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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 : A61M 31/00; G03B 21/46 A61F 1/16	A1	**(11) International Publication Number:** WO 84/ 01297 **(43) International Publication Date:** 12 April 1984 (12.04.84)

(21) International Application Number: PCT/US83/01531

(22) International Filing Date: 29 September 1983 (29.09.83)

(31) Priority Application Numbers: 432,409
444,376

(32) Priority Dates: 30 September 1982 (30.09.82)
26 November 1982 (26.11.82)

(33) Priority Country: US

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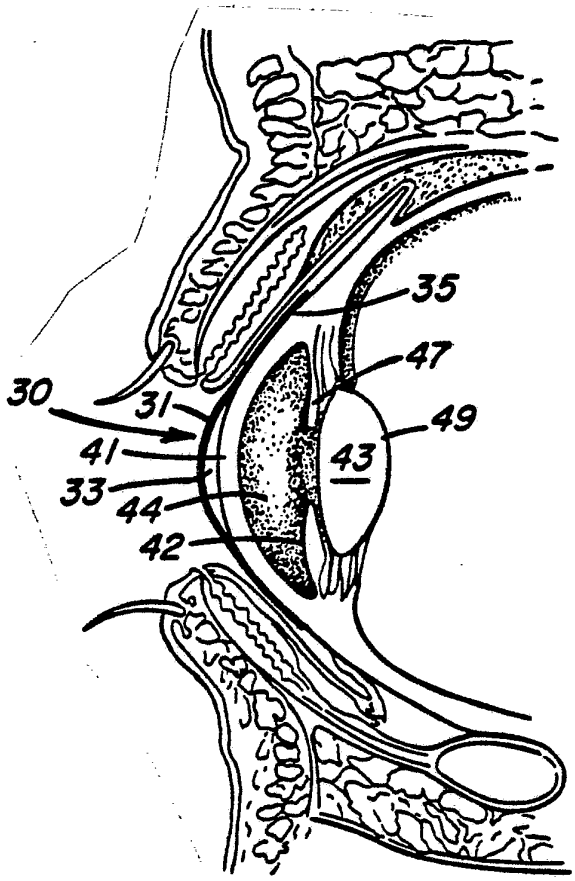
(81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.

(54) Title: OSMOTIC DEVICE FOR VARIOUS PHYSIOLOGICAL APPLICATIONS

(57) Abstract

An osmotic device (10) for immersion in a physiological fluid, including a semipermeable sheath (19) defining a fully enclosed cavity (18) and being imperforate except for a plurality of pores for permitting the flow of the physiological fluid into the cavity (18). At least one macromolecule is disposed within the cavity (18) and has a size larger than the pores in the sheath (19) so that the macromolecule is prevented from leaving the cavity (18) when the device is immersed in the physiological fluid, such physiological fluid being caused to flow into the cavity (18) through the pores under the influence of osmotic pressure. The cavity (18) will always contain a molecular concentration greater than the molecular concentration of physiological fluid surrounding the sheath (19).



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OSMOTIC DEVICE FOR VARIOUS PHYSIOLOGICAL APPLICATIONS

Technical Field

The present invention relates to an osmotic device for physiological applications, such as an improved delivery system for the time release of physiologically active agents, and an improved lens system which utilizes fluid as its primary lens medium.

Background Art

In recent years numerous devices have been devised which utilize osmotic flow for various physiological applications. For example, both U.S. Patent No. 4,265,874 to Bosen et al and U. S. Patent No. 4,298,003 to Theeuwes et al disclose methods and devices for the delivery of a drug where, as a result of osmotic flow, fluid passes through a semipermeable membrane and forces an insoluble drug or a solution of a soluble drug out of the device through an enlarged opening or passageway. The membrane of these devices allows the flux of water only, not the drug. The drug is forced out, under the influence of osmosis, through the enlarged opening or passageway which is separately drilled in the devices and whose size is orders of magnitude larger than the pores of the membrane. U. S. Patent No. 3,832,458 reveals a device in which a silicon polymer wall is utilized to vary permeability to an internal active agent. The permeability is adjusted by fabricating the wall with varying amounts of N-vinyl-pyrrolidone. While this device represents an improved drug delivery technique, it has a significant disadvantage in that it represents a

the driving force of drug delivered to the outside is the result of the internal concentration of drug alone. Thus the drug will be delivered at an initial rapid rate followed by a significantly lower rate until the active agent is expended.

U.S. Patent No. 4,309,996 by Theeuwes discloses a somewhat different mechanism for delivery of drugs whereby a separate compartment filled by a net osmotic inflow is utilized to expand against a flexible internal partition which forces the active agent out of a second compartment through a microporous structure thus attempting to approximate a steady delivery rate.

