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Kochinke et al.

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[54] **METHOD FOR INCREASING THE STORAGE STABILITY OF PHYSOSTIGMINE**

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[73] Assignee: **Pharmetrix Corporation,** Menlo Park, Calif.

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Related U.S. Application Data

[63] Continuation of Ser. No. 487,546, Mar. 2, 1990, abandoned.

[51] **Int. Cl.**[5] **A61F 13/00**

[52] **U.S. Cl.** **424/449;** 424/448

[58] **Field of Search** 424/448, 449

[56] **References Cited**

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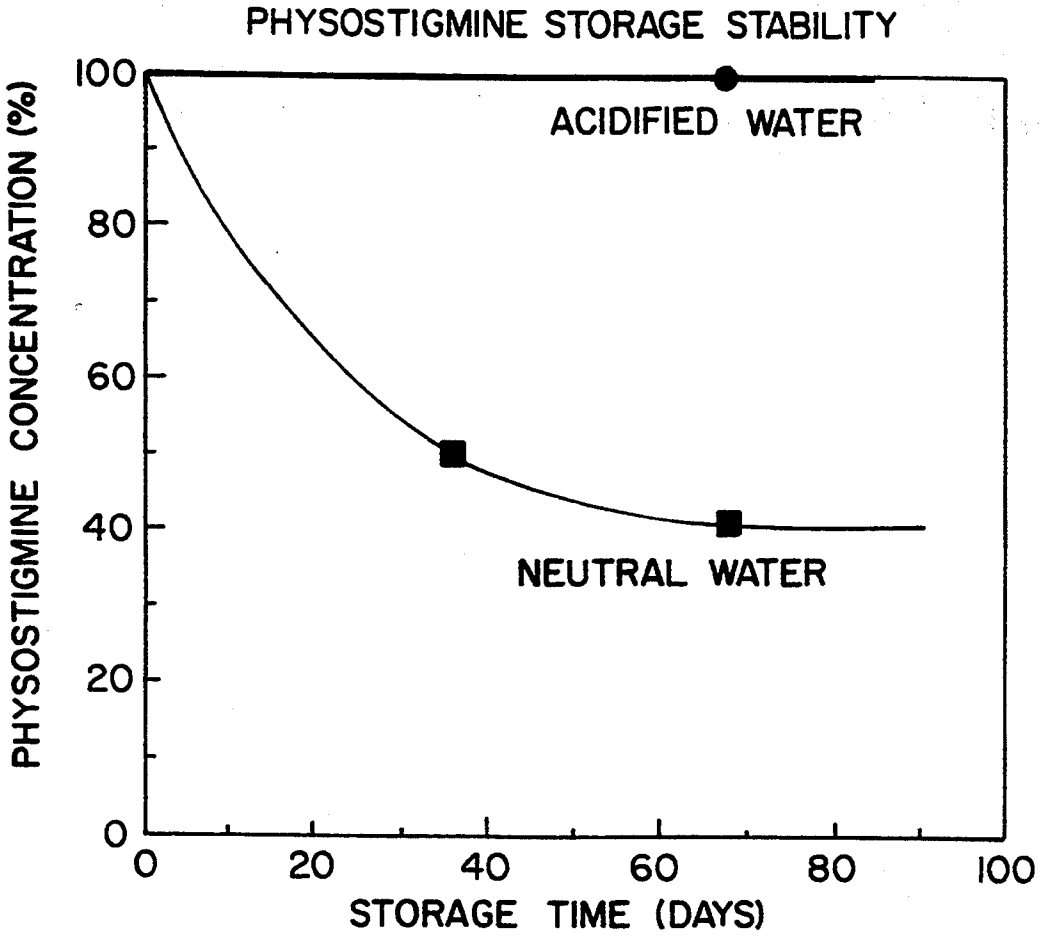
Attorney, Agent, or Firm—Townsend and Townsend Khourie and Crew

[57] **ABSTRACT**

This patent relates a method for increasing the storage stability of physostigmine free base and physostigmine analogs by incorporating the free base into a polymer matrix. Chemically compatible enhancers and adjuvants do not interfere with the stabilization of the free bases.

