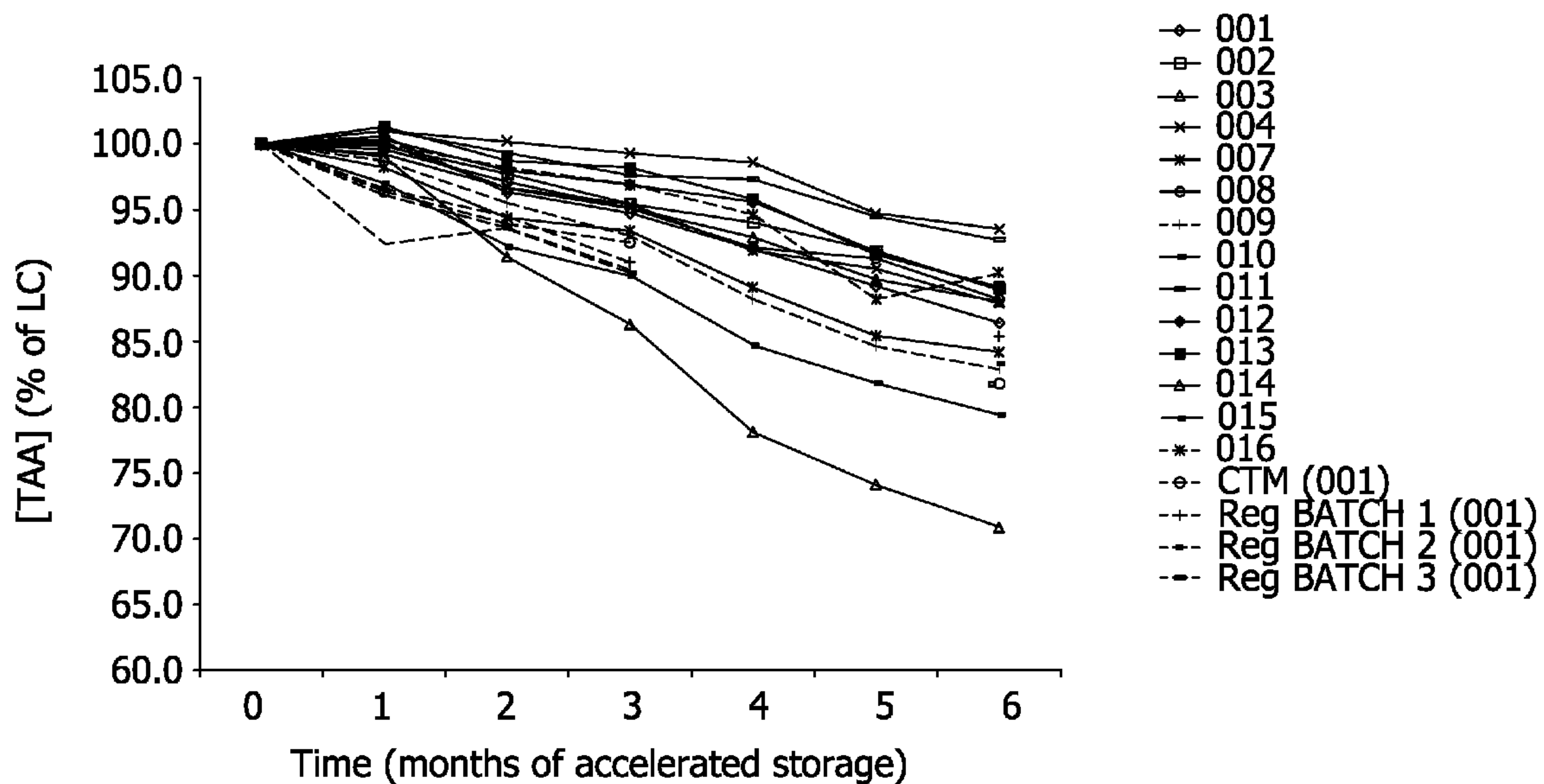




(86) **Date de dépôt PCT/PCT Filing Date:** 2007/05/08
 (87) **Date publication PCT/PCT Publication Date:** 2007/11/22
 (45) **Date de délivrance/Issue Date:** 2015/07/14
 (85) **Entrée phase nationale/National Entry:** 2009/10/30
 (86) **N° demande PCT/PCT Application No.:** US 2007/068496
 (87) **N° publication PCT/PCT Publication No.:** 2007/134071
 (30) **Priorité/Priority:** 2006/05/08 (US60/798,483)

(51) **Cl.Int./Int.Cl. A61K 31/58** (2006.01),
A61K 31/167 (2006.01), **A61K 9/10** (2006.01),
A61P 1/02 (2006.01), **A61P 17/02** (2006.01)
 (72) **Inventeurs/Inventors:**
 SHABANY, HOSSEIN, US;
 SUTTERER, ANGELA, US;
 REPKA, MICHAEL A., US
 (73) **Propriétaire/Owner:**
 UNIVERSITY OF MISSISSIPPI, US
 (74) **Agent:** GOWLING LAFLEUR HENDERSON LLP

(54) **Titre : FORMULE STABILISEE DE TRIAMCINOLONE ACETONIDE**
 (54) **Title: STABILIZED FORMULATION OF TRIAMCINOLONE ACETONIDE**



(57) **Abrégé/Abstract:**

A stabilized formulation of triamcinolone acetonide in a bioadhesive base material is provided. The present invention further includes a method of producing a stabilized non-aqueous TAA formulation and methods of measuring the stability of such TAA formulations.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 November 2007 (22.11.2007)

PCT

(10) International Publication Number
WO 2007/134071 A3

(51) International Patent Classification:
A61L 15/16 (2006.01)

(74) Agents: PETRILLO, Kathleen M. et al.; Senniger Powers, 1 Metropolitan Square, 16th Floor, St. Louis, MO 63102 (US).

(21) International Application Number:
PCT/US2007/068496

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 8 May 2007 (08.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/798,483 8 May 2006 (08.05.2006) US

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (for all designated States except US): FLEMING AND COMPANY, PHARMACEUTICALS [US/US]; 1733 Gilsinn Lane, Fenton, MO 63026 (US). THE UNIVERSITY OF MISSISSIPPI [US/US]; Thad Cochran Research Center, Room 1006, University, MS 38677 (US).

(72) Inventors; and

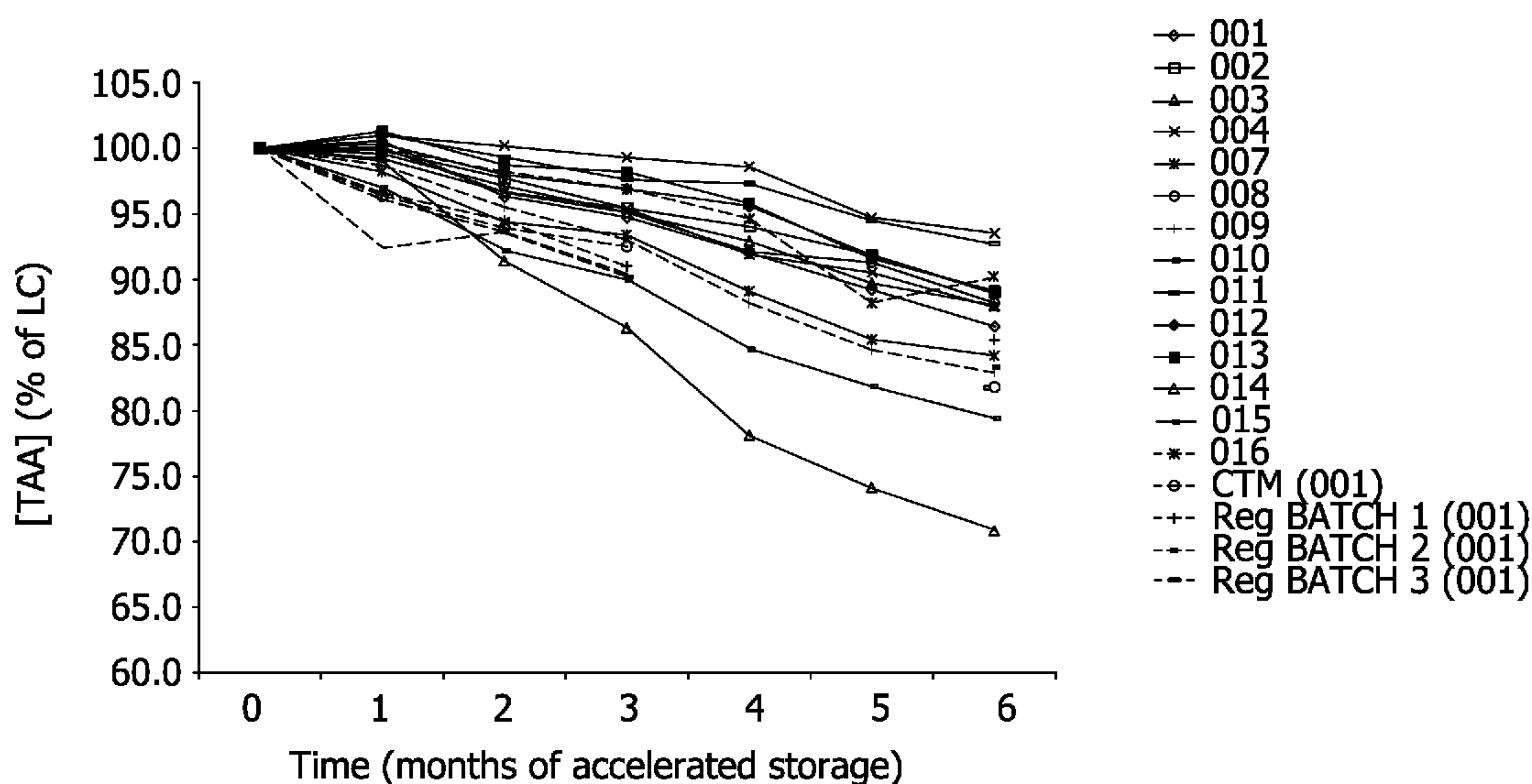
(75) Inventors/Applicants (for US only): SHABANY, Hossein [US/US]; 4351 Westhampton Place Court, St. Charles, MO 63304 (US). SUTTERER, Angela [US/US]; 1121 Dunston Drive, St. Louis, MO 63146 (US). REPKA, Michael A. [US/US]; 810 Brentwood Cove, Oxford, MS 38655 (US).

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
9 October 2008

(54) Title: STABILIZED FORMULATION OF TRIAMCINOLONE ACETONIDE



(57) Abstract: A stabilized formulation of triamcinolone acetonide in a bioadhesive base material is provided. The present invention further includes a method of producing a stabilized non-aqueous TAA formulation and methods of measuring the stability of such TAA formulations.

WO 2007/134071 A3

STABILIZED FORMULATION OF TRIAMCINOLONE ACETONIDE

FIELD OF THE INVENTION

[0001] The present invention is generally related to a storage stable triamcinolone acetonide (TAA) formulation. In particular, the present invention relates to bioadhesive formulations containing TAA and lidocaine or salt thereof, which are stable under standard storage conditions. In particular, the present invention relates to a process for the preparation of storage stable bioadhesive formulations containing TAA.

BACKGROUND OF THE INVENTION

[0002] Recurrent aphthous ulcers (RAU) or oral canker sores are the most common oral lesions afflicting humans. Studies have shown such ulcers affect 18% to 50% of the general population. As the name suggests, RAU lesions tend to recur in susceptible patients, often lasting for weeks. These lesions can be characterized as necrotizing ulcerations of oral mucosal tissue which are located on soft, non-keratinized mucosa. The lesions are painful, affect nutritional intake, and disrupt oral hygiene. They lead commonly to secondary infections by opportunistic organisms and sometimes result in scarring.

[0003] The etiology of RAU has been linked to several causative factors including allergies, trauma, stress, autoimmune dysfunction, nutritional deficiencies, microbial infection, hormonal changes, and systemic disease. However, several studies have shown that whatever the specific etiology in a particular patient, the clinical manifestations of RAU are due to an altered immune response. Immunosuppressive steroids such as triamcinolone acetonide are known to be effective in the treatment of RAU. A problem with steroidal therapy for RAU however, is that administration in large doses or over extended periods can cause adrenal suppression and atrophy. The dosage necessary for steroidal therapy to have therapeutic effect for RAU can be lessened, thereby decreasing the opportunity and magnitude of harmful side effects, if the therapy is applied topically rather than systemically. Furthermore, treatment periods necessary to achieve the desired therapeutic effect can be

shortened if the form of the product encourages patient compliance in applying the medication on a prescribed schedule.

[0004] Attempts at delivery of medication to the oral mucosa have included bioadhesive compositions based primarily on organic cellulose, such as disclosed in Reissue Patent No. RE 33,093 issued to Schiraldi et al., and polycarbophils disclosed in U.S. Pat. No. 4,615,697 issued to Robinson. The major disadvantages of such compositions is that they are aqueous systems which do not provide as rapid symptomatic relief as the compositions of the present invention, and which are relatively easily removed from the oral mucosa by the flow of saliva.

[0005] U.S. Pat. No. 4,948,580 to Browning describes a bioadhesive composition comprising a freeze-dried polymer mixture formed of the copolymer poly(methyl vinyl ether/maleic anhydride) and gelatin dispersed in an ointment base such as mineral oil containing dispersed polyethylene. The freeze-dried combination of polymer and gelatin is reported to be a synergistic combination having enhanced muco-adhesive properties compared to a simple mixture.

[0006] U.S Pat. Nos. 5,112,620 and 5,714,165 to Repka describe combining the therapeutic effect of steroids to counter the dysfunctional immune response associated with RAU, with a local anesthetic to provide immediate symptomatic relief, in an organic base material which provides delivery of the active medications to the lesions. The base material is a bioadhesive composition having wet adherent properties which is not readily displaced from the oral mucosa even in the presence of saliva, and which allows the active medications to remain concentrated and localized over the RAU lesions for an extended treatment period. A formulation prepared in accordance with the Repka patents, containing 0.1% TAA and 2% lidocaine, was able to maintain at least 90% of the initial TAA concentration for 3 months under accelerated storage conditions of 40°C and 75% relative humidity; however, surprisingly, the formulation was unable to maintain at least 90% of its initial concentration of TAA for more than 13 months under standard storage conditions of 25°C and 60% relative humidity.

[0007] Ideally, a therapeutic composition has an extended shelf life. Due to the realities of production, distribution, and retail sales, product preferably has a shelf life of at least 12 months, preferably at least 18 months, more preferably at least 24 months, and still more preferably at least 36 months. Such a characteristic is particularly advantageous in the treatment of RAU because the ulcers reoccur in susceptible patients. A TAA formulation with a long shelf life would speed healing by allowing susceptible patients to keep the therapeutic formulation on hand so they may apply the formulation at the first appearance of the ulcer(s).

[0008] The U.S. Food and Drug Administration measures shelf life as the time (days/months) for which a product retains, within specified limits, the same properties and characteristics that it possessed at the time of its manufacture. [Reference – Guideline for Industry – Stability Testing of New Drug Substances and Products, ICH]. The "specified limits" for Formulation B of Example 1 are: TAA concentration of 90 – 110% w/w and lidocaine concentration of 95-105% w/w of label claim.

[0009] Methods of stabilizing aqueous and alcoholic solutions of TAA are known. TAA has been stabilized in aqueous solutions with an acidic pH. Gupta reports that the optimum pH for TAA stability in aqueous solution was measured to be about 3.4 (Gupta, V.D., "Stability of triamcinolone acetonide solutions as determined by high-performance liquid chromatography," *J. Pharm. Sci.*, 72:1453-6 (1983)). Ungphaiboon et al. report that decomposition of TAA in aqueous solutions was minimal at pH 3.4 and that above pH 5.5 the rate of TAA decomposition increased rapidly (Ungphaiboon et al., "Formulation and efficacy of triamcinolone acetonide mouthwash for treating oral lichen planus," *Am. J. Health-Syst. Pharm.*, 62:485-91 (2005)). Ungphaiboon et al. suggest that buffering agents and antioxidants may be added to a TAA formulation to increase its stability. Xu et al. reported that solutions containing lidocaine hydrochloride, chlorhexidine gluconate, and TAA were stable with respect to TAA degradation after storage at room temperature for one year. (Xu et al., "Simultaneous determination of lignocaine hydrochloride, chlorhexidine gluconate, and triamcinolone acetonide in suspension by reversed-phase HPLC," *J. Liq. Chrom. & Re. Technol.*, 22(13):2071-91 (1999)).

[0010] The Repka patents suggest stabilizing a bioadhesive TAA formulation by the addition of antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole. However, it has been discovered that these antioxidants were not effective in adequately prolonging the storage stability of the Repka based formulation. Accordingly, there is a need for such compositions having enhanced storage stability.

SUMMARY OF THE INVENTION

[0011] Among the several features of the present invention are bioadhesive formulations with increased TAA stability and a process for producing such stable formulations.

[0012] Briefly, the present invention is directed to a storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 6 wt.% lidocaine or a salt thereof. The base material comprises from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of a polyalkylene glycol. The composition comprises either: at least 90% of the triamcinolone acetonide based on the amount of the triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity; no more than about 10% of compounds having the formulae I, II, and III based upon the amount of the triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity; at least 90% of the triamcinolone acetonide based upon the amount of the triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity; or no more than about 10% of the compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity. In an embodiment, a composition having wet adherent properties comprises a base material, about 0.1 wt.% triamcinolone acetonide, and about 2 wt.% lidocaine or a salt thereof, which comprises at least 0.09 wt.% triamcinolone acetonide and 1.8 wt.%

lidocaine or a salt thereof after 14 months; or comprises no more than about 0.01 wt.% of compounds having the formulae I, II, and III after 14 months.

[0013] Another aspect of the invention is directed to a composition for the treatment of mouth sores comprising a polyalkylene glycol, a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, lidocaine hydrochloride, triamcinolone acetonide, and a preservative.

[0014] In another aspect, the invention is directed to a method of making a therapeutic composition. The process comprises providing a base material and mixing lidocaine or a salt thereof and triamcinolone acetonide with the base material in an inert atmosphere.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is a graph depicting the stability of various TAA and lidocaine formulations as a percent recovery of TAA versus time as described in greater detail in the examples. "macc" is months of accelerated storage.

[0016] FIG. 2 is a graph depicting the normalized stability of TAA and lidocaine formulations as a percent recovery of TAA versus time as described in greater detail in the examples "macc" is months of accelerated storage.

[0017] FIG.3 is an HPLC chromatogram depicting the results of Experiment A as described in greater detail in the examples.

[0018] FIG. 4 is an HPLC chromatogram depicting the results of Experiment B as described in greater detail in the examples.

[0019] FIG. 5 is a graph depicting the stability of various TAA and lidocaine formulations as the concentration of TAA versus time under the accelerated storage conditions of 40°C and 75% relative humidity (RH) as described in greater detail in Example 6.

[0020] FIG. 6 is a graph depicting the stability of various TAA and lidocaine formulations as percent TAA degradation versus time as described in greater detail in Example 6.

[0021] FIG. 7 is a graph depicting the stability of various TAA and lidocaine formulations at room temperature storage over a twelve month period as the concentration of TAA versus time as described in greater detail in Example 6.

[0022] FIG. 8 graphically depicts the total percent of TAA degradants under accelerated storage conditions over a twelve month period as the percent of TAA degradants versus time as described in greater detail in Example 6.

[0023] FIG. 9 is an HPLC chromatogram depicting the results of experiments as described in greater detail in Example 6.

[0024] FIG. 10 is an HPLC chromatogram depicting the results of experiments as described in greater detail in Example 6.

