldon, R. ; 3060-D Colony Road, Durham, NC 27705 (US). MURAD, Saood ; 934 Lorain Avenue, Durham, NC 27704 (US). (74) Agents: WEST, William, K., Jr. et al.; Cushman, Darby & Cushman, Eleventh Floor, 1615 L Street, N.W., Washington, DC 20036 (US).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: STABLE ASCORBIC ACID COMPOSITIONS (57) Abstract A stable topical composition consists essentially of at least about 1 wt.% L-ascorbic acid, preferably from about 3 to 20 wt.% L-ascorbic acid, and more preferably about 5 to 10 wt. % L-ascorbic acid in water and a carrier for topical application is disclosed. Such a composition appears to allow ready penetration into the skin and retards the damage caused by ultraviolet light. Any composition containing at least about 1 wt. % L-ascorbic acid is expected to have beneficial effects, with the concentration of L-ascorbic acid being primarily limited by its solubility in the water/carrier system. The ratio of water to carrier is at least 1:1, and more preferably from 2:1 to 10:1, and the pH of the composition is no more than 3.0 to 3.5, preferably no more than about 2.5.		

STABLE ASCORBIC ACID COMPOSITIONS

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Background of the Invention

The present invention relates to stable topical compositions which contain L-ascorbic acid and which prevent ultraviolet damage to skin. More particularly, it relates to topical compositions containing L-ascorbic acid (vitamin C) which are stabilized in aqueous solutions by providing a concentration of L-ascorbic acid above about 1% (w/v) and maintaining the pH below about 3.5.

Considerable effort has been expended to find ways to prevent adverse changes in the skin brought about by ultraviolet (UV) exposure. Preventative approaches include physically blocking or absorbing the UV radiation before it can enter the skin. This technique is effective but is cumbersome because these prior art sunblockers or absorbers usually must be applied before every exposure and can be washed off with water. Thus, for example, after every swim they must be reapplied. Further, the long-term side effects of many of these prior art compositions are not known.

L-ascorbic acid has many known biological functions from enzymatic co-factor to "sparing" agent against vitamin E depletion. See, for example, Englard and Seifter, "The Biochemical Functions of Ascorbic Acid," Ann. Rev. Nutri. 6: 365-406, (1986); Kunert and Tappel, "The Effect of Vitamin C on in vivo Lipid Peroxidation in Guinea Pigs as Measured by Pentane and Ethane Production, Lipids 18: 271-74 (1983). The latter function may partly account for its "anti-oxidant" status.

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Additionally, at higher concentrations, ascorbic acid is known to react with both the superoxide and hydroxyl radicals. Superoxide and the subsequently generated hydrogen peroxide and hydroxyl radical are oxygen-containing free radicals now known to be generated in vivo under a variety of normal and pathological conditions. Quite simply, these radicals have been implicated as causative agents for everything from sunburn to aging. These radicals destroy lipid membranes, break down DNA, inactivate enzymes and so forth. An immense amount of work has been done in the last two decades documenting the deleterious behavior of oxygen radicals. Several recent texts on the subject include:

Oxy-radicals in Molecular Biology & Pathology, D. Cerutti, I. Fridovich, J. McCord, eds., (Alan R. Liss, Inc. New York, 1988);

Biological Role of Reactive Oxygen Species in Skin, O. Hayaishi, S. Inamura, Y. Mayachi, eds. (Elsevier Press, New York, 1987);

Free Radicals, Aging and Degenerative Diseases, J. E. Johnson, Jr., R. Walford, D. Harmon, J. Miquel, eds. (Alan Liss, Inc., New York, 1986);

Free Radicals in Biology and Medicine, B. Halliwell and J. M. C. Gutteridge, eds. (Clarendon Press, Oxford, 1985); and

Oxidative Stress Helmut Sies, ed. (Academic Press, 1985).

Also addressing the subject are several symposia, including "Oxygen Radicals and Tissue Injury" Proceedings from an Upjohn Symposium (April, 1987); and "Oxygen Free Radicals",

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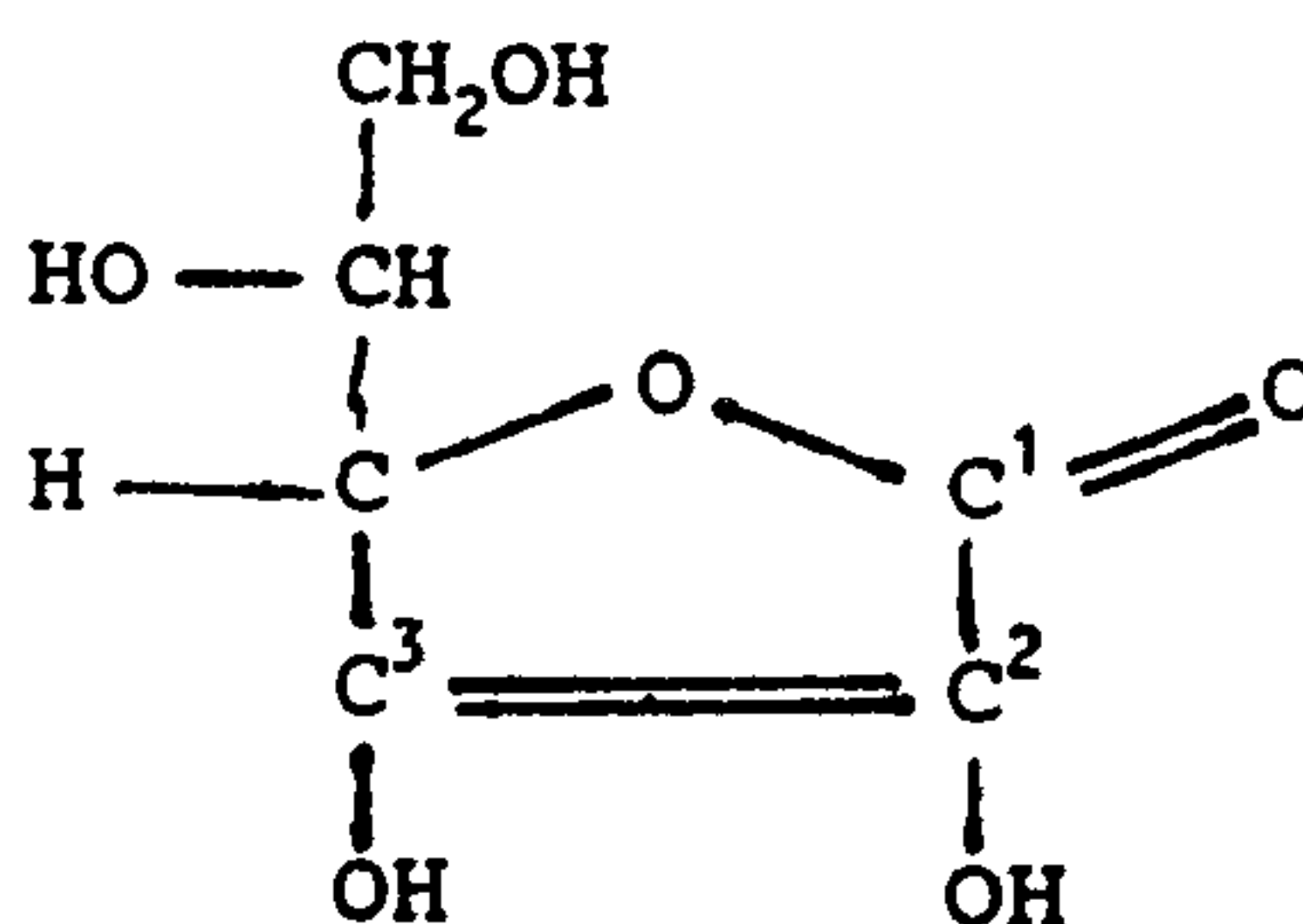
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Proceedings from National Heart, Lung & Blood
Institute (National Institute of Health,
Washington, D.C., Dec. 1987).

