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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**

References Cited

U.S. PATENT DOCUMENTS

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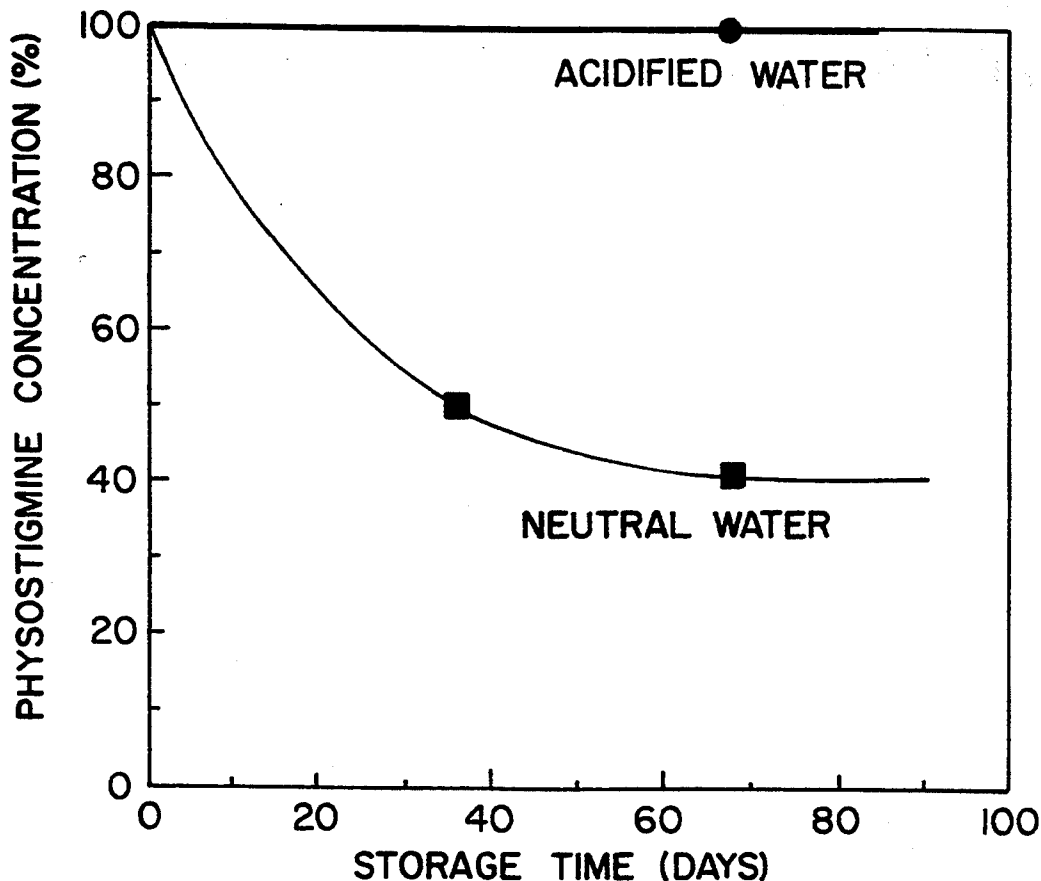
Primary Examiner—Gabrielle Phelan
Attorney, Agent, or Firm—Townsend and Townsend
 Khourie and Crew

