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(54) Title: STABILIZED COMPOSITIONS CONTAINING 1,2,5,6-TETRAHYDRO-1-METHYL-3-PYRIDINECARBOXY-ALDEHYDE-O-METHYL-OXIME

(57) Abstract

This invention is directed to a solid stable pharmaceutical formulation of the cognition activator CI-979 HCl comprising adipic acid as an excipient. The invention is further directed to the process of making a solid storage composition stabilizing CI-979 with adipic acid.

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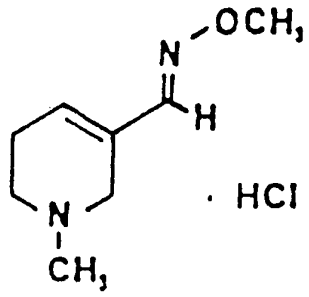
Stabilized compositions containing 1,2,5,6-tetrahydro-1-methyl-3-pyridinecarboxyaldehyde-O-methyl-oxime.

The present invention relates generally to stabilizing solid pharmaceutical compositions and, more particularly solid compositions for stabilizing the cognition activator CI-979 HCl using acidic excipients to reduce losses of the drug to hydrolysis and evaporation. In this context, a process is provided for preparing said compositions.

BACKGROUND OF INVENTION

Certain O - substituted - 1,2,5,6-tetrahydro-3-pyridine oximes and the process for making them, have been described in U.S. Patent No. 4,786,648 which disclosure is hereby incorporated by reference in the present specification. The compound CI-979 has been disclosed as an embodiment having pharmacological properties that make it useful as a cognition activator. Therefore, the compound has been under consideration for therapy of age-associated memory impairment and primary degenerative dementia. Furthermore, CI-979 HCl is being developed for the treatment of Alzheimer's disease.

The alkaloid derivative, namely CI-979 HCl, has the following structural formula (Ia):



(Ia)

As can be seen in formula (Ia), CI-979 contains a methyloxime group attached to a basic tetrahydropyridine ring (1,2,5,6-tetrahydro-1-methyl-3-pyridine carboxaldehyde, O-methyloxime). Similar to other pyridine derivatives, the free base form of CI-979 is a volatile oily liquid, whereas CI-979 hydrochloride is a stable crystalline salt.

In the course of preformulation testing, the storage stability of the drug and aqueous solutions of CI-979 HCl has been studied by exposure to heat, UV light, and the extreme ends of the pH range. Specifically, it has been found that the HCl salt converts in the presence of basic or neutral excipients and even minute amounts of water to a volatile free base form and consequently evaporates. Furthermore, in acidic environments, the drug undergoes hydrolysis to an aldehyde degradation product.

As illustrated in Figure 1, two major degradation pathways have been proposed for CI-979. One pathway

represents the hydrolysis of CI-979 to the 1,2,5,6-tetrahydro-pyridine carboxaldehyde under acidic conditions, e.g., at a pH of less than about 5.0. The second pathway consists of isomerization to the syn - (or Z-) isomer by exposure to UV light.

In particular, hydrolysis of CI-979 to the aldehyde form (A) is a temperature dependent first-order reaction. The isomerization reaction to the Z-isomeric structure of CI-979 (C) can be catalyzed by UV light energy. The light-catalyzed reaction of CI-979 in solution is apparently somewhat pH-dependent, with the highest rate of isomerization occurring at about pH 8.0. The UV light energy presumably weakens the oxime double bond and potentiates rotation to a thermodynamically less stable state.

However, the alkaloid drug, CI-979 HCl, has been found to be unstable in an acidic microenvironment even in the solid state and as a mixture with solid excipients. In fact, CI-979 HCl undergoes loss in mass balance when formulated in bulk with polyhydroxy excipients. However, only minimal isomerization has been observed. Further investigations demonstrated that the disappearance of the CI-979 peak on the HPLC elution profile was prevalent when incubated with "alkaline" or neutral excipients. The loss was apparently due to neutralization of the HCl salt to the free base which is volatile oil. Moreover, the large surface area afforded

by the excipient particles presumably enhanced evaporation of the drug from the excipient blend.