Ascorbic acid has been shown to stimulate
5 collagen synthesis in vitro which may provide
better understanding of pathologies related to
diminished collagen production in vivo. See for
example, S. R. Pinnell, "Regulation of Collagen
Biosynthesis by Ascorbic Acid: A Review", Yale J.
10 Biol. Med. 58: 554-59 (1985).

L-Ascorbic acid (or vitamin C), which has
a long and illustrious history, is chemically
defined as an α -keto-lactone with the following
structure:

15



20

The number 2 and 3 carbons are double-bonded and
contain an acid-ionizable hydrogen in water (pK =
4.2). Ascorbic acid is also a moderately strong
reductant. These properties, which lead to
25 instability in the ascorbic acid structure, are
well known and have been burdensome to
pharmacologists when attempting to formulate
active ascorbic acid solutions. Thus, at higher
pH's, the ascorbic acid increasingly becomes the
30 notoriously unstable ascorbate anion. This
instability may be due to several causes not
restricted to:

a) Stereochemical strain due to polar
repulsive forces. Thus, when the 2-hydroxy group

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is the one to ionize, it places two negative charges (the other being on the carboxyl oxygen) in close proximity which favors ring disruption.

b) Oxidative degradation due to the ascorbate anion's propensity to act as a reductant. The one-electron oxidation product (dehydroascorbate free radical) tends to disproportionate, forming another ascorbate molecule and the two-electron oxidation product, dehydroascorbate, which is extremely unstable in aqueous solutions and breaks down to ultimately form species such as L-threonic acid and oxalic acid. Transition metal ions can catalyze these reactions.

c) Degradation due to bulk water attack. Thus at lower ascorbate concentrations or ionic strength, water itself can react with and degrade the ascorbate molecule. For details of the above mentioned reactions, see Vitamin C: Its Molecular Biology and Medical Potential, Sherry Lewin, ed. (Academic Press, London, 1976).

For these reasons, among others, scientists working in the field have had difficulty in formulating stable solutions of ascorbic acid which would be useful for cosmetic, dermatologic, or ophthalmic needs. Nevertheless, because of the many beneficial pharmaceutical effects attributed to ascorbic acid, numerous attempts have been made to overcome these difficulties.

Thus, the literature describes ascorbic acid compositions formed by using a very low weight percent ascorbic acid, or a nonaqueous solvent, or by using derivatives of ascorbic acid,

usually in a solution buffered to a pH above 4.0. See, for example, Takashima et al, "Ascorbic Acid Esters and Skin Pigmentation," Am. Perfumer & Cosmetics 86: 29 (July 1971) (esterifying the hydroxyl group to form ascorbic acid-3-phosphate and maintaining an alkaline pH); Ciminera and Wilcox, "Stable Ascorbic Acid Solution for Parenteral Use", J. Am. Pharm. Assoc. Sci. Ed. 35: 363 (1946) (buffering an aqueous solution with an alkaline sodium salt). See also U.S. Patent No. 4,367,157 which discloses stabilizing an aqueous ascorbic acid solution by adding monothioglycerol and maintaining the pH between 4 and 7; U.S. Patent No. 2,400,171 which discloses stabilizing ascorbic acid by converting it to its calcium or zinc salt and preferably maintaining the pH at 7 to 7.3; U.S. Patent No. 2,442,461 which discloses stabilizing calcium ascorbate by adding an aliphatic thiocarboxylic acid and maintaining the pH between 5.2 and 5.6; U.S. Patent No. 2,585,580 which discloses stabilizing ascorbic acid with thio-sugars and maintaining the pH between 4.0 and 6.5; and U.S. Patent No. 4,372,874 which discloses actually removing the water to below 0.5 wt.% by using a desiccant. In many cases, these techniques have been successful in obtaining stable solutions but have been reasonably expensive and have yielded a product with less desirable properties than ascorbic acid in its unmodified form.

Disclosure of the Invention

We have now discovered a new, more economical, stable topical composition which consists essentially of at least about 1 wt.% L

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5 -ascorbic acid, preferably from about 3 to 20 wt.%
L-ascorbic acid, and more preferably about 5 to 10
wt.% L-ascorbic acid in water and a carrier for
topical application. Any composition containing
at least about 1 wt.% L-ascorbic acid is expected
to have beneficial effects, with the concentration
of L-ascorbic acid being primarily limited by its
solubility in the water/carrier system. The ratio
of water to carrier is at least 1:1, and more
10 preferably from 2:1 to 10:1, and the pH of the
composition is no more than about 3 to 3.5,
preferably no more than about 2.5. Such a
composition appears to allow ready penetration
into the skin and retards the damage caused by
15 ultraviolet light.

Carriers for topical application useful
in practicing the invention include, but are not
limited to, alkylene glycols, or alkylene glycols
in combination with one or more derivatives of
20 hydroxyalkylcellulose. In one embodiment, the
alkylene glycol is propylene glycol and the
hydroxyalkylcellulose is hydroxypropylcellulose.
When a combination of alkylene glycol and
hydroxyalkylcellulose is used, a useful ratio of
25 alkylene glycol to hydroxyalkylcellulose is from
about 30:1 to 5:1 and a particularly useful ratio
is 30:1. Without limitation, other carriers known
to those skilled in the art which are compatible
with water and are biologically acceptable are
30 expected to provide equivalent compositions within
the scope of this invention. For example,
alcohols such as ethanol and propanol, glycols
such as butylene or hexylene glycol, and polyols
such as sorbitol may be employed. Alternatively,

polyethylene or polypropylene glycols, mineral oil or glycerol can be used. Also contemplated by this invention are biologically acceptable hydroxyalkylcelluloses.

5 As one skilled in the art would recognize, the ascorbic acid may be provided by the addition of any reducing analog of ascorbic acid, such as D-isoascorbic acid or perhaps by the addition of other small reducing compounds such
10 as, but not limited to, glutathione, L-cysteamine, etc. Such forms would be expected to provide an equivalent composition to that claimed and are within the scope of the invention.

 The water used is preferably distilled
15 and/or deionized, but any water may be used which does not contain contaminants which would affect the stability of the ascorbic acid composition. The effects of water of varying purity on ascorbic acid stability is discussed in Meucci et al.,
20 "Ascorbic Acid Stability in Aqueous Solutions," Acta Vitaminol. Enzymol. 7(3-4): 147-54 (1985), incorporated herein by reference.

 A metal chelator, such as diethylene triaminepentaacetic acid (DTPA) or
25 ethylenediamine-di(o-hydroxyphenylacetic acid) (EDDHA), can be added to the composition in minor amounts (.001% to 0.1% (w/v)) to provide additional stability to the ascorbic acid, particularly when used at the lower concentration.

30 The required pH of the composition ensures that greater than 82% of the ascorbic acid remains in the protonated, uncharged form. Although not wishing to be bound by theory, we believe that the protonated form of ascorbic

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acid used in our invention is important dermatologically for several reasons. First, this form removes the ionic repulsion of the two oxygen groups, thus stabilizing the molecule. Second, because the protonated form of ascorbic acid is uncharged, entry into the skin (which itself has a pH of about 3-5) should be facilitated. See H. Schaefer et al., Skin Permeability 739-40 (Springer-Verlag Co., Berlin, 1982).

10 Brief Description of Drawings

FIGURE 1 Stability of various concentrations of L-ascorbic acid in aqueous cosmetic vehicle.

15 FIGURE 2 Effective of propylene glycol concentration on the stability of L-ascorbic acid.

FIGURE 3 Stability of a 5 percent aqueous solution of L-ascorbic acid at various pHs.