6 Claims, 2 Drawing Sheets



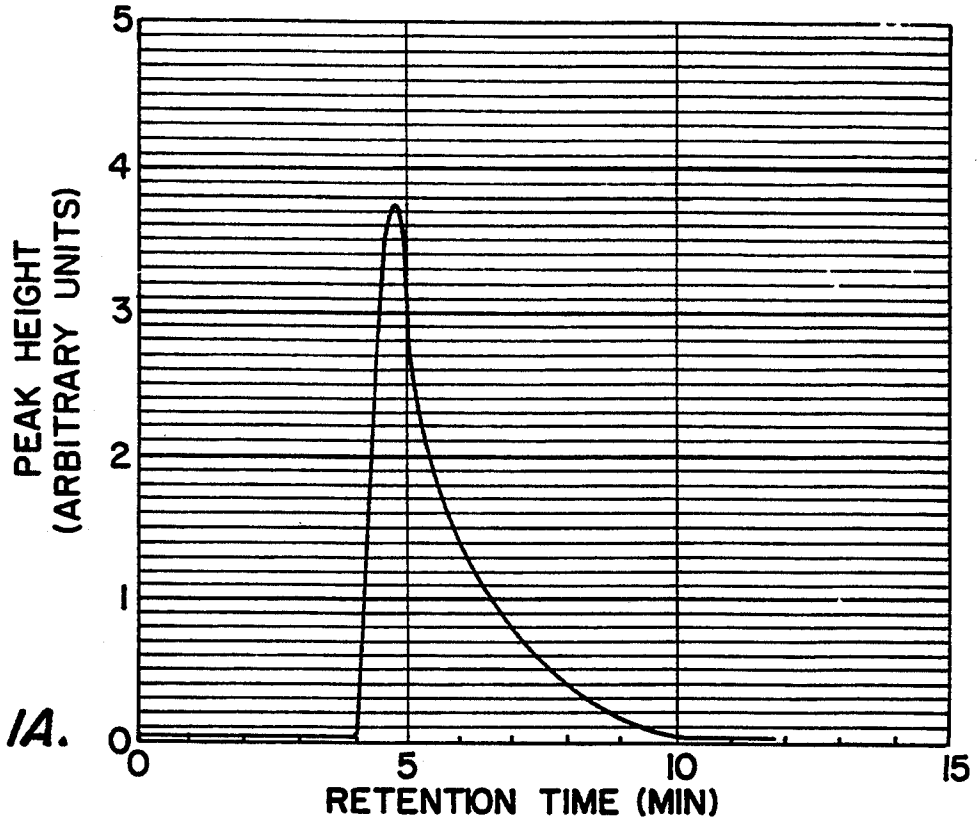


FIG. IA.

