

Filed On Behalf Of:

Novartis AG and LTS Lohmann Therapie-Systeme AG

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**NOVEN PHARMACEUTICALS INC.
AND MYLAN PHARMACEUTICALS INC.,**
Petitioners

v.

NOVARTIS AG AND LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owners

Inter Partes Review No. 2014-00549¹

U.S. Patent 6,316,023

**PATENT OWNERS' DEMONSTRATIVE
EXHIBITS PURSUANT TO 37 C.F.R. § 42.70(b)**

¹ Case IPR2015-00265 has been joined with this proceeding.

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Inter Partes Review Nos. 2014-00549, 2014-00265

U.S. Patent 6,316,023

**PATENT OWNERS' DEMONSTRATIVE
EXHIBITS FOR ORAL HEARING**

June 2, 2015

Professor Alexander M. Klibanov

- Professor of Chemistry and Bioengineering at M.I.T.
- Elected to the U.S. National Academy of Sciences
- Elected to the U.S. National Academy of Engineering
- Over 45 years as a practicing chemist
- Published over 300 scientific papers
- Given 370 invited lectures



Leo Recognizes That Discovery Of A Problem May Be A Patentable Invention

Paper 25 at 5, 7-8

1354

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(e.g., corticosteroids). See J.A. 6237. These researchers recognized possible advantages from combining a vitamin D treatment with topical corticosteroids, but nevertheless they recommended a two-drug regimen where patients applied the drugs at different times of a day or on alternating days. See *id.*

Although Dikstein and Serup attempt the combination of a vitamin D analog with a corticosteroid, neither discloses or addresses the stability problems of combining vitamin D analogs and corticosteroids into one pharmaceutical formulation. As evidenced by the experiments Leo Pharmaceuticals conducted, the prior art does not teach any composition that exhibits storage stable properties. Every example disclosed in Dikstein contains either almond oil or propylene glycol. Similarly, the examples disclosed in Serup contain not only water, but also almond oil, alcohol, or propylene glycol.

Leo Pharmaceuticals presented experimental evidence to the Board that each of these ingredients harmed the storage stability of the vitamin D analog and corticosteroid combination. See J.A. 562-64, 570 (Hoy Decls. discussing propylene glycol and almond oil); J.A. 566-68 (Didriksen Decl. discussing aqueous alcohol-based solvents). For example, the use of propylene glycol as a solvent resulted in 100% degradation of the vitamin D analog. J.A. 562-564, 692-702. Similarly, the use of aqueous solvents resulted in almost complete degradation of the vitamin D analog after three months of storage—98.3% degradation in one formulation and 100% degradation in another. J.A. 710-16, 1025-26. And, when almond oil was used as a solvent, vitamin D analogs degraded 13-29% after three months of storage. J.A. 570, 723-24. The vitamin D analogs were not the only components at risk for degradation. When commercial ointments with vitamin D analogs or corticosteroids were

combined, or 10% after four months of storage, as disclosed by almost all of the prior art. See J.A. 563; see also Serup (disclosing a corticosteroid of storage in an ointment analog).

Moreover, Serup recognized the problem, the ordinary artisan would have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To disclose a problem to an ordinary artisan would have required several months of testing. See '01, 1, 56; see also Serup (disclosing that the formulations would not be storage stable and advanced the use of propylene glycol and almond oil). The record shows that Dikstein and Serup have achieved the combination of Dikstein and Serup, but the combination does not solve the problem.

Although the Board found the prior art positions with respect to the stability of the formulations more storage stable than the formulations disclosed in Dikstein and Serup, the Board erred by collapsing the obviousness analysis into a hindsight-guided combination of elements. This record, however, discloses several reasons that a person of ordinary skill in

Moreover, because neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable.

Omeprazole Recognizes That Discovery Of A Problem May Be A Patentable Invention

Paper 25 at 5

1380

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ings in various pharmaceutical preparations in support of its argument that it would have been obvious to one of skill in the art to apply an inert subcoating to Example 12 of the '495 European application. None of the references on which Apotex relies, however, undermine the trial court's conclusion that the claims of the '230 and '505 patents would not have been obvious to a person of skill in the art.

Apotex was required to show by clear and convincing evidence that a person of skill in the art would have appreciated the need to include a subcoating in Example 12 of the '495 European application. The district court, however, found that the '495 European application does not disclose or suggest a negative interaction between the drug core containing the magnesium omeprazole salt and the enteric coating in Example 12. The court further found that a person of ordinary skill in the art would not have inferred from the '495 European application that a negative interaction would occur. Based on those findings, the court concluded that a person of ordinary skill would have had no reason to apply a subcoating to the tablets shown in Example 12 of the '495 European application.

To overcome that shortcoming of the '495 European application, Apotex relies on testimony from Dr. Block that "[a] person of ordinary skill would understand that cellulose acetate phthalate has free carboxylic acid groups and could interact with the omeprazole magnesium salt, the omeprazole being acid-labile." The district court was presented with ample evidence to support the contrary conclusion, however. Dr. Langer, Astra's expert, testified that the '495 European application does not suggest any problem relating to the interaction of the enteric coating and the drug core. Furthermore, Dr. Langer and Apotex's expert, Dr. Signorino, agreed that the disclosure in the '495 European application does not suggest any need to stabilize

omeprazole. Dr. Langer testified by inventor provided a person believed ate a pr omeprazole, C. lation of Gastroe The Pill that "an does not dissoluti transport part of the small intestine, enters the bloodstream." Based on that evidence, the district court reasonably concluded that a person not have ple 12 of teaching coatings

Even have re negative coating court fo obvious subcoati problem consider would h in the problem enteric problem the ente art show an alkali penion bonate, tered w applicat erburg,

Furthermore, Dr. Langer and Apotex's expert, Dr. Signorino, agreed that the disclosure in the '495 European application does not suggest any need to stabilize omeprazole beyond using the salt form.

Based on that evidence, the district court reasonably concluded that a person of ordinary skill in the art would not have seen any need to apply to Example 12 of the '495 European application the teachings of the references disclosing subcoatings.

Was Rivastigmine Known Or Reasonably Suggested To Have An Oxidative Degradation Problem?

Paper 25 at 11-13, 14-45

The Art Taught That Rivastigmine Was Chemically Stable

- Enz (Ex. 1002)
- Rosin (Ex. 1008)
- Elmalem (Ex. 1009)
- Enz 1991 (Ex. 2026)
- Weinstock 1994 (Ex. 2027)

A POSA Would Not Reasonably Have Predicted That Rivastigmine Would Oxidatively Degrade Based On Its Structure

- Benzylic C-H bond and an adjacent tertiary amine (nicotine)
- Amines (Sasaki) (Ex. 1005)

A POSA Would Not Have Been Motivated To Combine Rivastigmine With An Antioxidant Unless Required

- Ebert (Ex. 1006)
- Handbook of Pharmaceutical Excipients (Ex. 1003)

Prior Art Reported Greater Chemical Stability Of Rivastigmine And RA7 And/Or Did No Add An Antioxidant

Paper 25 at 14-15, 22, 25-26, 28-29, 36-37

Enz (Ex. 1002)	Did not add an antioxidant to rivastigmine
Rosin (Ex. 1008)	Did not add an antioxidant to RA ₇ RA ₇ 's greater in vivo activity over physostigmine "may be due to . . . greater chemical stability"
Elmalem (Ex. 1009)	RA ₇ has "a greater chemical stability and longer duration of action than that of physostigmine"
Enz 1991 (Ex. 2026)	Did not add an antioxidant to rivastigmine Rivastigmine "appears to have greater chemical stability . . . than does physostigmine."
Weinstock 1994 (Ex. 2027)	Did not add an antioxidant to rivastigmine "In animals and human subjects [rivastigmine] showed superior chemical stability . . . than physostigmine."

Prior Art Reported Greater Chemical Stability Of Rivastigmine And RA7 And/Or Did No Add An Antioxidant

Paper 25 at 14-15, 22, 25-26, 28-29, 36-37

Reference	Did Not Add An Antioxidant To Rivastigmine/RA7	Reported Rivastigmine/RA7 Has Greater Chemical Stability Than Physostigmine
Enz (Ex. 1002)	✓	
Rosin (Ex. 1008)	✓	✓
Elmalem (Ex. 1009)		✓
Enz 1991 (Ex. 2026)	✓	✓
Weinstock 1994 (Ex. 2027)	✓	✓

A POSA Would Not Add An Antioxidant Unless Required

Paper 25 at 10-12

Remington's (Ex. 2017):

Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation. Numerous examples are described in other sections of this book and the literature is replete with illustrations.

act chemically with the drugs they were intended to stabilize, without a noticeable change in the appearance of the preparation.

Because the stability of oxidizable drugs may be adversely affected by oxygen, certain pharmaceuticals may require an oxygen-free atmosphere during their preparation and storage. Oxygen may be present in pharmaceutical liquids as a headspace within the container or may be dissolved in the liquid vehicle. To avoid these sources, oxygen-sensitive drugs may be prepared in the dry state and they, as well as liquid preparations, may be packaged in sealed containers with the air replaced by an inert gas such as nitrogen. This is common practice in the commercial production of vials and ampuls of easily oxidizable preparations intended for parenteral use.

Trace metals originating in the drug, solvent, container, or stopper are a constant source of dif-

fer these parameters. In some instances it is necessary to use an container base that is less than ideal in order to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

Incompatibility

Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation. Numerous examples are described in other sections of this book and the literature is replete with illustrations. Thus, the subject need not be treated in detail here.

While undesirable reactions between two or more drugs are said to result in a "physical," "chemical" or "therapeutic" incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients which leads to a visibly recognizable change. The latter may be in the form of a gross precipitate, haze or color change.

On the other hand, a chemical incompatibility is classified as a reaction in which a visible change does not occur. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it, should it occur.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients which leads to (1) potentiation of the therapeutic effects of the ingredients, (2) destruction of the effectiveness of one or more of the ingredients or (3) occurrence of a toxic manifestation within the patient.

Oxidation-Reduction

Oxidation is a prime cause of product instability and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as autooxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide

with heavy metal ions during their manufacture, packaging or storage.

Hydronium and hydroxide ions. The rate of decomposition is more rapid in a maximum stability (minimum pH 8.4). There is a pH range in which antibiotic and vitamin products are achieved by adding an acid.

Oxidation may be inhibited by the use of so-called negative catalysis. Inhibiting pharmaceutical production chain reaction. The oxidizable, act by possessing the active ingredient. The oxidation or act as chain link in the activated molecule.

The ideal antioxidant should have a wide pH range, soluble in water, nonvolatile, nonirritating, thermostable and consistent system and formulation.

The commonly used antioxidants include sodium sulfite, sodium metabisulfite, sodium thiosulfate and ascorbyl-palmitate, hydroquinone, butylated hydroxytoluene and alpha-tocopherol.

Synergists, which increase the effectiveness of antioxidants, include organic compounds such as heavy metal ions (see Chelating agents), tetraacetic acid, ethylenediamine, tartaric acid, EDTA has been used to stabilize penicillin, epinephrine, and other drugs.

Reduction reactions are common in pharmaceuticals. The reduction of gold, silver, and other metals to their corresponding free metal ions is a common reaction.

H₂O₂

Drugs containing an ester group are susceptible to hydrolysis. Some examples are procaine, tetracaine, thiamine, and others. The rate of hydrolysis is dependent on the pH of the solution. For each 10¹ rise in pH, the reaction doubles or triples, depending on the drug.