FIGURE 4 Spectral analysis of an aqueous 5 percent L-ascorbic acid solution, pH 2.4.

20 FIGURE 5 Spectral analysis of an aqueous 5 percent L-ascorbic acid solution, pH 4.2.

FIGURE 6 A photomicrograph of ultraviolet irradiated porcine skin treated with an aqueous L-ascorbic formulation.

25 FIGURE 7 Effect of 5 percent L-ascorbic acid in aqueous formulation and of 5 percent L-ascorbic acid in "hydroalcoholic" vehicle on acute sunburn in the domestic pig.

30 FIGURE 8 Effect of post-exposure application of 5 percent L-ascorbic acid in an aqueous formulation (L-AA) on acute sunburn reaction in the pig.

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Best Mode of Carrying Out the Invention

The following examples are for illustrative purposes only and are not intended to limit the scope of the claimed invention. The spectrophotometric analyses were made on a Shimadzu UV-260 dual beam spectrophotometer under the following conditions: Samples of ascorbic acid were kept at room temperature (unless otherwise indicated), shielded from light with varying air headspace. At different times aliquots were taken from each sample and diluted into water in a quartz cuvette in the spectrophotometer "sample beam". The reference cell contained either vehicle diluted into water or water alone (no difference was detected). Spectra were then taken from 200 nm to 400 nm and the optical density at the absorption maximum (unless otherwise indicated) was used to determine concentration.

20

EXAMPLE I

Example I demonstrates the preparation of the claimed composition and the stability of compositions to the invention.

A concentrated solution of 10% L-ascorbic acid (w/v) is prepared by dissolving 10 g. of L-ascorbic acid (available from Sigma) in 80 ml distilled, deionized water, and adding propylene glycol (1,2 propanediol purchased from Aldrich Chemical) to 100 ml. Optionally, 1 g of hydroxypropylcellulose (average molecular weight of 300,000) may be added. For maximum stability, the solution should be stored in a light-impermeable bottle at a temperature of about $\leq 22^{\circ}\text{C}$ with minimal headspace and/or purged with

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nitrogen.

5 In Example I, four solutions of 1-10% L-ascorbic acid (w/v) in 80% H₂O (v/v):20% propylene glycol (v/v):1% hydroxypropylcellulose (w/v) were prepared and kept in the dark at room temperature and capped microfuge tubes (with an approximately 10% air headspace). At indicated times, aliquots were removed and the residual ascorbic acid
10 are illustrated in Figure 1.

EXAMPLE II

15 Example II illustrates that the stability of L-ascorbic acid is not influenced by the concentration of propylene glycol. A 2% solution of L-ascorbic acid was prepared in different concentrations of propylene glycol. These were stored in the dark, at room temperature in capped microfuge tubes with approximately 20% air headspace. At 4.5 and 8 weeks, aliquots were
20 removed and the residual ascorbic acid determined spectrophotometrically. The results are illustrated in Figure 2.

EXAMPLE III

25 Example III illustrates the effect of pH on the stability of L-ascorbic acid in 80% H₂O(v/v):20% propylene glycol (v/v):1% hydroxypropylcellulose (w/v). Five percent solutions of L-ascorbic acid were adjusted to different pH's and then stored in the dark, at 4°C
30 in capped microfuge tubes with approximately 25% air headspace. At 6 and 12 weeks, aliquots were removed and the residual ascorbic acid determined spectrophotometrically. These results are illustrated in Figure 3. It is apparent that even

at relatively high pH's, the L-ascorbic acid at a 5% concentration is quite stable.

EXAMPLE IV

Example IV illustrates that spectral changes occur in a 5% L-ascorbic acid solution in 80% H₂O(v/v):20% propylene glycol(v/v):1% hydroxypropylcellulose (w/v) at relatively high pH even though the ascorbic acid is stable. From Example III, compositions at pH 2.4 and pH 4.2 were scanned either immediately after preparation or after 12 weeks storage as in Example III. The spectra are illustrated in Figures 4 and 5. These results indicate that reactions are occurring at pH 4.2 which lead to spectral broadening of the major peak into the near UV, as manifested by an increased "yellowing" of the solution.

EXAMPLE V

Example V illustrates that by using distilled, deionized H₂O and high concentrations of ascorbic acid/ascorbate used in the formulation ($\geq 3\%$), chelators show only a slight tendency to to stabilize ascorbate. In comparison, when a 1% ascorbate solution in a propylene glycol/ethanol/H₂O vehicle was made with or without 0.1 mM DTPA, a slight protective effect of DTPA on the stability of ascorbate was found. With a 5% ascorbate solution in propylene glycol/H₂O however, DTPA no longer showed any protective effect when analyzed spectrophotometrically. The data are presented in Table I. The chelator effect is expected to increase in compositions which are formulated in less pure water than those used for Example V, or those in which any of the components

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are contaminated with metal ions.

EXAMPLE VI

Example VI illustrates the greater stability of L-ascorbic acid compared to that of Na-ascorbate in the cosmetic preparation of 80% H₂O:20% propylene glycol: 1% hydroxypropylcellulose at a concentration of 1% (w/v) and 10% (w/v). At 1%, L-ascorbic acid is slightly more stable than the sodium salt, ascorbate. At 10% concentration, both L-ascorbic acid and Na-ascorbate show pronounced stability based on the spectrophotometric analyses, but the Na-ascorbate shows considerable yellow discoloration at both concentrations after 2 weeks whereas L-ascorbic acid shows only slight changes even at 7 weeks. The results are tabulated in Table II.

EXAMPLE VII

Example VII illustrates the protection of skin from ultraviolet damage by topical application of the stabilized aqueous formulation of L-ascorbic acid. In this experiment a Yorkshire swine's back was shaved with clippers and areas pretreated 8 times in 6 days with 10% solution of L-ascorbic acid in 80% H₂O (v/v):20% propylene glycol (v/v):1% hydroxypropylcellulose (w/v) or the vehicle control. The back was then irradiated for 10 minutes from a distance of approximately 4 inches with a bank of two Westinghouse FS-40 sunlamps (This dose is equivalent to approximately 5 times the MED (minimal erythema dose). The areas were post-treated twice in the ensuing 24 hours. At 24 hours, 4 mm punch biopsies were taken from each

site and prepared for histology. Typical results are shown in the photomicrograph in Figure 6 in which A = L-ascorbic acid treated; B = vehicle treated. The presence of dysplastic basal cells ("sunburn" cells) in the epidermis in response to UV is a hallmark of short wavelength UV damage to skin. The section from the L-ascorbic acid-treated site shows markedly fewer of these cells. Another difference relates to the overall stain intensity, an indication of an edematous response in skin. Quite typically, the sections from non-treated, exposed skin stain less than sections taken from ascorbic acid-treated skin, indicating a decreased edematous response in protected skin.

EXAMPLE VIII

Example VIII illustrates the reservoir effect of L-ascorbic acid protection against UV damage to the skin. Animals treated as in Example VII receive the final pretreatment 4 hours before UV exposure. In addition all treated sites are washed with luke-warm water immediately prior to irradiation eliminating any residual solution acting as a sunblock. This establishes that protection is due to L-ascorbic acid which has been taken up by the skin. This is in contrast to typical, commercially available, sunscreens which have to be applied immediately prior to exposure for optimal performance.

EXAMPLE IX

Example IX illustrates the potential of topical applications of L-ascorbic acid to moderate severe ultraviolet-induced skin damage. In Example IX, the test animal was pretreated with a 5% formulation of L-ascorbic acid (in either an

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aqueous formulation or "hydroalcoholic" vehicle) five times in six days prior to irradiation. On the sixth day, the treated and control areas were irradiated for 60 minutes with a bank of two Westinghouse FS-40 bulbs. This dose is equivalent to 30 times the minimal erythema dose. The photograph was taken 11 days after irradiation showing the improvement in appearance of the L-ascorbic acid treated sites as compared to the control sites. The results are illustrated photographically in Figure 7.