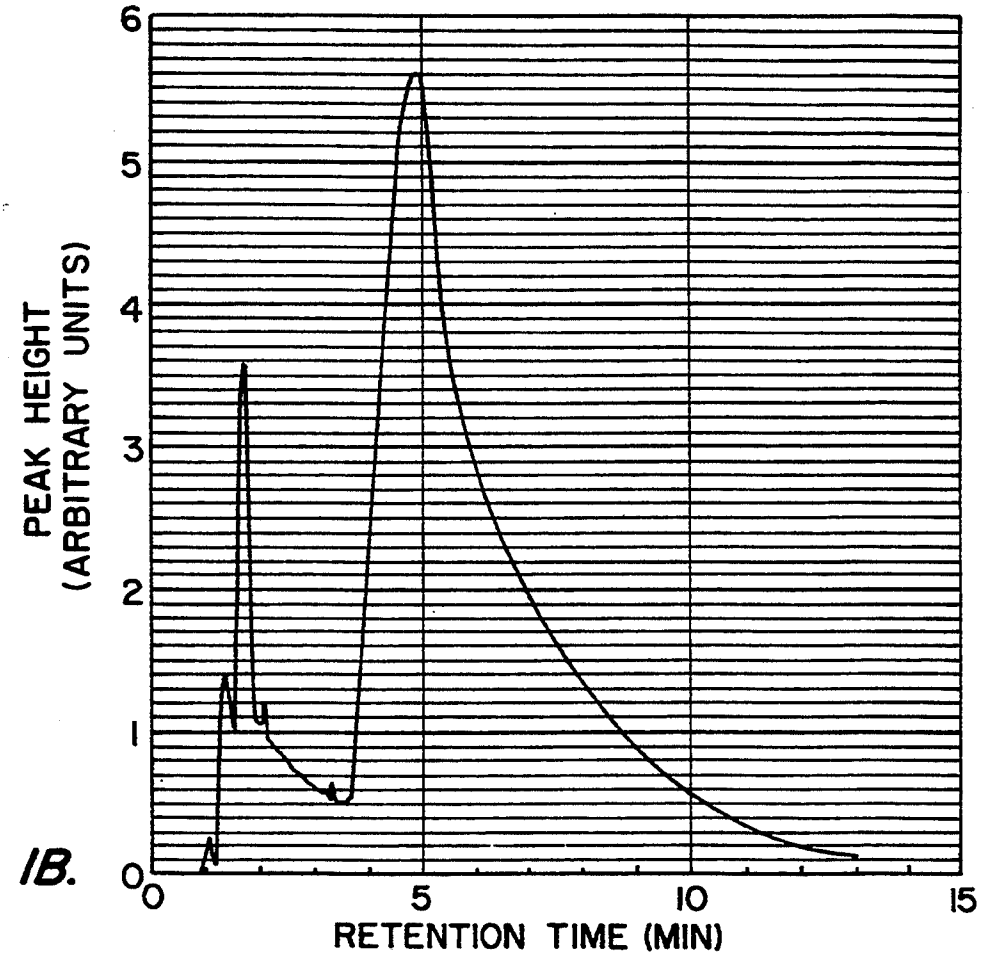


FIG. IB.