Such prior art drug delivery devices are either overly complex, adding to the cost of the devices, or unable to control the precise drug delivery rate. The osmotic device of the present invention overcomes these drawbacks by providing a drug delivery system which is flexible in that there are numerous variables which can be modified to control the delivery rate of the drug.

In another application of the osmotic device according to the invention, an improved lens is provided which utilizes fluid as its primary lens medium. The osmotic device according to the present invention is especially suited for use as an ocular lens, and the present invention further includes an improved method for the insertion of such an ocular lens.

It has long been recognized that ocular lenses made of glass or substantially rigid plastic result in irritation discomfort and alteration of the normal corneal physiology. Therefore, attempts have been made to reduce these effects by using softer, more permeable lens materials, particularly in the area of contact lenses. For example, U.S. Patent No. 2,241,415 to Moulton discloses an ophthalmic lens having a supporting portion formed of a thin, soft, pliable and slightly plastic material.

In recent years, so called "soft" contact lenses have been manufactured which utilize hydrogels as lens materials to reduce eye irritation and discomfort.

For example, in U.S. Patent No. 4,123,408 to Gordon, there is disclosed a contact lens of a hydrogel composition wherein the hydrogel utilizes a polymerized water-insoluble, water-swellable polymer composition. U.S. Patent No. 4,153,349 to Wichterle also discloses a method of making hydrogel contact lenses having improved lens properties. While "soft" contact lenses have reduced irritation and discomfort experienced while using prior art lenses, the soft contact lenses, while softer than prior art rigid lenses, must be sufficiently rigid to maintain the desired lens shape when utilized by the wearer and therefore a significant amount of foreign matter is introduced into the eye.

Any time foreign matter is introduced into the eye, there is a potential problem that irritation and discomfort will result even if the material is relatively soft. It will also hinder the passage of oxygen, nutrients, other gases and metabolites between cornea and tear film and thus potentially alter the normal physiology and clarity of the cornea. The ideal lens would utilize body fluids, such as lachrymal fluids, to form the desired lens and therby completely eliminate the need for introduction of foreign material into the eye. However, since it is not possible to retain such fluid in a desired lens configration, at least some type of structural member must be included to form the fluid into the shape of the lens.

The use of fluid in connection with ocular devices has been generally relegated to purposes other than the formation of a primary lens medium. For example, U.S. Patent No. 3,710,796 to Neefe discloses an opthlalmic dressing where a drug is impregnated into a transparent osmotic permeable material which serves to define the shape of the device. Diffusion of the drug out of its impregnated or dispersed state within this homogeneous polymer apparently determines the drug delivery rate. European Patent Application No. 32,517 published July 29th, 1981 discloses a lens which permits

the configuration of the device to a cornea by utilizing an insert filled with physiologically compatible fluid such as lachrymal fluid. However, the lens utilizes a soft contact material, not the fluid, as the primary lens medium.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide an improved osmotic device for a variety of physiological applications.

It is another object of the present invention to provide a new and improved system for delivering physiologically active agents.

It is a further object of the present invention to provide a new and improved system for the delivery of a physiologically active agent which is less complex than prior art devices.

It is an additional object of the present invention to provide a new and improved system for the delivery of physiologically active agents which permits more control and flexibility in the amount and rate of delivery of active agents than prior art devices.

It is another object of the present invention to provide a new and improved system for the delivery of physiologically active agents which utilizes the pores of a semipermeable membrane to deliver the active agent to a surrounding fluid environment.

It is yet another object of the present invention to provide a new and improved lens.

It is a further object of the invention to provide a new and improved lens which utilizes fluid as the primary lens medium.

It is an additional object of the present invention to provide a new and improved lens which utilizes fluid as the primary lens medium and is particularly suited for use as an ocular lens.

It is another object of the present invention to provide a new and improved lens which utilizes fluid

as the primary lens medium while keeping the structural material which forms the fluid in the shape of a lens to a minimum.

It is still a further object of the present invention to provide a new and improved lens which utilizes a semipermeable membrane to maintain a fluid body in a desired lens shape.

It is yet a further object of the present invention to provide a new and improved lens which utilizes a semipermeable membrane to maintain a fluid body in a desired lens shape and which retains the desired shape as a result of osmotic flow between the outside environment and the fluid body.

It is an additional object of the present invention to provide a new and improved lens which will permit the delivery of physiologically active agents.

It is a further object of the present invention to provide a new and improved lens which will permit the maximum exchange of gases, nutrients and metabolites between cornea, lachrymal fluid and the atmosphere, thus minimally compromising normal physiology.