EXAMPLE X

Example X establishes that topical application of the aqueous L-ascorbic acid formulation has beneficial, "wound healing", effects even when applied after UV irradiation, as illustrated photographically in Figure 8. In Example X, the test animal was pretreated and irradiated as in Example IX. One area on this animal (the bottom row in the illustration of Figure 8) received no pretreatment. After irradiation, the sites received either no post-treatment, or post-treatment on one, two, three, four, five, or seven days with 5% L-ascorbic acid, or post-treatment with the vehicle only for seven days. With 3 to 4 days post-treatment with the L-ascorbic acid solution (I-J in Figure 8), the appearance of skin improved as compared to those areas which were untreated or treated with vehicle only.

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TOXICITY STUDIES

Although no formal toxicity studies have been conducted, a 10% solution (w/v) has been applied to the face of a human one time per day, five times per week for thirty weeks without any adverse reaction. Additionally, in preliminary studies carried out by Dr. Lorraine Kligman at the University of Pennsylvania, hairless mice were treated 5 times per week with either a 5% or 10% solution of L-ascorbic acid at either pH 2.1 or 3, or with the pH controls for 4 weeks. No evidence (clinical or histological) was found for these topical applications being either toxic or irritating.

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TABLE I
Effect of a Metal Chelator on the Stability
of High Concentrations of Ascorbate

5	Sample	% Ascorbate remaining at	
		2.5 Weeks	3 Weeks
	1% Ascorbate	31	-
	1% Ascorbate + 0.1 mM DTPA	41	-
	5% Ascorbate	-	73
10	5% Ascorbate + 0.1 mM DTPA	-	73

1% ascorbate solutions were made in a water, propylene glycol, ethanol solution (10:60:30; v/v/v); 5% ascorbate solutions were made in a water, propylene glycol solution (80:20; v/v) with or without the indicated amount of DTPA. The samples were kept at room temperature in capped tubes (with significant air headspace). Aliquots were initially taken daily, then weekly and measured for residual ascorbate spectrophotometrically.

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TABLE II
Comparison of Stabilities of High Concentrations of
L-Ascorbic Acid and Na-Ascorbate

5	<u>% Remaining at</u>		
	<u>Sample</u>	<u>3 Weeks</u>	<u>7 Weeks</u>
	1% Na Ascorbate	79	60
	1% L-Ascorbic acid	93	74
	10% Na-Ascorbate	-	97.5
10	10% L-Ascorbic Acid	-	100

Ascorbic/ascorbate solutions were made in 80%
H₂O:20% propylene glycol:1% hydroxypropylcellulose.
The samples were kept in the dark at room
temperature in capped microfuge tubes (with an
15 approximately 10% air headspace). Aliquots were
taken at the indicated times and measured for
residual ascorbic acid/ascorbate
spectrophotometrically.

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Figure 1. Stability of various concentrations of L-ascorbic acid in aqueous cosmetic vehicle. Different concentrations of L-ascorbic acid were made in a vehicle composed of 80% H₂O, 20% propylene glycol and 1% hydroxypropylcellulose and stored shielded from light, at room temperature (with an approximately 10% air headspace). One day, 3 weeks and 7 weeks later, aliquots were diluted into a quartz cuvette and the resulting spectrum was scanned from 200 to 400 nm. The optical density of the 260-265 nm peak was recorded for lower concentrations while the optical density at 280 nm was recorded for changes in the higher concentrations of L-ascorbic acid.

1: 1% L-ascorbic acid 2: 3% L-ascorbic acid
3: 5% L-ascorbic acid 4: 10% L-ascorbic acid

Figure 2. Effect of propylene glycol concentration on the stability of L-ascorbic acid. Solutions (2% w/v) of L-ascorbic acid in water with various concentrations of propylene glycol were kept in the dark at room temperature in capped microfuge tubes (with an approximately 20% air headspace). At 4.5 and 8 weeks, aliquots were removed from each sample and the residual ascorbic acid recorded as in Figure 1.

○: 0% propylene glycol; □: 10% propylene glycol;
△: 20% propylene glycol; *: 40% propylene glycol;
◆: 60% propylene glycol

Figure 3. Stability of a 5% aqueous solution of L-ascorbic acid at various pH's. A 5% solution of L-ascorbic acid was prepared in a vehicle of 80% H₂O, 20% propylene glycol and 1% hydroxypropylcellulose at the indicated pH.

Samples were stored at 4°C, shielded from light (with approximately 25% air headspace). After one

day, six weeks and 12 weeks, aliquots were removed from each sample and the residual ascorbic acid recorded as in Figure 1.

1: pH 2.4; 2: pH 3.2; 3: pH 4.2; 4: pH 4.5;
5: pH 5.1

Figure 4. Spectral analysis of an aqueous 5% L-ascorbic acid solution, pH 2.4. Conditions were as in Figure 3. Spectra were taken immediately after preparation and after 12 weeks storage.

Figure 5. Spectral analysis of an aqueous 5% L-ascorbic acid solution, pH 4.2. Conditions were as in Figure 3. Spectra were taken immediately after preparation and after 12 weeks storage.

Figure 6. Photomicrograph of ultraviolet irradiated porcine skin treated with an aqueous L-ascorbic formulation or vehicle control. Sites on animals back were pretreated with the ascorbic acid or vehicle control eight times in the six days prior to irradiation, the last pretreatment being 4 hours before irradiation. Irradiation was for 10 minutes using a bank of two Westinghouse FS-40 sunlamps. Four millimeter punch biopsys were taken 24 hours later, routinely fixed and stained with (Hematoxylian and Eosin). Arrows point to sunburn cells.

Figure 7. Effect of 5% L-ascorbic acid in aqueous formulation and of 5% L-ascorbic acid in "hydroalcoholic" vehicle on acute sunburn in the domestic pig. The two ascorbic acid solutions (or their vehicle alone) were applied liberally 5 times in 6 days. On the seventh day, the animal was exposed for 60 minutes to ultraviolet irradiation (two FS-40 sunlamps at a distance of 4 inches). Photograph was taken 11 days post-

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irradiation. VC-I = 5% L-ascorbic acid in aqueous formulation; VC-I-V = VC-I vehicle alone; CB = 5% L-ascorbic acid in "Hydroalcoholic vehicle"; CBV = Hydroalcoholic vehicle alone.

5 Figure 8. Effect of post-exposure
application of 5% L-ascorbic acid in an aqueous
formulation (L-AA) on acute sunburn reaction in
the pig. The top row received pre-exposure
application of the ascorbic acid (A-F) or vehicle
10 (vehicle) 5 times in 6 days. The bottom row
received no pre-treatment. Selected sites in the
top and bottom rows then received L-AA application
for varying periods of time post-irradiation. A:
no further application; B: L-AA, one day; C:
15 L-AA, 2 days; D: L-AA, 3 days; E: L-AA, 5 days;
F: L-AA, 7 days post-exposure; G: L-AA, 1 day;
H: L-AA, 2 days; I: L-AA, 3 days; J: L-AA, 4 days;
K: L-AA, 5 days; L: L-AA, 7 days post-exposure.
Vehicle sites were treated with the VC-I vehicle
20 for the seven days post-exposure.