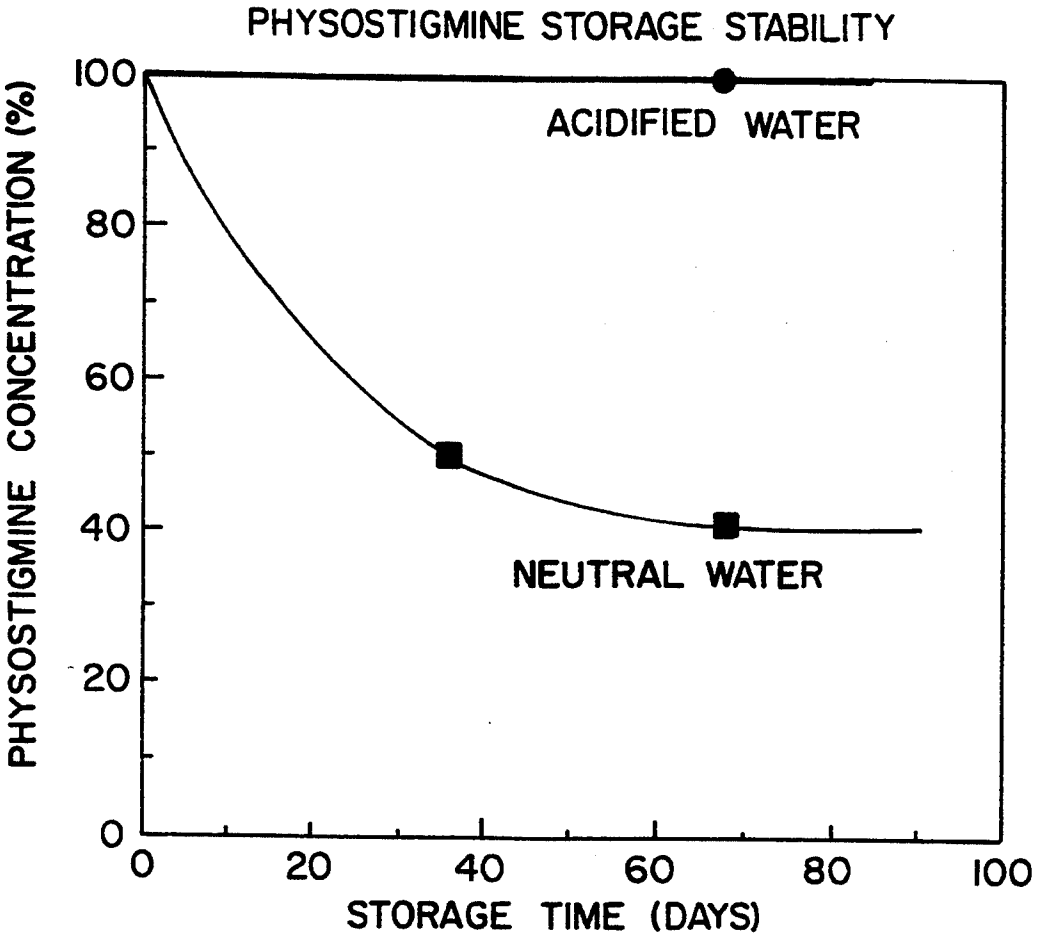


FIG. 2.

METHOD FOR INCREASING THE STORAGE STABILITY OF PHYSOSTIGMINE

This is a continuation of application Ser. No. 07/487,546 filed 2 Mar. 1990 now abandoned.

FIELD OF THE INVENTION

This invention is directed to devices and methods for the percutaneous administration of physostigmine and its closely related chemical analogs.

BACKGROUND OF THE INVENTION

Acetylcholine (ACh), an essential neurotransmitter, occurs both within the brain and in the peripheral parasympathetic nervous system. Impulses conducted along muscle fibers or axons depend upon the formation of ACh at the synaptic junction for transmission of the impulse to other fibers or axons. Acetylcholine's function as a transmitter is terminated (switched off) when it is converted to choline and acetic acid by the enzyme acetylcholinesterase (AChE). Modern biophysical methods have revealed that the amount of time consumed for the process of conversion of ACh to choline and acetic acid is less than one thousandth of a second. Drugs that have the ability to inhibit or inactivate AChE are called anticholinesterases or AChE inhibitors. As a result of AChE inhibition, acetylcholine accumulates in the synaptic cleft; since ACh is not Switched off, impulses are transmitted to the affected site for a longer period of time than would otherwise occur and results in a stronger or more prolonged neuromuscular action. Since these ACh parasympathetic synapses are widely distributed in the brain and peripheral nervous syslem, it is not surprising that AChE inhibitors produce a wide variety of effects on both the brain and body.

Physostigmine is one of the naturally occurring acetylcholinesterase inhibitorsl It has been isolated from the dry, ripe seed of the calabar or ordeal bean, a perennial plant (Physostigma venenosum), found in the Calabar region of Nigeria, West Africa. Also called Esre nut, chop nut or bean of Etu Esre, calabar bean was used as an ordeal poison. As a test of guilt, the suspect was forced to ingest a quantity of calabar beans. If he died, his guilt was proved. If the accused was confident of his innocence and ate the beans rapidly, the chances were high that he would regurgitate the beans and survive the ordeal. (It is reported that proof of guilt or innocence was not always left to chance. Apparently, a placebo was given to those prejudged to be innocent by the tribal elders in order to avoid any potential miscarriages of tribal justice), see *Plants in the Development on Modern Medicine,* Swain, T. ed., Harvard University Press, p. 303–360 (1972). Physostigmine, isolated from the calabar bean, was introduced into medicine for the treatment of wide angle glaucoma in 1877 by Laqueur.

Glaucoma is a disease characterized by an increase in intraocular pressure that, if sufficiently high and persistent, can lead to damage to the optic disc and result in permanent blindness. Wide angle glaucoma, or chronic, simple glaucoma occurs when the meshwork of pores of small diameter involved in the outflow of the aqueous humor lose their tone. Wide angle glaucoma has a gradual, insidious onset and is generally not amenable to surgical improvement. In this type of glaucoma, control of ocular pressure is only possible with continuous and permanent drug therapy.

Myasthenia gravis is a neuromuscular disease characterized by weakness and marked fatigability of skeletal muscles. Its clinical manifestations were described before the turn of the century, but it was not until the early 1930s that physostigmine was used in the management of this disease. The observation that physostigmine gave rise to increased strength of muscular contraction and the similarity between the symptoms of myasthenia gravis and curare poisoning in animals, suggested that physostigmine, an agent then known to antagonize curare, might be of therapeutic value for this disease. This observation led to the use of physostigmine in the treatment of myasthenia gravis.