Another object of the present invention is to provide a physiological lenticule capable of being introduced into the substance of the cornea with minimal disruption of its normal physiology while at the same time, altering significantly its shape and refractive power.

Yet another object of the present invention is to provide a new and improved method of placing a lens in the eye by insertion through a minimal incision.

Additional objects and advantages of the present invention will be set forth in part in the description which follows and in part will be obvious from the description or can be learned by practice of the invention. The objects and advantages are achieved by means of the processes, instrumentalities and combinations particularly pointed out in the appended claims.

To achieve the foregoing objects and in accordance with its purpose, the present invention provides, in its broadest aspect, an osmotic device for immersion in a physiological fluid. The device includes a semipermeable sheath defining a fully enclosed cavity and being imperforate except for a plurality of pores for permitting the flow of the physiological fluid into the cavity. At least one macromalocule is located within the cavity and has a size that is larger than the pores in the sheath so that the macromolecule is prevented from leaving the cavity when the osmotic device is immersed in the physiological fluid whereupon the physiological fluid surrounding the sheath is allowed to flow into the cavity through the pores under the influence of osmotic pressure and the molecular concentration of the physiological fluid within the sheath is maintained greater than the molecular concentration of the physiological fluid outside the sheath.

In one embodiment of the present invention a system is provided for the controlled delivery of a physiologically active agent to a fluid environment comprising a semipermeable sheath having a plurality of pores and being imperforate except for the plurality of pores and defining a fully enclosed cavity for holding a physiologically active agent. A physiologically active agent is contained in the fully enclosed cavity for delivery to a fluid environment, the plurality of pores being sized to permit both the flow of fluid from the fluid environment through the semipermeable sheath into the cavity and the flow of fluid and physiologically active agent in solution out of the cavity to the fluid environment whereby the physiologically active agent is delivered from the semipermeable sheath exclusively through the plurality of pores.

In another embodiment of the present invention a lens is provided comprising a semipermeable transparent sheath having opposite anterior and posterior portions joined at their edges and forming a closed interior space

between themselves. A body of liquid is provided within the sheath, fills the interior space and constitutes a lens whose anterior and posterior surfaces are bounded by the anterior and posterior portions of the sheath, respectively. Means are provided, in the body of liquid for producing within the interior space a concentration which is greater than the concentration of a liquid medium in association with which the lens is to be used, in consequence of which when the lens is in contact with such medium, the interior space will be kept filled with liquid under the influence of osmosis which causes the flow of liquid from the exterior of the sheath to the interior thereof, whenever the interior space is less than full.

An alternative embodiment of the present invention provides a lens in the form of a contact lens comprising a concave semipermeable transparent element adapted to seat on a human cornea to form therewith a closed interior space which contains a body of physiological solution produced by the wearer of the element and the body of liquid constitutes an optical lens whose anterior surface is bounded by the element and whose posterior surface is bounded by the cornea of the wearer. Means carried by the element at its interior is provided for producing within the interior space, when the same contains the body of liquid, a concentration which is greater than the concentration of the physiological solution produced by the wearer of the contact lens, in consequence of which when the element is worn on the cornea, the interior space will be kept filled with liquid under the influence of osmosis which causes the flow of liquid from the exterior of the space to the interior thereof whenever the interior space is less than full.

Furthermore, the present invention provides a method of locating an intraocular lens into an eye comprising the steps of providing a dehydrated semipermeable transparent sheath having opposite anterior and

posterior portions joined at their edges and forming a closed interior space between themselves and means within the interior space for producing within the interior spacing a concentration which is greater than the concentration of the physiological solution produced by the wearer of the lens, in consequence of which when the sheath is worn by the wearer, the sheath will hydrate such that the interior space will be kept filled with liquid under the influence of osmosis and therby form a lens, making an incision for insertion of the dehydrated semipermeable sheath into the eye and then inserting the dehydrated semipermeable sheathing into the eye whereby the dehydrated semipermeable sheath will contact the physiological solution produced by the wearer and hydrate to form a lens.

While the osmotic device of the present invention is particularly suited for an ocular lens, it is also suitable for any lens which is intended to be utilized in a fluid environment. In addition, the osmotic device of the present invention, whether or not it is in the form of a lens, permits the dispensing of physiologically active agents over a sustained period of time when the device is immersed in a physiological fluid

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of a device according to the invention.

Figure 2 is a sectional view along the section line II-II in Figure 1.

Figure 3 is a plot of the drug delivery rates of devices according to the invention.

Figure 4 is a perspective view of an alternative embodiment of a device in the form of a lens according to the invention.

Figure 5 is a sectional view of the alternative embodiment of the lens shown in Figure 4 in place on the cornea of the wearer.