Ansel (Ex. 2020):

The proper use of antioxidants involves their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances other pharmaceutical additives have been found to inactivate a given antioxidant when used in the same formulation. In other cases certain antioxidants have been found to react chemically with the drugs they were intended to stabilize, without a noticeable change in the appearance of the preparation.

A POSA Would Not Add An Antioxidant Unless Required

Paper 25 at 11

5. DEVELOPMENT PHARMACEUTICS

During the pharmaceutical development of the product the applicant should demonstrate:

- the necessity to add an antioxidant or a preservative to the finished product at the level chosen.
- the physical and chemical compatibility of the antioxidant and of the preservative with other constituents of the finished product, the container and the closures.

The concentration used must be justified in terms of efficacy and safety, such that the minimum concentration of preservative is used which gives the required level of efficacy. The appropriate test method for efficacy of antimicrobial preservation is that of the European Pharmacopoeia. This should be used to determine whether the required level of activity is achieved.

EMA Guidelines (Ex. 2019):

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space gas.

In the case of antioxidants, these should only be used once it has been shown that their use cannot be avoided, even if the manufacturing process is optimised to minimise the potential for oxidation, for example by manufacturing and filling products under an inert headspace gas.

6. CONTROL OF THE EXCIPIENTS

Antimicrobial preservatives and antioxidants are defined as excipients and as such should be controlled following the guidance given in The Rules Governing Medicinal Products in the European Union, Volume III "Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product".

7. CONTROL OF THE FINISHED PRODUCT

The finished product release specifications should include an identification test and limits for any antioxidants and antimicrobial preservatives present in the formulation. The finished product specification against which the product is tested throughout its shelf-life should also include limits for the antimicrobial preservatives present.

Where antioxidants are used up during the manufacture of the product, the release limits should be justified by batch data. The adequacy of specified limits should be justified on the

CPMP/CVMP/QWP/115/95

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NOVARTIS EXHIBIT 2019
Noven v. Novartis and LTS Lohmann
IPR2014-00550
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Petitioners Fail To Consider Elmalem And The Prior Art As A Whole

Paper 25 at 30-31

1066

ESTHER ELMALEM *et al.*

Each of the following drugs, physostigmine, (0.05 and 0.1 mg/kg); RA₆ (0.5 and 1 mg/kg); RA₇ (1 and 2 mg/kg) and RA₁₅ (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6-10 rabbits per drug. Nine other rabbits were given morphine alone with 0.1 ml/kg saline. An additional group of 6 rabbits received morphine

RESULTS

Antagonism of the respiratory depressant effect of morphine by antiAChE

Intravenous injection of morphine (8 mg) caused a significant fall in respiration rate of about 50% and a rise in paco₂ of 54% within 15 min, which lasted for 2-3 hr. Physostigmine significantly reduced from 35 to 45% the fall in respiration rate, while the pH fell at 15-60 min. Morphine caused a fall in heart rate by 70-120 beats per minute. Physostigmine caused a small but significant decrease in blood pressure (5.2 ± 1.8 mmHg) but significant decrease in blood

Elmalem (Ex. 1009):

All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

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homogenized in phosphate buffer (0.1 M) pH 8, containing 1% Triton. The mixture was centrifuged at 1000 g and the supernatant, which contained most of the solubilized enzyme, was used for the determination of the activity of AChE by the method of Ellman, Courtney, Andres and Featherstone (1961). The percentage inhibition of AChE by the drugs was computed by comparison with the pooled mean value for each of the appropriate saline-treated controls.

Estimation of plasma cholinesterase

Blood (0.5 ml) was withdrawn into a heparinized syringe, during the control period and at 5, 15, 30, 60, 90, 120, 150 and 180 min after injection of the AChE inhibitors. The blood was centrifuged at 4°C for 5 min at 1000 g and the activity of AChE of the plasma was measured by the method of Ellman *et al.* (1961).

Drugs

The agents tested were RA₆ (*N*-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate HCl. RA₇ (*N*-ethyl, *N*-methyl-3[1-(dimethylamino)ethyl] phenyl carbamate HCl. RA₁₅ (*N*-propyl-3[1-(dimethylamino)ethyl]phenyl carbamate HCl. Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

stress were accompanied by signs of peripheral cholinergic hyperactivity, including salivation, defaecation and slight muscular twitches.

The drug RA₇ (0.25 mg) significantly reduced the elevation in paco₂ and the fall in respiratory rate after morphine, only at 15 min after injection (Fig. 2). At a dose of 0.5 mg, both the change in paco₂ and in respiration rate, induced by morphine, were significantly antagonised for 3 hr (Fig. 2) but the brady-

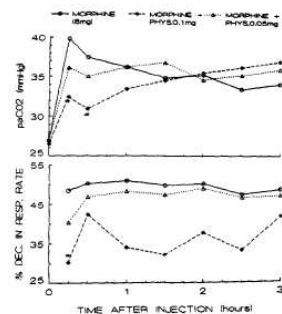


Fig. 1. The influence of physostigmine on the respiratory depressant effect of morphine. Physostigmine was injected intravenously at the same time as morphine. *Significantly different from morphine alone, $P < 0.05$.
Noven Ex. 1009

Page 2 of 6

Physostigmine Was Known To Undergo Hydrolysis

Paper 25 at 31-32

Rosin (Ex. 1008):

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PHENYL CARBAMATES

This application is a continuation of ap No. 185,451, filed on 04/25/88, entitled P... mates which in turn was a continuation of Ser. No. 835,466 filed Mar. 3, 1986, bo... done.

The present invention relates to novel mates which are useful as pharmaceutical The invention further relates to pharmace sitions having anticholinesterase activity.

Acetylcholine is a major neurotransm found in all parts of the body. Any re activity, either as a result of neuronal dan ation etc. or as induced by drugs or l marked changes in the function of the o tycholine itself has an extremely short ha is rapidly hydrolysed at its site of actio by specific cholinesterase enzymes. Dru acetylcholinesterase, markedly increas the action of acetylcholine, thereby enhan gic transmission. Three such agents are u i.e., physostigmine, a naturally occurring two synthetic analogues, neostigmine ar mine. The latter two agents are strongly ic ological pH and therefore are only poe from the gastro-intestinal tract, and do not central nervous system to any significant t stigmine is absorbed after oral admin readily enters the brain. As a therapeuti several disadvantages. It is chemically

must be prepared in solution with an an protected from light. It has a relatively short half-life (20-40 mins) thereby necessitating frequent administration. The latter is of particular importance when the drug is to be administered chronically. It has a low therapeutic ratio, a value of

majority of studies in labora therapeutic window, i.e. sma can be given without the acc Although physostigmine is intestinal tract, this is report predictable, and therefore it minister the drug parenteral back if it is to be used chronic

There are a number of cli ditions which are associate activity which can be improv an anticholinesterase agent. cholinergic transmission ind nos substances acting in the vous system. Peripherally ac

d-tubocurarine and pancuro muscle relaxants. Their action can readily be overcome by an anticholinesterase drug. Drugs which interfere with central cholinergic transmission are numerous, anticholinergic, atropine-like drugs including anti-parkinson drugs, tricyclic antidepressants, neuroleptics, opiate analgesics, benzodiazepines and some types of general anaesthetics. So far the only agent that has proved to be of any value in reversing the effects of the latter group of drugs is physostigmine. In all reported cases of drug overdose or lack of recovery when the agent was used peri-operatively, physostigmine is usually administered parenterally, and administration is repeated every 20-30 minutes as required.

curative dyskinesias. The widespread use of agents hav...

Physostigmine is absorbed after oral administration and readily enters the brain. As a therapeutic agent it has several disadvantages. It is **chemically unstable and must be prepared in solution with an antioxidant, and protected from light.**

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The monomethyl derivatives tend to be unstable in solution and **hydrolyse** readily at physiological pH.

The

35 tubocurarine, an antagonist of acetylcholine. The second group consists of various organophosphorus compounds, such as diisopropyl fluorophosphate, paraxon etc. The vast majority of the compounds of both these

opate, a quaternary ammonium organophosphorus compound, employed in eye drops for the treatment of glaucoma.

The synthetic anticholinesterase agents currently employed as pharmaceuticals all contain a charged nitrogen function and can be broadly classified into 3 groups.

- (1) Reversible inhibitors which contain a charged nitrogen function attached to an aromatic ring, e.g. edrophonium.
- (2) Dimethyl carbamates with an aromatic or heterocyclic ring containing a charged nitrogen, neostigmine, pyridostigmine.

Noven Ex. 1008
Page 2 of 8

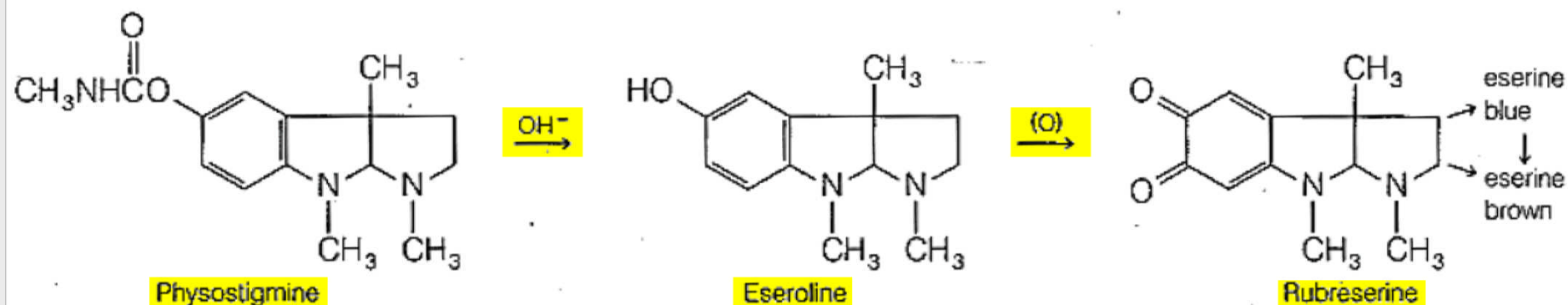
An Antioxidant Prevents The Oxidation Of Physostigmine's Hydrolytic Degradant

Paper 25 at 31-32

456 | CHOLINERGIC DRUGS AND RELATED AGENTS

Wilson & Gisvold (Ex. 2038):

...in a red coloration
...may be taken as an
...physostigmine solu-

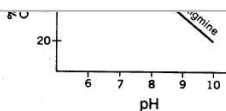


Physostigmine Salicylate, USP. Eserine salicylate. The salicylate of physostigmine may be prepared by neutralizing an ethereal solution of the alkaloid with an ethereal solution of salicylic acid.

Physostigmine is a relatively poor carbamylating agent of AChE and is often considered a reversible inhibitor of the enzyme. It has a K_i value (i.e., k_{-1}/k_{+1}) on the order of $10^{-8} M$ and is considered

The addition of sulfite or ascorbic acid prevents the oxidation of the phenol, eseroline, to rubreserine.