[0025] FIG. 11 is a graphical depiction of the crystal structure of Compound II as described in greater detail in Example 3.

[0026] FIG. 12 is a graph depicting the accelerated stability of various TAA and lidocaine formulations as a percent recovery of TAA versus time as described in greater detail in Example 7.

[0027] FIG. 13 is a graph depicting the stability of various TAA and lidocaine formulations as a percent recovery of TAA versus time as described in greater detail in Example 7.

DETAILED DESCRIPTION

[0028] In accordance with the present invention, improved formulations with increased stability of TAA have been discovered. The present invention improves the shelf life of TAA and lidocaine or lidocaine salt bioadhesive formulations. It has been discovered that the shelf life of a TAA-containing formulation is significantly increased by selecting a lidocaine salt, such as lidocaine hydrochloride, rather than lidocaine free base for incorporation in the formulation because TAA degradation is reduced. While not being bound by any particular theory, it is believed that lidocaine hydrochloride is a more effective stabilizing agent within the formulation than is lidocaine free base. The present invention also includes a method of preparing the improved formulations in an inert atmosphere to minimize oxidative degradation of the formulations during

storage. TAA-containing formulations including lidocaine or a salt thereof exhibit increased storage stability when prepared in an inert atmosphere as compared to formulations prepared under conventional conditions.

[0029] The formulations of the present invention comprise a base material and active ingredients.

BASE MATERIAL

[0030] The therapeutic compositions of the present invention comprise a base material having wet adherent properties and a therapeutically effective amount of one or more medicaments incorporated in the base material. The base material is a bioadhesive composition comprising a polyalkylene glycol, and in particular polyethylene glycol (PEG), and from about 3 to 15 wt.% of a water-soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or maleic anhydride. The PEG preferably comprises a mixture of a low molecular weight PEG which is a liquid at 30°C and a high molecular weight PEG which is a waxy solid at 30°C in proportions which result in the mixture having an ointment like consistency at room temperature. Suitable mixtures comprise from about 40 to about 60 wt.% PEG having a molecular weight of less than 600, most preferably PEG 400, admixed with about 20 to about 50 wt.% PEG having a molecular weight above 600, most preferably PEG 3350. The PEG component of the bioadhesive composition may conform to that described for ointments in the official monograph of the U.S. Pharmacopoeia (1990) at page 1963.

[0031] The alkyl vinyl ether/maleic acid or anhydride copolymers suitable for use in the base material are described in U.S. Pat. No. 4,910,247.

In general, these copolymers have from about 40 to about 90%, preferably from about 70 to 90%, of the initial carboxyl groups reacted with a metal, and have a molecular weight of between about 18,000 and about 80,000, preferably between about 40,000 and about 60,000 as measured by membrane osmometry in 2-butanone (1-10 grams/1000 ml solution). The various metal salts of the copolymer can be prepared by reacting the desired amount of metal hydroxide with a lower alkyl vinyl ether/maleic acid or maleic anhydride copolymer having a molecular weight of from about 18,000 to about

80,000. Such alkyl vinyl ether/maleic acid or anhydride copolymers are commercially available from ISP Corporation and sold as GANTREZ™ S series (MW approximately equal to 18,000-70,000; MS series (MW approximately equal to 60,000-75,000) and AN series (MW approximately equal to 18,000-80,000). The resultant metal salt product in which a portion of the original carboxyl groups are neutralized, is then dried and milled to a suitable particle size.

[0032] For purposes of the present invention, the copolymer is preferably a blend comprising a divalent calcium salt and a monovalent sodium salt of a methyl vinyl ether/maleic acid copolymer wherein the concentration of Ca is between about 10 and 15 wt.% of the blend; the concentration of Na is between about 1.5 and about 4 wt.% of the blend, and free acid-COOH represents between about 9 and about 25 wt.% of the blend. Alternatively, a commercially available mixed calcium and sodium salt of a methyl vinyl ether/maleic acid or anhydride copolymer can be used in the present mixture. Such a polymeric salt blend is supplied by ISP Corporation as GANTREZ™ MS-955 (CAS #62386-95-2) wherein the concentration of Ca is between about 11 and 13 wt.% of the blend, the concentration of Na is between about 2 and 2.5 wt.% of the blend, the proportion of Ca:Na is about 5-6:1 and the molecular weight is about 65,000-70,000.

ACTIVE INGREDIENTS

[0033] The medicament incorporated in the therapeutic compositions of the present invention may be any therapeutically active agent or combination of agents useful in the topical treatment of wounds, rashes, ulcers, and other conditions. For the treatment of aphthous ulcers, the medicament is preferably the immunosuppressive steroid TAA.

[0034] In addition, the therapeutic composition also includes a topical anesthetic such as lidocaine, benzocaine, bupivacaine, cocaine, dyclonine, mepivacaine, procaine, prilocaine, propoxycaine, chlorprocaine, tetracaine or salts thereof. Preferably, the anesthetic is lidocaine or a salt thereof, more preferably the anesthetic is lidocaine hydrochloride.

[0035] As will be described in Example 1 below, the addition of lidocaine to the formulation has a stabilizing effect on TAA in the base material. This stability effect can be seen by comparing Tables 1 and 2. Lidocaine hydrochloride had a marked effect on the stability of TAA in the formulation. In Example 2, a parallel five-month accelerated stability investigation revealed that the use of lidocaine hydrochloride increased the stability of the TAA formulation approximately 50%. The lidocaine hydrochloride was found to be a better stabilizer than lidocaine in the free base form. This result was particularly surprising because it was counterintuitive to add the salt of an active ingredient to a non-aqueous mixture rather than adding free base.

[0036] In addition to the active medicaments and anesthetic, the therapeutic compositions of the present invention can contain other components to modify the physical or esthetic properties thereof, such as coloring agents, flavoring agents, viscosity modifiers, gelling agents, antioxidants, preservatives and the like. Conventional preservatives such as methylparaben and propylparaben, and mixtures thereof and antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) may also be included to prevent bacterial contamination. However, it has been found through experimentation that the addition of butylated hydroxytoluene or butylated hydroxyanisole did not increase the stability of TAA in the formulations described in the Repka patents. Therefore, these additives need not be added to increase stability, but can be added to facilitate another characteristic of the formulation such as antibacterial properties. Moreover, these additives need not be present in the therapeutic compositions at all. Therefore, particular embodiments of the therapeutic compositions may be free of additives such as, for example, butylated hydroxytoluene, butylated hydroxyanisole, and EDTA. Accordingly, in one embodiment, the compositions are free of butylated hydroxytoluene, butylated hydroxyanisole, or both. In another embodiment, the compositions are free of EDTA. In another embodiment, the present compositions are free of butylated hydroxytoluene, butylated hydroxyanisole, EDTA, or any combination thereof. In a particularly preferred embodiment, the compositions are free of butylated hydroxytoluene, butylated hydroxyanisole, and EDTA.

[0037] In addition, the therapeutic compositions may also contain antioxidants, and in particular, antioxidants that act as reducing agents or oxygen scavengers. Without being bound by any particular theory, it is believed that the instability of TAA is at least in part due to the presence of oxygen in the prior formulated TAA containing compounds. Accordingly, the use of antioxidants capable of scavenging oxygen, and in particular oxygen free radicals, that may otherwise contribute to TAA degradation, is contemplated. Examples of suitable antioxidants include, for example, citric acid, ascorbic acid (vitamin C), tocopherols and tocotrienols (vitamin E), vitamin K, fumaric acid, malic acid, lactic acid, oxalic acid, and glutathione. Accordingly, the therapeutic compositions may also comprise an antioxidant. Preferably, the antioxidant acts as a reducing agent or oxygen scavenger. In one embodiment, the compositions comprise an antioxidant selected from the group consisting of oxalic acid, citric acid, ascorbic acid, fumaric acid, malic acid, lactic acid, and combinations thereof. In another embodiment, the compositions comprise an antioxidant selected from the group consisting of citric acid, ascorbic acid, fumaric acid, and combinations thereof. In another embodiment, the compositions comprise an antioxidant selected from the group consisting of ascorbic acid, fumaric acid, and combinations thereof. In a particularly preferred embodiment, the compositions comprise ascorbic acid.

[0038] Components such as acids or bases can also be added to adjust the pH of the compositions of the invention. Preferably, these compositions have a pH of less than 8.0, 7.9, 7.8, 7.7, 7.6, 7.5, 7.4, 7.3, 7.2, 7.1, 7.0, 6.9, 6.8, 6.7, 6.6, 6.5, 6.4, 6.3, 6.2, 6.1, 6.0, 5.9, 5.8, 5.7, 5.6, 5.5, 5.4, 5.3, 5.2, 5.1, 5.0, 4.9, 4.8, 4.7, 4.6, 4.5, 4.4, 4.3, 4.2, 4.1, or 4.0. Acids which may be included in the compositions include: citric acid, ascorbic acid, fumaric acid, malic acid, and lactic acid.

[0039] In one embodiment of the present invention, the base material of the formulation comprises a mixture of from about 3 to 15 wt.% GANTREZ™ MS-955, from about 40 to 60 wt.% PEG 400, and from about 20 to 50 wt.% PEG 3350. The active ingredients of the composition comprise from about 0.01 to about 0.3 wt.%, and most preferably from about 0.01 to 0.25 wt.% triamcinolone acetonide, and from about 0.25 to 6 wt.%, most preferably from about 1.5 to 2.5

wt.% lidocaine or a salt thereof. Any reference herein to a weight percentage of lidocaine salt is based upon the molar equivalent of lidocaine free base. Therefore, a composition of the invention including 5.0 wt.% lidocaine free base would be formulated with 6.0 wt.% lidocaine hydrochloride. Such compositions, when applied to an aphthous ulcer in the oral cavity, are found to adhere well to the mucosal surface and to dissolve slowly in the saliva such that the medicament is delivered and the treatment maintained for a period of 15 minutes or longer. In comparison therewith, compositions based only on the PEG ointment without the GANTREZ™ copolymer component do not adhere well to the applied surface, dissolve more rapidly in the saliva, and are effective for a period of only a few minutes.

[0040] In another embodiment, the therapeutic composition contains about 0.1 wt.% triamcinolone acetonide, about 2.5 wt.% lidocaine hydrochloride, and a base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyalkylene glycol, and in particular PEG.

[0041] In another embodiment, the therapeutic composition contains polyethylene glycol 400, polyethylene glycol 3350, a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, lidocaine or a salt thereof, triamcinolone acetonide, methylparaben, and propylparaben.

[0042] In yet another embodiment, the therapeutic composition contains about 52.6 wt.% polyethylene glycol 400, about 39.0 wt.% polyethylene glycol 3350, about 6.0 wt.% water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, about 2.3 wt.% lidocaine hydrochloride, about 0.1 wt.% triamcinolone acetonide, about 0.2 wt.% methylparaben, and about 0.02 wt.% propylparaben.

[0043] In one embodiment, the therapeutic composition contains about 52.6 wt.% polyethylene glycol 400, about 39.0 wt.% polyethylene glycol 3350, about 6.0 wt.% water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, about 2 wt.% lidocaine hydrochloride, about 0.1 wt.% triamcinolone acetonide, about 0.2 wt.% methylparaben, about 0.02 wt.%

propylparaben, up to about 0.02wt.% butylated hydroxytoluene, and up to about 0.01 wt.% butylated hydroxyanisole.

[0044] In yet another embodiment, the therapeutic composition is a composition, preferably an ointment composition, for the treatment of mouth sores comprising a polyalkylene glycol, a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, lidocaine hydrochloride, triamcinolone acetonide, and a preservative. In a particular embodiment, the composition for the treatment of mouth sores comprises polyethylene glycol 400, polyethylene glycol 3350, a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride, lidocaine hydrochloride, triamcinolone acetonide, methylparaben, and propylparaben. The composition may comprise about 0.01 to about 0.3 wt.% triamcinolone acetonide, about 0.01 to about 0.25 wt.% triamcinolone acetonide, or about 0.075 to about 0.125 wt.% triamcinolone acetonide,. In a particularly preferred embodiment, the therapeutic composition comprises about 0.1 wt.% triamcinolone acetonide.

[0045] The therapeutic composition may also comprise about 0.25 to about 6 wt.% lidocaine hydrochloride, about 0.25 to about 5 wt.% lidocaine hydrochloride, about 1 to about 5 wt.% lidocaine hydrochloride, or about 1.5 to about 2.5 wt.% lidocaine hydrochloride. In a particularly preferred embodiment, the therapeutic composition comprises 2 wt.% lidocaine hydrochloride. In an even more particularly preferred embodiment, the therapeutic composition comprises about 0.1 wt.% triamcinolone acetonide and about 2 wt.% lidocaine hydrochloride.

METHOD OF USE

[0046] While the compositions of the present invention are particularly useful in the treatment of aphthous ulcers, the utility of the compositions is not so limited. The compositions of the present invention may also be used in the topical application of medicaments to other mucous membranes in nasal, rectal and vaginal applications as well as oral applications. In addition, the compositions of the present invention may be used in the general treatment of wounds, abrasions and other epidermal conditions where topical medicaments

commonly find application. The compositions of the present invention are also useful for the treatment of eczema, bug bites, burns in mouth and, external mouth sores. The clinical efficacy of TAA and lidocaine containing formulations is known from the Repka patents and bioadhesive formulations prepared according to the Repka patent.

METHOD OF PRODUCTION

[0047] Stability of TAA may also be increased by reducing the amount of oxygen introduced into the formulation during production or packaging. This can be achieved in a number of ways, including, for example, by the production of any of the therapeutic compositions disclosed herein under an inert atmosphere. In one embodiment, the base material is mixed with the TAA and lidocaine or a salt thereof, under an inert atmosphere. The base may be purchased or produced as described herein.

[0048] In one embodiment, the base is produced by:

mixing a liquid polyalkylene glycol, preferably polyethylene glycol, a solid polyalkylene glycol, preferably polyethylene glycol, and a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride at a temperature at or above the melting point of the solid polyethylene glycol to produce a homogenized mixture; and

mixing a preservative, preferably methylparaben or propylparaben or a mixture of methylparaben and propylparaben with the homogenized mixture to form the base material.

[0049] In one embodiment, butylated hydroxytoluene (BHT), and/or butylated hydroxyanisole (BHA) may be added with the methylparaben and propylparaben to produce the base.

[0050] In another embodiment, the liquid PEG is PEG having a molecular weight of less than 600 such as PEG 400, and the solid PEG is PEG having a molecular weight above 600, such as PEG 3350.

[0051] In an embodiment, the base material and/or the homogenized mixture is produced under an inert atmosphere. In another embodiment, the

composition is packaged under an inert atmosphere. The inert atmosphere comprises nitrogen, helium, or any inert gas or inert mixture of gases as known in the art. In a preferred embodiment, the inert atmosphere is nitrogen gas.

[0052] It is advantageous to add the active ingredients last because it reduces their exposure to oxygen and heat which could degrade the active ingredients. Furthermore, once it was discovered that lidocaine hydrochloride increased the stability of TAA in the formulation it became preferable to avoid dissolving the lidocaine hydrochloride in the PEG during the first step of base material production, as was described in the Repka patents, in order to increase shelf life of the composition.

[0053] In a preferred embodiment, a composition of the invention is prepared by first adding the liquid PEG into a homogenizer or other suitable mixer as known in the art. In one embodiment, the homogenizer is bottom fed and is under continuous vacuum to further minimize oxygen within the homogenizer. The liquid PEG is heated to a temperature at or above the melting temperature of the solid PEG. The solid PEG and the water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride (such as Gantrez™ MS-955) are then fed into the homogenizer and mixed with the liquid PEG until the solid PEG dissolves. Optionally, other solid components (such as methyl paraben, propyl paraben, BHA, or BHT) are then added to the homogenized mixture and well mixed. The base material is then cooled to about 55°C. Active ingredients, such as TAA and lidocaine or a salt thereof, are added to the cooled base material and well mixed to form the therapeutic composition. The composition is then further cooled and packaged. In one embodiment, the base material is prepared in an inert atmosphere.

PACKAGING

[0054] The stability of the present formulations may also be increased by packaging the formulations, preferably under an inert atmosphere, in containers designed to reduce the degradation of the TAA. Without being bound by a particular theory, it is believed that reduced exposure to oxygen increases the stability of the present formulations. As such, packaging that is designed or able

to limit the amount of oxygen to which the formulations are exposed when contained therein is contemplated.

[0055] As the formulations are typically in the form of an ointment or gel, any conventional packaging that reduces exposure of the ointment or gel to oxygen, such as, for example, an oxygen impermeable container, but which also allows for dispensing or application of the ointment or gel is contemplated. Examples of such packaging include containers constructed of glass, plastic, metal, and in particular metal foil, or any combination thereof, or containers having a metal overwrap. In a particular embodiment, the ointment or gel is packaged in a flexible oxygen impermeable container such as a conventional metal foil container allowing for dispensing or application of the ointment or gel by the application of pressure to the container. In another embodiment, the container is wrapped in a metal overwrap or placed in a foil-lined or foil pouch such as Kapak VWR 2004/2005 Cat# 11213-852.

Stability Analysis

[0056] The storage stability of a composition of the invention can be determined by measuring the concentration of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II and III as described in Example 3. For example, the concentration of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II and III can be measured by liquid chromatography using methods well known in the art. One method measures the concentration of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II, and III by reverse phase high pressure liquid chromatography. The instrument parameters used to measure the experimental stability of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II and III are set out below.

Instrument Parameters

Injector	Hewlett Packard 1050 or 1100 Series		
Pump	Hewlett Packard 1050 or 1100 Series		
Detector	Hewlett Packard 1050 or 1100 Series		
Software	Hewlett Packard Chemstation or Equivalent		
Column	Agilent C8, zorbax, 3.5 μ , 4.6 X 150 mm		
Column Temperature	30° C		
Wavelength	238 nm and 280 nm (at 7.8 min)		
Flow Rate	1.2 mL/min		
Injection Volume	60 μ L		
Mobile Phase A	0.05% TFA in DI water		
Mobile Phase B	0.05% TFA in Acetonitrile		
Gradient	Time (min)	Mobile Phase	
	0 min	85% A	15% B
	11 min	0% A	100% B
	13 min	0% A	100% B
	Post time 2 min		

Elution Time= Lidocaine (3.777 min), Methylparaben (5.161 min), formulae II (6.109 min), formulae I (5.881 min), TAA (6.316 min), formulae III (6.803 min), Propylparaben (6.990 min), BHA (8.488 min), BHT (11.774 min)

[0057] The storage stability of a therapeutic composition as disclosed herein may be determined by measuring the concentration of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II, and III after exposure of the therapeutic composition to standard storage conditions. Typically, standard stability storage conditions comprise storage conditions in which the temperature is about room temperature and the relative humidity is generally about 60%. The International Conference on Harmonization (IHC) guidelines dictate standard stability storage conditions to be at a temperature of 25°C \pm 2°C and at a relative humidity of 60% \pm 5%. A particularly preferred standard stability storage condition is at a temperature of about 25°C and a relative humidity of about 60%. Once the particular conditions are selected, the composition is then subject to the standard stability conditions for a period of time sufficient to determine the

effects of the conditions on the tested composition. By way of example, the therapeutic compositions disclosed herein may be subjected to the standard stability storage conditions for a period of time sufficient to determine the point at which the concentration of certain active ingredients falls below an acceptable concentration or when the concentration of an undesirable degradant exceeds an acceptable concentration. This period of time may be anywhere from a 6 month period, a 12 month period, an 18 month period, a 24 month period, a 30 month period, or even a 36 month period. It may also include any period in between, including, for example 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 31, 32, 33, 34, or 35 month periods.