Figure 6 is a perspective view of an eye in

partial section showing an alternative embodiment of the invention partially inserted therein.

BEST MODES FOR CARRYING OUT THE INVENTION

The osmotic device according to the invention will first be described in the context of a delivery system for physiologically active agents.

In accordance with the invention, as shown in Figure 1, an osmotic device 10 which is generally of circular configuration, but whose shape may vary as appropriate for differing sites of application, consists of a semipermeable sheath 19 which is made of two thin sheets 12 and 14. The thin sheets 12 and 14 are bound along their espective edges to form a sheath with an outside edge 16. As will be apparent hereafter, the osmotic device, when employed as a delivery system according to the invention, is intended to be used in a fluid environment with sufficient fluid present to enable the system to operate as intended. Furthermore, as with the prior art devices, the system according to the invention, is particularly suitable for the delivery of active agents to animals and may be located with respect to the animal to be treated by positioning or implanting the system in a variety of locations such as the animals rectum or gastrointestinal tract, etc.

As can be seen in Figure 2, thin sheets 12 and 14 define a cavity 18 which is intended to contain a physiologically active agent. Thin sheets 12 and 14 are provided with a plurality of pores in order to be semipermeable and permit the passage of fluid therethrough. The semipermeable thin sheets 12 and 14, when joined to form edge 16, result in a semipermeable sheath.

The present invention utilizes the principle of osmotic flow which results from a difference in molecular concentration being present across a semipermeable membrane.

According to this embodiment of the invention, cavity 18 will contain at least a physiologically active agent which will go into solution with fluid which will

enter cavity 18. The physiologically active agent may or may not be fully soluble as long as it can be delivered from device 10 at a suitable and predictable rate. As will be described in more detail hereinafter, in a preferred embodiment of the invention, a macromolecule is also present in cavity 18. The term macromolecule is intended to mean a large molecule such as a protein, carbohydrate, rubber or other natural or synthetic higher polymer.

The presence of an active agent in cavity 18 results in a net molecular concentration gradient being set up between the cavity 18 and the fluid environment in which the lens is used. This net molecular concentration gradient will result in flow of fluid from the fluid environment through the semipermeable sheath into cavity 18. This flow of fluid, generally referred to as osmotic flow, results from the net higher molecular concentration or net higher osmotic pressure which is present in cavity 18 due to the presence of a physiologically active agent alone or the physiologically active agent and the macromolecule. That is, the body of fluid inside the semipermeable sheath is hypertonic with respect to the fluid outside of the semipermeable sheath, i.e., the fluid inside the semipermeable sheath has a higher osmotic pressure than the fluid outside the semipermeable sheath.

When measured at any given instance, the osmotic pressure inside cavity 18 will be higher than that of the fluid surrounding the device and, therefore, there will be a net inward flow of fluid. However, over a period of time fluid continuously enters and leaves cavity 18 which results in a dispersion of the active agent from cavity 18. While there will be continuing "steady-state" flux of fluid between the environment and internal fluid of the device, the net inflow of fluid volume will occur in the initial states under the influence of osmosis until the osmotic pressure and fluid inflow result in the device achieving its natural pre-

molded configuration. The burst strength of the encapsulating polymer film and its seal exceed the maximum achievable osmotic pressure by at least several orders of magnitude. The continuing steady-state flux of fluid across the walls of the device will result in the dispersion of any active agent whose molecular size is such as to allow passage through the preselected pore diameter of the membrane wall.

The osmotic flow which results due to molecular concentration differences is independent for each molecule involved. For example, in the above example if the macromolecule, designated A, and another molecule, designated B, were added to cavity 18, and went into solution and became part of the body of liquid in cavity 18, molecule B would set up a concentration gradient across the semipermeable sheath independent of the gradient present as a result of macromolecule A. The osmotic flow resulting from the presence of molecule B would be independent of the osmotic flow resulting from the presence of macromolecule A.

Preferably, in this embodiment of the invention a macromolecule would be complexed with the physiological agent and the macromolecule selected such that it would be larger than the pores of the semipermeable sheath, yet the complex would decay over a period of time thereby allowing the active agent to slowly disperse from the semipermeable sheath.

The macromolecule, according to the invention, may be selected from any class of compounds with molecular weight and configuration sufficiently large to be excluded passage of the desired pore size. Generally suitable are the dextrans, amylopectins (hydroxyethylstarch), polyvinylpyrrolidone, polyethylene glycol, albumin and various other soluble polymers and/or proteins. Alternatively, emulsions with droplets containing active agent can be utilized as well. Microemulsions with droplets of a diameter range 0.01 to 0.1 microns are transparent and optically clear and thus, preferable for

optical systems whereas macroemulsions with droplet of size 0.1 to 1 or 2 micrometers may be satisfactory in other uses.