Physostigmine salicylate occurs as a white, shining, odorless crystal, or white powder that is soluble in water (1:75), alcohol (1:16), or chloroform (1:6), but is much less soluble in ether (1:250). Upon prolonged exposure to air and light, the crystals turn red. The red may be removed by washing the crystals with alcohol, although this causes loss of the compound as well. Aqueous solutions are neu-



NOVARTIS EXHIBIT 2038
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IPR2014-00550
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Elmalem States That RA₇ Has Greater Chemical Stability Than Physostigmine

Paper 25 at 28-29

Neuropharmacology Vol. 30, No. 10, pp. 1059-1064, 1991
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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTICHOLINESTERASE

Elmalem (Ex. 1009):

Department

Summary—The effects of 10 mg/kg of morphine in rabbits, which was measured in terms of respiratory depression, were antagonized by physostigmine. The drugs R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₃₈, R₃₉, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₆, R₄₇, R₄₈, R₄₉, R₅₀, R₅₁, R₅₂, R₅₃, R₅₄, R₅₅, R₅₆, R₅₇, R₅₈, R₅₉, R₆₀, R₆₁, R₆₂, R₆₃, R₆₄, R₆₅, R₆₆, R₆₇, R₆₈, R₆₉, R₇₀, R₇₁, R₇₂, R₇₃, R₇₄, R₇₅, R₇₆, R₇₇, R₇₈, R₇₉, R₈₀, R₈₁, R₈₂, R₈₃, R₈₄, R₈₅, R₈₆, R₈₇, R₈₈, R₈₉, R₉₀, R₉₁, R₉₂, R₉₃, R₉₄, R₉₅, R₉₆, R₉₇, R₉₈, R₉₉, R₁₀₀, R₁₀₁, R₁₀₂, R₁₀₃, R₁₀₄, R₁₀₅, R₁₀₆, R₁₀₇, R₁₀₈, R₁₀₉, R₁₁₀, R₁₁₁, R₁₁₂, R₁₁₃, R₁₁₄, R₁₁₅, R₁₁₆, R₁₁₇, R₁₁₈, R₁₁₉, R₁₂₀, R₁₂₁, R₁₂₂, R₁₂₃, R₁₂₄, R₁₂₅, R₁₂₆, R₁₂₇, R₁₂₈, R₁₂₉, R₁₃₀, R₁₃₁, R₁₃₂, R₁₃₃, R₁₃₄, R₁₃₅, R₁₃₆, R₁₃₇, R₁₃₈, R₁₃₉, R₁₄₀, R₁₄₁, R₁₄₂, R₁₄₃, R₁₄₄, R₁₄₅, R₁₄₆, R₁₄₇, R₁₄₈, R₁₄₉, R₁₅₀, R₁₅₁, R₁₅₂, R₁₅₃, R₁₅₄, R₁₅₅, R₁₅₆, R₁₅₇, R₁₅₈, R₁₅₉, R₁₆₀, R₁₆₁, R₁₆₂, R₁₆₃, R₁₆₄, R₁₆₅, R₁₆₆, R₁₆₇, R₁₆₈, R₁₆₉, R₁₇₀, R₁₇₁, R₁₇₂, R₁₇₃, R₁₇₄, R₁₇₅, R₁₇₆, R₁₇₇, R₁₇₈, R₁₇₉, R₁₈₀, R₁₈₁, R₁₈₂, R₁₈₃, 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Key words—

In previous studies in tal animals it was reduce the respiratory without interfering (Snir-Mor, Weinstock, Erez, Davidson, Rosin and potential therapy of receiving opiates, a serious disadvantage is its relatively high appearance of distress doses (Christie, Shear). Its low chemical stability also necessitate an attempt to overcome novel anticholinesterase this laboratory. The central nervous system stability and longer duration of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

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In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

Elmalem Quantitatively Compared The Effects Of Different Drugs On Morphine-Induced Respiratory Depression

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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTICHOLINESTERASE AGENTS

Elmalem (Ex. 1009):

MARTA WEINSTOCK**
School of Pharmacy, Hebrew University,
Israel

(Accepted 12 May 1991)

Summary—This study compared the effects of 3 novel antiAChE agents (derivatives of dimethylaminoethyl-phenyl carbamate) with that of physostigmine on the respiratory depression induced by morphine in rabbits. Each drug, RA₆ (1 mg i.v., 2 mg s.c.) RA₇ (1 or 2 mg i.v.); RA₁₅ (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6–10 rabbits.

Key words—respiratory depression; cholinesterase inhibition; medullar, carbamates, rabbit.

In previous studies in human subjects and experimental animals it was shown that physostigmine could reduce the respiratory depressant effect of morphine, without interfering with the analgesic effect (Snir-Mor, Weinstock, Bahar and Davidson, 1983; Weinstock, Erez and Roll, 1981a; Weinstock, Davidson, Rosin and Schnieden, 1982). However, as potential therapy for concomitant use in patients receiving opiates, physostigmine has a number of serious disadvantages. The most important of these is its relatively high toxicity, which results in the appearance of distressing side effects at therapeutic doses (Christie, Shering, Ferguson and Glenn, 1981). Its low chemical stability and short duration of action also necessitate frequent administration. In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

The purpose of this study was twofold; to compare the abilities of three of these novel anticholinesterase agents with that of physostigmine to antagonize the respiratory depressant effect of morphine and to determine whether there is a correlation between the degree of such antagonism and the amount of inhibition of acetyl-cholinesterase (AChE) in the medulla oblongata.

METHODS

Antagonism of the cardiovascular and respiratory depressant effects of morphine by the anticholinesterase compounds

Male and female rabbits, weighing 2.5–3 kg, were prepared with catheters in the central ear artery and marginal ear vein, as previously described (Weinstock *et al.*, 1981a). Rectal temperature was monitored on a telethermometer with the aid of a thermistor probe inserted into the rectum. Respiration rate was counted visually for periods of 30 sec. Blood gases and pH were measured on a blood gas analyzer (Instrumentation Laboratories) after correction for the appropriate body temperature from samples of blood taken from the ear artery. Blood pressure and heart rate were monitored on a Brush Gould recorder.

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Elmalem Was A Well-Controlled Study

Paper 25 at 29, 32-33

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ANTAGONISM OF MORPHINE-INDUCED DEPRESSION BY NOVEL ANTI-CHOLINERGIC AGENT

ESTHER ELMALEM,¹ M. CHOREV² and

¹Departments of Pharmacology and ²Medical Chemist
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(Accepted 13 May 1991)

Summary—This study compared the effects of 3 novel laminoethyl-phenyl carbamate) with that of physostigmine morphine in rabbits. Each drug, RA₁ (1 mg i.v., 2 mg s.c.) physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected into groups of 6–10 rabbits. Respiration rate, blood gases was measured before and at 15 min intervals after injection rabbits, which were sacrificed at the time of maximal anti-morphine, in order to measure the activity of AChE in the

Physostigmine (0.1 mg) only antagonized the increase in The drugs RA₁ (0.5 mg), RA₂ (2.5 mg) and RA₃ (2 mg) depression, without obvious signs of peripheral cholinergic relationship between the degree of antagonism of the inhibition of ChE in plasma. In contrast, a highly significant the former and the amount of inhibition of AChE in the
It is suggested that the novel carbamates may have potential respiratory depression of opiates, without impairing anal

Key words—respiratory depression, cholinesterase inhibition

In previous studies in human subjects and experimental animals it was shown that physostigmine could reduce the respiratory depressant effect of morphine, without interfering with the analgesic effect (Snir-Mor, Weinstock, Bahar and Davidson, 1983; Weinstock, Erez and Roll, 1981a; Weinstock, Davidson, Rosin and Schnieden, 1982). However, as potential therapy for concomitant use in patients receiving opiates, physostigmine has a number of serious disadvantages. The most important of these is its relatively high toxicity, which results in the appearance of distressing side effects at therapeutic doses (Christie, Shering, Ferguson and Glenn, 1981). Its low chemical stability and short duration of action also necessitate frequent administration. In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

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Formulation Controls:

- All drugs formulated with an antioxidant

Route Of Administration Controls:

- All drugs administered by injection

Test Subject Controls:

- At least 4 rabbits/treatment
- All rabbits similar size (2.5 to 3 kg)
- Dosages calculated per kg body weight
- Blood samples analyzed before treatment
- Changes in body temperature monitored
- Differences in respiration rates normalized

Weinstock 1994 Did Not Suggest That Rivastigmine Requires An Antioxidant In Any Formulation

Paper 25 at 36

Weinstock 1994 (Ex. 2027):

J Neural Transm (1994) [Suppl] 43: 219–225
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Pharmacological evaluation of phenyl-carbamates as CNS-selective acetylcholinesterase inhibitors

M. Weinstock¹, M. Razin¹, M. Chorev², and A. Enz³

esterase. If memory impairments in AD are related to a lack of cholinergic activity in cortical and hippocampal brain areas, SDZ ENA 713 should produce significant symptomatic improvement.

Introduction

Summary. The pharmacological and clinical properties of a novel phenyl carbamate acetylcholinesterase (AChE) inhibitor, SDZ ENA 713 are described. In animals and human subjects this compound showed superior chemical stability, oral bioavailability and a longer duration of action than physostigmine.

NOVARTIS EXHIBIT 2027
Noven v. Novartis and LTS Lohmann
IPR2014-00550
Page 2 of 8

Petitioners' Reading Of Elmalem Adds A Variable To The Well-Controlled Study

Paper 25 at 33-34

Elmalem (Ex. 1009):

1060

Each of the following drugs, RA₆ (0.5 and 1 mg/kg) and RA₁₅ (0.25 and 0.5 mg/kg) and RA₇ (1 and 2 mg/kg) were injected intravenously (i.v.) with groups of 6-10 rabbits per drug. Nine other rabbits were given morphine alone as an additional group of 6 rabbits (8 mg/kg) plus RA₆ (2 mg/kg) (s.c.). Blood samples were taken at least twice before and 30 min after injection intervals, for 3 hr.

Measurement of anticholinergic areas of the brain of rabbits

Rabbits were injected with physostigmine or each of the doses designated, or with saline. 4 animals were used for each dose at the stated times after the injection. The rabbits were sacrificed by air embolism and were injected with saline or morphine at the same times as the anticholinesterases, i.e. each after 15 and 30 min. The brain was rapidly dissected out on ice, homogenized in phosphate buffer containing 1% Triton. The supernatant at 1000 g and the supernatant of the solubilized enzyme, was used for the determination of the activity of AChE by the method of Ellman, Courtney, Andres and Featherstone (1961). The percentage inhibition of AChE by the drugs was computed by comparison with the pooled mean value for each of the appropriate saline-treated controls.

Estimation of plasma cholinesterase

Blood (0.5 ml) was withdrawn by syringe, during the control period, 90, 120, 150 and 180 min after injection of inhibitors. The blood was centrifuged at 1000 g and the plasma was measured by the method of Ellman (1961).

Drugs

The agents tested were RA₆ (N-(2-aminoethyl)phenyl carbamate HCl), RA₇ (N-methyl-3-(1-(dimethylamino)ethyl)phenyl carbamate HCl), RA₁₅ (N-propyl-3-(1-(dimethylamino)ethyl)phenyl carbamate HCl), Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

Each of the following drugs, physostigmine, (0.05 and 0.1 mg/kg); RA₆ (0.5 and 1 mg/kg); RA₇ (1 and 2 mg/kg) and RA₁₅ (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6-10 rabbits per drug. Nine other rabbits were given morphine alone with 0.1 ml/kg saline.