[0058] Thus, in some embodiments, the therapeutic composition is a storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 5 wt.% lidocaine or a salt thereof, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol and having particular characteristics as determined by exposure to particular standard stability storage conditions. In particular, the storage stable therapeutic composition may comprise at least about 85% and preferably at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, and 99% of the amount of triamcinolone acetonide based on the amount of triamcinolone acetonide within the composition at the time of manufacture or about 85% and preferably at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, and 99% of the amount of lidocaine or a salt thereof based on the amount of lidocaine or salt thereof within the composition at the time of manufacture after about 12, preferably about 18, more preferably about 24, even more preferably about 30, and most preferably about 36 months, and in particular at standard stability storage conditions of 25°C ± 2°C and 60% ± 5% relative humidity, and in particular, standard stability storage conditions of 25°C and 60% relative humidity. In particularly preferred embodiments, the storage stable therapeutic composition having wet adherent properties comprises a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 6 wt.% lidocaine or a salt thereof, the base material comprising from

about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol, wherein (a) the composition comprises at least 90% of triamcinolone acetonide based on the amount of triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity or (b) the composition comprises no more than about 10% of compounds having the formulae I, II, and III based upon the amount of triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity.

[0059] In another embodiment, the therapeutic composition is a storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 6 wt.% lidocaine or a salt thereof, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol and having particular characteristics as determined by exposure to particular standard stability storage conditions. In particular, the storage stable therapeutic composition may comprise at least about 0.01 wt.% and preferably at least about 0.05 wt.%, 0.075 wt.%, 0.1 wt.%, 0.125, 0.15 wt.%, 0.2 wt.%, 0.25 wt.%, 0.3 wt.% triamcinolone acetonide and about 0.25 wt.% and preferably about 0.5 wt.%, 0.75 wt.%, 1 wt.%, 1.25 wt.%, 1.5 wt.%, 1.75 wt.%, 2 wt.%, 2.25 wt.%, 2.5 wt.%, 2.75 wt.%, 3 wt.%, 3.25 wt.%, 3.5 wt.%, 3.75 wt.%, 4 wt.%, 4.25 wt.%, 4.5 wt.%, 4.75 wt.%, 5 wt.%, 5.25 wt.%, 5.5 wt. % or 5.75 wt.% lidocaine or a salt thereof after about 12, preferably about 18, more preferably about 24, even more preferably about 30, and most preferably about 36 months, and in particular at standard stability storage conditions of 25°C ± 2°C and at a relative humidity of 60% ± 5%, and in particular standard stability storage conditions of 25°C and 60% relative humidity. In a particularly preferred embodiment, the storage stable therapeutic composition having wet adherent properties comprises a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 5 wt.% lidocaine or a salt thereof, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and

from about 85 to 97 wt.% of polyethylene glycol, wherein: (a) the composition comprises at least 0.09 wt.% triamcinolone acetonide and 1.8 wt.% lidocaine, and preferably 1.9 wt.% lidocaine, or a salt thereof after 14 months or (b) the composition comprises no more than about 0.01 wt.% of compounds having the formulae I, II, and III after 14 months.

[0060] In one embodiment, the therapeutic composition maintains a minimum TAA concentration of 0.09 wt.% for at least 14 months. Preferably, the composition maintains a minimum TAA concentration of 0.09 wt.% for at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 months or more. In one embodiment, the therapeutic composition has a maximum TAA concentration of 0.15% and a minimum TAA concentration of 0.09 wt.% for at least 14 months.

[0061] The storage stability of a therapeutic composition as disclosed herein may also be determined by measuring the concentration of TAA, lidocaine or a salt thereof, or degradation products of formulae I, II, and III after exposure of the therapeutic composition to accelerated stability storage conditions. Typically, accelerated stability storage conditions comprise storage conditions in which the temperature is in excess of room temperature and the relative humidity is in excess of 60%. The International Conference on Harmonization (IHC) guidelines dictate accelerated stability storage conditions to be at a temperature of $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and at a relative humidity of $75\% \pm 5\%$. A particularly preferred accelerated stability storage condition is at a temperature of about 40°C and a relative humidity of about 75%. Once the particular conditions are selected, the composition is then subject to the accelerated stability conditions for a period of time sufficient to determine the effects of the conditions on the tested composition. By way of example, the therapeutic compositions disclosed herein may be subject to the accelerated stability storage conditions for a period of time sufficient to determine the point at which the concentration of certain active ingredients falls below an acceptable concentration or when the concentration of an undesirable degradant exceeds an acceptable concentration. This period of time may be anywhere from a one month period to a 6 month period, a 12 month period, an 18 month period, or even a 24 month period. It may also include any

period in between, including, for example 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, and 23 month periods.

[0062] Thus, in one embodiment, the therapeutic composition is a storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 6 wt.% lidocaine or a salt thereof, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol and having particular characteristics as determined by exposure to particular accelerated stability storage conditions. In particular, the storage stable therapeutic composition may comprise at least about 85%, preferably at least about 90%, still more preferably at least about 95%, even more preferably about 97%, and most preferably about 99% of the amount of triamcinolone acetonide based on the amount of triamcinolone acetonide within the composition at the time of manufacture or and about 85%, preferably at least about 90%, still more preferably at least about 95%, even more preferably about 97%, and most preferably about 99% of the amount of lidocaine or a salt thereof based on the amount of lidocaine or salt thereof within the composition at the time of manufacture after about 6, preferably about 12, more preferably about 18, and most preferably about 24 months of accelerated stability storage conditions of $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75 \pm 5\%$ relative humidity, and in particular, accelerated stability storage conditions of 40°C and 75% relative humidity. In a particularly preferred embodiment, the storage stable therapeutic composition having wet adherent properties comprises a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 5 wt.% lidocaine or a salt thereof, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol, wherein (a) the composition comprises at least 90% of said triamcinolone acetonide based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity; or (b) the composition comprises no more than about 10% of the compounds having the formulae I, II, and III based upon the amount of said

triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity.

[0064] Having described the invention in detail, it will be apparent that modifications and variations are possible without departing the scope of the invention defined in the appended claims. Furthermore, it should be appreciated that all examples in the present disclosure are provided as non-limiting examples.

EXAMPLES

[0065] The following non-limiting examples are provided to further illustrate the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the invention, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1: STABILITY TESTS FOR FORMULATIONS CONTAINING TAA ONLY AND TAA AND LIDOCAINE

[0066] Stability tests were conducted to determine the stability of TAA in a base material with wet adherent properties. The tests were conducted under accelerated and standard storage conditions.

[0067] Tests were conducted on formulation comprising a base material and TAA. The first formulation was identified as Formulation A and comprised the raw materials listed in the table below.

Formulation A

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	53.7%
Polyethylene Glycol (PEG) 3350	39.9%
Gantrez™ MS-955	6.0%
Methylparaben	0.2%
Triamcinolone Acetonide (TAA)	0.1%
Edetate Disodium, Dihydrate	0.05%
Propylparaben	0.02%
Butylated Hydroxytoluene (BHT)	0.02%
Butylated Hydroxyanisole (BHA)	0.01%
Total	100%

[0068] Formulation A was produced on a production scale, the formulation was prepared by first adding the PEG 400 into a Ross VersaMix kettle. The PEG 3350 was then added and the mixture heated with mixing to 60 – 65°C. The PEGs were mixed at this temperature for 10 minutes. The BHA, BHT, propyl paraben, and methyl paraben were added to the kettle and the mixture maintained at 60 – 65°C with mixing for 10 minutes. The EDTA and Gantrez™ MS-955 were then added and the heated mixture was then stirred an additional 10 minutes. TAA was then added and the mixture was maintained at 60 – 65°C with mixing for 10 minutes. The formulation was then cooled to 44 - 54°C, deaerated via vacuum, and packaged for storage.

[0069] The results of the stability studies for formulation A are summarized in the tables below.

Table 1a – Accelerated Storage (40°C / 75% relative humidity)

Months of Storage	Measured % of theoretical concentration
Initial Preparation	100.8
1	96.5
2	93.0
3	87.9
6	78.7

Table 1b – Room Temperature Storage (25°C / 60% relative humidity)

Months of Storage	Measured % of theoretical concentration
Initial Preparation	100.8
3	97.1
6	95.2
9	89.2
12	84.2

[0070] The stability tests were repeated on a formulation comprising a base material, TAA, and lidocaine. The formulation was identified as Formulation B and comprised the raw materials listed in the table below.

Formulation B

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.6
Polyethylene Glycol (PEG) 3350	39.0
Gantrez™ MS-955	6.0
Lidocaine (LID)	2.0
Methylparaben	0.2
Triamcinolone Acetonide (TAA)	0.1
Edetate Disodium, Dihydrate	0.05
Propylparaben	0.02
Butylated Hydroxytoluene (BHT)	0.02
Butylated Hydroxyanisole (BHA)	0.01
Total	100%

[0071] Formulation B was produced on a production scale, the formulation was prepared by first adding the PEG 400 into a Ross VersaMix kettle. The PEG 3350 was then added and the mixture heated with mixing to 60 – 65°C. The PEGs were mixed at this temperature for 10 minutes. The BHA, BHT, propyl paraben, and methyl paraben were added to the kettle and the mixture maintained at 60 – 65°C with mixing for 10 minutes. The EDTA and Gantrez™ MS-955 were then added and the heated mixture was then stirred an additional 10 minutes. TAA and lidocaine were then added and the mixture was maintained at 60 – 65°C with mixing for 10 minutes. The formulation was then cooled to 44 – 54°C, deaerated via vacuum, and packaged for storage.

[0072] The results of the test for formulation B are summarized in the tables below.

Table 2a – Accelerated (40°C / 75% relative humidity)

Months of Storage	Measured % of theoretical concentration
Initial Preparation	100.4
1	96.8
2	94.3
3	92.9
6	82.2

Table 2b – Room Temperature (25°C / 60% relative humidity)

Months of Storage	Measured % of theoretical concentration
Initial Preparation	100.4
3	96.5
6	96.1
9	93.9
12	90.4

[0073] The data in table 1b shows Formulation A would fail the FDA shelf life storage stability requirement for TAA between 6 and 9 months of storage under standard storage conditions. Extrapolation of the data in table 2b shows formulation B's TAA concentration would fail after 13 months. Comparison of Formulation A and B, surprisingly, shows that the addition of lidocaine had a stabilizing effect.

EXAMPLE 2: STABILITY TESTS FOR FORMULATIONS CONTAINING VARIOUS FORMS OF LIDOCAINE

[0074] Five formulations were prepared and tested to determine the effect of lidocaine and lidocaine hydrochloride in formulations comprising a base material and TAA.

[0075] Each formulation was prepared on a laboratory scale. The dry ingredients, including active ingredients, were added to a 1 L beaker and mixed well with a mechanical stirrer for thirty minutes. The PEG 400 was added to the beaker with continuous stirring and heating to 65°C over a period of thirty

minutes to form a hot gel. The hot gel was then transferred into 11 glass vials and allowed to cool to room temperature.

[0076] The five formulations contained varying combinations of lidocaine, lidocaine hydrochloride, and TAA, as well as benzoic acid to lower the pH of the formulations. The components of each formulation are summarized in the tables below.

Formulation A (Only TAA)

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	53.7%
Polyethylene Glycol (PEG) 3350	39.9%
Gantrez™ MS-955	6.0%
Methylparaben	0.2%
Triamcinolone Acetonide (TAA)	0.1%
Edetate Disodium, Dihydrate	0.05%
Propylparaben	0.02%
Butylated Hydroxytoluene (BHT)	0.02%
Butylated Hydroxyanisole (BHA)	0.01%
Total	100%

Formulation B (TAA+Lid)

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.6
Polyethylene Glycol (PEG) 3350	39.0
Gantrez™ MS-955	6.0
Lidocaine (LID)	2.0
Methylparaben	0.2
Triamcinolone Acetonide (TAA)	0.1
Edetate Disodium, Dihydrate	0.05
Propylparaben	0.02
Butylated Hydroxytoluene (BHT)	0.02
Butylated Hydroxyanisole (BHA)	0.01
Total	100%

Formulation C (Lid-Bz)

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.9%
Polyethylene Glycol (PEG) 3350	38.3%
Gantrez™ MS-955	6.0%
Lidocaine	2.0%
Methylparaben	0.2%
Triamcinolone Acetonide (TAA)	0.1%
Edetate Disodium, Dihydrate	0.05%
Propylparaben	0.02%
Butylated Hydroxytoluene (BHT)	0.02%
Butylated Hydroxyanisole (BHA)	0.01%
Benzoic acid	0.4%
Total	100%

Formulation D (Lid.HCl)

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.3%
Polyethylene Glycol (PEG) 3350	38.8%
Gantrez™ MS-955	6.0%
Lidocaine Hydrochloride (LID.HCl)	2.5%
Methylparaben	0.2%
Triamcinolone Acetonide (TAA)	0.1%
Edetate Disodium, Dihydrate	0.05%
Propylparaben	0.02%
Butylated Hydroxytoluene (BHT)	0.02%
Butylated Hydroxyanisole (BHA)	0.01%
Total	100%

Formulation E (Lid.HCl+Bz)

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.6%
Polyethylene Glycol (PEG) 3350	38.2%
Gantrez™ MS-955	6.0%
Lidocaine Hydrochloride (LID.HCl)	2.3%
Methylparaben	0.20%
Triamcinolone Acetonide (TAA)	0.1%
Edetate Disodium, Dihydrate	0.05%
Propylparaben	0.02%
Butylated Hydroxytoluene (BHT)	0.02%
Butylated Hydroxyanisole (BHA)	0.01%
Benzoic acid	0.5%
Total	100%

[0077] The pH of the five formulations was measured. To determine the pH of each formulation approximately 1 g of sample was placed into a beaker and diluted with 50 mL of DI water. Two drops of a saturated solution of KCl

were added and the pH was then measured using a calibrated pH meter. The results of the pH measurements are reported in the table below.

Table 3

Formulation Identification Name	Components of formulation	pH
Formulation A (Only TAA)	No lidocaine, only TAA in the base formulation	6.81
Formulation B (TAA+Lid)	TAA + lidocaine in the base formulation	8.10
Formulation C (Lid-Bz)	TAA + lidocaine + benzoic acid in base formulation	7.32
Formulation D (Lid-HCl)	TAA + lidocaine hydrochloride in the base formulation	6.79
Formulation E (Lid-HCl+Bz)	TAA + lidocaine hydrochloride + benzoic acid in base formulation	6.07

[0078] The formulations were stored under accelerated storage conditions as in Example 1. Periodic measurements were made to determine the concentration of TAA in the formulations.

[0079] The results of the five month accelerated storage test at 40°C and 75% relative humidity are illustrated in Table 4A and 4B below and in Figures 1 and 2. The data contained in Tables 4A and 4B and in Figures 1 and 2 shows that the formulation with TAA and lidocaine hydrochloride (Lid-HCl) was the most stable formulation of TAA in the bioadhesive base.

Table 4A.

TAA % after months of accelerated storage				
Formulation	1 mo.	3 mos.	4 mos.	5 mos.
A (Only-TAA)	101.4	95	85.9	84.2
B (TAA+Lid)	103.2	93.5	90.2	87.9
C (Lid-Bz)	98	90.7	78	73.8
D (Lid-HCl)	101.6	100.5	95.3	93.3
E (Lid-HCl+Bz)	95.5	91.5	83.4	82

Table 4B.

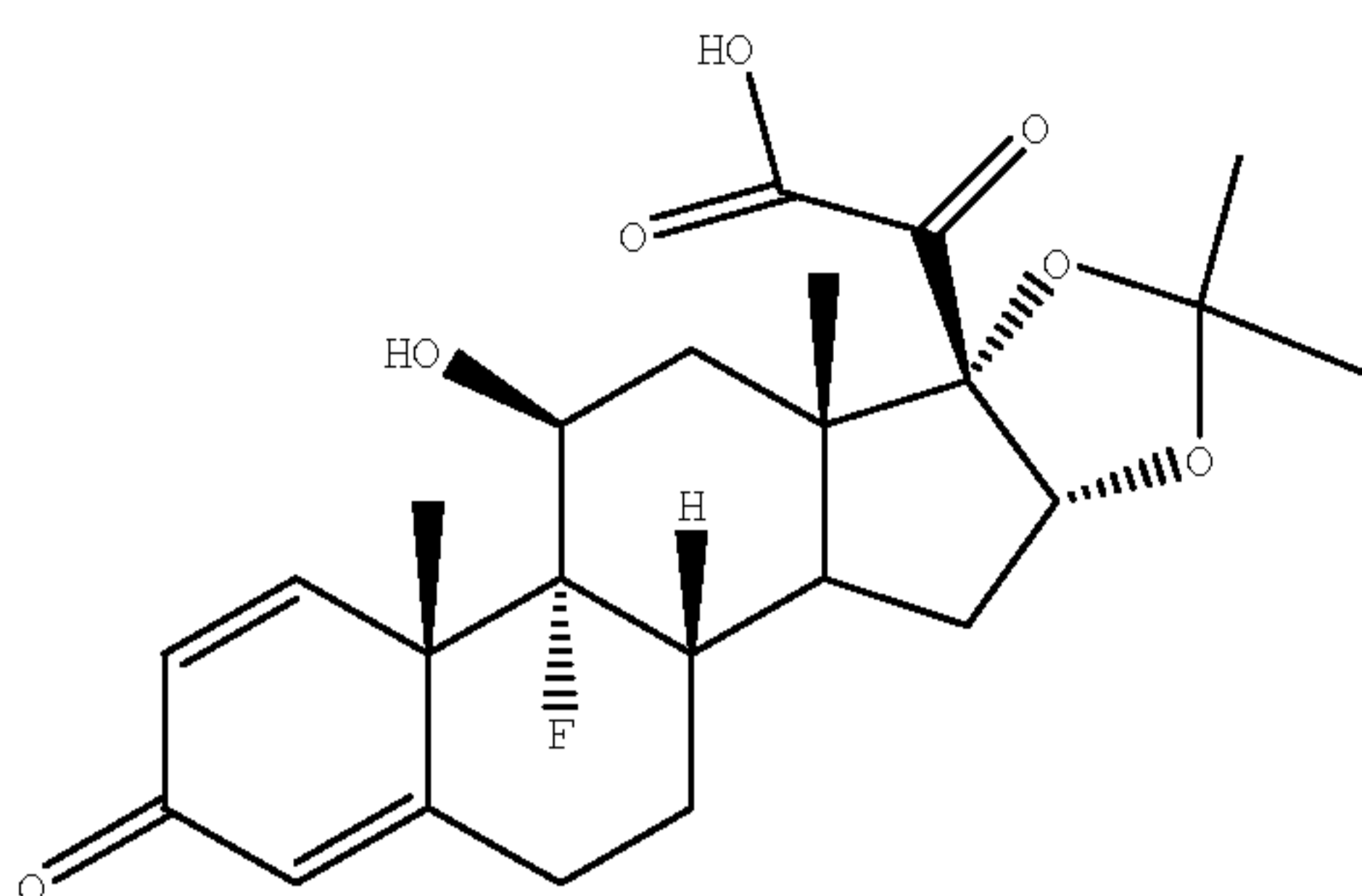
Normalized TAA % after months of accelerated storage				
Formulation	1 mo.	3 mos.	4 mos.	5 mos.
A (Only-TAA)	100	93.6	84.5	82.8
B (TAA+Lid)	100	90.3	87	84.7
C (Lid-Bz)	100	92.7	80	75.8
D (Lid-HCl)	100	98.9	93.7	91.7
E (Lid-HCl+Bz)	100	96	87.9	86.5

[0080] By comparing formulation B (pH 8.10) to formulation C (pH 7.32) and formulation D (pH 6.79) to formulation E (pH 6.07) it is shown that TAA in a bioadhesive formulation is degraded faster in a formulation with acid added than in a formulation without acid added. Therefore, decreasing the pH of the bioadhesive formulation did not increase stability of TAA as reported by Gupta and Ungphaiboon for TAA solutions. It appears that the benzoic acid interfered with the stabilizing properties of lidocaine and lidocaine hydrochloride.