The active agents suitable for use in connection with the present invention include for examples: oxygen, preferentially bound to fluorocarbons; salicylates, catechols, halogens, barbiturates or other compounds complexed to a macromolecule such as polyethylene glycols; antibiotics such as chloramphenicol, sulfa or other medications complexed with a macromolecule such as polyvinylpyrrolidone; antiepileptic medications such as phenytoin complexed to albumin; antihistamines, quinine, procaine or other compounds complexed to a macromolecule such as sodium carboxymethylcellulose; salicylates complexed to the antibiotics oxytetracycline or tetracycline or other compounds complexed to a macromolecule such as salicylates or other macromolecules could be utilized such as caffeine or albumin. The above identified complexes have well known dissociation constants. See generally Remington's Pharmaceutical Sciences, 16th Edition, Arthur Osol, Editor, Mack Publishing Co. 1980, pp. 182-193 and Physical Pharmacy, 2d Edition, Martin et al, Lea & Febiger, 1969, pp. 325-352.

A given delivery rate of active agent and/or complexing molecule can be achieved through selection of appropriate membrane pore size, density, environmental conditions and binding molecule. Active agent and binding molecule form a molecular complex with an affinity for each other which can be expressed as a dissociation constant, an easily determined quantity related to concentration and physiocochemical environment. This constant is directly proportional to the concentration of the complex and inversely proportional to the product of the concentrations of active agent uncomplexed and binding molecule uncomplexed. It can thus be seen that if a nondiffusable binding molecule is chosen, the further dampening of a potentially rapid or exponential rate of delivery of active agent can be achieved. In

simple form, if the dissociation constant is represented as K, the molar concentration of the drug as (D), the binding molecule concentration as (B), and the bound complex as (B-D), the following represents the relationship described:

$$K = \frac{(B\text{-}D)}{(B)(D)}.$$

The thickness of the semipermeable sheet material, utilized in connection with the invention, will depend on a number of factors and is directly related to the intended use of the delivery system. Generally, the membrne thickness will range from 5-10 micrometers, depending upon the material used and the intended configuration and concentration gradient. Sheet material could be selected from cellulose acetate, cellulose acetate butyrate, cellulose triacetate, poly-1, 4 butylene terephthalate (such as MYLAR^{R}), polymethylmethacrylate, polypropylene (such as CRYOVAC^{R}), polystyrene, polyvinyl acetate, polyvinyl chloride, polyvinyl fluoride polyvinylidene chloride (such as SARAN^{R}), polycarbonate or silicon-polycarbonate copolymers (such as NUCLEPORE^{R}) and others.

The sheet material can be made porous in a variety of ways. For example, the technique of nuclear track etching can be used, in which the polymer films are exposed to radioactive decay particles and products and then treated chemically to "etch" permanently the tracks of the particles through the film, thus creating pores of a size and density determined by the exposure time and etching process. The particle dose determines the hole density while the pore diameter is a function of etching time. The specific particles, dose, etchants, and other conditions to achieve desired pore sizes and density for the aforementioned polymer films are well known in the prior art. See Nuclear Tracks in Solids, Principals and Applications, R. L. Fleischer et al, University of California Press, 1975. For example, polycabonate

filters (such as NUCLEPORE^{R}) are produced by exposure to U^{235} followed by sodium hydroxide etching. Polyvinylidene chloride (such as SARAN^{R}) can be made microporous by exposure to fission fragments of Californium 252 followed by etching with potassium permanganate at 55 degrees Centrigrade. As an alternative to nuclear tracking etching, the newer advanced lasers such as frequency-doubled Neodymium-YAG, Excimer, tunable dye or other lasers may be used to produce pores of the desired size and density.

Pores may also be created by forming membranes as integrated sheets of polymer containing "pore-formers," molecules which subsequently can be leached or dissolved out, leaving a predictable pore size. The leaching or dissolution can be accomplished prior to use or so selected to occur in the environment of use. For example, certain polymer films made of various polycarbonates, polyamides, or polyesters can include such pore formers as lithium carbonate, calcium phosphate, and various polysaccharides, such as mannitol, CARBOWAX^{R}, etc. The microporous paths then fill with a medium, compatible with or identical to the medium of the environment in which active agent, complexing (binding) molecule and complex are soluable, thus permitting diffusion of active agent and fluid medium out of cavity 18 and the generation of an osmotic gradient across semipermeable sheets 12 and 14. These above processes, and others for creating microporous membranes, are noted in the prior art literature and are compiled in such works as Synthetic Polymer Membranes, R. E. Kesting, McGraw-Hill Inc., 1971.