The drug (0.05 mg/kg) significantly reduced the elevation in paco₂ and the fall in respiratory rate after morphine, only at 15 min after injection (Fig. 2). At a dose of 0.5 mg, both the change in paco₂ and in respiration rate, induced by morphine, were significantly antagonised for 3 hr (Fig. 2) but the brady-

All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

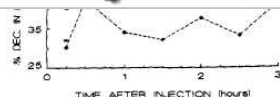


Fig. 1. The influence of physostigmine on the respiratory depressant effect of morphine. Physostigmine was injected intravenously at the same time as morphine. *Significantly different from morphine alone, $P < 0.05$.

Noven Ex. 1009
Page 2 of 6

Antioxidant Amount Is Not Calculated Based On The Amount Of Drug

Paper 43 at 9-10; see *also* Paper 25 at 33-34

Dr. Kydonieus (Ex. 1049):

9 Q. And Dr. Kydonieus, I'm asking you when
10 the Handbook of Pharmaceutical Excipients refers
11 to a percent weight by weight, it is a
12 percent -- percentage based on the total weight
13 of the pharmaceutical composition, correct?

14 A. Yes, in --

15 MR. COULSON: Objection to form.

16 A. Excuse me.

17 MR. COULSON: Objection. Form.

18 A. In the -- if you want, I can read it
19 for you, but I believe it is on the total
20 weight.

Elmalem And Weinstock 1981 Studies Were Conducted For Different Purposes

Paper 25 at 35 n.7

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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTIACHE AGENTS ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTIACHE AGENTS

Elmalem (Ex. 1009):

M. WEINSTOCK*

*Departments of Pharmacology and *Medicinal Chemistry, School of Pharmacy, Hebrew University, Jerusalem, Israel

Summary—This study compared the effects of 3 novel antiAChE agents (derivatives of dimethylaminoethyl-phenyl carbamate) with that of physostigmine on the respiratory depression induced by morphine in rabbits.

Physostigmine (0.1 mg) only antagonized the increase in $\text{p}a\text{C}_2$ induced by morphine at 15 and 30 min. The drugs RA₁ (0.5 mg), RA₂ (2.5 mg) and RA₃ (2.5 mg) almost completely reversed the respiratory depression, without obvious signs of inhibition of ChE in plasma. In contrast to the former and the amount of inhibition of ChE in plasma. It is suggested that the novel carbamate respiratory depression of opiates, without impairing analgesia.

Key words—respiratory depression

In previous studies in human subjects and in animals it was shown that physostigmine reduces the respiratory depressant effect of morphine without interfering with the analgesia (Snir-Mor, Weinstock, Bahar and Davidson, 1981; Weinstock, Erez and Roll, 1981a; Davidson, Rosin and Schnieden, 1982). The potential therapy for concomitant use of physostigmine with opiates, receiving opiates, physostigmine has several serious disadvantages. The most important are its relatively high toxicity, which results in the appearance of distressing side effects at high doses (Christie, Shering, Ferguson and Davidson, 1981). Its low chemical stability and short duration of action also necessitate frequent administration. In an attempt to overcome these drawbacks, novel anticholinesterase agents were synthesized in this laboratory. These agents readily cross the blood-brain barrier, have a greater stability and longer duration of action than physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Choren and Tashma, 1986).

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Antagonism of the Cardiovascular and Respiratory Depressant Effects of Morphine in the Conscious Rabbit by Physostigmine¹

MARTA WEINSTOCK, ELI EREZ and DORON ROLL

Department of Pharmacology and Experimental Therapeutics, Hebrew University, Hadassah School of Medicine, Jerusalem, Israel (M.W., D.R.)

The influence of physostigmine was studied on the effect of morphine on the cardiovascular and respiratory systems in conscious rabbits. Morphine (4 mg/kg i.v.) caused analgesia, bradycardia, hypotension and respiratory depression, as indicated by a fall in respiratory rate of 50%, a rise in blood $\text{P}a\text{CO}_2$ from 25.1 to 37.2 mm Hg and a fall in pH from 7.40 to 7.24. These effects lasted 2 to 3 hr and were completely antagonized by naloxone. Physostigmine (2.5 or 5 $\mu\text{g}/\text{kg}/\text{min}$) given by

intravenous infusion of morphine remained unimpaired by physostigmine. Naloxone (2.5 $\mu\text{g}/\text{kg}/\text{min}$) potentiated the bradycardia induced by morphine and did not antagonize its hypotensive and respiratory depressant effects. The results support the hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous system.

Weinstock 1981 (Ex. 2046):

The influence of physostigmine was studied on the effect of morphine on the cardiovascular and respiratory systems in conscious rabbits.

rate in decerebrate cats, pretreated with physostigmine (Miller, 1967), with central cholinergic activity as well as with respiratory

The results support the hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous system.

IPR2014-00550
Page 1 of 5

Elmalem And Weinstock 1981 Used Different Experimental Designs

Paper 25 at 35 n.7; Paper 43 at 10-11

1060

ESTHER ELMALEM *et al.*

Each of the following drugs, physostigmine, (0.05 and 0.1 mg/kg); RA₆ (0.5 and 1 mg/kg); RA₁ (1 and 2 mg/kg) and RA₁₅ (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6-10 rabbits per drug. Nine other rabbits

RESULTS

Antagonism of the respiratory depressant effect of morphine by antiAChE

Intravenous injection of morphine (8 mg) caused a fall in respiration rate of about 50% and CO₂ of 54% within 15 min, which lasted 5 ± 5 at 15 and 30 min, while the pH fell from 7.27 ± 0.01 at 15-60 min. Mor-

Elmalem (Ex. 1009):

...at least twice before administration of drug, ...

All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

the frontal cortex, hippocampus and medulla were rapidly dissected out on ice, weighed individually and homogenized in phosphate buffer (0.1 M) pH 8, containing 1% Triton. The mixture was centrifuged at 1000 g and the supernatant, which contained most of the solubilized enzyme, was used for the determination of the activity of AChE by the method of Ellman, Courtney, Andres and Featherstone (1961). The percentage inhibition of AChE by the drugs

...physostigmine potentiated the bradycardia induced by morphine at 15 and 30 min. These effects were accompanied by signs of peripheral cholinergic hyperactivity, including salivation, defecation and slight muscular twitches.

The drug RA₁₁ (0.25 mg) significantly reduced the elevation in paco₂ and the fall in respiratory rate after morphine, only at 15 min after injection (Fig. 2). At a dose of 0.5 mg, both the change in paco₂ and

Weinstock 1981 (Ex. 2046):

Estimation of plasma cholinesterase

407 R

Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation.

(Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

TIME AFTER INJECTION (hours)

Fig. 1. The influence of physostigmine on the respiratory depressant effect of morphine. Physostigmine was injected intravenously at the same time as morphine. *Significantly different from morphine alone, P < 0.05.

Noven Ex. 1009

Page 2 of 6

1981

Physostigmine Antagonism of Morphine 505

25 µl/ml of heparin. Blood pressure and heart rate were recorded on a Brush Gould recorder by means of a transducer attached to one arterial cannula. Drugs were administered through a butterfly needle (no. 23) placed in a marginal ear vein. Physostigmine or neostigmine was infused i.v. in a volume of 0.09 ml/min by means of a Harvard constant infusion pump.

Rectal temperature was monitored on a telethermometer (Yellow Springs Instrument Company, Yellow Springs, OH) with the aid of a thermistor probe inserted into the rectum. Respiration rate was counted visually and blood gases and pH were measured on Corning automatic blood gas analyzer after adjustment to the appropriate body temperature.

injection of 4 and 10 mg/kg of morphine respectively. The peak hypotensive response (9.8 ± 2.2 and 12.4 ± 1.8 mm Hg) occurred 20 to 30 min after injection of 2 and 4 mg/kg, respectively. The response to 10 mg/kg of morphine was inconsistent, with some rabbits displaying a rise of 5 to 10 mm Hg during the first 10 min and others, a small nonsignificant fall. Both the bradycardia and hypotensive response to 4 mg/kg of morphine lasted 2.5 to 3 hr.

A dose of 4 mg/kg of morphine was therefore chosen for all subsequent experiments since it produced the most extensive and consistent vasodepression and bradycardia.

Pretreatment with ATMN (0.5 mg/kg) completely prevented the bradycardia and reduced the fall in blood pressure.

Morphine (4 mg/kg) caused more than a 50% reduction in respiratory rate, which was associated with a 48% increase in arterial Paco₂. Blood pH was reduced from 7.40 to 7.24 (see fig. 1). Maximum respiratory depression occurred between 30 and 90 min after morphine administration and lasted 3 hr.

A considerable degree of analgesic activity was also seen at this dose level, 30 min after injection of morphine, with most of the rabbits failing to respond to the highest degree of pressure (table 1).

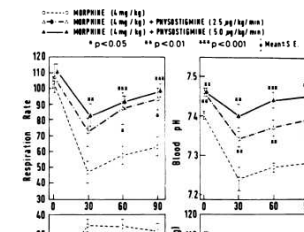
Naloxone, given by continuous i.v. infusion at a dose of 0.1 mg/min completely prevented all the above effects of morphine (4 mg/kg) in four rabbits.

Influence of anticholinesterase agents on actions of

infusion of physostigmine, and at 30, 60 and 90 min after injection of morphine. The volume of blood taken was replaced each time with an equal volume of sterile saline. In five rabbits, neostigmine (2.5 µg/kg/min) was infused for 30 min and then continued after injection of morphine (4 mg/kg). Blood pressure, heart and respiration rates and blood gases were measured as above. In six other rabbits, ATMN (0.5 mg/kg), or in four animals, hyoscine (10 mg/kg), was given, 15 min before the infusion of physostigmine, 5 µg/kg/min.

In four rabbits, naloxone was infused i.v. at a concentration of 0.1 mg/kg/min for 15 min before and for 90 min after injection of 4 mg/kg of morphine. Blood pressure, heart and respiration rates were recorded as described above.

Estimation of plasma cholinesterase. Blood (0.3-0.5 ml) was withdrawn into a heparinized syringe during the predrug control period and at 30 and 60 min after commencement of physostigmine infusion (i.e., 30 min after morphine injection). The blood was centrifuged



Effect of morphine on blood pressure, heart rate, respiration and pain threshold. Intravenous injection of morphine (2 mg/kg) caused significant bradycardia (reduction of 72 ± 10 beats/min) within 5 min, whereas 1 mg/kg only reduced heart rate by 30 ± 9 beats at 60 min. Reductions in heart rate of 108 ± 12 and 102 ± 10 beats/min occurred 5 to 30 min after

Control	21	1.38 ± 0.13
Morphine (4 mg/kg)	9	4.55 ± 0.24
Physostigmine (5 µg/kg/min, 30 min)	7	1.71 ± 0.28
Physostigmine (5 µg/kg/min, 30 min) + morphine (4 mg/kg)	12	4.91 ± 0.08

NOVARTIS EXHIBIT 2046
Noven v. Novartis and LTS Lohmann
IPR2014-00550
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Rosin Discloses Millions Of “Compounds Of The Invention”

Paper 25 at 24-25

Rosin (Ex. 1008):

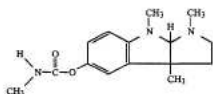
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(3) Bisquaternary structures, e.g. Demacarium, Ambenonium. These agents tend to be more selective inhibitors of acetylcholinesterase than butyrylcholinesterase, compared with the monoquaternary molecules.