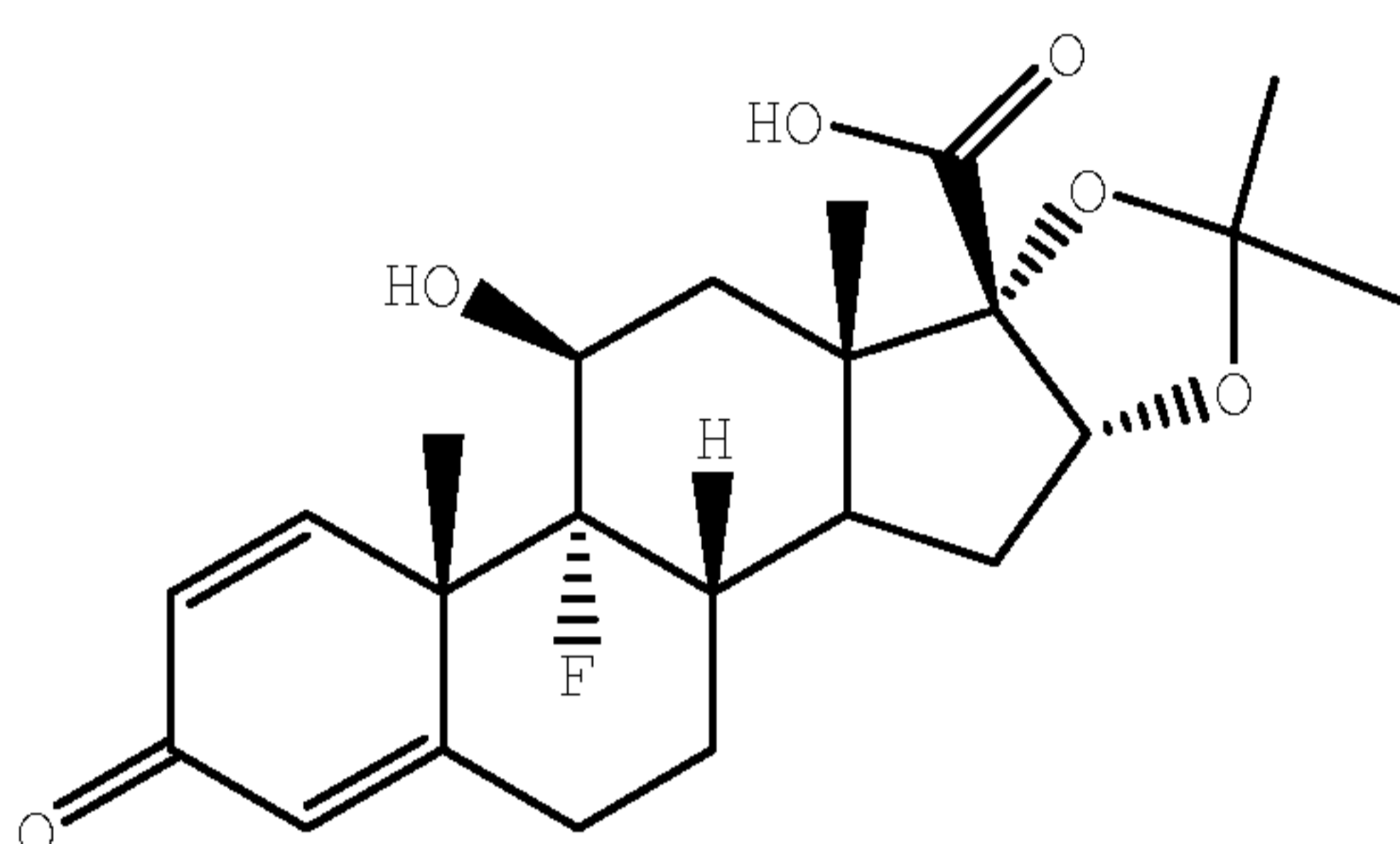
EXAMPLE 3: DETERMINATION OF DEGRADANTS

[0081] LC-MS studies have found the degradation of TAA in formulation B results in the formation of three key oxidative degradation compounds having the formulae:

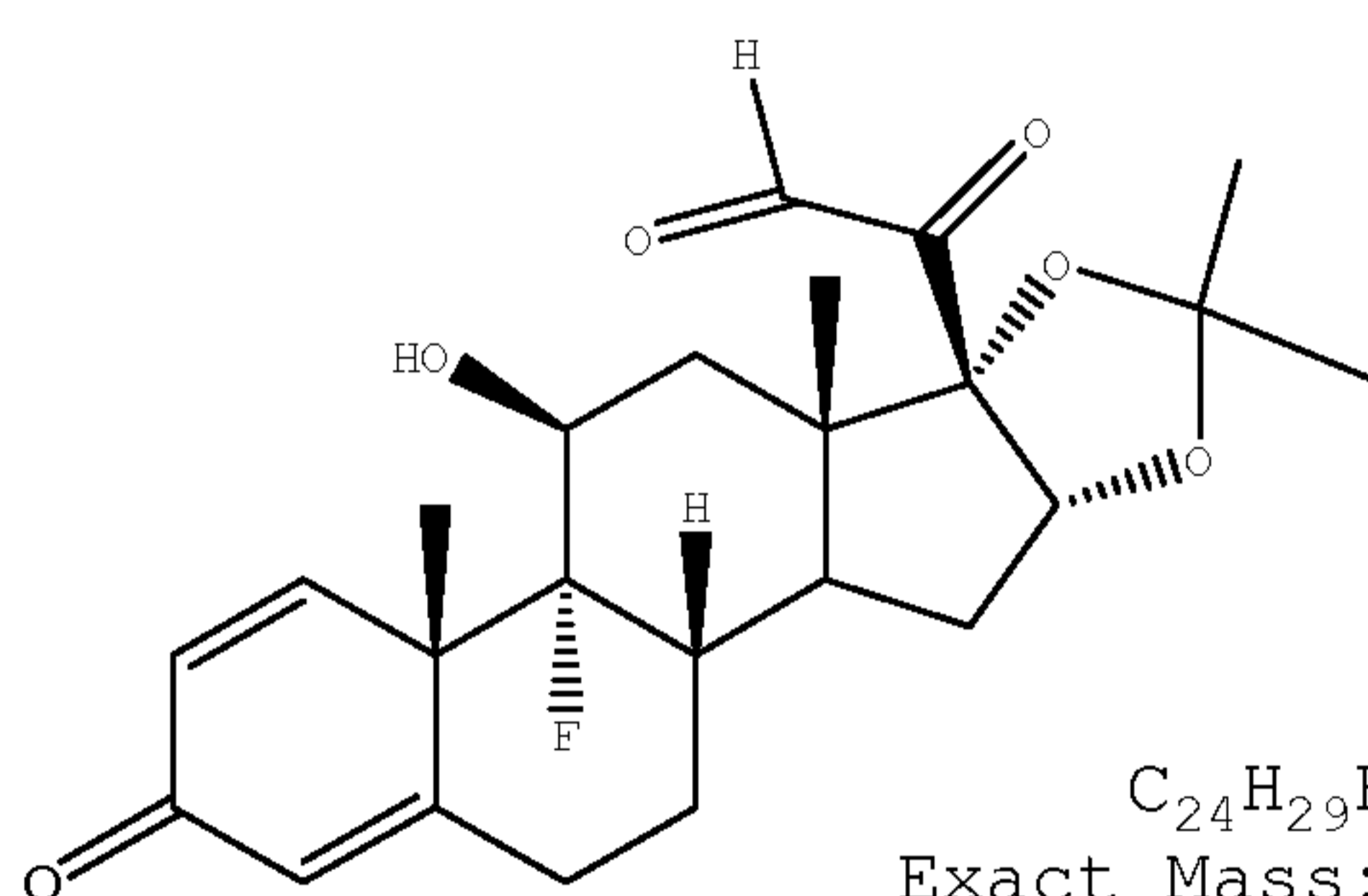
31



$C_{24}H_{29}FO_7$
 Exact Mass: 448.19
 Mol. Wt.: 448.48
 C, 64.27; H, 6.52; F, 4.24; O, 24.97 (I);



$C_{23}H_{29}FO_6$
 Exact Mass: 420.19
 Mol. Wt.: 420.47
 C, 65.70; H, 6.95; F, 4.52; O, 22.83 (II); and



$C_{24}H_{29}FO_6$
 Exact Mass: 432.19
 Mol. Wt.: 432.48
 C, 66.65; H, 6.76; F, 4.39; O, 22.20 (III).

[0082] These degradation products were found in both degraded TAA (degraded drug substance) and degraded formulation B (degraded drug product sample). HPLC chromatograms of these decomposed samples indicate that the combined peak areas of formulae I, II, and III correspond to the loss of area in the TAA peak due to oxidative degradation. Therefore, with due consideration of

the margin of analytical error, mass balance can be achieved as the relative total area count of these three indicator compounds and can be used to monitor the stability of TAA in the formulation. International Conference on Harmonization (ICH) Guidance Document Q1A, "Stability Testing of New Drug Substances and Products."

EXAMPLE 4: AIR OXIDATION OF TAA-LIDOCAINE HYDROCHLORIDE AND TAA-LIDOCAINE FREE BASE IN A MIXTURE OF METHANOL AND WATER

[0083] The purpose of this investigation was to demonstrate that formulation D, using lidocaine hydrochloride, is more stable to air exposure than formulation B, using lidocaine.

[0084] *Experiment A* – A solution of TAA (29 mg) in methanol (20 mL) was treated with lidocaine (580 mg), and air bubbled through the mixture using a glass pipette.

[0085] *Experiment B* – A solution of TAA (32 mg) in methanol (20 mL) was treated with lidocaine hydrochloride (640 mg) and air bubbled through the mixture using a glass pipette.

[0086] The progress of each experiment was monitored by HPLC. The HPLC results showed there was no significant difference between the experiments after 24 hrs. To each of these reactions was added water (1 mL) and the reaction was allowed to continue over two days. The HPLC results showed a significant difference between experiment A, illustrated as the HPLC chromatogram of Figure 3, and experiment B, illustrated as the HPLC chromatogram of Figure 4. Experiment A (TAA- Lidocaine) showed significant impurities (Im) versus experiment B (TAA-Lidocaine-hydrochloride).

[0087] The area of the TAA peak decreased as the experiment continued (data not shown). It was found that the increase in peak area of the impurities was directly proportional to the decrease of the TAA peak area.

EXAMPLE 5: STABILITY OF FORMULATIONS B AND D UNDER OXIDATIVE STRESS CONDITIONS

[0088] In separate beakers 1.543 g of formulation B and 1.560 g of the formulation D were dissolved in methanol (20 mL). To these solutions was added copper(II) acetate (6.89 mg). In formulation B, the color of the solution changed from blue to green immediately. In formulation D, the color of the solution changed from blue to green only after heating for 5 min. The color of copper (II) is blue and the color of the copper (I) is green. This experiment shows formulation D is more resistant to oxidation than formulation B.

EXAMPLE 6: STABILITY OF FORMULATIONS CONTAINING ANTIOXIDANTS

[0089] The purpose of this investigation is to determine the effects of individual ingredients such as EDTA, BHA, BHT, lidocaine free base, and lidocaine hydrochloride on the stability of TAA in the formulations listed in Table 5 and the specific Formulation Detail Tables listed thereafter. The method of preparation of the formulations is the same as listed in Method of Production above using pilot scale manufacturing equipment (5 kg scale).

Table 5

Formulation ID	Formulation Constituents
001	Using Lidocaine free base
002	Using Lidocaine.HCl Monohydrate
003	Using Lidocaine.HCl Monohydrate
004	Using Lidocaine.HCl Monohydrate
005	Using Lidocaine.HCl Monohydrate minus BHA & BHT
006	Using Lidocaine.HCl Monohydrate minus EDTA
007	Using Lidocaine.HCl Monohydrate minus BHA /BHT/EDTA
008	Using Lidocaine.HCl Monohydrate minus BHA /BHT/EDTA
009	Using Lidocaine.HCl Monohydrate minus BHA /BHT/EDTA
010	Current Formulation, TAA only, minus LID
011	Current Formulation, TAA only, minus LID,BHA, BHT, EDTA
012	Using LID.HCl Monohydrate minus TAA
013	Using LID.HCl Monohydrate minus TAA, BHT/BHA, EDTA
014*	Using LID.HCl Monohydrate with TAH, minus TAA, BHT/BHA, EDTA
015*	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus Oxalic Acid
016*	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus Citric Acid
017	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus Ascorbic Acid
018	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus Fumaric Acid
019*	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus DL Malic Acid
020*	Using LID.HCl Monohydrate minus BHT/BHA, EDTA, Plus Lactic Acid

*study numbers 014 – 016, 019, and 020, as discussed in greater detail below, were not further examined.

FORMULATION DETAILS**Formulation 001**

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.600
Polyethylene Glycol (PEG) 3350	39.000
GANTREZ™ MS-955	6.000
Lidocaine	2.000
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.050
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.020
Butylated Hydroxyanisole (BHA)	0.010
Total	100.000

Formulation 002- 004

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.312
Polyethylene Glycol (PEG) 3350	38.823
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.050
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.020
Butylated Hydroxyanisole (BHA)	0.010
Total	100.000

Formulation 005

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.329
Polyethylene Glycol (PEG) 3350	38.836
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.050
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Total	100.000

Formulation 006

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.341
Polyethylene Glycol (PEG) 3350	38.844
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.020
Butylated Hydroxyanisole (BHA)	0.010
Total	100.000

Formulation 007- 009

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.358
Polyethylene Glycol (PEG) 3350	38.857
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Total	100.000

Formulation 010

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	53.748
Polyethylene Glycol (PEG) 3350	39.852
GANTREZ™ MS-955	6.000
Lidocaine	0.000
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.050
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.020
Butylated Hydroxyanisole (BHA)	0.010
Total	100.000

Formulation 011

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	53.794
Polyethylene Glycol (PEG) 3350	39.886
GANTREZ™ MS-955	6.000
Lidocaine	0.000
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Total	100.000

Formulation 012

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.369
Polyethylene Glycol (PEG) 3350	38.866
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.000
Edetate Disodium, Dihydrate	0.050
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.020
Butylated Hydroxyanisole (BHA)	0.010
Total	100.000

Formulation 013

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	52.415
Polyethylene Glycol (PEG) 3350	38.900
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.000
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Total	100.000

Formulation 017

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	51.210
Polyethylene Glycol (PEG) 3350	38.005
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Ascorbic Acid	2.000
Total	100.000

Formulation 018

Raw Material	% of Product by Wt.
Polyethylene Glycol (PEG) 400	51.210
Polyethylene Glycol (PEG) 3350	38.005
GANTREZ™ MS-955	6.000
Lidocaine.HCL (LID.HCL)	2.465
Methylparaben	0.200
Triamcinolone Acetonide (TAA)	0.100
Edetate Disodium, Dihydrate	0.000
Propylparaben	0.020
Butylated Hydroxytoluene (BHT)	0.000
Butylated Hydroxyanisole (BHA)	0.000
Fumaric Acid	2.000
Total	100.000

[0090] Twenty bio-adhesive gel pilot batches, designated 001 through 020, were formulated. Formulation 001 contains Lidocaine free base. Formulations 002 to 004 contain Lidocaine Hydrochloride in place of the Lidocaine free base. Formulations 005 and 006 were designed to assess the roles of EDTA, BHA, and BHT. The formulation used in 007 to 009 was designed to assess the impact of removing all of these preservatives/antioxidants. Trials 010 and 011 were designed to assess the impact of removing Lidocaine from the formulation completely to better understand the effect on the TAA. Formulations 012 and 013 established the impact of preservative/antioxidant removal on the Lidocaine stability. In addition they help to assess the presence of lidocaine degradation products in the absence of TAA. In Formulation 014, TAA was replaced with triamcinolone hexanoide (TH), a derivative of TAA, to assess TH stability versus TAA. Formulations 015 through 020 were designed to establish the effect of individual organic acids/antioxidants on the oxidative degradation of TAA.

[0091] Normalized TAA assay results for six months of accelerated stability storage are represented in Table 6 and in Figure 5.

Table 6. Normalized TAA assay results for 6 months of accelerated stability storage

Lot#	0 m	1 m	2 m	3 m	4 m	5 m	6 m
001	100	96	93.9	91.8	90.5	89.7	84.3
002	100	100.5	99.9	99.1	99.3	100	98.4
003	100	98.4	96.7	97.2	98.5	97.6	96.1
004	100	98.4	97.9	97.4	97.5	97.9	96.3
005	100	97.9	96.7	96.7	97.4	96.8	94.2
006	100	98.8	97.4	97.0	97.1	97.3	96.1
007	100	98.4	98.3	97.5	97.7	97.2	96.0
008	100	100	98.7	97.5	98.9	98.1	97.4
009	100	99.2	98.8	97.7	98.2	97.2	97.2
010	100	95.3	93.0	90.9	90.1	88.7	87.9
011	100	95.9	97.1	96.9	95.0	93.1	93.7
017	100	98.0	99.1	99.5	97.8	97.6	98.8
018	100	97.1	97.9	98.8	96.7	97.5	97.1

*study numbers 014 – 016, 019, and 020, as discussed in greater detail below, were not further examined.

[0092] Total percent of TAA degradants for the six months of accelerated storage were calculated by totaling the individual percent degradants for each of formulae I, II, and III, each individual percentage being determined according to the following formula, and are listed in Table 7 and depicted graphically in Figure 6.

$$\% \text{ Imp} = \frac{(\text{Area Imp})}{(\text{Area TAA} + \text{Area Imp I} + \text{Area Imp II} + \text{Area Imp III})} \times 100\%$$

Table 7. Total % TAA Degradants for 6 months of accelerated storage

Lot#	0-time	1m	2m	3m	4m	5 m	6m
001	0	3.2	4.63	6.74	8.2	9.16	11.92
002	0	0.96	1.18	1.97	2.29	2.59	3.43
003	0	0.91	1.1	1.8	2.11	2.39	3.21
004	0	0.98	1.22	2.05	2.36	2.67	3.66
005	0	0.75	1.2	1.88	2.51	2.89	4.92
006	0	0.76	1.21	1.78	2.2	2.58	3.33
007	0	0.79	1.33	2.04	2.59	2.95	4.43
008	0	0.77	1.25	1.88	2.38	2.96	4.59
009	0	0.82	1.33	2.01	2.53	3.05	4.03
010	0	3.4	5.03	7.06	8.26	10.22	10.98
011	0	NA	2.11	3.18	4.81	4.66	4.98
017	0	NA	0.69	2.18	1.5	1.61	1.78
018	0	NA	1.3	1.81	1.86	2.14	2.77

[0093] The total percent TAA degradants, as listed in Table 7 above and Table 9 below, represents the percentage of the 0.1 wt.% TAA degraded. Thus, for example, 001 has 11.92% degradation of the 0.1 wt.% TAA, or 0.012 wt.% TAA degradants, and 002 has 3.43% degradation of the 0.1 wt.% TAA, or 0.003 wt.% TAA degradants. The total percent of TAA degradants listed in the table is the sum of percent TAA degradants of formulae I, II, and III.