[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

PHYSOSTIGMINE STORAGE STABILITY



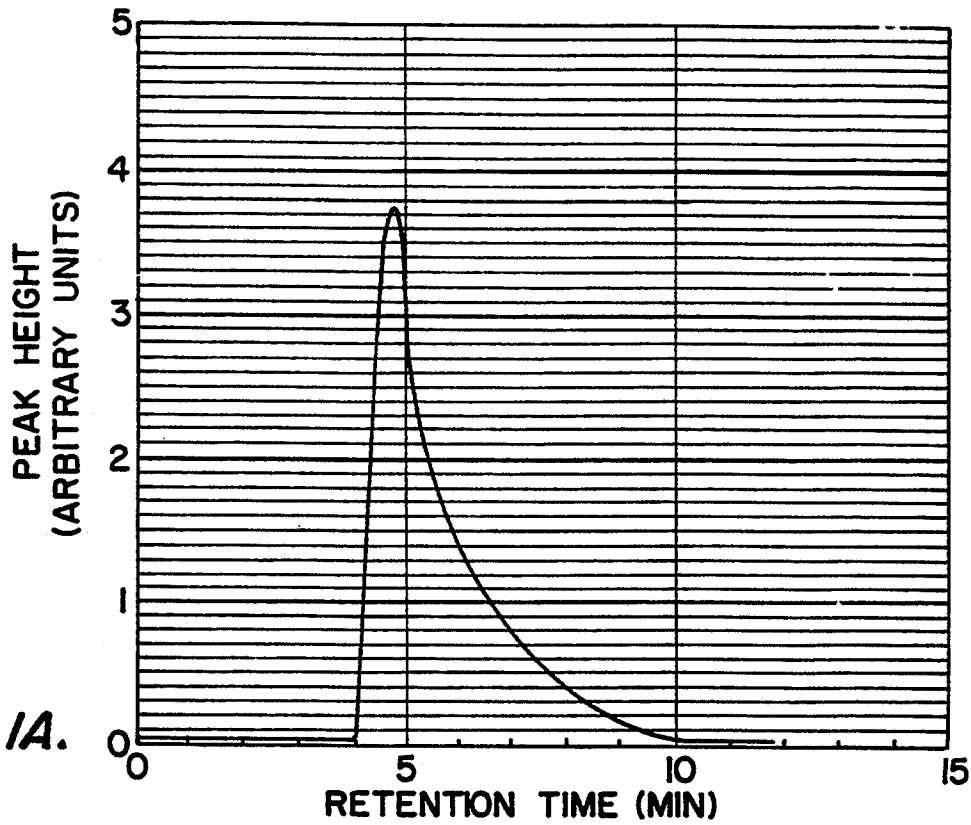


FIG. 1A.

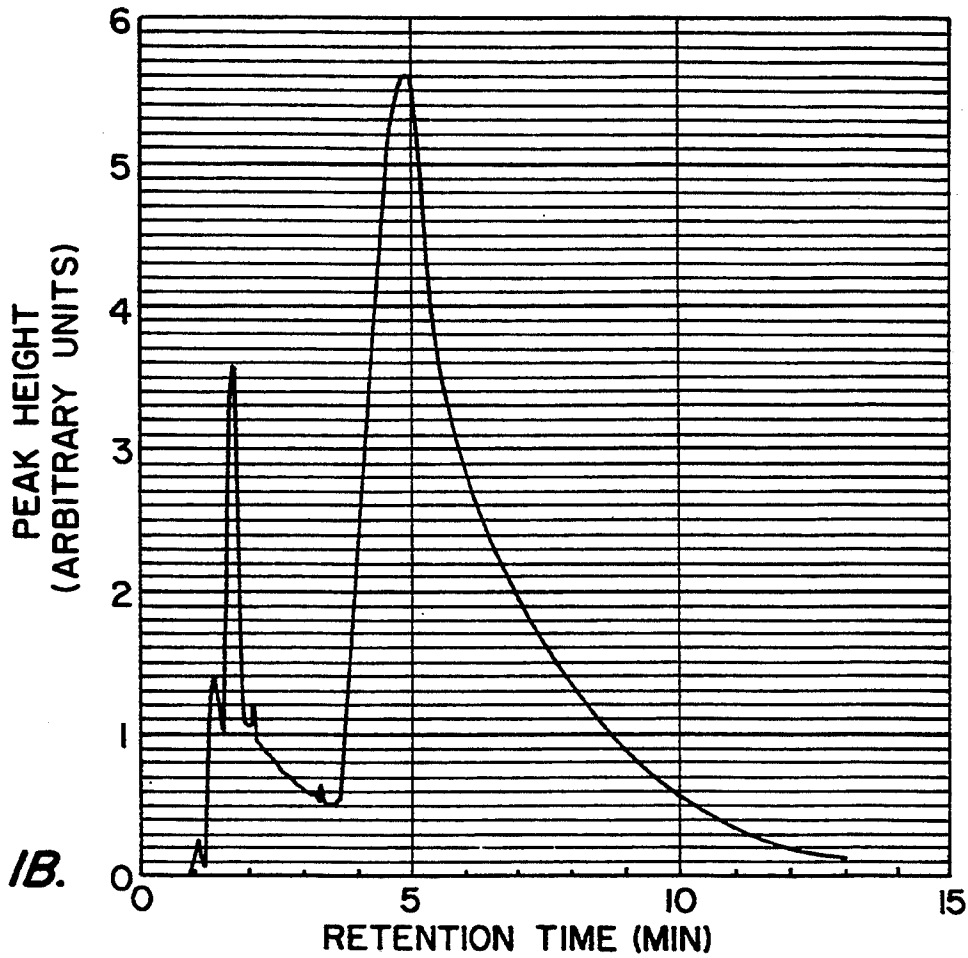


FIG. 1B.