The pharmaceutical application of the quaternary anticholinesterase agents is limited because of their poor penetration through cell membranes. They are therefore used for actions outside the central nervous system, and are usually given parenterally, since they are not reliably absorbed from the gastrointestinal tract. Edrophonium, neostigmine and pyridostigmine and the bisquaternary analogues are used in anesthetic practice for the reversal of the action of muscle relaxants. They are also used for the treatment of myasthenia gravis, and paralytic ileus.

Physostigmine is the only potent anti-cholinesterase agent which has been used clinically to treat conditions in which an elevation of brain acetylcholine activity is desired. These include, Alzheimer's disease, tardive dyskinesia, Down's syndrome and Huntington's chorea. Physostigmine is also used to reverse the effects of overdose of anticholinergic agents, anti-Parkinson drugs, benzodiazepines and opiate analgesics.

Physostigmine is a natural alkaloid extracted from calabar beans and the seeds of the vine *Physostigma venenosum* and has the formula



There is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine.

Furthermore there is a need to provide new compounds which inhibit acetylcholinesterase in the brain for periods exceeding 3 hours but not more than 12 hours after a single administration.

There is also a need to provide new compounds which will be completely and reliably absorbed after oral administration.

There is also a need to provide new compounds which will be relatively less toxic than physostigmine. This means that the therapeutic ratio, defined as

$$\frac{\text{dose to produce therapeutic effect}}{\text{dose to produce mortality in 50\% of animals}}$$

should be significantly higher than those of physostigmine and that the incidence and severity of side effects should be less than those of physostigmine at therapeutic doses.

There is also a need to provide new compounds which can be given orally or parenterally to treat chronic conditions in which it is desired to raise cholinergic activity in the central nervous system. These include, Alzheimer's disease, Down's syndrome, Huntington's chorea, Friedrich's ataxia.

There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neuroleptics and general anesthetics.

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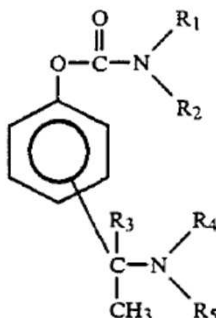
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There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neuroleptics and general anesthetics.

Thus according to the present invention there is now provided a pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system of mammals comprising a compound of the general formula I



wherein

- 35 R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,
- 40 R₂ is hydrogen, methyl, ethyl or propyl, or R₁ and R₂ together with the nitrogen to which they are attached form a morpholino or piperidino radical,
- 45 R₃ is hydrogen or lower alkyl,
- 50 R₄ and R₅ are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position, or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor. Hereinafter these compounds are called compounds of the invention.

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Rosin Discloses Compositions For Oral And Parenteral Administration

Paper 25 at 25

4,948,807

7
stir at ambient temperature for 15-24 hours. Removal of the acetonitrile under reduced pressure (20 mm Hg) is followed by the addition of water (10-25 ml). The pH of the aqueous solution is adjusted to pH=11 by the addition of the appropriate amount of NaOH 0.1N followed by extraction with ether (3x25 ml). The combined organic phases are washed with brine (25 ml) dried over MgSO₄ anhydride which is then filter cooled ethereal filtrate is saturated with (g) resulting in the formation of a heavy anticipated carbamate which is collected washed with dry ether (20 ml) and dried weight in a desiccator under high vacuum over KOH pellets.

The compounds of the invention e.g. salt form can be utilized by formulating them in compositions such as tablets, capsules for oral administration or in sterile solutions for parenteral administration. A mixture of compounds of formula (I) or acceptable salt(s) thereof is compounded with a logically acceptable vehicle, carrier, preservative, stabilizer, flavor, etc., in form as called for by accepted pharmaceutical practice. The amount of active substance in the or preparations is such that a suitable dose. Illustrative of the adjuvants which are used in tablets, capsules and the like as a binder such as gum tragacanth, acacia gelatin; an excipient such as dicalcium disintegrating agent such as corn starch; stearate; a lubricant such as talc; a sweetening agent such as sucrose; a sweetening agent such as saccharin; a flavoring agent such as peppermint, wintergreen or cherry. When the dosage capsule, it may contain in addition to above type a liquid carrier such as a fl other materials may be present as co-solvent or to modify the physical form of the preparation. Tablets may be coated with a film. A syrup or elixir may contain alcohol, glycerol, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavour.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.

Preferred antioxidants for use with the compounds of the present invention include sodium metabisulfite and ascorbic acid.

While the invention will now be described in connection with certain preferred embodiments in the following examples, it will be understood that it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description

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of procedures as well as of the principles and conceptual aspects of the invention.

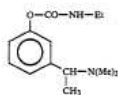
EXAMPLE I

0.5 g (3.03 mmole) of α -m-hydroxyphenylethylidimethylamine are dissolved in 15 ml of dry acetonitrile and 0.70 g (5.2 mmole) of diethylcarbamoylchloride are

Rosin (Ex. 1008):

The compounds of the invention e.g. in free form or salt form can be utilized by formulating one or more of them in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration.

causes a heavy precipitation. The product is filtered, washed with ether and dried in a desiccator over KOH pellets. The carbamate is obtained as a white powder 800 mg (75%) mp. 177°-179° C. and identified as N-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate having the formula



The compounds of the present invention are useful as pharmaceuticals. In particular they show the following activities in vitro and in vivo in the tests specified below.

The values are correct when taken in comparison with the standard drug physostigmine.

IN VITRO EXPERIMENTS

Tests for anticholinesterase activity

A solubilized preparation of acetylcholinesterase was prepared from mouse whole brain (minus cerebellum). The brain was homogenized with (100 mg/ml) phos-

Noven Ex. 1008
Page 5 of 8

Rosin Discloses Use Of Antioxidants In Sterile Compositions For Injection Only As Required

Paper 25 at 25-26

4,948,807

7
stir at ambient temperature for 15-24 hours. Remove the acetonitrile under reduced pressure (20 mm) followed by the addition of water (10-25 ml). The aqueous solution is adjusted to pH=11 by the addition of the appropriate amount of NaOH 0.1N by extraction with ether (2x25 ml). The organic phases are washed with brine (25 ml) and dried over MgSO₄ anhydride which is then filtered off. The cooled ethereal filtrate is saturated with a strong (g) resulting in the formation of a heavy precipitate (anticipated carbamate) which is collected by filtration, washed with dry ether (20 ml) and dried to constant weight in a desiccator under high vacuum (0.1 mm) over KOH pellets.

The compounds of the invention e.g. in their salt form can be utilized by formulating one or more of them in compositions such as tablets, capsules for oral administration or in sterile solutions for parenteral administration. A composition of compounds of formula (I) or physiologically acceptable salt(s) thereof is compounded with a logically acceptable vehicle, carrier, excipient, preservative, stabilizer, flavor, etc., in a unit form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage can be administered.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, polyvinylpyrrolidone, and the like; a lubricant such as stearate; a sweetening agent such as sucrose, saccharin; a flavoring agent such as peppermint, wintergreen or cherry. When the dosage unit is a capsule, it may contain in addition to material above type a liquid carrier such as a fatty acid or other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shells of cellulose. A syrup or elixir may contain the active ingredient, sucrose as a sweetening agent, methylparaben as preservatives, a dye and flavor such as cherry or orange flavour.

Sterile compositions for injection can be prepared according to conventional pharmaceutical practice by dissolving or suspending the active substance in a suitable vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.

Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

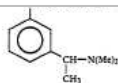
While the invention will now be described in connection with certain preferred embodiments in the following examples, it will be understood that it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description

Rosin (Ex. 1008):

8
dried over 0.70 g (5.2 mmole) of diethylcarbamoylchloride are

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.

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Tests for anticholinesterase activity

A solubilized preparation of acetylcholinesterase was prepared from mouse whole brain (minus cerebellum). The brain was homogenized with (100 mg/ml) phos-

Noven Ex. 1008
Page 5 of 8

Enz Confirms That Rosin Does Not Suggest An Oxidative Degradation Problem For RA₇

Paper 25 at 26-27

Enz (Ex. 1002):

3-[(1-dimethylamino)ethyl]-
m of its hydrochloride is known
tion 193,926 where it is

The racemic mixture (\pm)-N-ethyl-3-[(1-dimethylamino)ethyl]-
N-methyl-phenyl-carbamate in form of its hydrochloride is known
from the European patent application 193,926 where it is
identified as RA₇ HCl.

the optically active centre, is mainly responsible for the
acetylcholinesterase inhibiting activity of the phenyl
carbamates.

The compounds according to the invention have never been
specifically disclosed in the literature. The free base may be
prepared from the racemate by separation of the enantiomers in
accordance with known methods, e.g. using di-0,0'-p-toluyll-
tartaric acid. The acid addition salts may be prepared from the
free base in known manner. These include e.g. the hydrogen
tartrate.

Noven Ex. 1002
Page 3 of 23

Rosin Discloses Millions Of “Compounds Of The Invention”

Paper 25 at 24-25

Rosin (Ex. 1008):

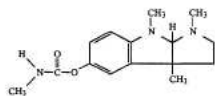
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(3) Bisquaternary structures, e.g. Demacarium, Ambenonium. These agents tend to be more selective inhibitors of acetylcholinesterase than butyrylcholinesterase, compared with the monoquaternary molecules.

The pharmaceutical application of the quaternary anticholinesterase agents is limited because of their poor penetration through cell membranes. They are therefore used for actions outside the central nervous system, and are usually given parenterally, since they are not reliably absorbed from the gastrointestinal tract. Edrophonium, neostigmine and pyridostigmine and the bisquaternary analogues are used in anesthetic practice for the reversal of the action of muscle relaxants. They are also used for the treatment of myasthenia gravis, and paralytic lens.

Physostigmine is the only potent anti-cholinesterase agent which has been used clinically to treat conditions in which an elevation of brain acetylcholine activity is desired. These include, Alzheimer's disease, tardive dyskinesia, Down's syndrome and Huntington's chorea. Physostigmine is also used to reverse the effects of overdose of anticholinergic agents, anti-Parkinson drugs, benzodiazepines and opiate analgesics.

Physostigmine is a natural alkaloid extracted from calabar beans and the seeds of the vine *Physostigma venenosum* and has the formula



There is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine.

Furthermore there is a need to provide new compounds which inhibit acetylcholinesterase in the brain for periods exceeding 3 hours but not more than 12 hours after a single administration.

There is also a need to provide new compounds which will be completely and reliably absorbed after oral administration.

There is also a need to provide new compounds which will be relatively less toxic than physostigmine. This means that the therapeutic ratio, defined as

$$\frac{\text{dose to produce therapeutic effect}}{\text{dose to produce mortality in 50\% of animals}}$$

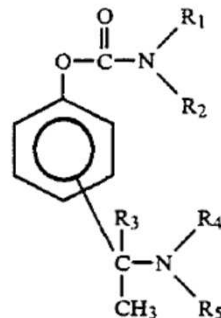
should be significantly higher than those of physostigmine and that the incidence and severity of side effects should be less than those of physostigmine at therapeutic doses.

There is also a need to provide new compounds which can be given orally or parenterally to treat chronic conditions in which it is desired to raise cholinergic activity in the central nervous system. These include, Alzheimer's disease, Down's syndrome, Huntington's chorea, Friedrich's ataxia.

There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neuroleptics and general anesthetics.