Tardive dyskinesia is a disease characterized by abnormal, involuntary movements, usually of oral and facial musculature but often involving the trunk and extremities. Typical of oral and facial movements are puffing of the cheeks, grimacing, protrusion and licking of the tongue, and incessant blinking of the eyes. The abnormal movements are rhythmic and repetitive and may interfere with speech, salivation, chewing, and swallowing. Patients, many times, are not aware of the symptoms. Tardive dyskinesia is usually irreversible and considered to be incurable at the present time. Therefore, prevention of the manifestations of this disease is considered to be the only known effective method for dealing with the problem. Tardive dyskinesia is most frequently found in geriatric patients who have been taking neuroleptic drugs. All neuroleptic drugs may cause tardive dyskinesia. However, the low-dose, high potency drugs which produce the greatest degree of blockage, and thus a greater degree of pyramidal side effects are the most likely to cause tardive dyskinesia. Such high potency drugs include the phenothiazines, the thioxanthenes, the butyrophenones, the benxodiazepines and the dihydroindolones. In recent years, the greater use of psychotropic drugs has aggravated the incidence of tardive dyskinesia. The increasing use of neuroleptic drugs in geriatric care facilities has resulted in dramatic increase in the incidence of tardive dyskinesia. See Geriatrics, Volume 34, Number 7, pages 59–66, July 1979, by Harcourt Brace Jovanovich, Inc. An investigation in the use of anticholinergic drugs reported in American Journal of Psychiatry, Volume 134, Number 7, July 1979, pages 769–774 indicates that the use of physostigmind and choline have positive therapeutic effects on tardive dyskinesia. Although the data presented is not unequivocal, tests have shown that physostigmine injections reduce tardive dyskinesia in from 20% to 80% of the patients suffering from tardive dyskinesia. Continuous and permanent drug therapy is necessary to control tardive dyskinesia.

Senile dementia of the Alzheimer's type (SDAT) is a progressive, incurable, and irreversible disease characterized by long term memory impairment. Studies in humans and animals have implicated cholinergic processes in memory functioning. Investigations with anticholinergics and cholinomimetics indicate that fluctuations in cholinergic activity can profoundly affect storage and retrieval of information in memory. Davis, et al. in a study by reported in Science, Volume 201, p.272 (1978) concluded that physostigmine significantly enhanced storage of information into long-term memory. This study moreover indicates that retrieval of information from long-term memory was also improved by physostigmine therapy.

Treatment of tardive dyskinesia, wide angle glaucoma, SDAT, and the like, by injection of physostig-

mine is not practical therapy. Physostigmine exhibits a short half-life (about 1 to 2 hours) due to rapid metabolism following systemic administration. Thus, treatment would require injections of physostigmine every 30 minutes to 1 hour at a minimum, to maintain efficacious blood levels. Additionally, physostigmine has a narrow therapeutic window which necessitates constant patient monitoring for safety in order to avoid side effects which limit physostigmine's systemic use. Recently, physostigmine has been formulated into tablets for oral dosage. Determination of drug blood levels for multiple oral doses show typical variations in blood concentration ranging from a maxima above the required level (and possibly in the toxic range) to a minima which may be below the effective dose. The dysfunctions mentioned above, as well as many others, are more prevalent among the elderly. This population group endures more memory impairment and physical disability than other age groups and consistent therapy is necessarily more difficult to attain. Percutaneous administration of physostigmine has many advantages over systemic therapy. It is well known that patient compliance is improved where therapy can be attained with fewer numbers of drug applications within a twenty-four hour period. Transdermal administration offers the possibility that application of an appropriate device need occur but once in a twenty four hour period. Therapy can be terminated by removal of the transdermal device. Stable blood levels can be obtained using dose-controlled devices, thus limiting the toxic side effects caused by overdosing and the lack of effect due to underdosing. Pharmacologically active agents with short metabolic lifetimes are particularly suited to transdermal methods of drug delivery.