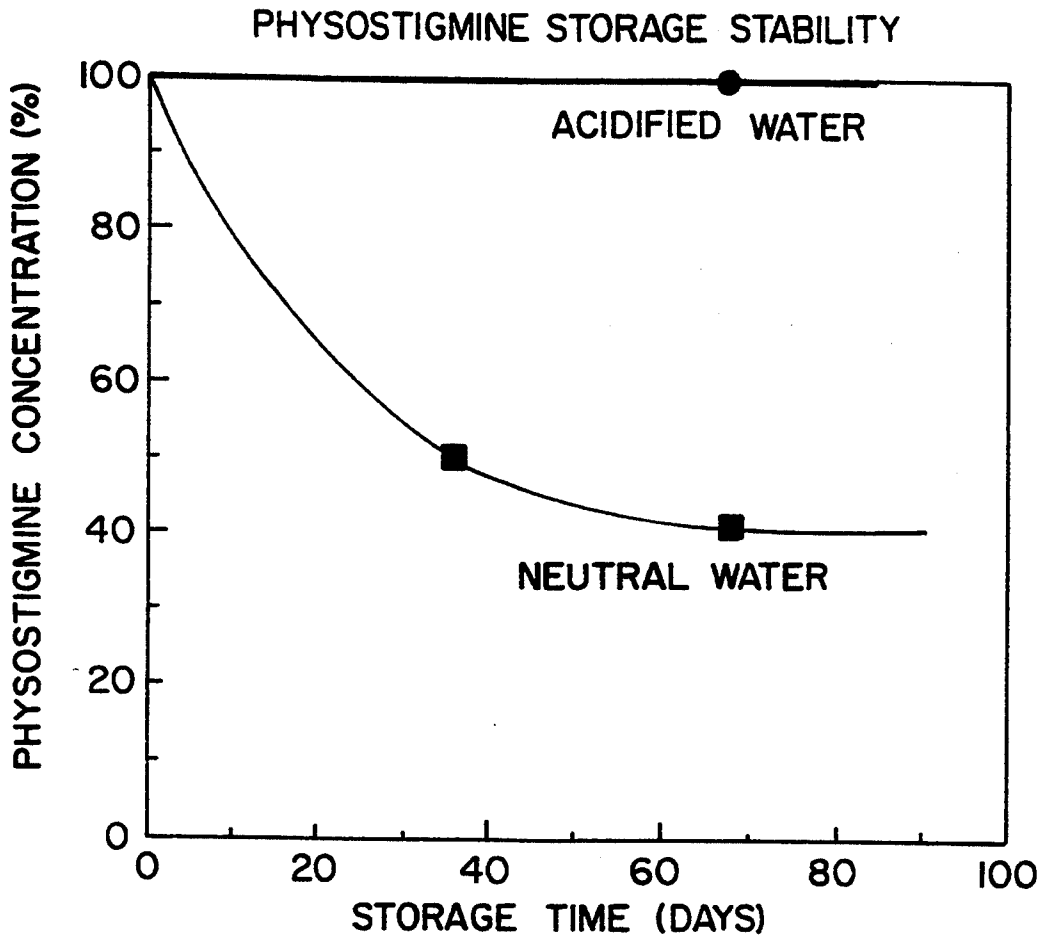


FIG. 2.

METHOD FOR INCREASING THE STORAGE STABILITY OF PHYSOSTIGMINE

This is a continuation of application Ser. No. 5
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 para-
sympathetic 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 func-
tion 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 con-
sumed 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 inhibi-
tors. As a result of AChE inhibition, acetylcholine ac-
cumulates 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 neu-
romuscular action. Since these ACh parasympathetic
synapses are widely distributed in the brain and periph-
eral nervous system, 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 ace-
tylcholinesterase inhibitors. It has been isolated from
the dry, ripe seed of the calabar or ordeal bean, a peren-
nial plant (*Physostigma venenosum*), found in the Cal-
abar 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 sur-
vive 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 miscar-
riages 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 persis-
tent, 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 grad-
ual, 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 charac-
terized by weakness and marked fatigability of skeletal
muscles. Its clinical manifestations were described be-
fore 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 cu-
rare, might be of therapeutic value for this disease. This
observation led to the use of physostigmine in the treat-
ment of myasthenia gravis.

Tardive dyskinesia is a disease characterized by ab-
normal, 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 dis-
ease is considered to be the only known effective
method for dealing with the problem. Tardive dyskine-
sia 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 pyra-
midal side effects are the most likely to cause tardive
dyskinesia. Such high potency drugs include the pheno-
thiazines, the thioxanthenes, the butyrophenones, the
benzodiazepines and the dihydroindolones. In recent
years, the greater use of psychotropic drugs has aggra-
vated the incidence of tardive dyskinesia. The increas-
ing 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 Jovano-
vich, Inc. An investigation in the use of anticholinergic
drugs reported in *American Journal of Psychiatry*, Vol-
ume 134, Number 7, July 1979, pages 769-774 indicates
that the use of physostigmine 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 charac-
terized by long term memory impairment. Studies in
humans and animals have implicated cholinergic pro-
cesses in memory functioning. Investigations with anti-
cholinergics and cholinomimetics indicate that fluctua-
tions in cholinergic activity can profoundly affect stor-
age 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 en-
hanced storage of information into long-term memory.
This study moreover indicates that retrieval of informa-
tion from long-term memory was also improved by
physostigmine therapy.

Treatment of tardive dyskinesia, wide angle glau-
coma, 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 ambient conditions, would be quickly converted to the expected degradation products. Consequently, 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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