[0094] Normalized TAA assay results for twelve months of room temperature stability storage were determined and are listed in Table 8 and depicted graphically in Figure 7.

Table 8. Normalized TAA assay results for 12 months of room temperature stability storage

Lot#	0-time	3m	6m	9m	12m
001	100	96.7	92.5	93.1	90.6
002	100	100.8	99.6	100.8	98.8
003	100	98.5	95.1	97.0	97.0
004	100	99.2	97.0	98.6	96.8
005	100	98.5	96.0	97.1	95.4
006	100	98.9	97.9	98.1	96.3
007	100	99.8	97.9	98.4	96.8
008	100	100.7	98.3	99.4	97.4
009	100	99.0	98.2	99.4	98.1
010	100	95.9	93.5	93.2	91.2
011	100	96.7	94.9	94.6	93.1
017	100	99.7	98.6	99.8	96.2
018	100	98.9	98.1	99.0	96.2

[0095] Total percent of TAA degradants for the twelve months of room temperature storage were calculated by totaling the individual percent TAA degradants for each of formulae I, II, and III, each individual percentage being determined according to the following formula and are listed in Table 9 and depicted graphically in Figure 8.

$$\% \text{ Imp} = \frac{(\text{Area Imp})}{(\text{Area TAA} + \text{Area Imp I} + \text{Area Imp II} + \text{Area Imp III})} \times 100\%$$

Table 9. Total % TAA Degradants for 12 months of room temperature storage

Lot#	0-time	3m	6m	9m	12m
001	0	2.84	4.92	6.3	7.83
002	0	0.72	0.94	1.53	2.1
003	0	0.81	0.99	1.44	2.09
004	0	0.73	0.97	1.6	2.29
005	0	0.69	0.96	1.59	2.12
006	0	0.74	1	1.61	2.29
007	0	0.8	1.44	1.79	2.43
008	0	0.84	1.65	1.88	2.38
009	0	0.79	1.32	1.74	2.35
010	0	2.89	4.68	6.5	8.57
011	0	2.58	3.21	4.35	5.93
017	0	0.73	0.68	1.28	2.07
018	0	0.88	0.93	1.45	1.47

[0096] Trials 001 and 003 were subjected to HPLC analysis. The results are represented in Figures 9 and 10, respectively, and demonstrate the reduced degradation of TAA (and likewise the decreased presence of compounds having the formulae I, II, or III) in formulation 003 versus formulation 001.

EXAMPLE 7 – USE OF A BLANKET OF INERT GAS

[0097] This purpose of the following investigation was to determine the affects of producing a therapeutic compound under a blanket of inert gas. The S-001 batch listed in Table 10 was prepared using the Fryma MaxxD semi-solid manufacturing equipment. Studies S-002 through S-017 were performed at the Fryma process lab in Germany. S-017 was found to have inconsistent results indicating non-homogeneous product. As this material was from the same batch as studies S-015 & 016, it was concluded that the inconsistencies may have stemmed from a heating band malfunction which occurred during the packaging

of S-017 (the last material in the batch to be packaged). Study S-017, which is a repeat of the data for S-013, was therefore excluded from further study.

Table 10

Batch #	Study Code	Experiment Description
	S-001	Formulation 001 of Example 6
1	S-002	Lab scale of S-001
2	S-003	Repeat of S-002
3	S-004	Lab scale of S-001 with process change to introduce the Gantrez with the PEG 3350
4	S-005	Repeat of S-004 except heat premix under vacuum to remove any water (premix sample held at 65 deg C with 4 vacuum cycles ~ 30 min)
	S-006	Repeat of S-004 except heat premix under vacuum to remove any water (premix sample held at 85 deg C for an additional 3 vacuum cycles ~ 25 min)
	S-007	Repeat of S-004 except heat premix under vacuum to remove any water (the final product formulated from the above premix S-006)
5	S-008	Repeat of S-002 with extended heating (65 deg C) hold under vacuum to remove water (3 vacuum cycles ~ 35 min)
	S-009	Repeat of S-002 with extended heating (85 deg C) hold under vacuum to remove water (S-008 product held at 85 deg C for 3 vacuum cycles ~ 30 min)
6	S-010	S-001 with dried Gantrez
7	S-011	S-001 with manufacturing and packaging under nitrogen as well as secondary nitrogen filled foil pouch

Batch #	Study Code	Experiment Description
	S-012	S-001 with manufacturing and packaging under nitrogen (S-011 without foil pouch)
	S-013	S-001 with manufacturing under nitrogen (S-011 without nitrogen blanket on tube filler/sealer)
8	S-014	S-001 without Gantrez
9	S-015	Repeat of S-011
	S-016	Repeat of S-012
	S-017	Repeat of S-013

[0098] The percent TAA recovery, obtained according to the accelerated stability storage methods discussed above for a six month period, is represented graphically in Figure 12. The TAA recovery, obtained according to the standard stability storage methods discussed above for a 24 month period, is represented graphically in Figure 13. For these studies, data regarding months 7, 8, 10, 11, 13-17, and 19-23 were calculated values based on observed values using data obtained for months 1-6, 9, 12, 18, and 24 (the standard test periods per the IHC). For the clinical trial material (CTM) batch and registration (Reg 1, Reg 2, and Reg 3) batches (the same formulation as Formulation 001 of example 6), data regarding months 7, 8, 10, and 11 were calculated values based on observed values using data obtained for months 1-6, 9, and 12.

[0099] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a," "an," "the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

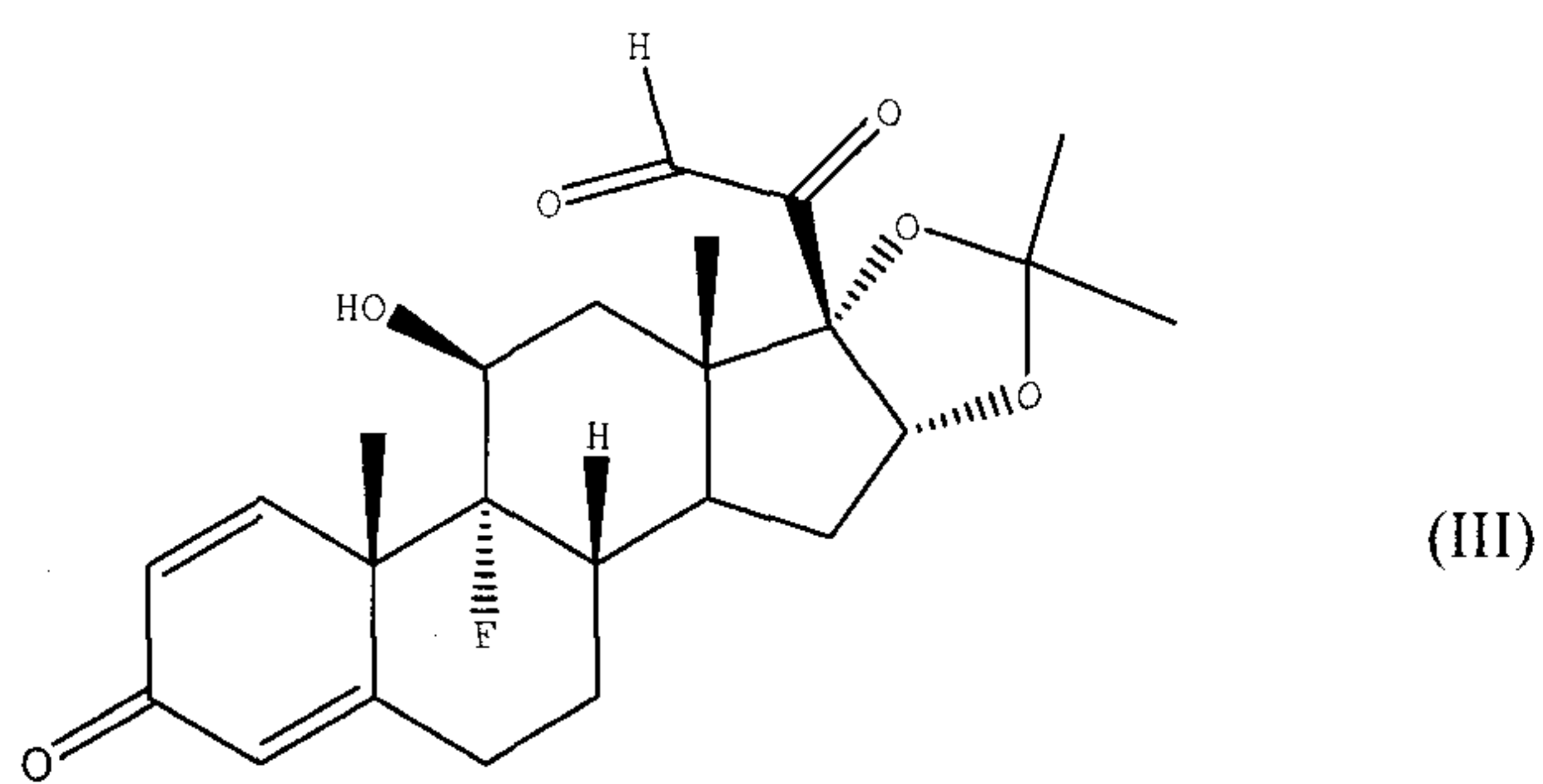
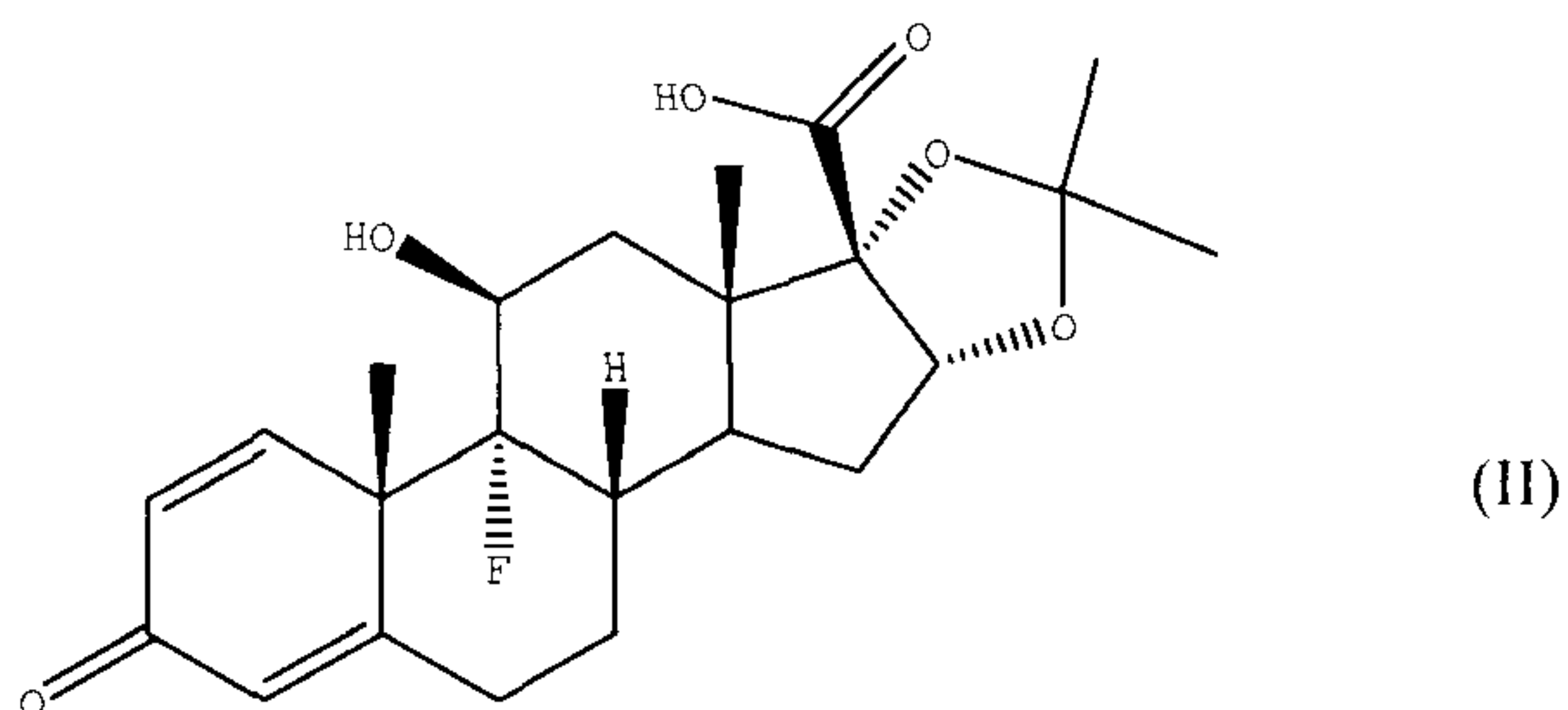
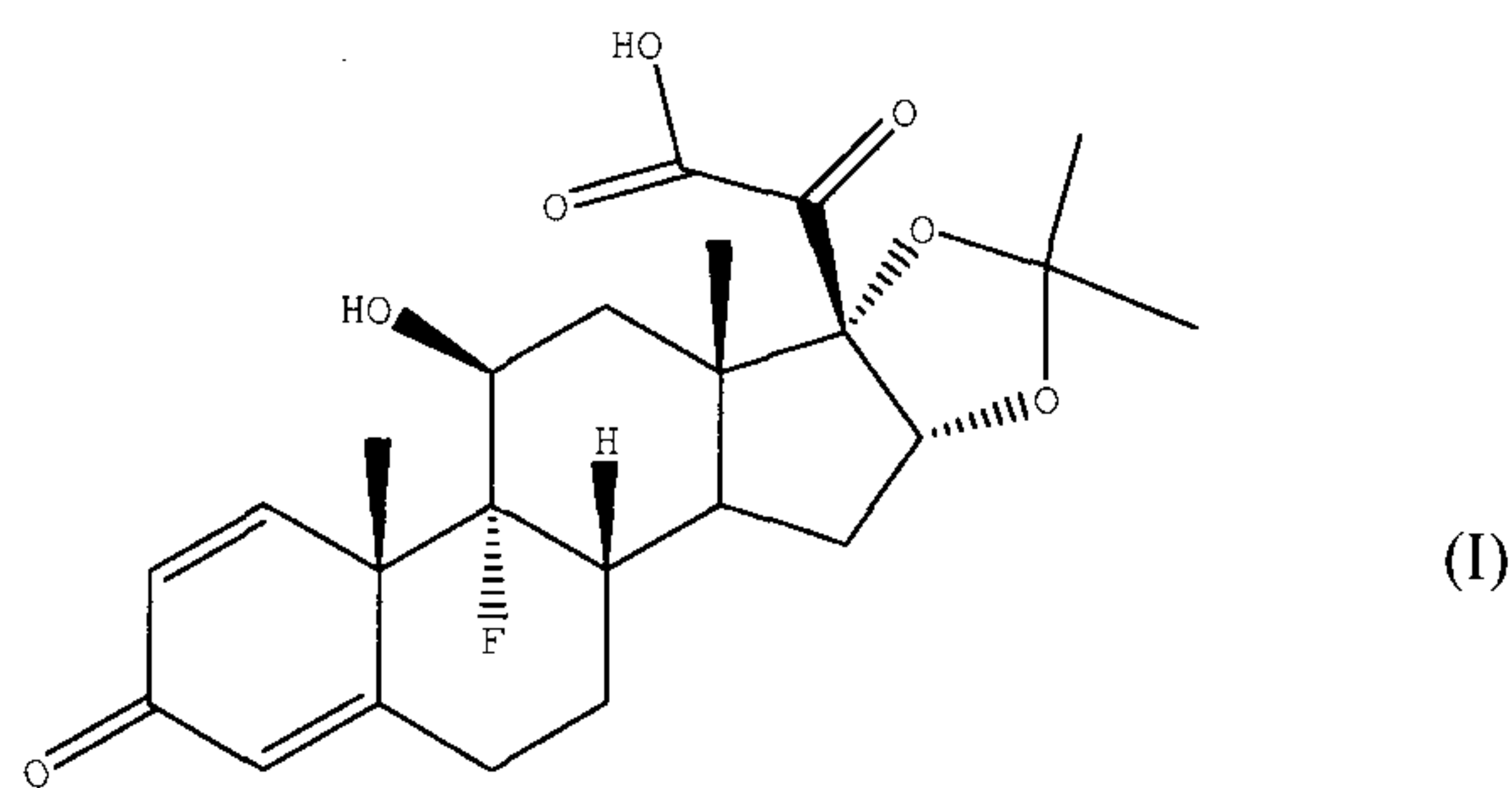
[00100] In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained. As various changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description and shown in any accompanying figures shall be interpreted as illustrative and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.01 to about 0.3 wt.% triamcinolone acetonide, and about 0.25 to about 6 wt.% salt of lidocaine, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of a polyalkylene glycol, wherein:

(a) the composition comprises at least about 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity;

(b) the composition comprises no more than about 10% of compounds having the formulae of any one of I, II, or III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity



(c) the composition comprises at least about 90% of said triamcinolone acetonide based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity; or