There is a need to provide new compounds which inhibit acetylcholinesterase in the central nervous system of mammals comprising a compound of the general formula I

Thus according to the present invention there is now provided a pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system of mammals comprising a compound of the general formula I



wherein

R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₂ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₃ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₄ and R₅ are the same or different and each is a lower alkyl,

R₅ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor.

Hereinafter these compounds are called compounds of the invention.

Especially preferred are those compounds in which the nitrogen atom to which the benzene ring is attached is part of a morpholino or piperidino radical.

Certain of these compounds have previously been described in the literature.

R₅ = CH₃

wherein

R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₂ is hydrogen, methyl, ethyl or propyl, or

R₁ and R₂ together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R₃ is hydrogen or lower alkyl,

R₄ and R₅ are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor. Hereinafter these compounds are called compounds of the invention.

Hereinafter

these compounds are called compounds of the invention.

The "Compounds Of The Present Invention" Include The Large Class Of Eight Million-Plus Compounds

Paper 43 at 7-8; see also Paper 25 at 24-25 & n.4

Rosin Priority Application (Ex. 2058):

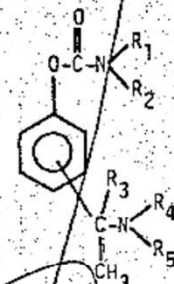
Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

15 this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of procedures as well as of the principles and conceptual aspects of the invention.

NOVARTIS EXHIBIT 2058
Noven & Mylan v. Novartis & LTS Lohmann
IPR2014-00550
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WHAT IS CLAIMED IS:

1. A pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system comprising a compound of formula I



wherein

- R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,
- R₂ is hydrogen, methyl, ethyl or propyl, or
- R₁ and R₂ together with the nitrogen to which they are attached form a morpholino or piperidino radical,
- R₃ is hydrogen or lower alkyl,
- R₄ and R₅ are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor.

NOVARTIS EXHIBIT 2058
Noven & Mylan v. Novartis & LTS Lohmann
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Neither Rosin Nor Elmalem Discloses Transdermals

Paper 43 at 13; Paper 45 at 12-13; see *also* Paper 25 at 3-4, 27-28, 36

Dr. Kydonieus (Ex. 1026):

16 Q. Okay. It does not -- the '807 patent does
17 not discuss transdermal formulations; right?

18 A. No, it does not discuss.

17 Q. And Elmalem did not prepare any
18 transdermal formulations; right?

19 A. Right.

Whether Rivastigmine Undergoes Oxidative Degradation Is Formulation-Specific

Paper 25 at 4, 13, 27, 36

Dr. Schöneich (Ex. 1026):

24 Q. And you agree with the general principle
1 that the extent of degradation depends on the
2 chemical environment in which a drug is
3 formulated?

4 A. So if you have a drug which is susceptible
5 to degradation, the extent to which it actually
6 happens, that depends on the environment.

Whether Rivastigmine Undergoes Oxidative Degradation Is Formulation-Specific

Paper 25 at 4, 13, 27, 36

Dr. Kydonieus (Ex. 1026):

8 Q. So if you have oxidative degradation in a
9 solution, you cannot conclude that it would also
10 be a problem, for instance, in a transdermal
11 patch; right?

12 A. I said that many times. That is
13 formulation dependent.

Dosage Form Can Determine Whether An Antioxidant Is Required

Paper 45 at 12-13; see *also* Paper 25 at 13-14

**Dr. Schöneich
(Ex. 1048):**

3 Q And it's your opinion that the
4 dosage form is significant? That's what you
5 say in the first line of 48; is that right?
6 A Yes.

21 Q And my question was whether or not
22 the dosage form that is selected can
23 determine whether or not an antioxidant is
24 required.

25 MR. GLYNN: Objection to form.

2 Q It's your opinion that it could;
3 correct?

4 MR. GLYNN: Objection to form.

5 Also, compound question.

6 A The formulation, if you -- if you
7 say the formulation is equivalent to the
8 dosage form, it can make a difference, so,
9 yes.

10 Q It can make a difference whether or
11 not an antioxidant is required?

12 A Yes.

Hydrolysis Of Carbamates Had Been Studied Experimentally Since The 1930s

Paper 25 at 31-32; Paper 45 at 13

Dr. Schöneich (Ex. 1048):

17 Q And you would agree with me that
18 the hydrolysis of monomethyl carbamates has
19 been studied experimentally since the 1930s?

20 A That's what Dr. Klibanov states.

21 Q And you don't dispute that, do you?

22 A I don't dispute it.

23 Q And you also don't dispute that the
24 hydrolysis of dialkyl carbamates has been
25 studied experimentally since the 1930s?

2 A Yes.

Mechanisms Of Hydrolysis Of Carbamates Had Been Experimentally Determined As Of 1998

Paper 25 at 31-32; Paper 45 at 13

Dr. Schöneich (Ex. 1048):

11 Q Okay. And you agree that the
12 mechanism by which monomethyl carbamates
13 undergo hydrolysis had been experimentally
14 determined as of 1998?

15 A I think so.

16 Q And you don't dispute that the
17 mechanism by which dialkyl carbamates undergo
18 hydrolysis had been experimentally determined
19 by 1998?

20 A I don't dispute that.

Oxidative Mechanisms Were Poorly Understood As Of 1998

Paper 25 at 18-19

Chemical Kinetics and Drug Stability

183

Oxidation

Oxidation reactions are important pathways of drug decomposition. In pharmaceutical dosage forms, oxidation is usually mediated through reaction with atmospheric oxygen under ambient conditions, a process commonly referred to as autoxidation. Oxygen is, itself, a diradical, and most autoxidations are free-radical reactions. A free radical is a molecule or atom with one or more unpaired electrons. Of considerable importance to pharmaceutical scientists is a reliable

Modern Pharmaceuticals (Ex. 2014):

are initiated by trace amounts of impurities, such as metal ions or hydroperoxides. Thus, ferric

The mechanisms of oxidation reactions are usually complex, involving multiple pathways for the initiation, propagation, branching, and termination steps.

change in, color in a dosage form is suggestive of the occurrence of oxidative degradation.

Photolysis

Normal sunlight or room light may cause substantial degradation of drug molecules. The energy from light radiation must be absorbed by the molecules to cause a photolytic reaction. If that

Connors (Ex. 1015):

Examples

Oxidative and photochemical reactions are, for the most part, one-electron reactions as opposed to reac-

tial stability problems for these molecules. That is, many molecules tend to be converted to a more oxidized state. Kinetically, however, there is a sufficient energy barrier to many such reactions (the energy of activation) that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation. The radiation from the sun and artificial light, particularly visible and ultraviolet light, is also ubiquitous, so that molecules capable of rearranging upon absorption of radiation energy must be

Our overall mechanistic understanding of oxidative and photochemical reactions is poor.

Classes	Chemical Structures	Examples
Thiols	RCH_2SH	Dimercaprol (BAL)
Thioethers	$R-S-R'$	Phenothiazines (chlorpromazine)
Carboxylic acids	$RCOOH$	Fatty acids
Nitrites	RNO_2	Amyl nitrite
Aldehydes	$RCHO$	Paraldehyde

NOVARTIS EXHIBIT 2014
Noven v. Novartis and LTS Lohmann
IPR2014-00550
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Noven Ex. 1015
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Testing Was Required To Determine Intrinsic Stability

Paper 25 at 19

Dr. Kydonieus (Ex. 1010):

Indeed,

regulatory guidelines in effect as of January 1998 recommended that applicants

perform stability tests on the drug substance and drug product. This included

stress testing on the drug substance to determine its intrinsic stability and

degradation pathways, as well as formal studies on the drug substance to show that

it will remain within specification during the re-test period if stored under the

recommended storage conditions. (See ICH Topic Q 1 A, Stability Testing

Guidelines: Stability Testing of New Drug Substances and Products

(CPMP/ICH/380/95) (Ex. 1014).)

Bond Strengths Do Not Indicate The Conditions Under Which A Radical Will Form

Paper 45 at 1; see also Paper 25 at 16-17

Dr. Schöneich (Ex. 1048):

6 Q And if you turn back to paragraph
7 nine.

8 A Yes.

9 Q And you also discuss there relative
10 radical stabilities; correct?

11 MR. GLYNN: Objection to form.

12 A What we see in this table, which is
13 on page five, paragraph nine, first of all,
14 on the right-hand column, absolute values,
15 these are bond dissociation energies which
16 are measured, and just for comparison, in the
17 middle column, they are radical -- relative
18 radical stabilities.

19 Q So, you are saying that methane is
20 relatively less stable than the C-H bond to a
21 tertiary carbon (CH₃)₃CH?

22 A So, the carbon-hydrogen bond in
23 methane is stronger than the carbon-hydrogen
24 bond in the tertiary -- in the tertiary
25 carbon-hydrogen --

2 Q And that is a relative assessment;
3 correct?

4 MR. GLYNN: Objection to form.

5 A It's a relative assessment within
6 this group of compounds. But there are
7 certainly absolute numbers to support that.

8 Q And those numbers don't tell us
9 under what conditions the radicals were
10 formed, do they?

11 A These numbers are absolute values
12 of bond dissociation energies, so, they
13 should be independent of the measurement.
14 These are absolute numbers.

15 Q But they don't tell me under what
16 conditions the radical will form, do they?

17 MR. GLYNN: Objection to form.

18 A The bond dissociation energy is
19 just by its mere fact a bond dissociation
20 energy. It does not tell you under which
21 conditions you form radicals in any chemical
22 reaction.

Testing Is Required To Determine Whether Rivastigmine Oxidative Degrades Under Pharmaceutically Relevant Conditions

Paper 25 at 2-3, 13-14, 16, 20, 22, 23, 27, 36, 42

Dr. Schöneich (Ex. 1026):

10 Q. So whether rivastigmine oxidatively
11 degrades in a specific formulation is something
12 that has to be shown?

13 A. Well, whether rivastigmine is susceptible
14 to degradation that can be deduced from the
15 structure, whether it actually happens, that
16 needs to be shown experimentally and the extent
17 to what it happens needs to be shown
18 experimentally.

Testing Is Required To Determine Whether Rivastigmine Oxidative Degrades Under Pharmaceutically Relevant Conditions

Paper 25 at 2-3, 13-14, 22, 23, 27, 36, 42

Dr. Kydonieus (Ex. 1026):

6 Q. So let me go back to my question. Just
7 knowing that a compound as you put it is
8 susceptible to oxidation doesn't tell you how
9 much oxidative degradation will occur over any
10 particular time; right?

11 A. Over any particular time? It doesn't tell
12 you how much degradation you will get period
13 depending on that formulation.