CLAIMS

1. A topical composition consisting essentially of from at least about 1% ascorbic acid (w/v) in water and a carrier suitable for topical application wherein the volumetric ratio of water to carrier is at least 1:1 and wherein the composition has a pH of no more than about 3.5.
2. The composition of claim 1 wherein the cosmetic carrier comprises an alkylene glycol.
3. The composition of claim 2 wherein the alkylene glycol is propylene glycol.
4. The composition of claim 1 wherein the carrier is a combination of an alkylene glycol and hydroxyalkylcellulose.
5. The composition of claim 4 wherein the alkylene glycol is propylene glycol and the hydroxyalkylcellulose.
6. The composition of claim 1 wherein the volumetric ratio of water to carrier is from about 2:1 to about 10:1.
7. The composition of claim 2 wherein the volumetric ratio of water to carrier is from about 2:1 to about 10:1.
8. The composition of claim 3 wherein the volumetric ratio of water to carrier is from about 2:1 to about 10:1.

9. A topical composition consisting essentially of between 3 and 20% ascorbic acid (w/v) and 80% to 97% water and a carrier suitable for topical application wherein the volumetric ratio of water to carrier is at least about 1:1 and wherein the composition has a pH of no more than about 3.5.

10. The composition of claim 9 wherein the carrier is a combination of an alkylene glycol and hydroxyalkylcellulose.

11. The composition of claim 10 wherein the volumetric ratio of alkylene glycol to hydroxyalkylcellulose is from about 30:1 to 5:1.

12. The composition of claim 11 wherein the alkylene glycol is propylene glycol and the hydroxyalkylcellulose is hydroxypropylcellulose.

13. A topical composition consisting essentially of from at least about 1% ascorbic acid (w/v) in water and a carrier suitable for topical application wherein the volumetric ratio of water to carrier is at least 1:1, and from about 0.01 to about 0.1% metal chelator (w/v) and wherein the composition has a pH of no more than about 3.5.

14. The composition of claim 13 wherein the metal chelator is selected from the group consisting of diethylenetriamine pentaacetic acid, ethylenediamine di(o-hydroxyphenylacetic acid), ethylene glycol bis (β -aminoethyl ether) - N,N,N',N'-tetraacetic acid and combinations thereof.

15. The composition of any one of the preceding claims wherein the pH is no more than about 2.5.

16. The composition of claim 1 wherein the water is selected from the group consisting of distilled, deionized and distilled deionized water.

17. The composition of claim 16 wherein the pH is no more than about 2.5.

18. A topical composition consisting essentially of about 5 to 10% ascorbic acid (w/v) and about 90 to 95% water and a carrier suitable for topical application wherein the volumetric ratio of water to carrier is at least about 1:1 and wherein the composition has a pH of no more than about 3.5.

19. The composition of claim 18 wherein the carrier is a combination of an alkylene glycol and hydroxyalkylcellulose.

20. The composition of claim 19 wherein the volumetric ratio of alkylene glycol to hydroxyalkylcellulose is from about 30:1 to 5:1.

21. The composition of claim 20 wherein the alkylene glycol is propylene glycol and the hydroxyalkylcellulose is hydroxypropylcellulose.

22. The composition of claim 18 wherein the water is distilled, deionized, or distilled deionized water.

23. The composition of any one of the preceding claims wherein the composition is a dermatological composition and the carrier is a dermatological carrier.

24. The topical use of the composition of any of the preceding claims for retarding damage to skin by ultraviolet light.

5 25. The topical use of the composition of any one of claims 1 to 23 for preventing skin pathologies.

26. The topical use of claim 25 wherein the skin pathology is an inflammation of the skin.

10 27. The topical use of the composition of any one of claims 1 to 23 for increasing the rate of wound healing.

15 28. The topical use of claim 25 wherein the skin pathology is the incidence of skin neoplasms due to ultraviolet radiation damage to the skin.

20 29. The use of the composition of any one of claims 1 to 23 preventing or rectifying pathologies of the eye.

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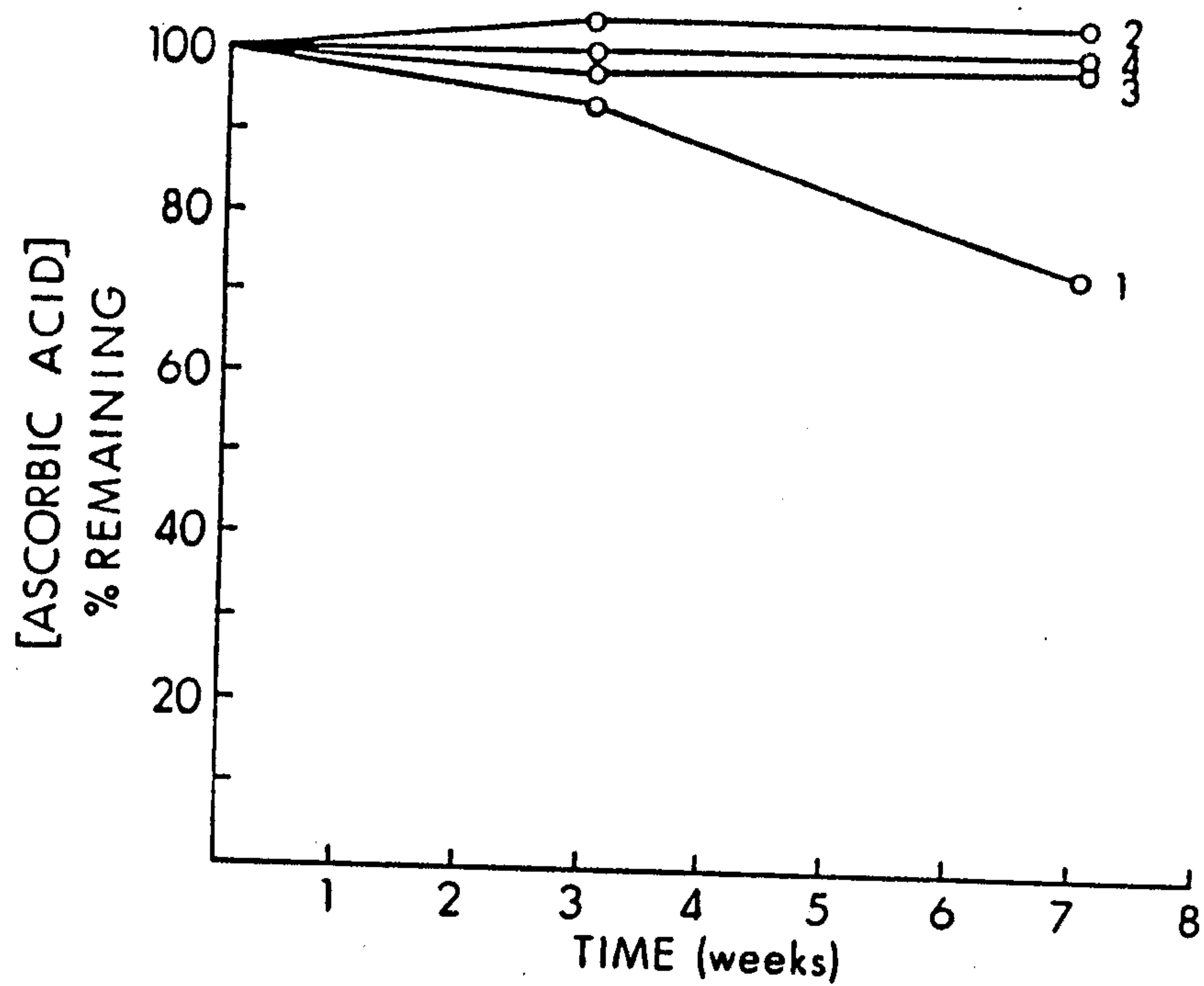