The pore size will preferably range between 50 Angstroms diameter to 1,000 Angstroms; however, it may be possible to have pore sizes smaller than 50 Angstroms, if desired. The pore size is selected depending on the molecular weight and configuration of the macromolecule. For example, a pore size of approximately 60 Angstroms will exclude a molecule having a molecular weight of about 10,000. A 100 Angstrom pore size will exclude a

molecule having a 100,000 molecular weight. The exact three dimensional configuration of the molecules may, of course, produce exceptions. Pore density would be on the order of 10^5 to 10^{10} per square cm; however, depending on the application of the device, pore densities less than 10^5 per square cm may be used.

The thin sheets 12 and 14 may be joined at their respective edges to form edge 16 in a variety of ways. Various heat and impulse sealers can be used with variations in temperatures, frequency, and times allowing for substantial flexibility depending upon the particular polymer. Various one-part and two-part compatible adhesive bonding systems such as EASTMAN 910^R, EPON 828^R and 3M CONTACT CEMENT^R could also be used. In addition, some materials are suitable for bonding without using conventional bonding methods. For example, vinylidene chloride may be sealed to itself while in the so-called "supercooled" state to form a strong bond without conventional dielectric heat or adhesive methods.

Osmotic pressures generated in cavity 18 obviously will be significantly less than the burst strength of the semipermeable membranes. For example, the pressure generated by the macromolecule will be on the order of less than 0.34 atmosphere (5 pounds per square inch), while, for example, the burst strength of vinylidene chloride 1 mil thick is 30 pounds per square inch.

The following specific examples of delivery systems, in accordance with the invention, are set forth as illustrative only, and should not in any way limit the scope and purpose of the present invention.

A delivery system for the drug phenytoin, is constructed by forming a sheath made from planar sheets of polycarbonate membrane, with pore size of 0.015 micrometers, porosity $12 \times 10^8/cm^2$ and thickness 6 micrometers. The polycarbonate membrane is heated to 220 degrees Centrigrade, and molded by vacuum or pressure

to a spherical cap of 6.0 mm diameter with radius of curvature, 6.4 mm. A 1/2 mm wide planar circumferential cuff is left about each empty spherical cap. Then, 25 µg of phenytoin, along with 100 µg of albumin are placed into one cap after which the opposing cap is utilized as a cover and the circumferential cuff of 1/2 mm is sealed together at 230-275 degrees Centigrade. This creates an envelope of potential volume 11.92 mm^3. Placed in the fluid environment of use, the delivery system will fill to its normal volume.

Figure 3 is a plot of the delivery rate of systems according to the invention comparing the delivery rate of a system containing phenytoin-albumin complex with the delivery rate of a system containing phenytoin alone. In the first half-hour the system utilizing the drug phenytoin-albumin complex shows that 0.74% of its drug content by weight will have been expended and after one hour a total of 1.7% will have been expended, and so on for the following intervals: 2 hrs, 3.4%; 4 hrs, 5.4%; 10 1/2 hours, 12%; 24 hrs, 20.2%; 33 1/2 hrs, 27.2%.

By contrast, an identical device containing only phenytoin without albumin will deliver at the identical time intervals as noted above, the following percentages of the initial amount of drug placed in the device: 1/2 hr, 1.47%; 1 hr, 2.97%; 2 hrs, 5.7%; 4 hrs, 9.6%; 10 1/2 hrs, 22.4%; 24 hrs, 38%; 33 1/2 hrs, 47.2%.

The osmotic device according to the invention will now be described in its embodiment as a lens. Again referring to Figures 1 and 2, when osmotic device 10 is employed as a lens, thin sheets 12 and 14 are made of transparent material and are bound along their respective edges to form sheath 19 which defines cavity 18 for retaining a body of fluid. In accordance with this embodiment of the invention, the body of fluid comprises the primary lens medium. The primary function of the transparent thin sheets 12 and 14 is not to constitute part of the lens medium, but is to retain the body of

fluid in a shape that will enable it to serve as the primary lens medium. As will be apparent hereafter, the lens according to the invention, is intended to be used in a fluid environment with sufficient fluid present to enable the lens to operate as intended. The body of fluid retained by the sheath formed by the thin transparent sheets 12 and 14 will not necessarily be present when the lens is not being used in its intended environment.

As in the delivery system described above sheets, 12 and 14 are provided with a plurality of pores in order to be semipermeable and permit the passage of fluid therethrough. The semipermeable thin transparent sheet 12 and 14, when joined to form edge 16 result in a semipermeable sheath.