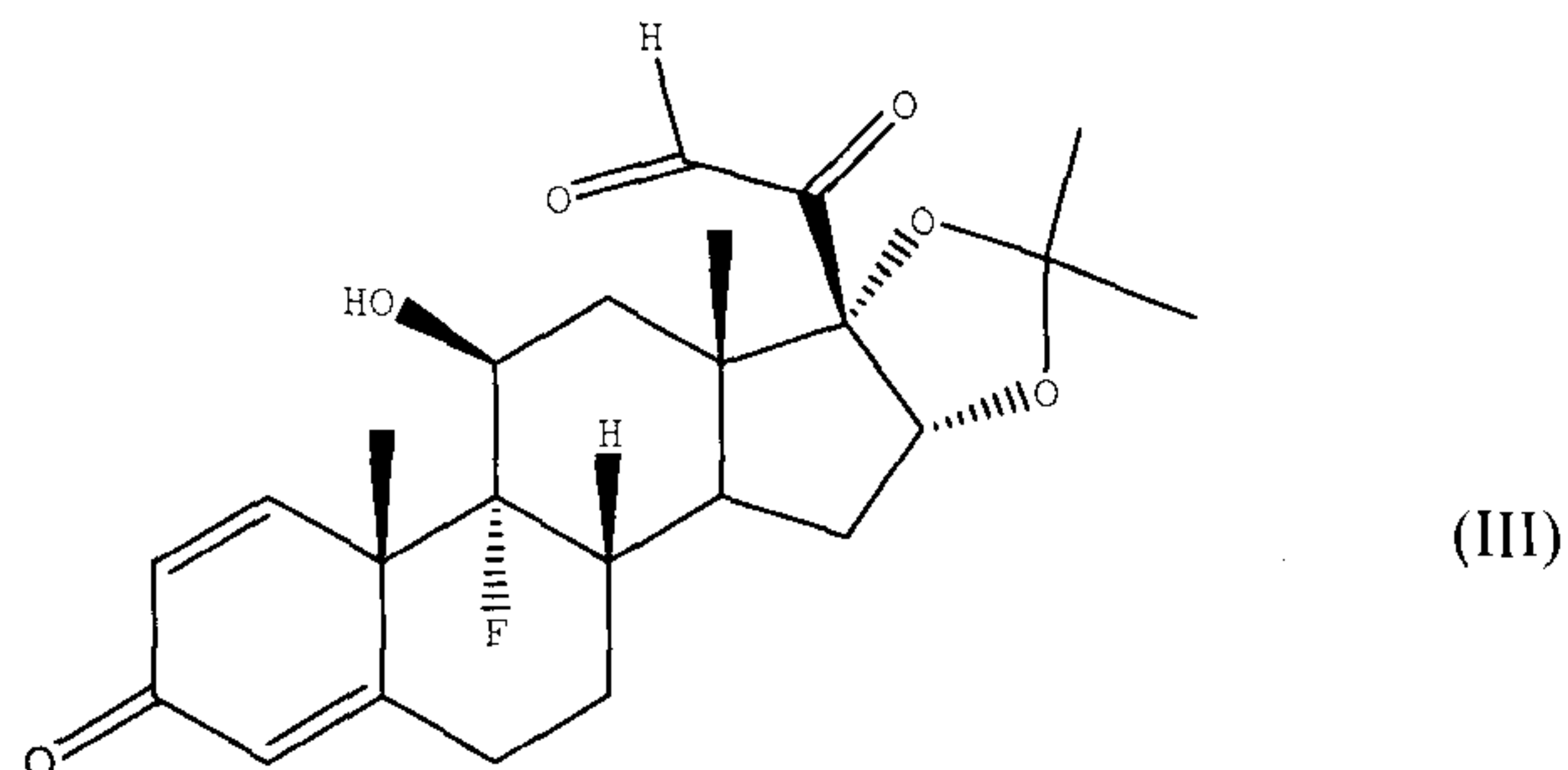
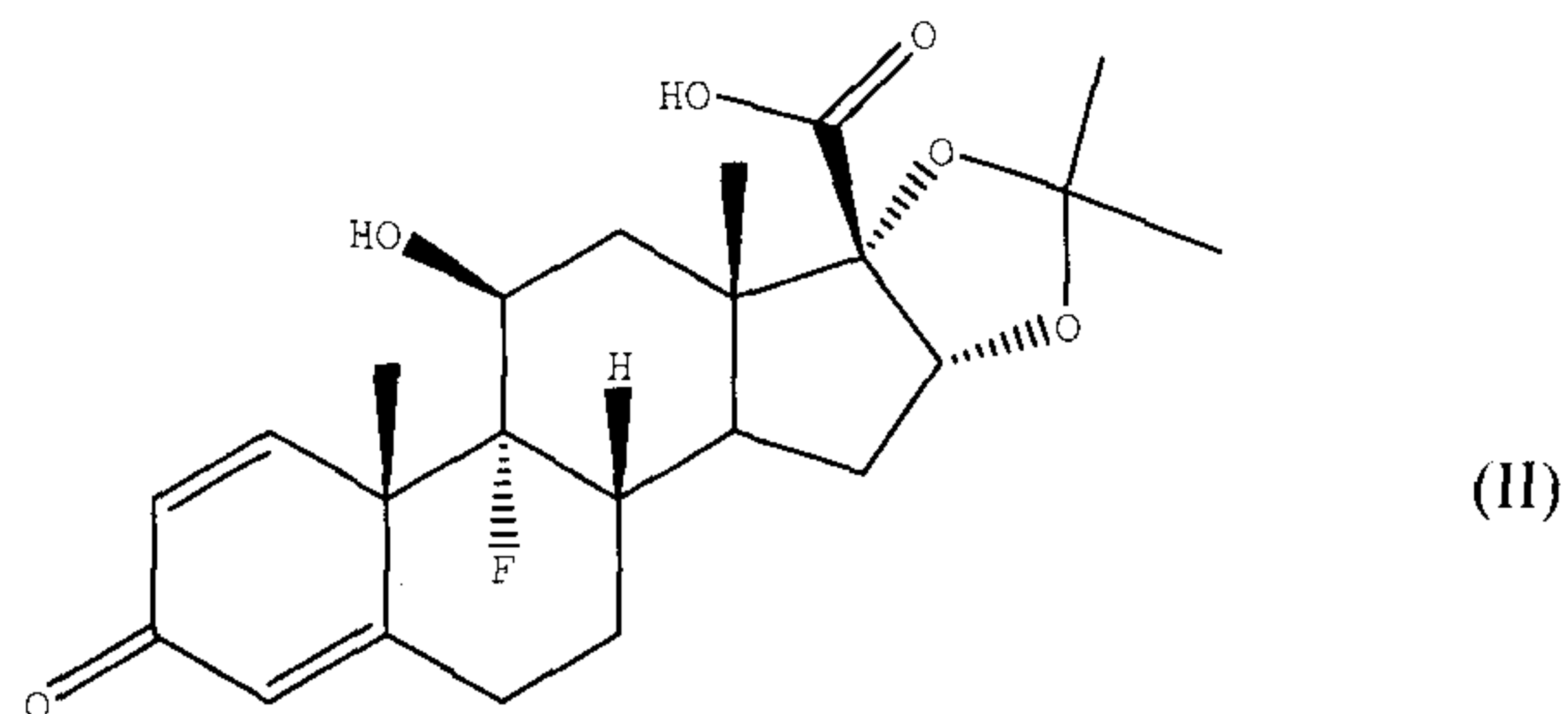
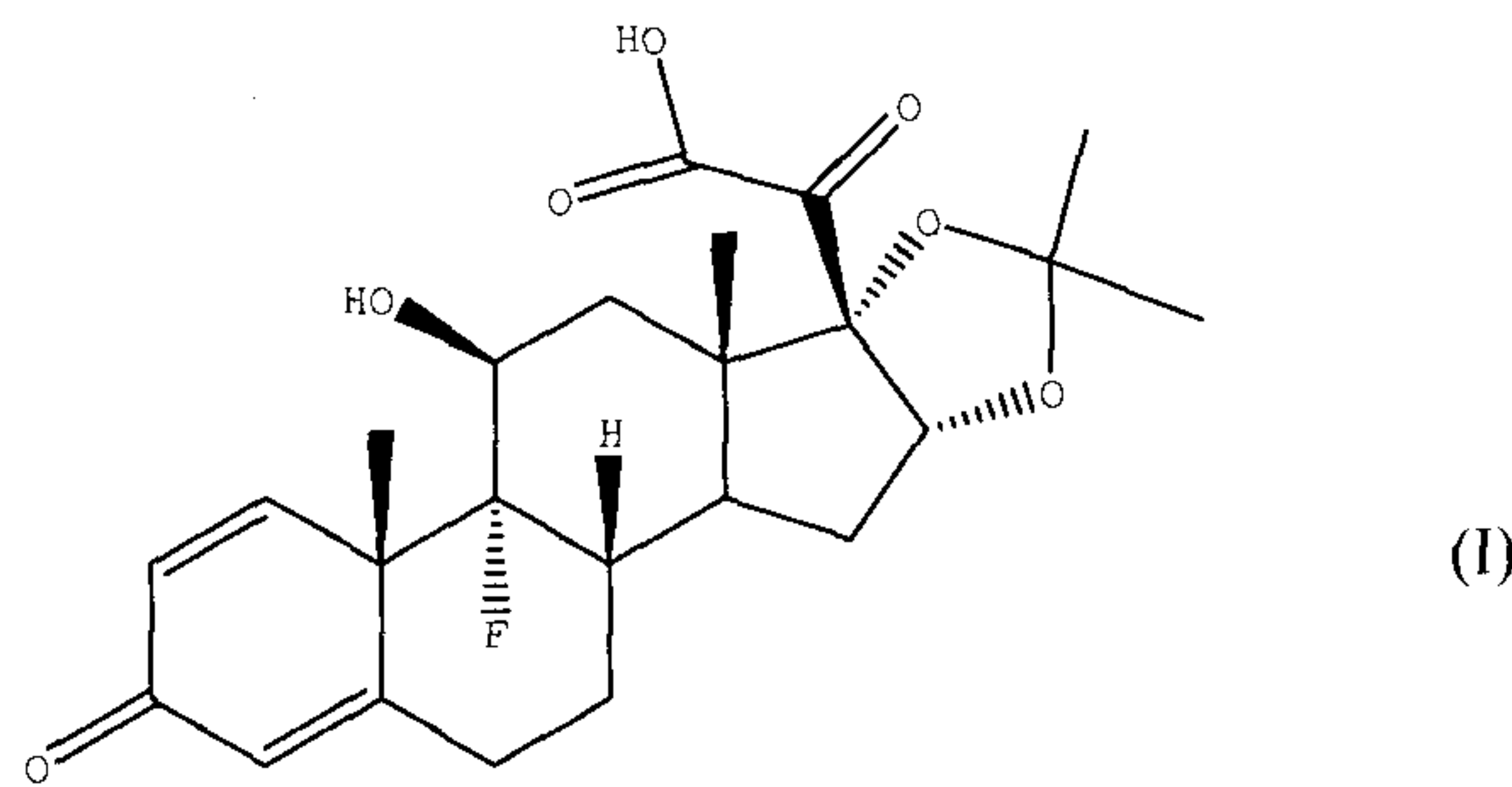
(d) the composition comprises no more than about 10% of the compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 6 months accelerated stability storage at 40°C and 75% relative humidity.

2. A storage stable therapeutic composition having wet adherent properties comprising a base material, about 0.1 wt.% triamcinolone acetonide, and about 2 wt.% salt of lidocaine, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol, wherein:

(a) the composition comprises at least about 0.09 wt.% triamcinolone acetonide and about 1.8 wt.% salt of lidocaine after 14 months; or

(b) the composition comprises no more than about 0.01 wt.% of compounds having the formulae of any one of I, II, or III after 14 months

49



3. The composition of claim 1 wherein the polyalkylene glycol comprises polyethylene glycol.
4. The composition of any one of claims 1-3, wherein the copolymer is a sodium salt, a calcium salt, or a mixture thereof.
5. The composition of any one of claims 1-4 wherein the copolymer comprises a blend of divalent calcium salt and monovalent sodium salt wherein the concentration of calcium is between about 10 and 15 wt.%, the concentration of sodium is between about 1.5 and 4 wt.%, and the free acid is between about 9 and 25 wt.%.
6. The composition of any one of claims 1-5, wherein the copolymer is methyl vinyl ether/maleic acid and the concentration of calcium is between about 11 and 13 wt.%, the concentration of sodium is between about 2 and 2.5 wt.%, the ratio of Ca:Na is about 5-6:1, and the molecular weight of the copolymer is about 65,000-70,000.

7. The composition of any one of claims 1 and 3-6, wherein the composition comprises at least 90% of said salt of lidocaine based on the amount of said salt of lidocaine within the composition at the time of manufacture after 14 months storage at 25°C and 60% relative humidity.
8. The composition of any one of claims 1 and 3-7, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 18 months storage at room temperature and 60% relative humidity.
9. The composition of any one of claims 2 and 4-6, wherein the composition comprises at least 0.09 wt.% triamcinolone acetonide and at least 1.8 wt.% salt of lidocaine or lidocaine hydrochloride after 18 months.
10. The composition of any one of claims 1 and 3-7, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 24 months storage at 25°C and 60% relative humidity.
11. The composition of any one of claims 2 and 4-6, wherein the composition comprises at least 0.09 wt.% triamcinolone acetonide and at least 1.8 wt.% salt of lidocaine or lidocaine hydrochloride after 24 months.
12. The composition of any one of claims 1 and 3-7, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 30 months storage at 25°C and 60% relative humidity.
13. The composition of any one of claims 2 and 4-6, wherein the composition comprises at least 0.09 wt.% triamcinolone acetonide and at least 1.8 wt.% salt of lidocaine or lidocaine hydrochloride after 30 months.
14. The composition of any one of claims 1 and 3-7, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 36 months storage at 25°C and 60% relative humidity.
15. The composition of any one of claims 2 and 4-6, wherein the composition comprises at least 0.09 wt.% triamcinolone acetonide and at least 1.8 wt.% salt of lidocaine or lidocaine hydrochloride after 36 months.

16. The composition of any one of claims 1 and 3-7 wherein the composition comprises no more than about 10% of compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 18 months storage at 25°C and 60% relative humidity.
17. The composition of any one of claims 2 and 4-6, wherein the composition comprises no more than 0.01 wt.% of the compounds of formulae I, II, and III after 18 months.
18. The composition of any one of claims 1 and 3-7 wherein the composition comprises no more than about 10% of compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 24 months storage at 25°C and 60% relative humidity.
19. The composition of any one of claims 2 and 4-6, wherein the composition comprises no more than 0.01 wt.% of the compounds of formulae I, II, and III after 24 months.
20. The composition of any one of claims 1 and 3-7 wherein the composition comprises no more than about 10% of compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 30 months storage at 25°C and 60% relative humidity.
21. The composition of any one of claims 2 and 4-6, wherein the composition comprises no more than 0.01 wt.% of the compounds of formulae I, II, and III after 30 months.
22. The composition of any one of claims 1 and 3-7 wherein the composition comprises no more than about 10% of compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 36 months storage at 25°C and 60% relative humidity.
23. The composition of any one of claims 2 and 4-6, wherein the composition comprises no more than 0.01 wt.% of the compounds of formulae I, II, and III after 36 months.
24. The composition of any one of claims 1 and 3-6, wherein the composition comprises at least 90% of said salt of lidocaine based on the amount of said salt of lidocaine within the composition at the time of manufacture after 6 months storage at 40°C and 75% relative humidity.
25. The composition of any one of claims 1, 3-6 and 24, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said

triamcinolone acetonide within the composition at the time of manufacture after 8 months accelerated stability storage at 40°C and 75% relative humidity.

26. The composition of any one of claims 1, 3-6 and 24, wherein the composition comprises at least 90% of said triamcinolone acetonide based on the amount of said triamcinolone acetonide within the composition at the time of manufacture after 9 months accelerated stability storage at 40°C and 75% relative humidity.

27. The composition of any one of claims 1, 3-6 and 24, wherein the composition comprises no more than about 10% of the compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 8 months accelerated stability storage at 40°C and 75% relative humidity.

28. The composition of any one of claims 1, 3-6 and 24, wherein the composition comprises no more than about 10% of the compounds having the formulae I, II, and III based upon the amount of said triamcinolone acetonide within the composition at the time of manufacture after 9 months accelerated stability storage at 40°C and 75% relative humidity.

29. The composition of any one of claims 1-28 further comprising methylparaben and propylparaben.

30. The composition of any one of claims 1 and 3-6, wherein the composition comprises at least 0.01 to about .25 wt.% triamcinolone acetonide and about 1 to about 5 wt.% salt of lidocaine.

31. The composition of any one of claims 1 and 3-6, wherein the composition comprises at least 0.075 to about .125 wt.% triamcinolone acetonide and about 1.5 to about 2.5 wt.% salt of lidocaine.

32. The composition of any one of claims 1-31 wherein the salt of lidocaine is in the form of lidocaine hydrochloride.

33. The composition of claim 2 consisting essentially of a base material, about 0.1 wt.% triamcinolone acetonide, and about 2 wt.% lidocaine hydrochloride, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol.

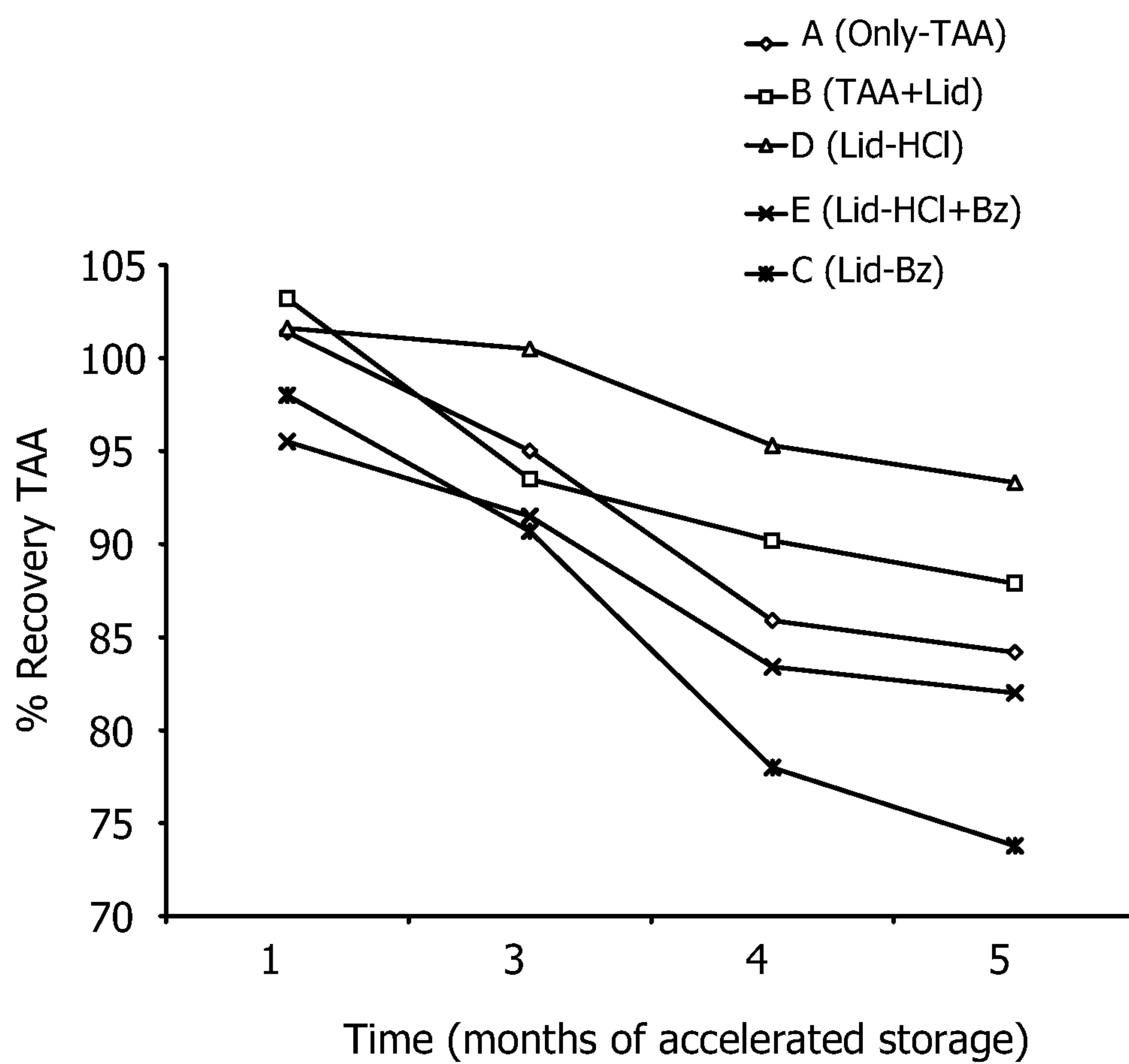
34. The composition of claim 2 consisting essentially of a base material, about 0.1% triamcinolone acetonide, about 2 wt.% lidocaine hydrochloride, about 0.2 wt.%

methylparaben, and about 0.02 wt.% propylparaben measured by weight, the base material comprising from about 3 to 15 wt.% of a water soluble salt of a copolymer of a lower alkyl vinyl ether and maleic acid or anhydride and from about 85 to 97 wt.% of polyethylene glycol.