Dextromethorphan Is “Especially Susceptible” To Oxidative Degradation But “Very Stable”

Paper 25 at 17; Paper 45 at 2-4

Carey & Sundberg
(Ex. 1018):

- Benzylic positions are “**especially susceptible**” to oxidation

Dr. Schöneich’s opinion
(Exs. 1011, 1032):

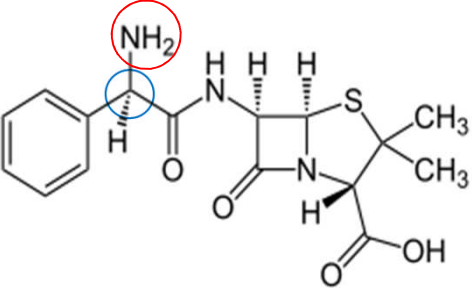
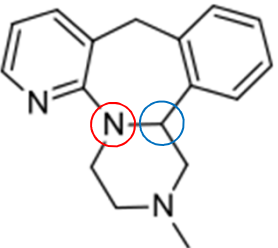
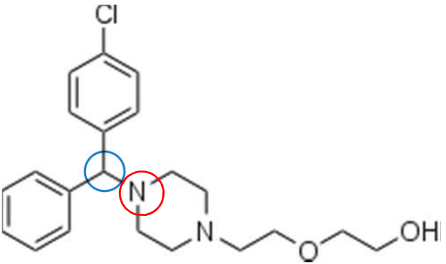
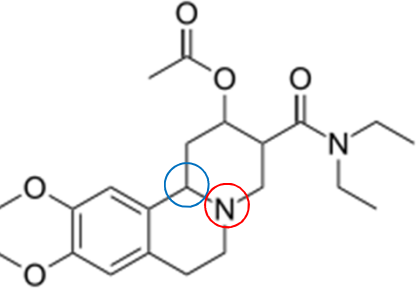
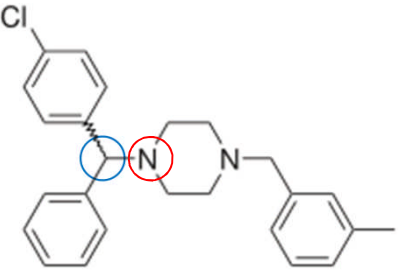
- “Dextromethorphan Was **Known To Be Susceptible To Oxidation**”
- Dextromethorphan was “**prone to oxidation**”

The prior art teaches
(Exs. 2050, 2051):

- Dextromethorphan is “**very stable**”
- Dextromethorphan is “**stable** under **all normal conditions** of storage”
- Dextromethorphan has “**excellent stability**” under pharmaceutically relevant conditions

Drugs With Structural Features Of Rivastigmine Were Not Reported To Undergo Oxidation

Paper 25 at 18

Ampicillin		Mirtazapine	
Hydroxyzine		Benzquinamide	
Meclizine			

Dr. Schöneich Provided No Evidence To Show Dr. Klibanov's Real-World Pharmaceuticals Were Unstable

Paper 45 at 5-6; see also Paper 25 at 18

Dr. Schöneich (Ex. 1048):

13 Q That wasn't my question. I was
14 asking you about whether you had done any
15 literature searches relating to any of the
16 five compounds, real world examples, that
17 Dr. Klibanov relied on saying that they
18 undergo oxidative degradation in any
19 formulation.

20 MR. GLYNN: Objection to form.

21 A I have not done literature research
22 to that respect.

Dr. Schöneich Provided No Evidence To Show Dr. Klibanov's Real-World Pharmaceuticals Were Unstable

Paper 45 at 5-6; see also Paper 25 at 18

Dr. Schöneich (Ex. 1048):

5 Q Okay. And you have a testing lab
6 at Kansas, don't you?

7 A I have a laboratory, yes.

8 Q Okay. And that lab could have run
9 some tests on any one of these drugs to
10 determine whether or not they undergo
11 oxidative degradation under a certain set of
12 conditions; correct?

13 A Well, certainly we have the
14 capacity, but we haven't done it.

15 Q You chose not to do that; correct?

16 A We chose not to do that.

PDR Reports Chemical Instability Of Nicotine

Paper 45 at 8; see also Paper 25 at 17-18

Physicians' Desk Reference (Ex. 2022):

Nicotine has a characteristic pungent odor and turns brown on exposure to air or light.

Dr. Schöneich (Ex. 1048):

13 Q And "turns brown on exposure to
14 air" is a reference to the oxidation of
15 nicotine?

16 A It implies oxidation.

12 Q So, but a person of ordinary skill

13 in the art would understand that to be a

14 reference to oxidative instability of

15 nicotine; correct?

16 A A POSA would certainly see this as

17 a warning that nicotine would undergo

18 oxidation.

the suppository must come out immediately, it was not inserted high enough and should be pushed higher.
Children under 12 years of age: One-half of one 10 mg suppository once daily.
If the suppository seems soft, hold in foil wrapper under cold water for one or two minutes. In the presence of anal fissure or hemorrhoids, suppository may be coated at the tip with petroleum jelly before insertion.
Preparation for a rectal enema: For barium enemas, no food should be given. Following oral administration to prevent reaccumulation of material in the rectum, no suppository should be administered one to two hours prior to examination.
HOW SUPPLIED
Dulcolax, brand of bisacodyl, is supplied as either light orange enteric coated tablets of 5 mg each in sample package of 2 or boxes of 4, 10, 25, 50, 100 (OTC) as well as hospital bulk doses and 500, or as suppositories of 10 mg each in sample packages of 7 or boxes of 4, 8, 15, 50, and 500.
NDC 0067-6200 (tablets)
NDC 0067-6100 (suppositories)
Store Dulcolax tablets and suppositories at temperatures below 77°F (25°C). Avoid excessive humidity.
Dulcolax is also supplied in a Boost Prep Kit. Each kit contains one Dulcolax suppository (10 mg), four Dulcolax tablets (5 mg each), and complete patient instructions.
BIBLIOGRAPHY
Balk, V. W. et al. "Pharmacokinetics and Laxative Effect of Bisacodyl after Administration of Various Doses." *Pharmazie*, 38 (1), No. 4, pp. 370-4 (1983).
Additional literature references available upon request.
Shown in Product Identification Guide, page 308.
HABITROL®
Laxative (transdermal system)
Systemic delivery of 2.1, 14, or 7 mg/day over 24 hours
Prescribing Information
DESCRIPTION
Habitrol is a transdermal system that provides systemic delivery of nicotine following its application to intact skin for 24 hours.
Nicotine is a tertiary amine composed of a pyridine and a pyrolidine ring. It is a colorless-to-yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of the two stereoisomers, S-nicotine is the more active and is the more prevalent form in tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.
Structural Formula
CN1CCCC1c2cccnc2
Chemical Name: 5-(3) methyl-2-pyrrolidyl)pyridine
Molecular Formula: C₁₀H₁₄N₂
Molecular Weight: 162.2
Ionization Constants: pK_{a1} = 7.84, pK_{a2} = -3.04
Octanol/Water Partition Coefficient: 1.81 at pH 7
Habitrol systems are round, flat, 0.6mm-thick, multi-layer units containing nicotine as the active agent. Proceeding from the inside surface toward the surface attached to the skin are: (1) a tan-colored aluminum backing film; (2) a pressure sensitive adhesive substrate; (3) a layer containing a methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose rayon; (4) an adhesive layer similar in composition to (3) above; (5) a protective aluminum release liner which overlies the adhesive layer and must be removed prior to use.
[See Figure at top of next column.]
Nicotine is the active ingredient; other components of the system are pharmacologically inactive.

There Are Reasons Other Than Oxidative Instability To Select A Dry Dosage Form

Paper 45 at 11; see *also* Paper 25 at 18

Dr. Schöneich (Ex. 1048):

21 Q Well, just generally speaking,
22 there are reasons to select a dry dosage form
23 other than chemical instability?

24 A Well, the mode of application. If
25 you want to give a tablet, it's a dry dosage
2 form, yeah.

3 Q Yes. So there are other reasons.

4 A Okay.

5 Q Do you agree?

6 A But that doesn't exclude the
7 oxidation sensitivity as a problem.

8 Q I understand that, but just taking
9 this one step at a time. Okay. There are
10 reasons other than chemical stability for
11 selecting a dry dosage form; correct?

12 A Let me think a moment.

13 I would say predominantly dry
14 dosage forms are selected if you have

15 chemically unstable molecules, but, okay,
16 there could be some other reasons.

17 Q Well, how about convenience to the
18 patient of taking a dry dosage form, such as
19 a tablet?

20 A Yeah, that could be. I said that,
21 yeah.

22 Q And what about reasons other than
23 oxidative instability? There are reasons --
24 strike that.

25 There are reasons other than
2 oxidative instability for selecting a dry
3 dosage form; correct?

4 A Yes.

5 Q And one of those would be, for
6 example, avoiding hydrolysis?

7 A For example.

The Salt Form Of A Drug May Undergo Oxidative Degradation

Paper 43 at 4-5; see *also* Paper 25 at 18

Dr. Kydonieus (Ex. 1049):

6 Q. And it's your opinion that the salt of
7 morphine needed to be mixed with an antioxidant
8 prior to use to prevent oxidative degradation,
9 correct?

10 A. Yes, there's saline -- first of all,
11 what that statement basically says that you have
12 to dissolve it. I mean, you cannot inject a
13 crystal into a person or an animal. You can
14 cause thrombosis and whatever else, so you have
15 to dissolve it, and you dissolve it and you know
16 that morphine is susceptible to oxidation. You
17 would use saline plus an antioxidant.

18 Q. So even though it's a salt, you would
19 still use an antioxidant, correct?

20 MR. COULSON: Objection.

21 A. Okay, I will give you my opinion, my
22 extensive opinion -- my extensive experience.
23 Salts are always better than the bases. Not
24 always. Again, never always. 95 percent of the
25 time, as far as oxidation is concerned, are
2 better than the base. But that does not mean,
3 necessarily, that the salt does not degrade. It
4 degrades to a lesser extent most of the time,
5 but it doesn't mean that it will not degrade.

Formulation In A Dry Dosage Form Does Not Indicate The Real-World Pharmaceuticals Are Susceptible To Oxidation

Paper 45 at 11; see *also* Paper 25 at 18

Petitioners' Response (Paper 52):

Response to p. 11 ¶¶ 1-2: Patent Owners mischaracterize Dr. Schöneich's testimony. Patent Owners incorrectly assert that Dr. Schöneich testified that formulation of a compound in a dry dosage form establishes that is susceptible to oxidation or that measures were taken to avoid oxidation. Dr. Schöneich testified that the so-called "real world examples" selected by Dr. Klibanov from the PDR were formulated as a dry dosage form, as a salt, or both. (Ex. 1032 ¶ 47.)

Whether Rivastigmine Would Degrade In An Acrylic Adhesive Could Not Be Reasonably Predicted From Its Structure

Paper 25 at 42

Dr. Kydonieus (Ex. 1026):

12 Q. Could you turn to your deposition, Page
13 89?

14 Let's put it on the screen. It will
15 be easier. Page 89, and 18, Line 18. And you
16 were asked the question: "So am I right that
17 it's your opinion that when rivastigmine's in an
18 acrylic adhesive, it will not necessarily undergo
19 oxidative degradation?"

20 "Answer: I don't know the answer."

21 A. Absolutely correct. Yes.

22 Q. Now, Dr. Kydonieus --

23 A. May I finish. It is formulation
24 dependent.

Enz Discloses Rivastigmine In An Acrylic Adhesive Without Requiring An Antioxidant

Paper 25 at 43-44

Enz (1002):

EXAMPLE 2: Preparation of a transdermal composition containing a hydrophilic polymer

Composition

Compound of formula I', e.g. compound A
Hydrophilic polymer, e.g. Eudragit E 100*
Non swellable acrylate polymer, e.g. Durotack 280 - 2416**
Plasticizer, e.g. Brij 97***

* : Registered Trade Mark, available from Röhm, Darmstadt, W. Germany
** : Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands
***: Registered Trade Mark, available from Atlas Chemie, W. Germany

The components are added to acetone and an appropriate volatile organic solvent to form a mass. The mass is spread on top of a substrate (thickness 23 microns) using a coating knife to form a film of thickness 0.2 mm when viewed at room temperature over 4 to 6 hours. The film is cut up into patches about 10 sq cm.