In accordance with the present invention the lens utilizes the principle of osmotic flow which results from a difference in molecular concentration being present across a semipermeable membrane.

According to this embodiment of the invention, cavity 18 will contain at least one macromolecule which will go into solution with the fluid in cavity 18 and the macromolecule along with the fluid in cavity 18 will form the body of fluid which constitutes the lens medium. The presence of the macromolecule in solution in the body of fluid in cavity 18 results in a molecular concentration gradient being set up between the body of fluid in cavity 18 and the fluid environment in which the lens is used. As described in connection with the embodiment of the delivery system, this molecular concentration gradient results in a net flow of fluid from the fluid environment through semipermeable sheath 19 into cavity 18, because the fluid inside the semipermeable sheath has a higher osmotic pressure than the fluid outside the semipermeable sheath due to the presence of the macromolecule in cavity 18.

To assure that this concentration gradient is maintained, the macromolecule and semipermeable sheath are selected such that the macromolecule will not flow

out of cavity 18 through the semipermeable sheath, yet the semipermeable membrane will permit the flow of fluid from the environment in which the lens is used into cavity 18. Because the macromolecule cannot leave cavity 18, the molecular concentration inside cavity 18 and the molecular concentration outside cavity 18 will never equalize. Since, normally, osmotic flow will continue until the molecular concentrations are equalized, there is always a tendency for the surrounding fluid to flow through the semipermeable sheath. The size of cavity 18, however, is determined by sheath 19, and the tensile strength of sheath 19 is stronger than the osmotic pressure exerted due to the molecular concentration differences. Cavity 18 thus always remains full when disposed in its intended environment.

When osmotic device 10 is utilized in connection with an ocular lens, the surrounding fluid environment will generally consist of lachrymal fluid and cavity 18 will fill with such lachrymal fluid. As a intraocular lens, aqueous humor will surround the lens and be at an equilibrium with the intralenticular fluid. As an intracorneal lens, the interstitial fluid of the cornea will comprise the fluid within cavity 18.

In this embodiment of the invention, the macromolecule, should generally be photostable and inert to assure proper performance of the lens. The macromolecule may be selected from any class of compounds with molecular weight and configuration sufficiently large to be excluded passage by the desired pore size. Generally suitable are the dextrans, amylopectins (hydroxyethylstarch), polyvinylpyrolidone, polyethylene glycol and various other soluble polymers, proteins and/or physiologically active agents.

Osmotic device 10 may serve the dual function of a lens as well as a delivery system due to the principle that, as discussed above, the osmotic flow which results from molecular concentration differences is

independent of each molecule involved. Thus, a lens according to this aspect of the invention can be utilized for the delivery of physiological agents by incorporating such agents within cavity 18 and selecting the active agent such that it has a molecule size sufficiently small to pass through the semipermeable sheath. Preferably, a second macromolecule would be tagged with the physiological agent and the macromolecule selected such that it would be larger than the pores of the semipermeable sheath, yet it would decay over a period of time thereby allowing the active agent to slowly disperse from the semipermeable sheath. All the while, however, the first macromolecule, which is larger than the pore size of the semipermeable sheath, is confined within cavity 18. Because of the osmotic pressure generated by the first macromolecule, as soon as any active agent leaves the cavity, the surrounding fluid will still enter cavity 18 to maintain the lens configuration.

The active agents suitable for use in connection with the lens of the present invention include for example: oxygen, preferentially bound to fluorocarbons; salicylates, catechols, halogens, barbiturates or other compounds complexed to a macromolecule such as polyethylene glycols; antibiotics such as chloramphenicol, sulfa or other medications complexed with a macromolecule such as polyvinylpyrrolidone; antihistamines, quinine, procaine or other compounds complexed to a macromolecule such as sodium carboxymethylcellulose; salicylates complexed to the antibiotics oxytetracycline or tetracycline or other compounds complexed to a macromolecule such as salicylates or other macromolecules could be utilized such as caffeine or albumin. (See generally Remington's Pharmaceutical Sciences, and Physical Pharmacy, cited above).

The delivery rate of active agent and/or complexing molecule is determined as previously discussed in connection with the osmotic device as employed is a delivery system..

When concerned with ocular lenses, the membrane thickness will generally range from 5-10 micrometers, again depending upon the material used and the desired configuration and concentration gradient intended to be utilized. The sheet material for sheath 19 is the lens embodiment could be selected from among the same materials listed above relative to the use of the osmotic device as a delivery system, and the same processes as described above may be used to create the pores in the transparent sheets and to join the respective edges to form edge 16. Also, the pore size will preferably be the same as previously discussed.