Consequently, the storage stability of the drug as a solid oral formulation presents a two-fold dilemma. On the one hand, an acidic microenvironment causes hydrolysis of CI-979 HCl, while preventing conversion of the HCl-salt to the free base and subsequent volatilization. On the other hand, even a mildly alkaline microenvironment allows formation of the free base of the drug while diminishing CI-979 degradation (as shown in Fig. 1).

The object of the present invention is therefore directed to a pharmaceutical composition of a solid mixture stabilizing the alkaloid ether oxime salt against hydrolysis and evaporation.

The object of the present invention is also directed to a low dose mixture which comprises a uniform particulate consistency throughout the composition.

The further object of the present invention is directed to process for preparing a stable solid pharmaceutical composition by preparing a dilute aqueous solution of an alkaloid ether oxime salt; triturating the aqueous alkaloid solution onto the acidic solid excipient while mixing; drying the alkaloid/excipient mixture of the previous step on trays for about 4 hours at about 40° - 45°C; again blending the dried material of step (c); and storing and/or processing the triturate composition

into a suitable solid oral dosage form (tablets or hard-gelatin capsules).

SUMMARY OF THE INVENTION

It has been surprisingly found that solid formulations of an alkaloid ether oxime salt such as CI-979 HCl with certain acidic excipients result in an acceptable reduction of hydrolysis and a concomitant reduction in loss upon storage of the active compound.

The present invention provides, therefore, a stable composition comprised of a solid mixture of an alkaloid ether oxime salt and at least one acidic excipient, effective in stabilizing the alkaloid salt.

Specifically, the present invention is directed to a pharmaceutical composition of a solid uniform low dose blend comprising an alkaloid ether oxime salt and at least one acidic excipient, the blend giving stability against both hydrolysis and neutralization and/or evaporation of the alkaloid ether oxime salt.

Further to the present invention, the solid pharmaceutical composition contains acidic excipients comprising adipic acid or fumaric acid.

More particularly, the present invention is directed to the low dose drug excipient mixture wherein the excipient adipic acid simultaneously stabilizes the drug CI-979 HCl both against degradation and conversion to the free base.

The present invention, moreover, provides a process for preparing a solid excipient complex for stability of the O-substituted oxime of 1, 2, 5, 6-tetrahydro-1-methyl pyridine against hydrolysis and evaporation comprising the steps of: (a) preparing a dilute aqueous solution of an alkaloid oxime ether salt, (b) spraying the aqueous alkaloid solution of step (a) onto a solid acidic excipient along with thorough mixing, (c) spreading the alkaloid/excipient mixture of step (b) onto trays for drying at about 40°-45° C for about 4 hours, (d) again thoroughly mixing the dried material of step (c), and (e) processing the triturated composition to formulate the solid oral dosage form (either tablets or hard-gelatin capsules) of acceptable uniformity.

This process is particularly directed to preparing a solid triturate of acidic excipients wherein the alkaloid drug is the cognition activator, CI-979 HCl salt.

Brief Description of Drawings

Fig. 1 Schematic of degradative pathways of CI-979.

Fig. 2 An elution profile of a typical reverse phase high performance liquid chromatograph of CI-797 and its breakdown products.

DETAILED DESCRIPTION OF INVENTION

In order to avoid having to store the alkaloid ether oxime salt and solid excipient mixtures thereof under vacuum in closed containers, requiring an elaborate process to keep moisture from entering the ambient atmosphere and eventually the solid triturate composition itself, the excipients are usually selected so as to buffer the active ingredient at the pH range found suitable for preventing hydrolytic degradation.

In view of the two-fold lability of CI-979 HCl in terms of both highly acidic and neutral to basic environments, as described above, the present invention is directed to produce a solid formulation which stabilizes the active ingredient, CI-979 HCl, in association with certain suitable excipients. Accordingly, solid blends of the alkaloid drug have been found to keep the microenvironment of the active ingredient at a weakly acidic range of less than about pH 6.0, as shown in the following examples.