EXAMPLE 2: Preparation of a transdermal composition containing a hydrophilic polymer

Composition

Compound of formula I', e.g. compound A	20 %
Hydrophilic polymer, e.g. Eudragit E 100*	30 %
Non swellable acrylate polymer, e.g. Durotack 280 - 2416**	44 %
Plasticizer, e.g. Brij 97***	6 %

* : Registered Trade Mark, available from Röhm, Darmstadt, W. Germany
** : Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands
***: Registered Trade Mark, available from Atlas Chemie, W. Germany

A POSA Would Not Believe That All Amines Break Down In Acrylic Adhesives Based On Two Amines In Sasaki

Paper 25 at 42

Sasaki (Ex. 1005):

Here, it is possible to prevent the dissipation and photodecomposition of the drug by way of sealing and light shielding with aluminum laminate packaging or the like, but with drugs blended with a plaster comprising an adhesive substance as described above, and especially phenolic hydroxyl group-containing compounds, amine compounds and the like, breakdown of the drug will still proceed, even with aluminum laminate packaging, and there are more than a few drugs that cannot withstand usage involving storage for two to three years.

(19) Japanese Patent Office (JP)
 (12) Kokai Unexamined Patent Application Bulletin
 (11) Laid Open Patent Application No. 59-1
 (43) Publication Date Oct
 Number of Claims 1
 Number of Pages 3
 Examination Request not y

(51) Int. Cl. ²	Identification Code	Internal File No.
A61K 9/70 //A61K 31/355		7057-4C

(54) Acrylic Plaster			
(21) Application No.:	58-57689	(72) Inventor:	
(22) Application Date:	March 31, 1983	(71) Applicant:	
(72) Inventor:	SASAKI, Hiroaki Nitto Electric Industry Co., Ltd. 1-1-2 Shimohodumi, Ibaraki-shi	(74) Agent:	
(72) Inventor:	HORIUCHI, Tetsuo		

SPECIFICATION
 1. Title of the Invention
 Acrylic Plaster
 2. Claims
 (1) An acrylic adhesive plaster characterized by blending at least one toopherol selected from toopherols with a plaster comprising an acrylic adhesive substance.
 (2) The plaster recited in claim (1), wherein a

preparation, in which plaster comprising an preparation in which plaster comprising an is stored for a long tendency for the preparation to be breakdown and dissipat Here, it is possible

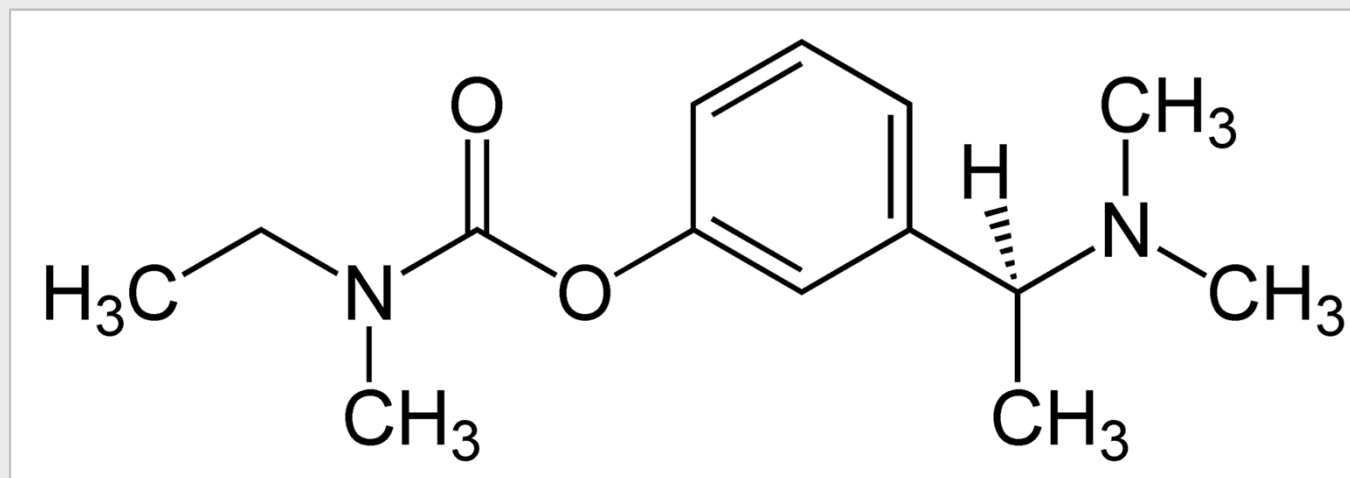
Dr. Klivanov (Ex. 2012):

drug by way of aluminum laminate s blended with a substance as phenolic hydroxyl

156. The disclosure in Sasaki of just two amine-containing compounds in one prototype transdermal formulation would not have taught or suggested to a POSA that all amine-containing compounds break down in any acrylic adhesive.¹⁷

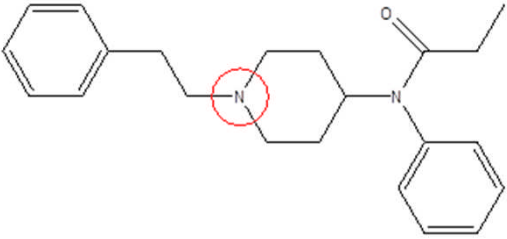
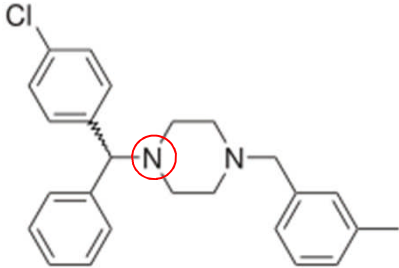
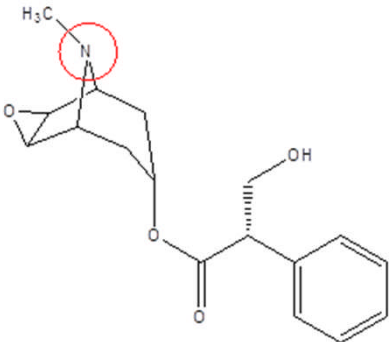
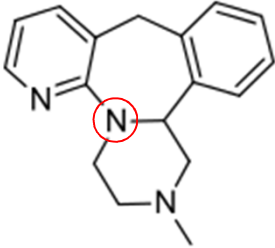
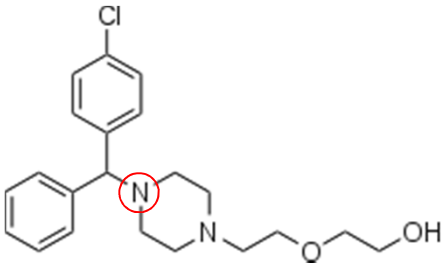
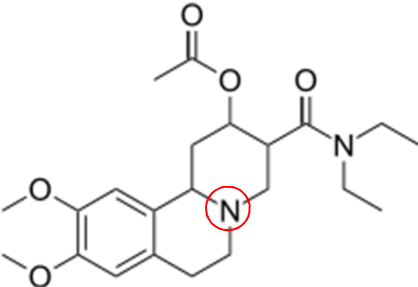
Rivastigmine

Paper 25 at 17-18



Amine-Containing Drugs Were Not Reported To Contain Antioxidants In Commercial Formulations

Paper 25 at 42-43

Fentanyl		Meclizine	
Scopolamine		Mirtazapine	
Hydroxyzine		Benzquinamide	

Amine Or Phenolic Hydroxyl Compounds In An Acrylic Adhesive Were Not Reported To Contain An Antioxidant

Paper 25 at 42-43 & n.11

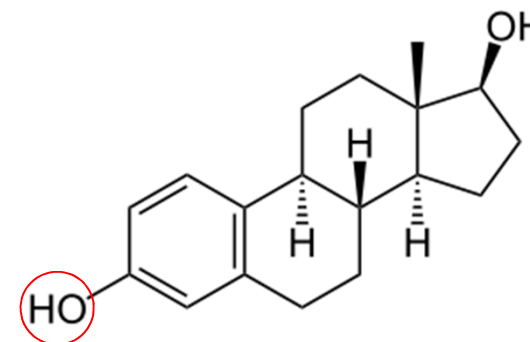
Physicians' Desk Reference (Ex. 2022):

The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP.

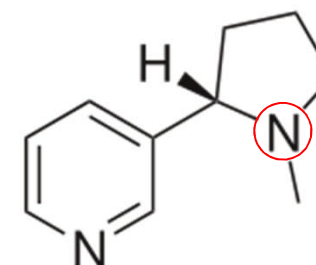
The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol,

Habitrol systems are round, flat, 0.6-mm-thick multi-layer units containing nicotine as the active agent. Proceeding from the visible surface toward the surface attached to the skin are: (1) a tan-colored aluminized backing film; (2) a pressure-sensitive acrylate adhesive; (3) a layer containing a methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton;

Estradiol



Nicotine



“Susceptibility” Does Not Indicate Whether Rivastigmine Will Undergo Any Oxidative Degradation

Paper 43 at 4; see also Paper 25 at 13-14, 16-17

Dr. Kydonieus (Ex. 1031):

10. Of course, whether rivastigmine would actually undergo oxidative degradation in a particular pharmaceutical formulation depends on the specific formulation. This is why, for a particular formulation, a POSA would conduct testing to confirm to what extent, if any, the drug in the formulation oxidatively degrades.

Ebert Discloses An Unconventional Method

Paper 25 at 37-38

Dr. Klibanov (Ex. 2012):

169. Ebert discloses a *non-conventional* method for manufacturing transdermal devices containing “volatile or heat-sensitive drugs, enhancers or other components cannot be subjected to drying or heating, such as would occur in an oven.” (Ex. 1006, Ebert at 5, ll. 16-21.)

171. To address such nicotine-specific problems, Ebert discloses a method of manufacturing transdermal devices wherein an “active gel” of nicotine, BHT (thus notably in contradiction to Sasaki), and hydroxypropyl cellulose (HPC) is prepared by stirring for an “extended period of time.” (*Id.* at 19, l. 34-20, l. 3.) In Example 1, nicotine was mixed with HPC for 26.5 hours in air, thereby amply exposing nicotine to air. (*Id.* at 20, ll. 10-12.) The active gel is then extruded onto an adhesive layer. (*Id.* at 1, ll. 13-20.)

Rivastigmine Transdermal Can Be Prepared Using Conventional Methods

Paper 25 at 37-38

Enz (Ex. 1002): tion ⁽¹⁹⁾ GB ⁽¹¹⁾ 2 203 040 ⁽¹³⁾ A
(43) Application published 12 Oct 1988

The present invention furthermore provides a pharmaceutical composition comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner.

The active agents may be administered in any conventional liquid or solid transdermal pharmaceutical composition

mass. The mass is spread on top of an aluminised polyester foil (thickness 23 microns) using a conventional apparatus, to produce a film of thickness 0.2 mm when wet.

Respectfully submitted,

Dated: May 26, 2015

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CERTIFICATE OF SERVICE

I certify that a copy of the foregoing PATENT OWNERS' DEMONSTRATIVE EXHIBITS PURSUANT TO 37 C.F.R. § 42.70(b) were served on May 26, 2015 by causing them to be sent by email to counsel for Petitioners at the following email addresses:

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