The literature is filled with descriptions of transdermal devices for the slow or sustained or controlled release of medicaments. These devices may take the form of monolithic reservoir devices, osmotically driven devices, membrane controlled devices, enhancer controlled devices, microencapsulated drugs, bioerodable devices and almost every conceivable combination of the above. For a general review of the art see, "Controlled Release of Biologically Active Agents", R. W. Baker, John Wiley and Sons, 1987. All of the dosing methods and devices used in drug therapy carry an implicit and many times unstated assumption, that the drug released has not been altered upon storage in any way to significantly decrease its efficacy or accumulate undesirable or unacceptable break-down products. It is well known that most free base alkaloids are not stable against air oxidation, actinic radiation, heat etc. Physostigmine free base is a particularly labile compound because its two basic tertiary amine groups facilitate hydrolysis of its phenolic carbanilide group. Once hydrolysis has taken place, contact with atmospheric oxygen will rapidly oxidize the phenolic hydroxyl group to the highly colored ortho-quinone, rubreserine, see, *Studies on Physostigmine and related substances, IV Chemical Studies on Physostigmine Breakdown Products and Related Epinephrine Derivatives,* S. Ellis, J. Pharmacol. Exp. Ther., 79 (1943) pp 364–372. See Reaction I. Consequently, chemicals of this class are commonly stored and administered as their salts. For example, because physostigmine is difficult to store as its free base, the salicylate salt is sold as a commercial preparation with the admonition that solutions should be kept well closed in light-resistant, alkali-free glass containers and used within a week of opening. The practitioner is cautioned to discard the preparation if it is discolored. In almost all cases, the free base is preferred for transdermal permeation because the free base will quickly cross the stratum corneum skin barrier while the salt form is poorly, if at all, transported and absorbed. Many approaches have been tried to solve this conflicting problem of storage vs permeability. For example, Banerje, in U.S. Pat. No. 4,692,462, binds the free base of drug on an ion exchange resin and relies upon the absorption of an equilibrium concentration of the free base form of the drug by the skin for utility. Lee and Yum in U.S. Pat. No. 4,781,924, store a variety of basic drugs in their salt form in combination with a dry basic compound. Upon moisture absorption, a solution is formed which permits the reaction between the alkaline compound and the salt form of the organic base, liberating the free base. The free base migrates through the device to the skin surface where it rapidly permeates the skin barrier. These inventions serve to illustrate the lengths to which those skilled in the art have gone in order to contain the therapeutic agent in its stable form as the salt, and administer the drug in its most biologically useful form, the free base. The foregoing discussion illustrates the need and value of a device or method that contains the target drug in its most active and bioavailable form (free base) while maintaining adequate storage stability.

Conventional wisdom has indicated that effective protection against the deleterious effects of oxygen and moisture could not be achieved by employing the various polymers as monolithic matrices for sensitive drugs. Diffusion of atmospheric oxygen and water vapor are thought to be so high that drugs sensitive to hydrolysis or oxidation, stored for any significant length of time under ambidnt conditions, would be quickly converted to the expected degradation products. Comequently, past efforts toward dealing with the problem of drug instability have been dedicated to converting the target drug into a chemical form that has adequate storage stability.

OBJECTS OF THE INVENTION

It is the object of this invention to disclose a novel means for increasing the storage lifetime of drugs.

It is another object of this invention to disclose a novel means for increasing the storage lifetime of physostigmine free base and its closely related analogs.

It is another object of this invention to disclose novel transdermal devices for the release of physostigmine free base and its closely related analogs.

It is another object of this invention to disclose devices and methods for controlled release of compounds effective in the treatment of memory impairment, glaucoma, tardive dyskinesia and myasthenia gravis.

It is another object of this invention to provide a means for treatment of disorders resulting from a deficiency of acetylcholine.

It is a further object of this invention to provide a means for symptomatic treatment of disorders resulting from a deficiency of acetylcholine.

Further objects of the invention will be apparent from the description of the invention to those skilled in the art.

SUMMARY OF THE INVENTION

The present invention stabilizes compounds containing chemically labile functional groups, such as physo-

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