EXAMPLES

In consideration of the submilligram dosages anticipated for the therapeutic use of CI-979 HCl, the solid blends were prepared as follows: Each solid excipient was triturated with dilute aqueous solution of the drug to insure content uniformity. The final concentration of CI-979 HCl in a given blend was kept at

about 0.01% or about 0.05% by weight. Each solid triturate mixture was dried at a controlled temperature ranging from 40°-45°C.

The pH of the microenvironment in the solid drug blend according to the present invention was estimated to be less than 6.0 which may be considered a critical threshold for the long-term storage stability of solid oral formulations or excipient mixtures of CI-979 HCl. As previously described, the diminished conversion to CI-979 free base at the low pH of the excipient microenvironment appears to preclude its conversion to the free base and subsequent evaporation. Moreover, the stabilizing efficacy of certain acidic carriers, e.g. adipic acid or fumaric acid, was surprising in view of the acid labile character of the instant ether oxime salt, CI-979 HCl.

TABLE I: EXCIPIENTS TESTED FOR THE STABILIZATION OF CI-979 IN THE SOLID STATE

EXAMPLE NO.	EXCIPIENT	COMPENDIUM	pH (20%)*
1	TARTARIC ACID	USP/NF	1.6
2	MALIC ACID	FCC	1.7
3	ASCORBIC ACID	USP/NF	2.1
4	FUMARIC ACID	FCC	2.3
5	ADIPIC ACID	FCC	2.7
6	LACTOSE, FAST-FLO®	USP/NF	4.1
7	SODIUM PHOSPHATE MONOBASIC	USP/NF	4.2
8	PRIMOGEL®	USP/NF	6.0
9	SODIUM CITRATE	USP/NF	8.4

* solution or suspension

HPLC PROCEDURE

The blends were individually sampled and then analyzed by reverse phase high performance liquid chromatography (HPLC) a highly sensitive method for assessing even trace amounts of breakdown products as well as assaying any change in the overall mass balance due to degradation or evaporation losses. The HPLC procedure was used to measure the concentrations of CI-979 and its aldehyde breakdown product. The apparatus was comprised of a Hewlett-Packard 1090L, equipped with a Zorbax CN Folum, 250 mm x 4.6 mm I.D. with 5 mm bead. Beckman Dijimentry MKS Instrument Complex and a Kratos model 783 Detector. The data analysis utilized a Beckman LIMS running "Peak Pro" software. The buffer was 0.001 M Pic B8^R (octanesulfonic acid, sodium salt) 0.0025M triethylamine, adjusted to pH 3.0 with H_3PO_4. Acetonitrile was added as modifier for the mobile phase at 99:1 (Buffer:Modifier).

The elution flow rate was 1.3 ml/minutes for a 15 minute run. The injection volume was 20 μl. The detection light wavelength was 225 nm. Taking reference to Figs. 1 and 2, the retention times were 3.8 minutes for the alkaloid carboxylic acid (B), (not observed in Fig. 2), 4.6 minutes for the aldehyde (A), 9.6 minutes for the Z-isomer (C), and 10.5 minutes for CI-979. The method was validated previously and was tested for system suitability according to the USP.

Approximately 10 mg of CI-979 HCl analytical reference standard was prepared as an aqueous solution of a final concentration of 0.02 mg/ml. Approximately 100 mg of the CI-979 HCl/excipient mixture equivalent to about 1.0 mg (or 5.0 mg) CI-979 HCl was weighed and mixed in about 50 ml water to give an approximate concentration of 0.02 mg CI-979 HCl/ml.

Figure 2 shows a typical HPLC elution profile of CI-979 HCl in solution and some of its identified breakdown products, the aldehyde (A), and the Z-isomer (C), as proposed on Fig. 1.

The amounts of CI-979 free base in the reference standard was corrected for moisture and molecular weight of the salt. The amounts of CI-979 free base in the nine test preparations of Examples 1-9 (see Tables) were calculated by comparison of the peak areas of the examples with that of the external standard. Area normalization was used to provide an estimate of degradation products of CI-979 HCl due to lack of pure samples of the potential degradation products indicated in Fig. 1.