35. The composition of any one of claims 1-34 which is free of EDTA.
36. The composition of any one of claims 1-34, wherein the composition is free of butylated hydroxytoluene, butylated hydroxyanisole, or EDTA.
37. The composition of claim 36, wherein the composition is free of butylated hydroxytoluene, butylated hydroxyanisole, and EDTA.
38. The composition of any one of claims 1-37 further comprising an acid selected from the group consisting of citric acid, ascorbic acid, fumaric acid, malic acid, and lactic acid.
39. The composition of any one of claims 1-38 wherein the composition has a pH of less than 8.0, 7.9, 7.8, 7.7, 7.6, 7.5, 7.4, 7.3, 7.2, 7.1, 7.0, 6.9, 6.8, 6.7, 6.6, 6.5, 6.4, 6.3, 6.2, 6.1, 6.0, 5.9, 5.8, 5.7, 5.6, 5.5, 5.4, 5.3, 5.2, 5.1, 5.0, 4.9, 4.8, 4.7, 4.6, 4.5, 4.4, 4.3, 4.2, 4.1, or 4.0.
40. Use of the composition of any one of claims 1-39 for treating recurrent aphthous ulcers.
41. Use of the composition of any one of claims 1-39 in the preparation of a medicament for treating recurrent aphthous ulcers.
42. The composition of any one of claims 1-39 for use in treating recurrent aphthous ulcers.
43. Use of the composition of any one of claims 1-39 for treating eczema, bug bites, burns in mouth, or external mouth sores.
44. Use of the composition of any one of claims 1-39 in the preparation of a medicament for treating eczema, bug bites, burns in mouth, or external mouth sores.
45. The composition of any one of claims 1-39 for use in treating eczema, bug bites, burns in mouth, or external mouth sores.

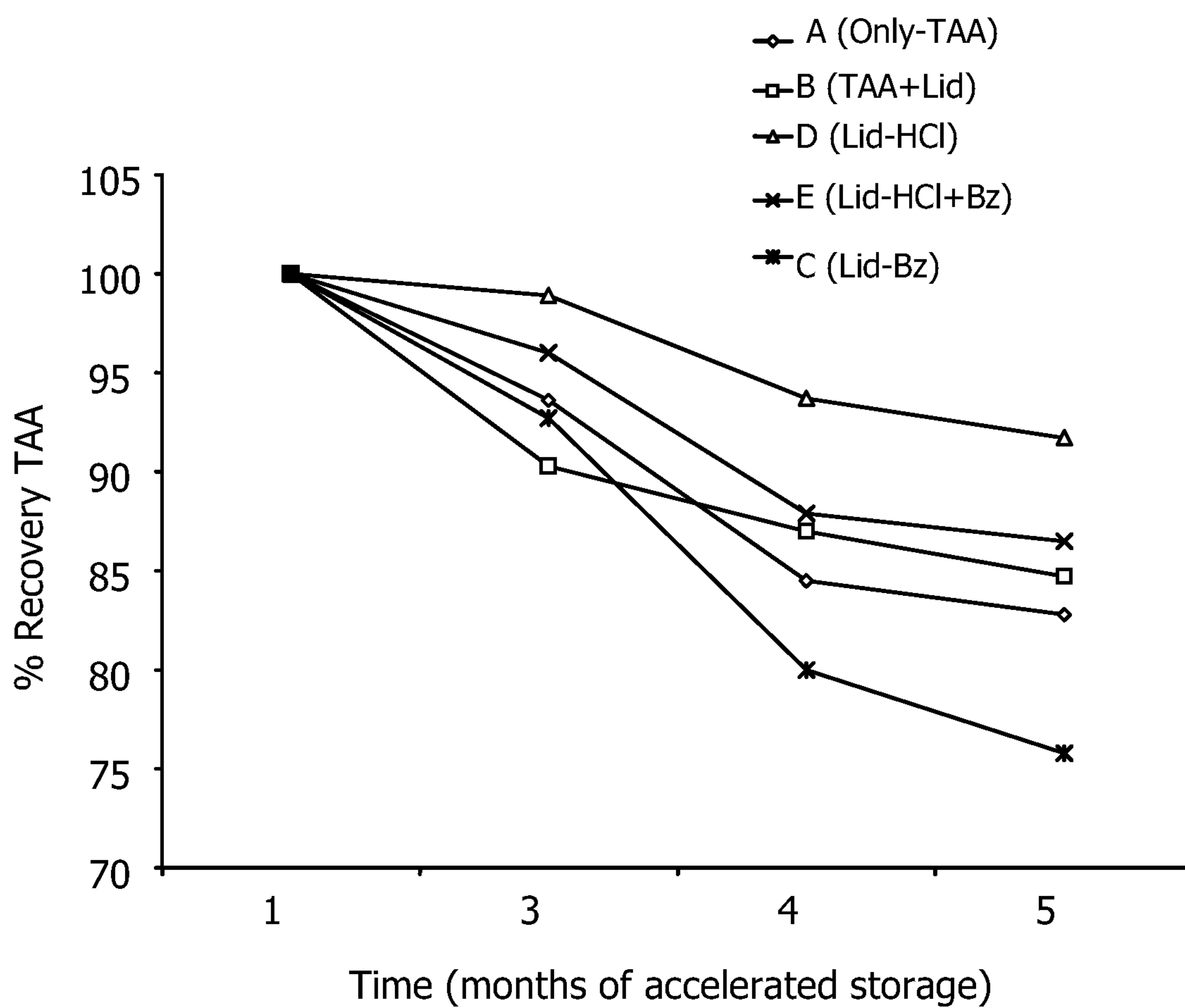
1/13

FIG. 1



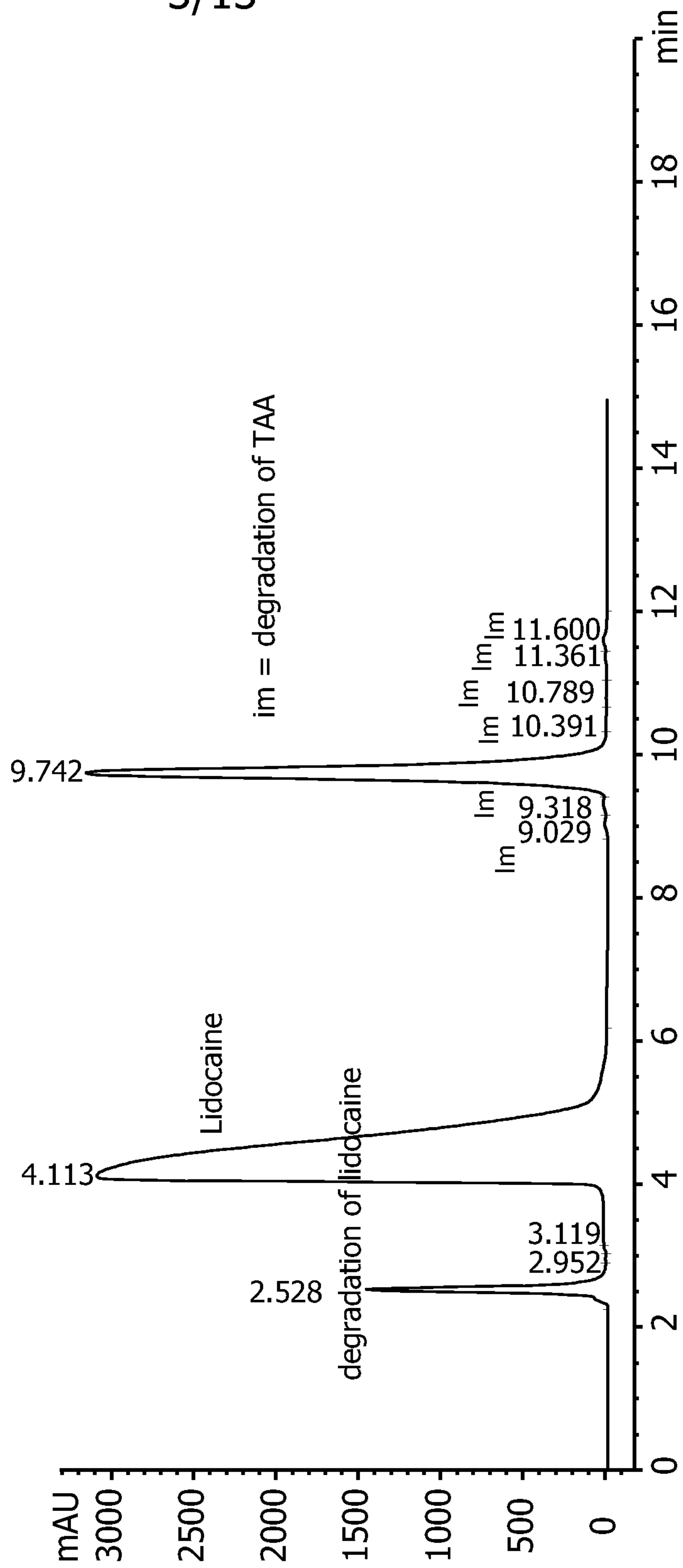
2/13

FIG. 2



3/13

FIG. 3



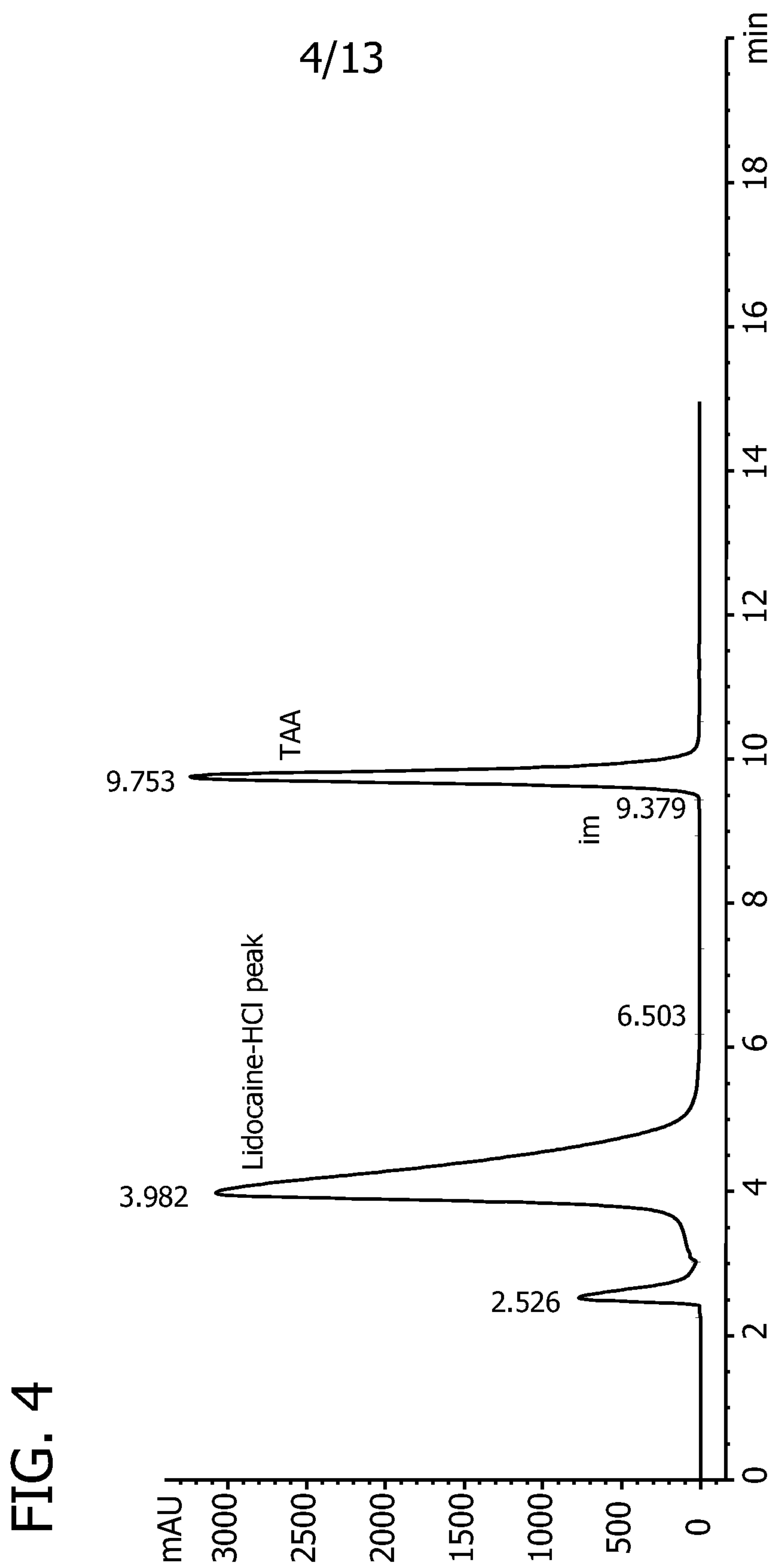
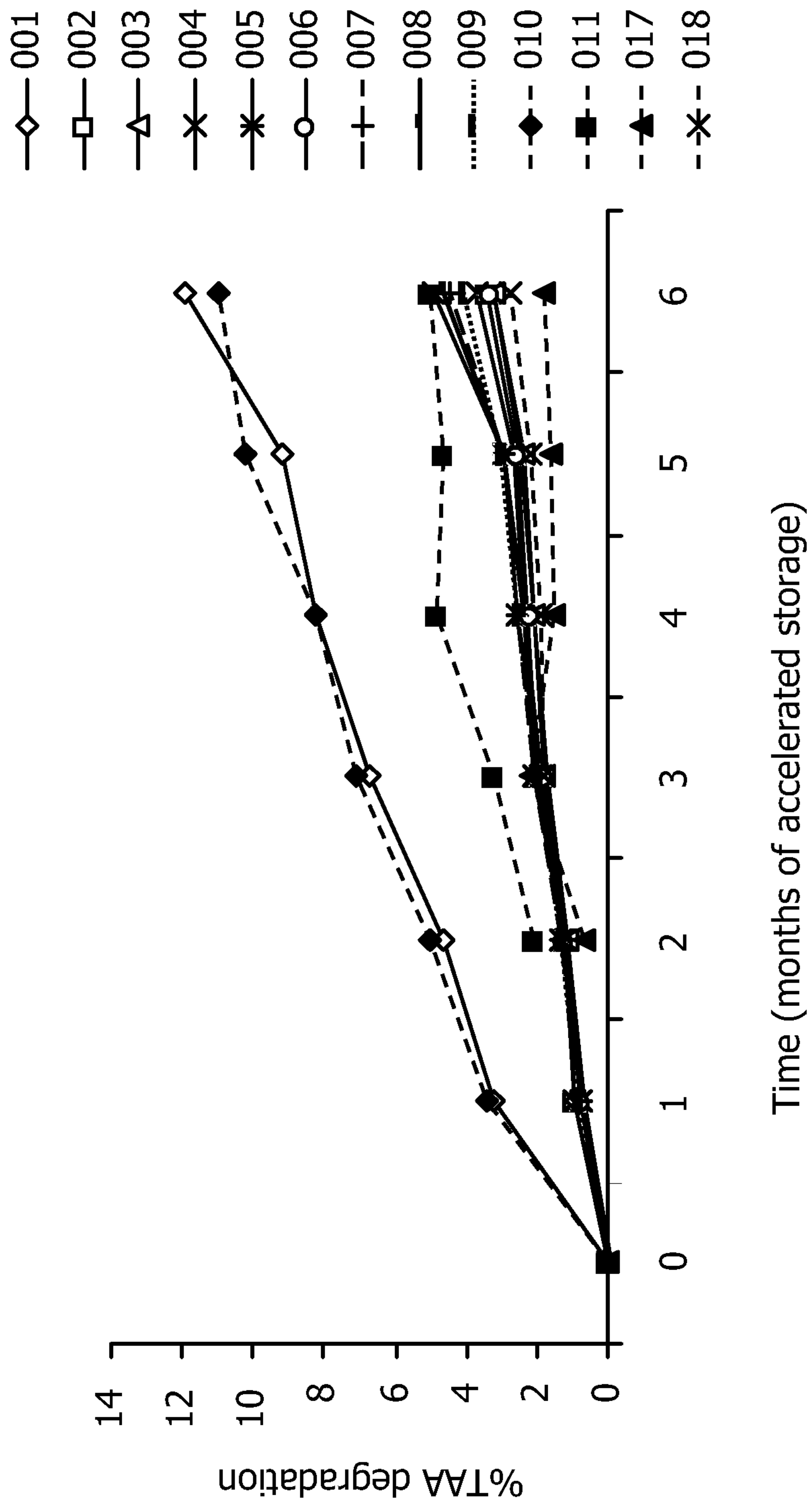