FIGURE 1

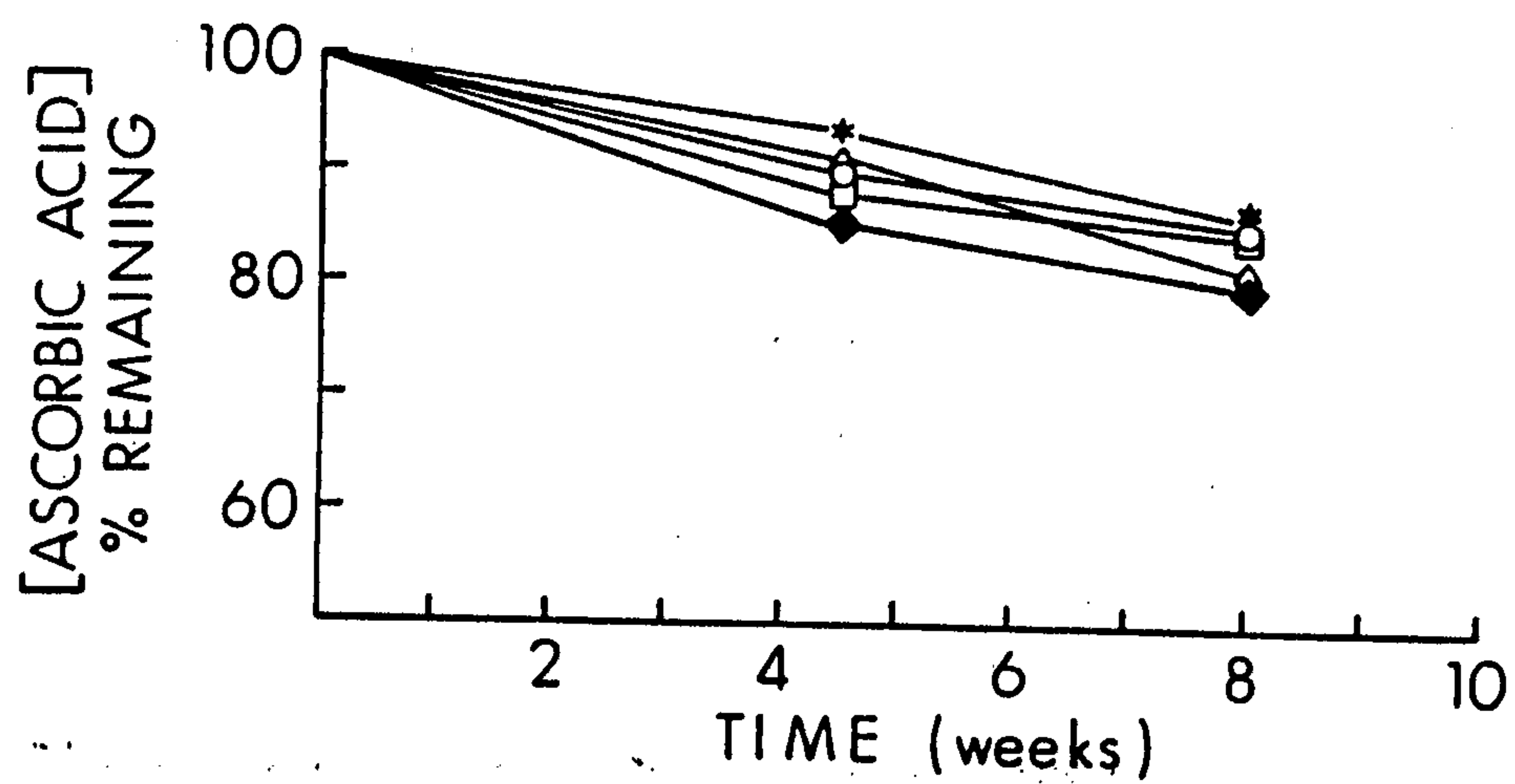


FIGURE 2

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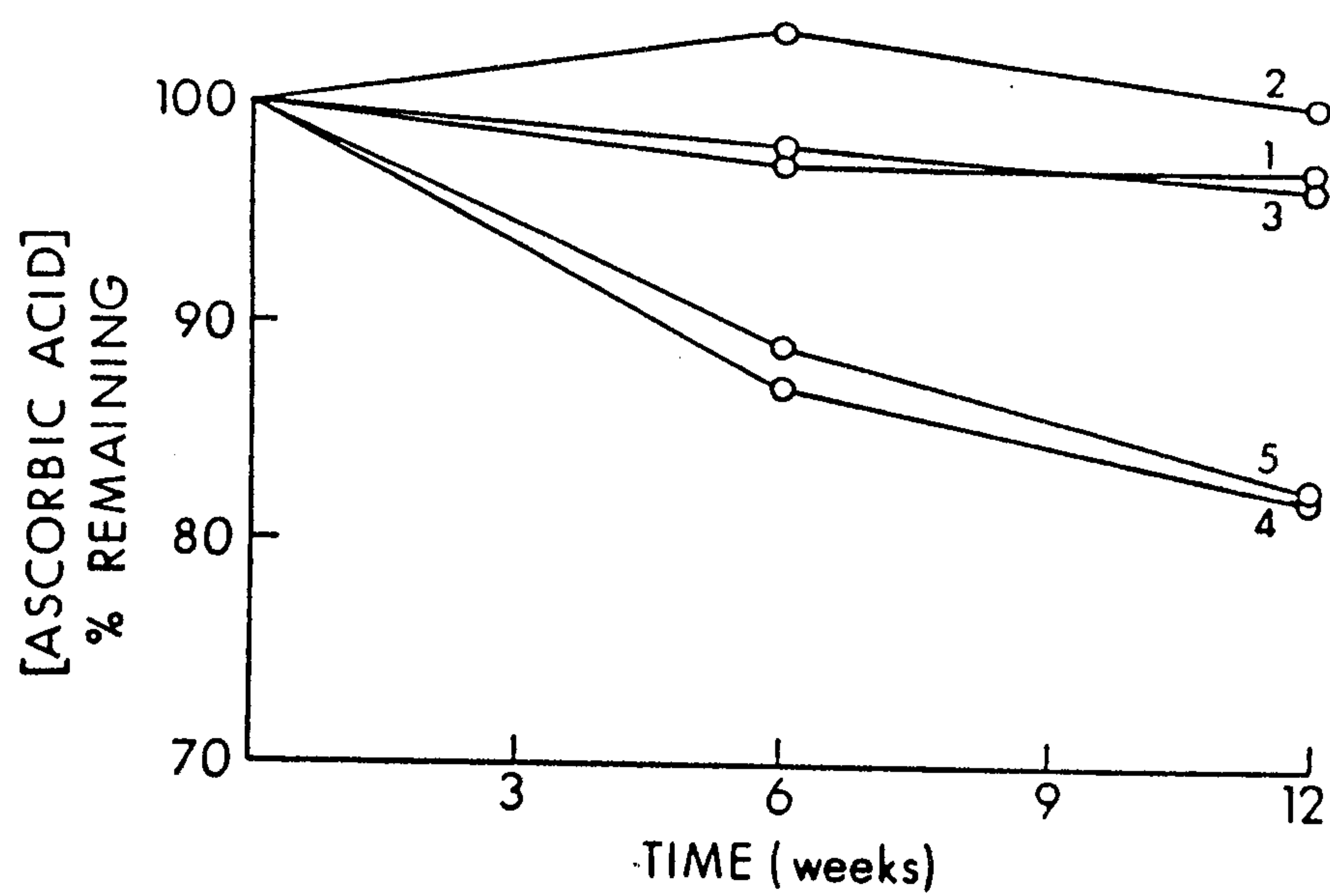