The nine excipients tested by comparative methods are listed in Table I along with the observed pH of a 20% (w/w) solution or suspension of each excipient in purified water, depending on the respective solubilities. In particular, 20% solutions or suspensions of certain acid compounds such as fumaric and

adipic acid which are known to be poorly or only slightly soluble in water were found to exhibit low pH values varying from 2.3 to 2.7. In addition, commonly known additives such as e.g. lactose and sodium phosphate (monobasic) as shown in comparative Table I, provided pH values of 4.1 and 4.2, respectively. The additive substance Primogel® provided a 20% solution or suspension having pH 6.0. Sodium citrate (20% solution) having a pH 8.4 was also used for comparative excipient testing of the alkaloid compound.

It had been observed previously that after incubation of the bulk drug with certain polyhydroxy excipients, there was a marked loss of mass balance as determined by HPLC-chromatography. Upon further investigation, the disappearance of the CI-979 peak was seen most pronounced in the presence of so-called alkaline or neutral excipients. It may therefore be reasonably assumed that this reaction is generated by neutralization of the HCl salt to the free base, thereby causing formation of a volatile liquid. The extensive surface area inherent in the microparticulate structures of the excipient materials further facilitates or enhances the neutralization and evaporation of the drug from the excipient blend. The pKa of the active ingredient being approximately 8.0, a microenvironment of pH 6.0 or higher can be expected to generate the free base form which then evaporates. Thus the present

invention is directed to answer the need for a low dosage (submilligram) formulation which would provide long term storage stability for the active ingredient, CI-979 HCl.

This need for stability is complicated by the requirement that the solid formulation maintain a suitable molecular microenvironment of the the drug sufficiently alkaline or at least weakly acidic (at less than pH 6.0) to impede the hydrolytic degradation molecules while simultaneously preventing conversion of the HCl salt to the free base with subsequent volatilization.

Since the presumed dosages required for therapeutic formulations of CI-979 HCl involve submilligram quantities, each stability test sample was prepared with a final concentration of either about 0.01% or about 0.05% CI-979 HCl. The comparative stability of CI-979 triturated with various excipients is shown in the Tables II, III or IV.

TABLE II: CI-979 STABILITY IN THE PRESENCE OF EXCIPIENTS (INCUBATION FOR 24 HOURS AT 45°C)

EX. NO.	EXCIPIENT	INITIAL CI-979 HCL CONCENTRATION (g/100 g)[*/]	PERCENT CI-979 REMAINING (% initial)	PERCENT ALDEHYDE FORMED (% initial)	TOTAL
1	TARTARIC ACID	0.01	72.5	14.0	86.5
2	MALIC ACID	0.01	76.4	15.1	91.5
3	ASCORBIC ACID	0.01	88.4	4.2	92.6
4	FUMARIC ACID	0.01	102.9	0.0	102.9
5a	ADIPIC ACID	0.01	103.4	0.0	103.4
5b	ADIPIC ACID	0.05	104.6	0.0	104.6
6	LACTOSE	0.01	91.2	0.0	91.2
7	SODIUM PHOSPHATE MONOBASIC	0.05	99.4	0.0	99.4
8	PRIMOGEL®	0.05	71.0[**/]	0.0	71.0
9	SODIUM CITRATE	0.05	93.5	0.0	93.5

[*/] The 0.05g per 100g mixtures were prepared on a laboratory scale in a mortar and pestle in a manner simulating the larger scale preparation.

[**/] Results are based on theoretical value for initial concentration due to problem with omitted HPLC chromatogram.