FIG. 4

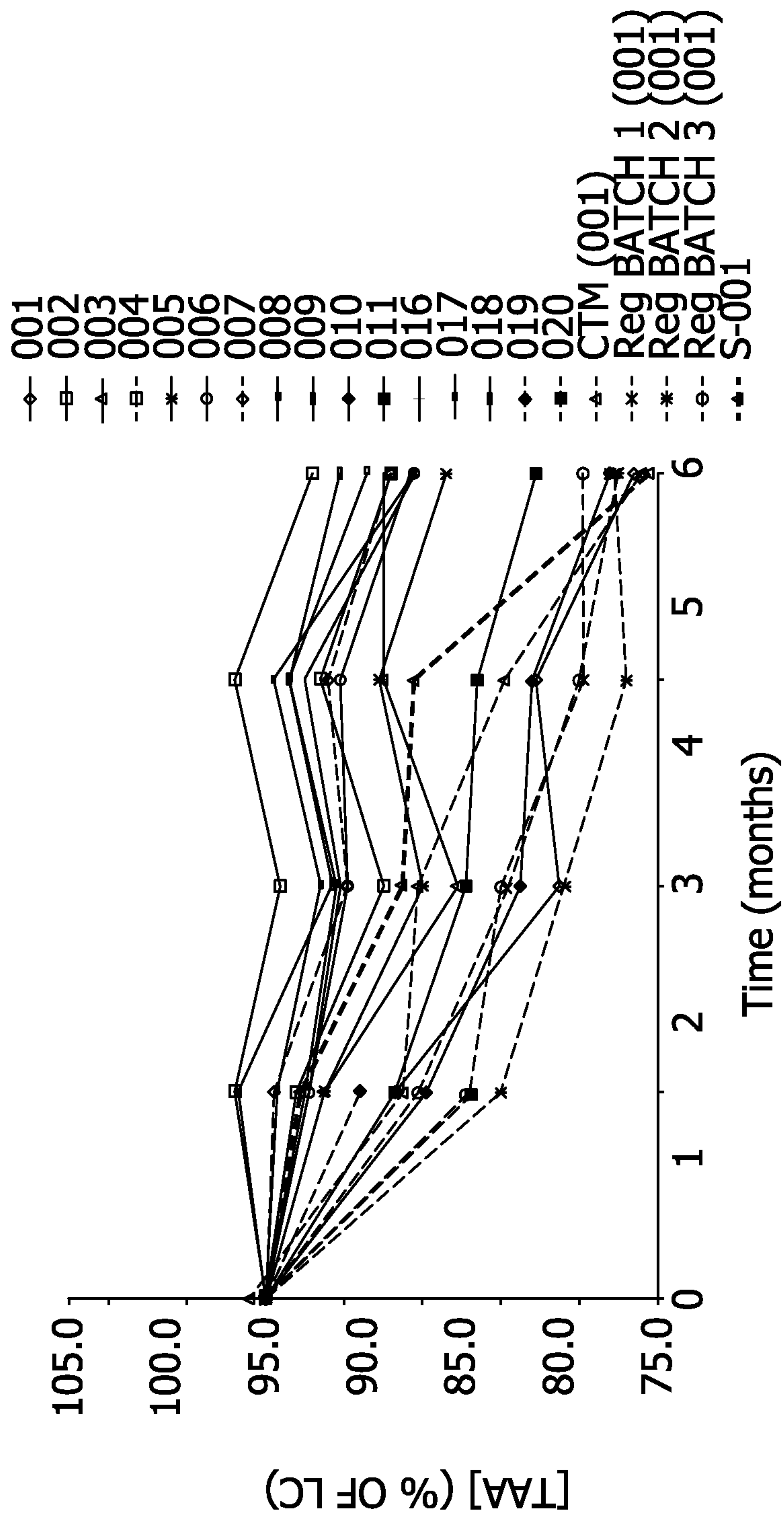
6/13

FIG. 6



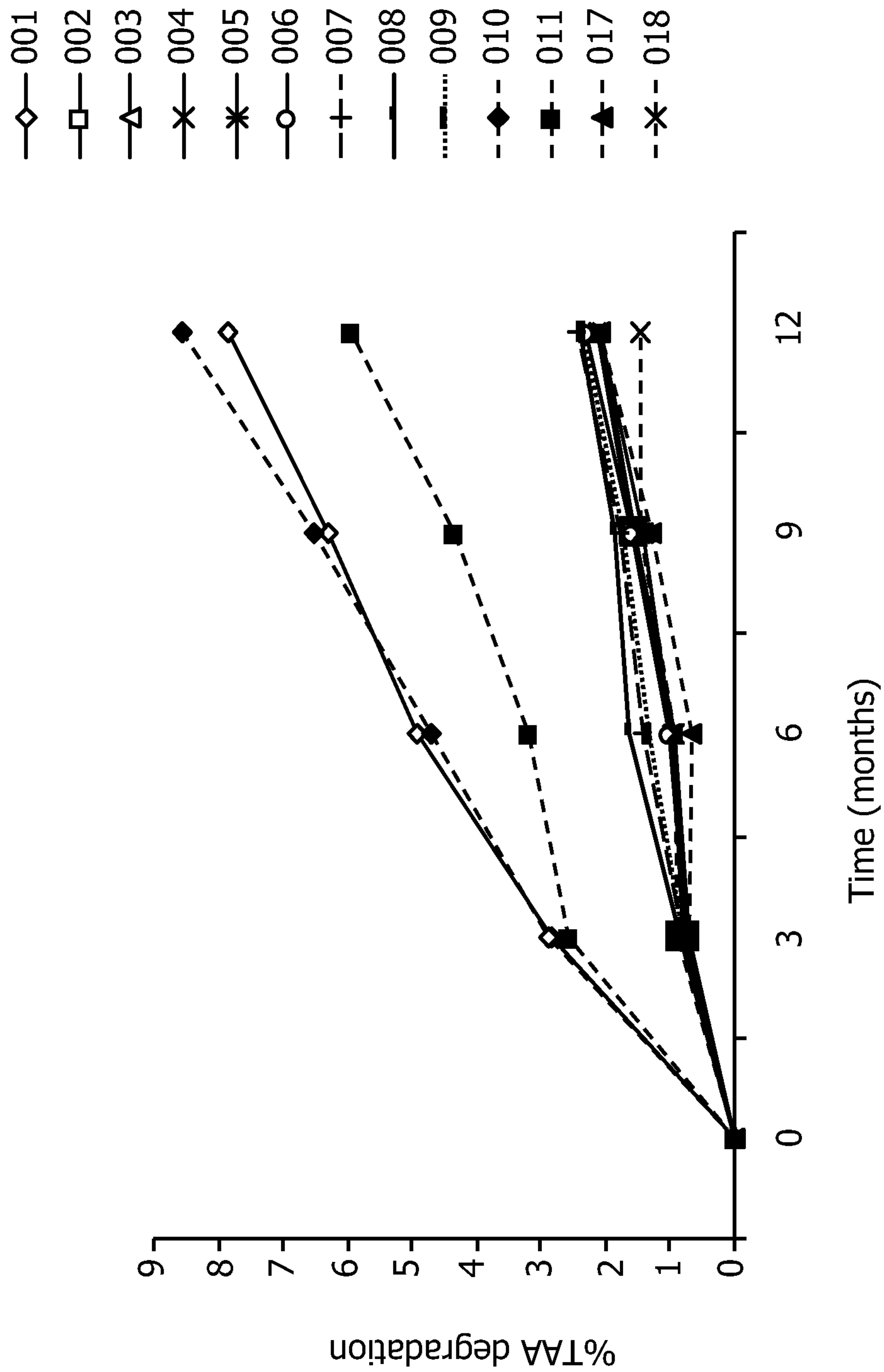
7/13

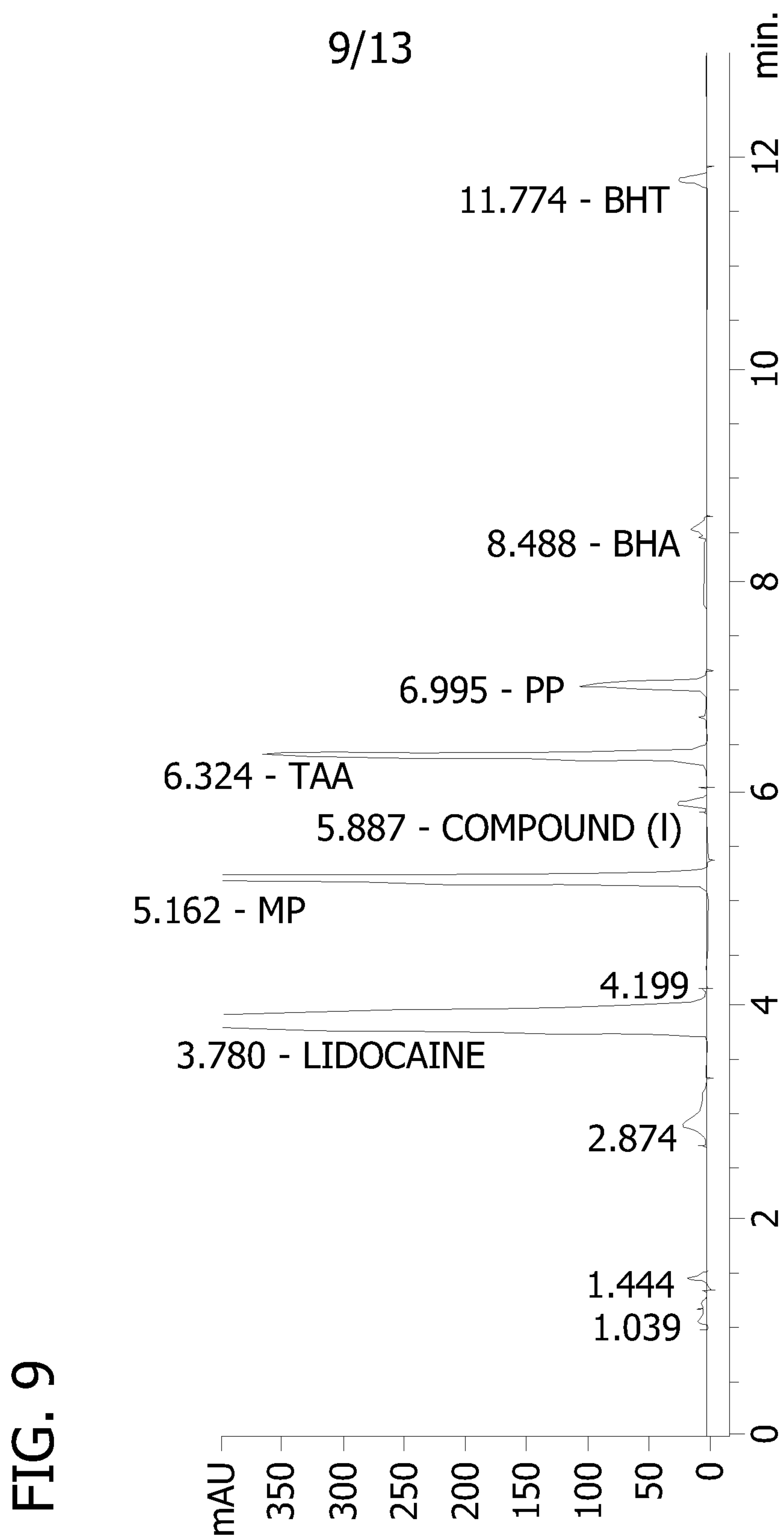
FIG. 7

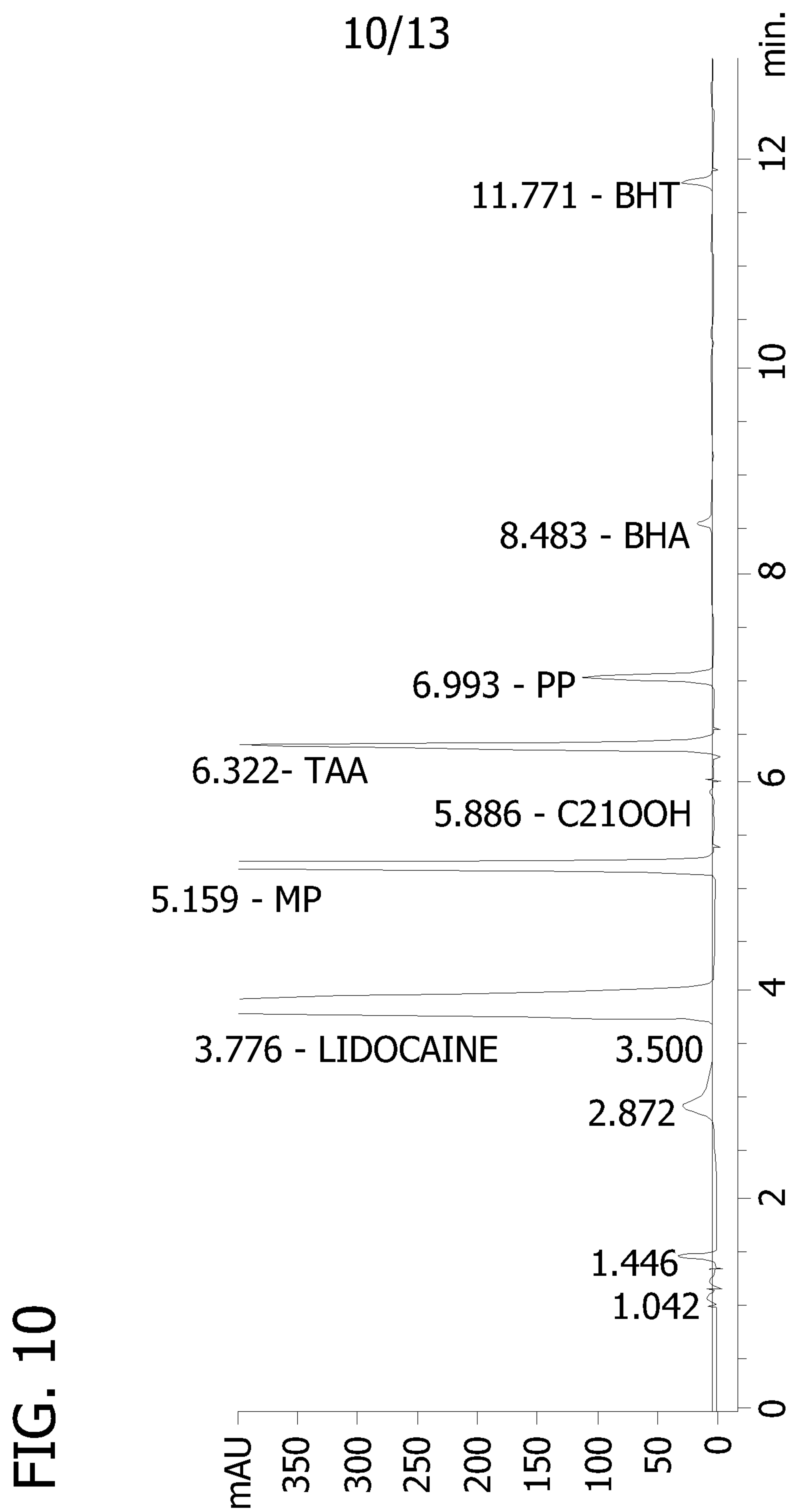


8/13

FIG. 8







11/13

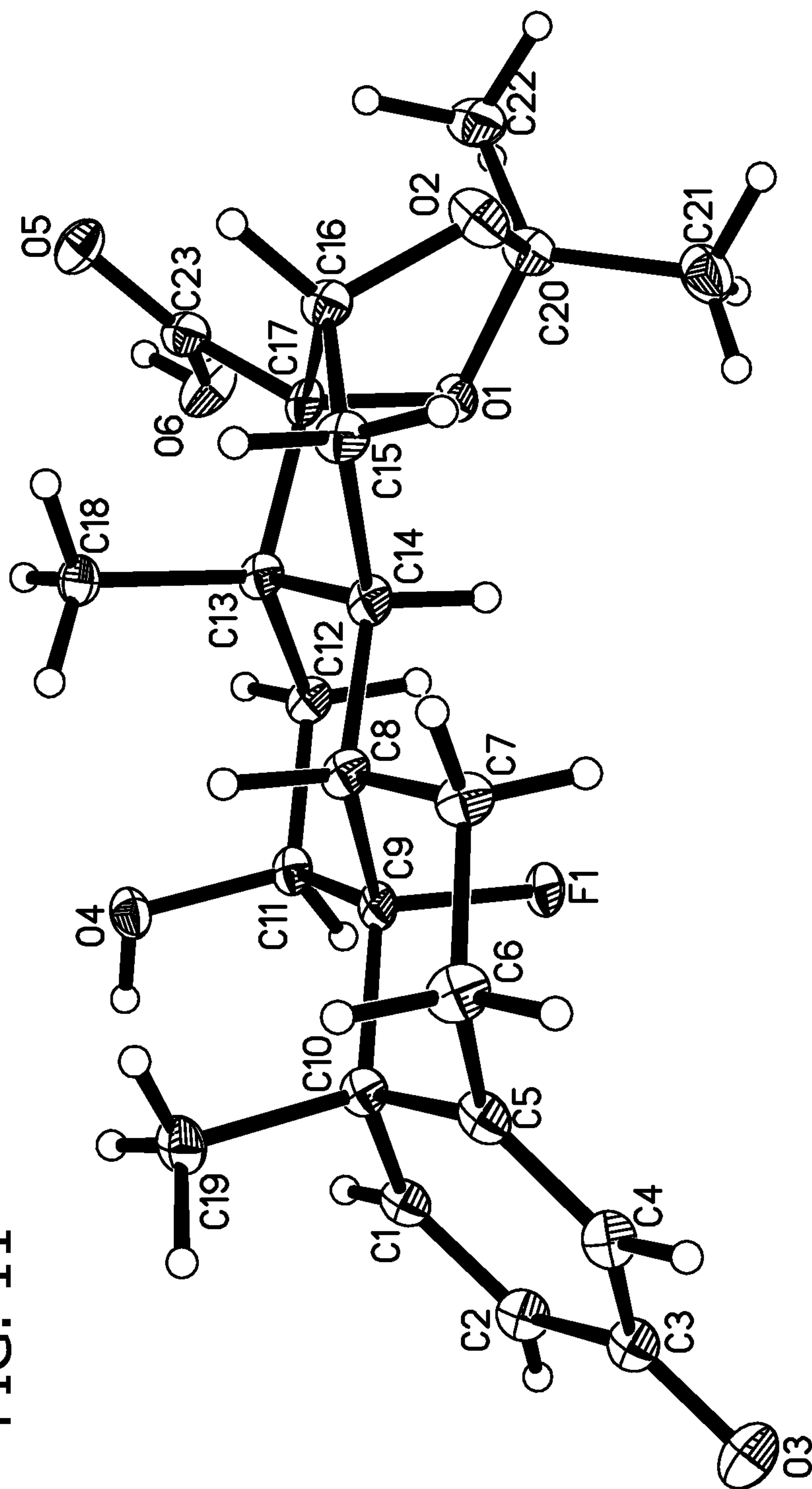


FIG. 11

12/13

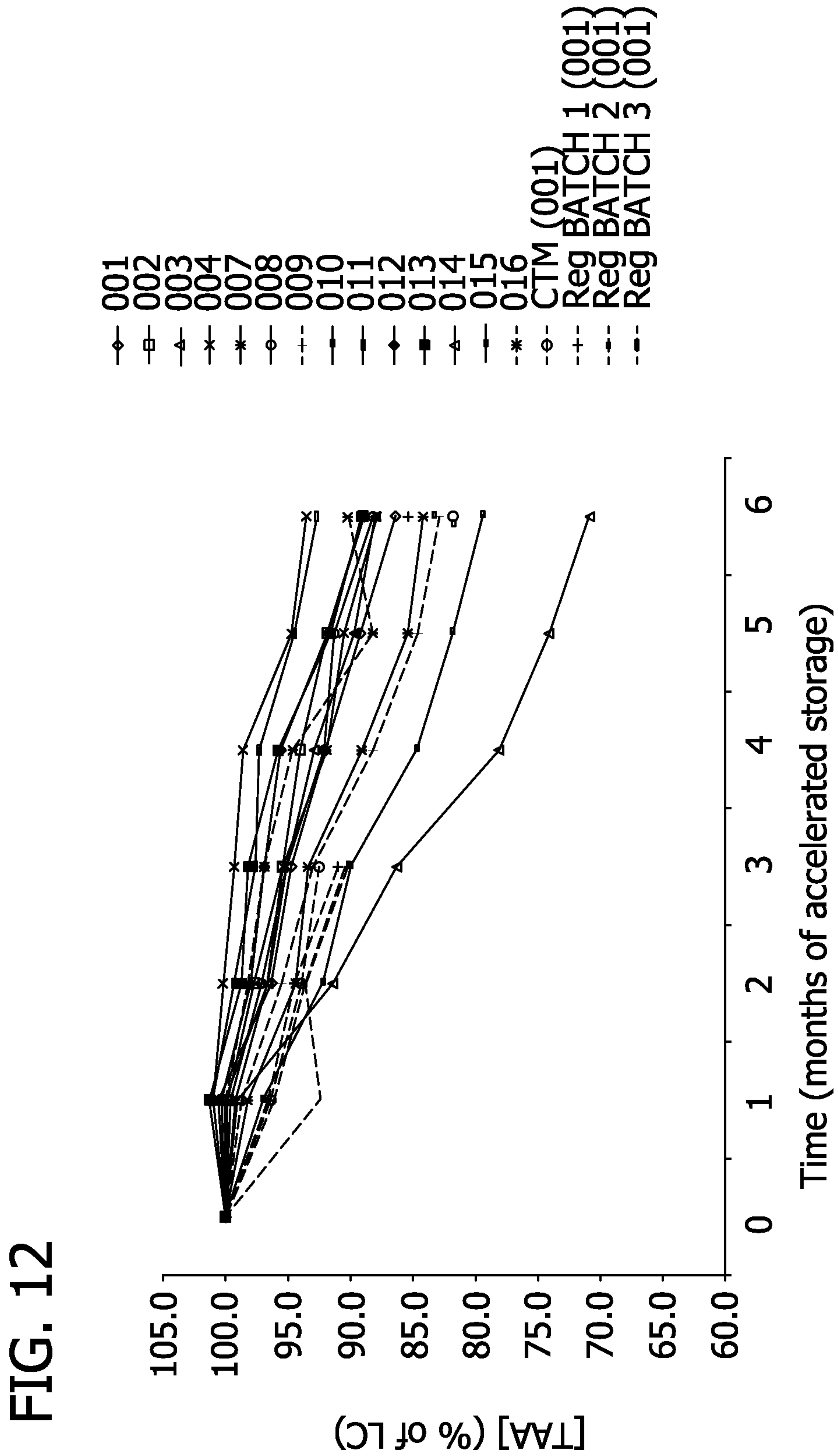


FIG. 13