FIGURE 3

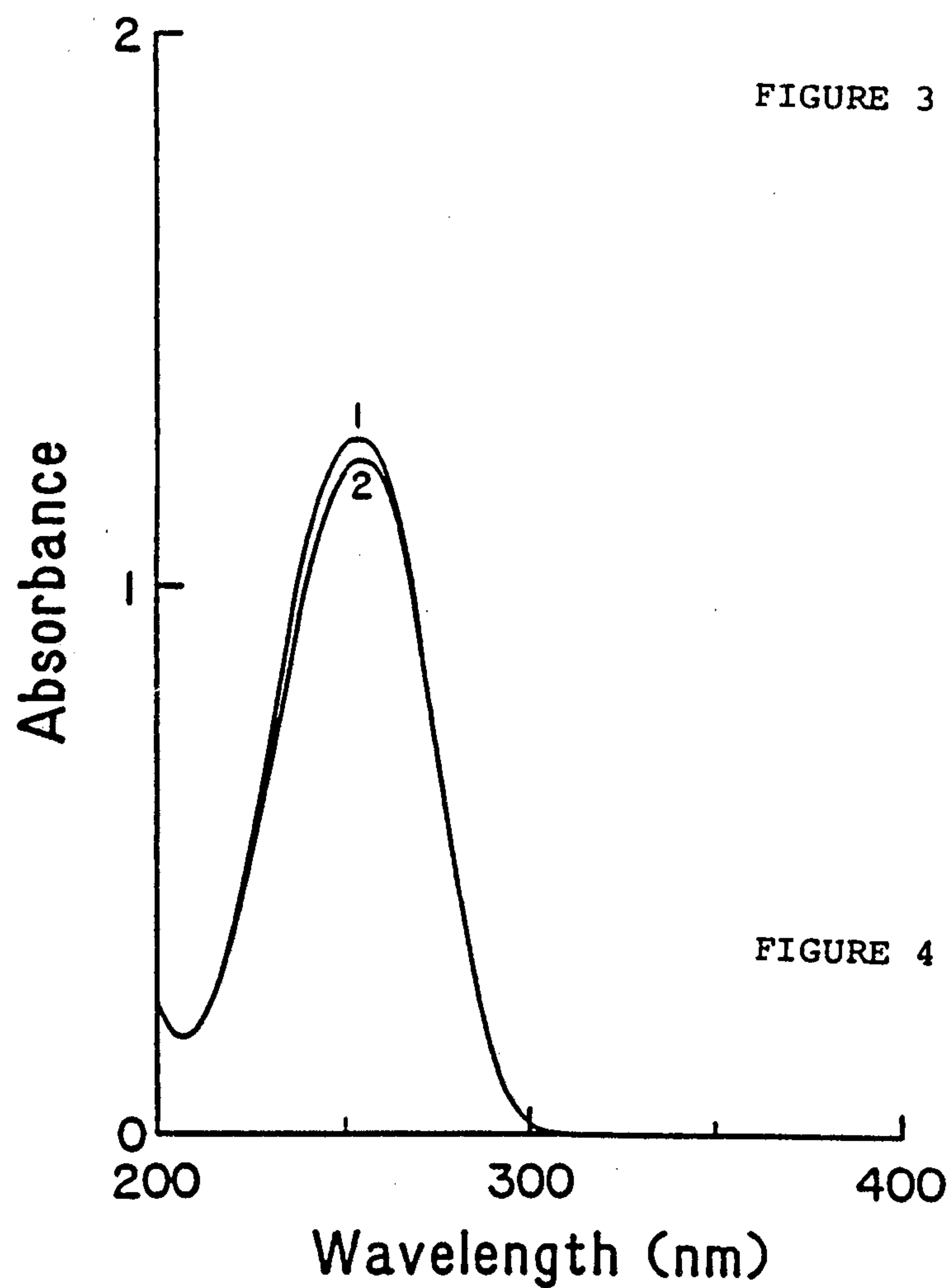


FIGURE 4

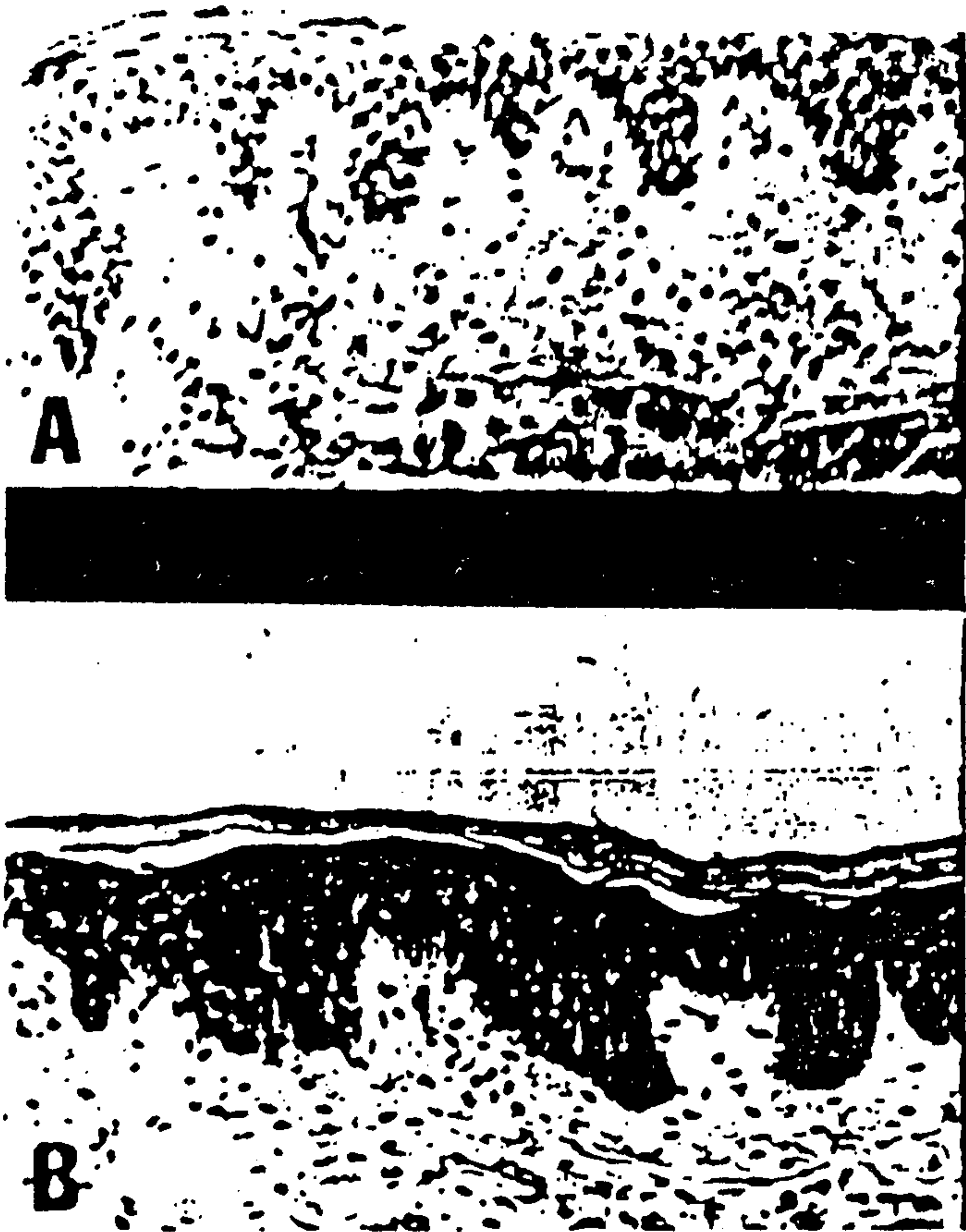


FIGURE 6