TABLE III: CI-979 STABILITY IN THE PRESENCE OF EXCIPIENTS (INCUBATION FOR 1 WEEK AT 45°C)

EX. NO.	EXCIPIENT	INITIAL CI-979 HCL CONCENTRATION (g/100 g)*	PERCENT CI-979 REMAINING (% initial)	PERCENT ALDEHYDE FORMED (% initial)	TOTAL
1	TARTARIC ACID	0.01	55.3	23.5	78.8
2	MALIC ACID	0.01	63.0	20.8	83.8
3	ASCORBIC ACID	0.01	50.8	5.6	56.4
4	FUMARIC ACID	0.01	93.5	4.7	98.2
5a	ADIPIC ACID	0.01	103.3	0.0	103.3
5b	ADIPIC ACID	0.05	99.8	0.0	99.8
6a	LACTOSE	0.01	90.1	0.0	90.1
6b	LACTOSE	0.05	107.1	0.9	108.0
7	SODIUM PHOSPHATE MONOBASIC	0.05	85.1	0.0	85.1
8	PRIMOGEL®	0.05	54.0**	0.0	54.0
9	SODIUM CITRATE	0.05	78.1	0.0	78.1

* The 0.05g per 100g mixtures were prepared on a laboratory scale in a mortar and pestle in a manner simulating the larger scale preparation.

** Results are based on theoretical value for initial concentration due to problem with omitted HPLC chromatogram.

TABLE IV: CI-979 STABILITY IN THE PRESENCE OF SELECTED EXCIPIENTS (INCUBATION FOR 2 WEEKS AT 45°C)

EX NO.	EXCIPIENT	INITIAL CI-979 HCL CONCENTRATION (g/100 g)*/	PERCENT CI-979 REMAINING (% initial)	PERCENT ALDEHYDE FORMED (% initial)	TOTAL
4	FUMARIC ACID	0.01	81.9	6.4	88.3
5a	ADIPIC ACID	0.01	102.3	0.0	102.3
5b	ADIPIC ACID	0.05	104.5	0.0	104.5
6	LACTOSE	0.05	99.6	1.3	100.9
7	SODIUM PHOSPHATE MONOBASIC	0.05	73.1	0.3	73.4

*/ The 0.05g per 100g mixtures were prepared on a laboratory scale in a mortar and pestle in a manner that stimulates the larger scale preparation.

As shown, Tables II, III, and IV contain data on the amount of activity lost after 1 day, 1 week, and 2 weeks, respectively. The results indicate that certain acid excipients, with presumed very low pH (see Table I) are deleterious to the stability of CI-979 by accelerated acid hydrolysis during solid storage. For example, as shown particularly in the third data column of Tables II and III, tartaric acid (Ex. 1) as well as malic acid (Ex. 2) produced significant amounts of the aldehyde breakdown product (A) of CI-979 HCl. Moreover, the mass balance of the mixture is severely affected by the further conversion of the aldehyde (A) to the acid (B) (see Fig. 1), which latter compound incidentally exhibits low absorptivity and is not readily analyzed by reverse phase HPLC-chromatography at this wavelength (225 nm).

At neutrality or higher pH values, the mass balance of the formulation is again found defective, due to the spontaneous conversion of the HCl salt to the volatile free base (Fig. 1). It should be noted, finally, that there is an observed amount of syn or Z - isomer present in all the blends tested, ranging fairly constantly from about 0.5% to about 0.6% by weight of the total applied drug. The process of trituration with the excipients as discussed above (see Table I) is illustrated in Example 10.

Specifically, the alkaloid CI-979 HCl preparations were triturated at about 0.01% (w/w) and/or about 0.05% (w/w) final concentration with the various excipients listed in Table I. In order to effect uniform content or distribution of active ingredient in the triturates, the excipients were blended with a very dilute aqueous solution of the drug. Each resulting solid drug triturate was dried at 40-45°C and again incubated at 45°C for specific time periods, e.g. one day, one week, or two weeks. Each mixture was sampled at the various intervals and analyzed by high performance liquid chromatography (HPLC). Accordingly, both hydrolytic degradation and mass balance of the alkaloid drug were monitored to determine the storage stability of the solid composition.

Example 10

Preparation of Triturates (Protocol)

(a) The dry alkaloid sample is dissolved in de-ionized water (0.31% w/v);

(b) the aqueous solution of drug is sprayed onto the solid excipient with simultaneous thorough mixing using an intensifier bar in a "V" blender;

(c) the beaker is rinsed to transfer all the remaining drug solution onto the excipient;

(d) upon complete mixing, the wet mass is removed from the blender vessel and spread on suitable drying trays and dried at about 40°C - 45°C for about 4 hours;

(e) the dry triturate lumps are rapidly dispersed in a "V" blender for about 2 minutes and suitably stored or immediately processed into a solid oral dosage form (either tablets or hard-gelatin capsules). Suitable conditions are protective from heat and moisture.

The drug excipient test mixtures of Tables II-IV prepared as described above had final concentrations of about 0.01% (w/w). In contrast, the 0.05 grams of CI-979 HCl per 100 gram of total mixture were prepared on a laboratory scale by a mortar and pestle method which was intended to simulate the conditions of a larger manufacturing-type preparation.

The results of the described processing conditions demonstrate that adipic acid stabilizes CI-979 HCl at the two test concentrations. In view of the observed absence of hydrolysis or neutralization, solid adipate triturates appear surprisingly stable when stored at 45°C for two weeks. On the other hand, the experimental use of lactose (milk sugar) triturates (Tables II and III) exhibited low level but measureable hydrolytic effects at 45°C.

Any variations of the invention described above are not to be regarded as a departing from the spirit and scope of the invention as claimed.

WHAT IS CLAIMED IS:

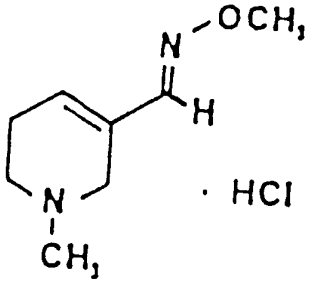
1. A pharmaceutical composition comprising in a solid mixture:

(a) an alkaloid ether oxime salt and

(b) acidic excipients;

the mixture being effective in stabilizing the alkaloid salt.

2. The pharmaceutical composition of claim 1 wherein the alkaloid ether oxime salt comprises CI-979 HCl, having formula Ia:



3. The pharmaceutical composition of claim 1, wherein the mixture stabilizes the alkaloid salt against hydrolysis and evaporation.

4. The pharmaceutical composition of claim 1, wherein the mixture comprises particulate excipients.

5. The pharmaceutical composition of claim 1, wherein the acidic excipients comprise adipic acid or fumaric acid.

6. An oral pharmaceutical composition of a uniform solid blend comprising an alkaloid oxime ether salt and at least one acidic excipient; the blend providing

stability against hydrolysis of the alkaloid oxime ether and neutralization and/or evaporation.

7. The oral pharmaceutical composition of claim 6 in a solid dosage form of the solid blend.

8. The oral pharmaceutical composition of claim 7 wherein the solid dosage is in the form of tablets or hard-gelatin capsules.

9. A process for stabilizing an alkaloid oxime ether salt in a solid pharmaceutical composition having stability against hydrolysis and evaporation comprising the steps of:

(a) preparing a dilute aqueous solution of an alkaloid oxime ether salt;

(b) spraying the aqueous alkaloid solution of step (a) onto a solid acidic excipient which is being thoroughly mixed;

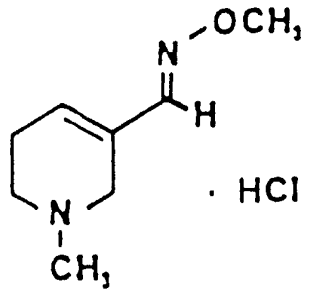
(c) spreading the alkaloid/excipient mixture of step (b) onto trays for drying at about 40°-45°C;

(d) again blending the dried material of step (c); and

(e) storing and/or processing the triturated composition into a solid oral dosage form (tablets or hard-gelatin capsules).