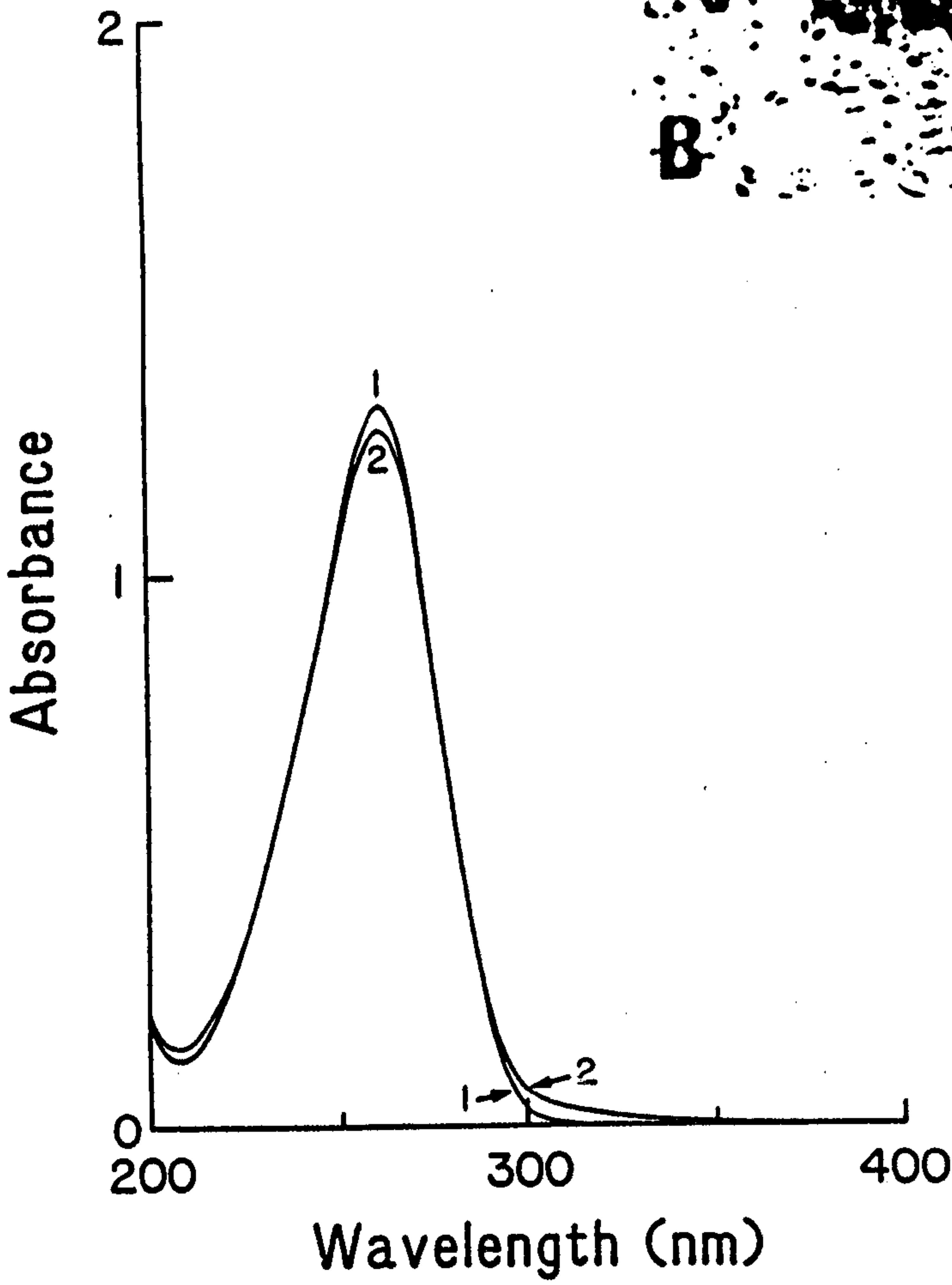


FIGURE 5



FIGURE 7

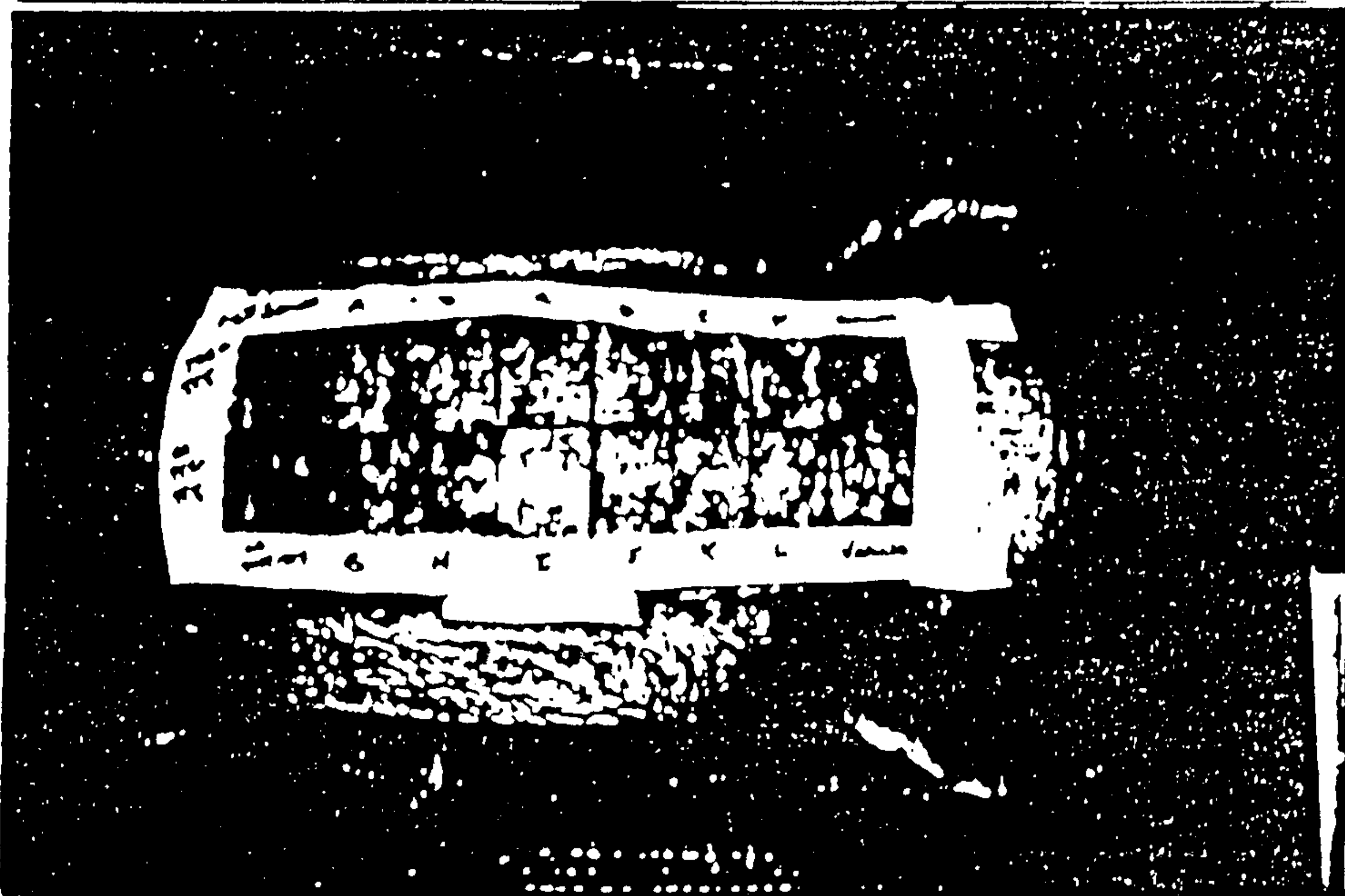


FIGURE 8