10. The process of claim 7, wherein step (b) takes place in a "V" blender equipped with a intensifier bar.

11. The process of claim 7, wherein the alkaloid is CI-979 salt represented by formula (Ia)



Ia

12. The process of claim 7, wherein the solid acidic excipient is adipic acid or fumaric acid.

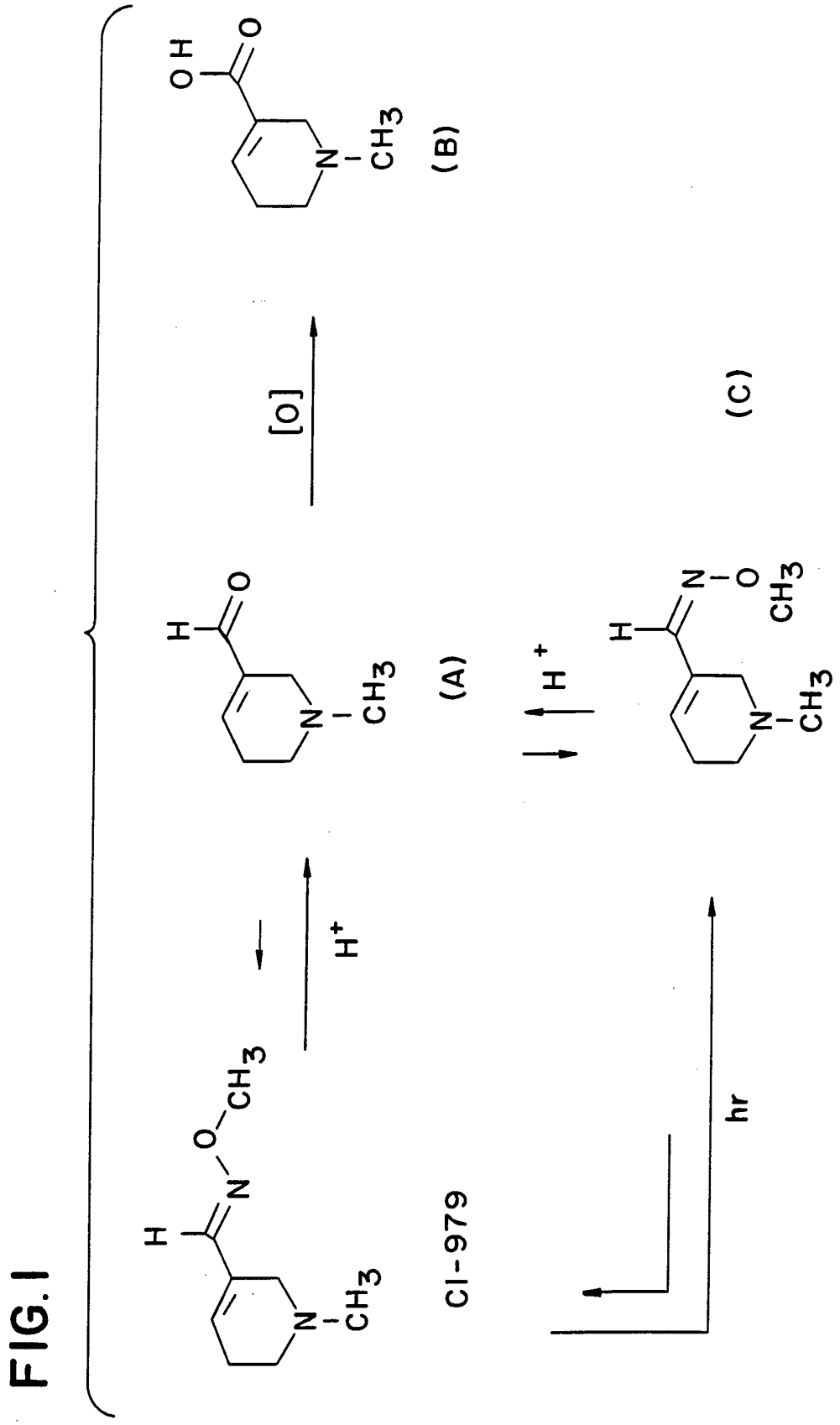


FIG. I

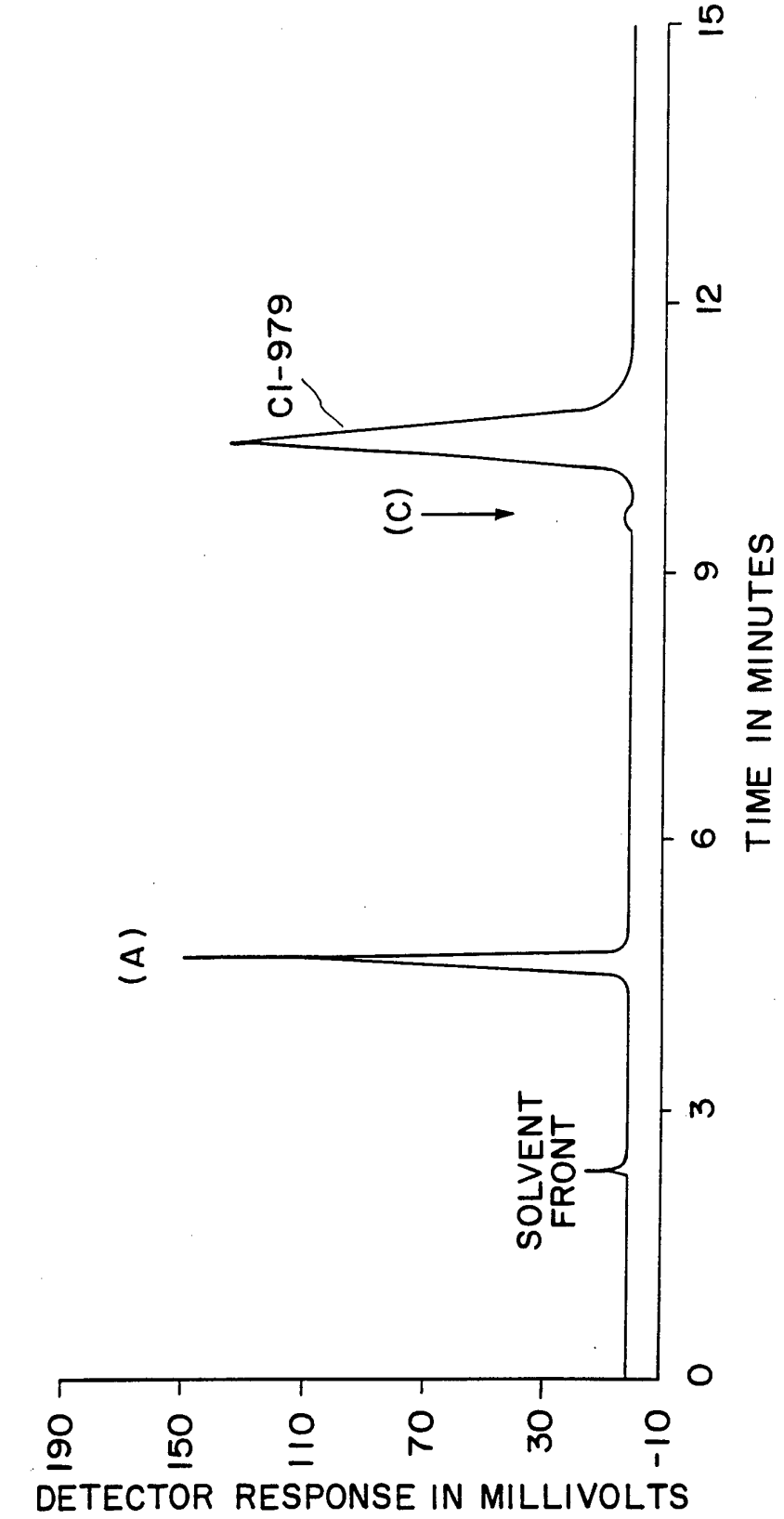

DETECTOR RESPONSE IN MILLIVOLTS
190
150
110
70
30
-10
TIME IN MINUTES
0
3
6
9
12
15
SOLVENT FRONT
(A)
(C)
CI-979

FIG.2

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/US 93/09425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/44 A61K47/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 271 798 (WARNER-LAMBERT) 22 June 1988 cited in the application see claims 1,11 see example 3 see page 11, line 35 - line 37	1,6,8
A	EP,A,0 239 445 (ROUSSEL-UCLAF) 30 September 1987 see claims 1,7-9 see example 1 see page 3, line 36 - line 44	1,6,8

☐ Further documents are listed in the continuation of box C.

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