The refractive index of the lens will be determined by composition and concentration of the body of liquid formed in cavity 18. For example, dilute solutions of dextran (average molecular weight 75,000) and amylopectin have a refractive index similar to that of plain water or saline solution, 1.336. (Amylopectin average molecular weight, 545,167). A 17% solution of amylopectin has a refractive index of 1.432.

Turning now to Figures 4 and 5, there is shown lenses 20, 30 in accordance with the invention, in the form of a contact lens. Lens 20 of Figure 4 is made of a thin transparent sheet 21 of semipermeable material as previously described. While the lens of Figure 4 is an ocular contact lens having a generally circular configuration, the principles of the invention are equally applicable to lenses of other shapes or other uses. Furthermore, while the lenses shown in Figures 3 and 4 are hyperopic contact lenses, the present invention is likelwise suitable for myopic contact lenses. As the anterior surface is regular and independent of the posterior curvature, it will neutralize corneal astigmatism and/or irregularity.

Lens 20 includes scaffolding 29 on the rear surface of the semipermeable sheet 21. The scaffolding 29 serves to give additional support to sheet 21.

Scaffolding 29 comprises polymethylmethacrylate, polypropylene, cellulose acetate butyrate, hydroxymethylmethacrylate or other rigid, semirigid or soft polymer strands. Scaffolding 29, as shown in Figure 4, is fish net in configuration; however, it may be a variety of designs such as concentric rings connected by radial spokes, arcuate crossing elements, radial strands, a mesh of criss-crossing meridional fibers, etc. In addition, while scaffolding 29 is shown in connection with contact lens 20 of Figure 4 and 5, it could also be used in connection with other lenses, in accordance with the invention, such as the lens shown in Figures 1 and 2. In addition, as was the case with the formation of the semipermable sheath, the scaffolding may be joined to the lens by known prior art methods such as by heat impulse sealing, adhesives, or during the manufacturing of the semipermeable sheath.

Turning now to Figure 5, lens 30 is shown, in place, on the cornea of the wearer. Figure 5 shows a human eye including a cornea 41, iris 42, eye lens 43, anterior chamber 44, posterior chamber 47 and posterior capsule 49. Thin transparent sheet 31 rests on cornea 41 and retains a body of fluid 33 which functions as the primary lens medium. As described in connection with the embodiment of Figures 1 and 2, the body of fluid 33 contains a macromolecule and has a higher concentration than the surrounding ocular fluid, primarily lachrymal fluids. Because the body is of higher concentration than the surrounding body fluids, the cavity defined by the thin, transparent sheet 31 and the cornea 41 will remain filled with fluid. Instead of being provided with scaffolding for added support, contact lens 30 includes a larger diameter outer portion 35 made of soft permeable material which serves as a lens carrier to support contact lens 30. Alternatively, the lenses, according to the invention, could utilize both scaffolding and a lens carrier if desired.

Figure 6 shows an intraocular lens 50 in accordance with the invention partially inserted in the eye cavity. Lens 50 is provided with haptic support struts which serve to anchor the lens to the eye cavity. According to the method of this embodiment of the invention, because lens 50 is flexible and can be inserted in the eye in a dehydrated state, the lens may be folded or rolled to a size smaller than its hydrated size. This permits the use of a small incision as compared with prior art methods of insertion and results in lessened trauma to the patient. Once the dehydrated lens is inserted in the eye, it can be unfolded or unrolled and then permitted to hydrate in order to function as a lens.

The following specific examples of lenses constructed in accordance with the invention are set forth as illustrative only, and should not in any way limit the scope and purpose of the present invention.

Example I

A contact lens according to this embodiment of the invention may be constructed for a moderately farsighted patient after a cataract extraction, a moderately extreme example of need for hyperopic or "+" correction of +14.00 diopters. A semipermeable sheath of polyvinylidene chloride is provided which has been exposed to Californium 252 to create a pore density of about 10,000 pores per square cm and then etched in potassium permanganate at 55 degrees Centigrade for a time appropriate to create a pore diameter of 100 Angstroms. A refractive index of 1.366 is arbitrarily chosen and will require a solution of 20% amylopectin. A wide and generous optical zone of 7.0 mm is selected. The lens is designated to be fitted to a cornea so that its posterior radius will conform, for example, with an average 7.8 mm radius of the cornea. Given these parameters, an anterior curvature of the lens of 6.0 mm radius will occur and result in an extremely favorable thin lens having a central maximum thickness of the lens of 0.3 mm. The

volume of the lens will be 6.19 mm^3 and thus 1.5 mg of amylopectin will create the desired 20% solution and refractive index of 1.366. The periphery of the lens can be heat-sealed at 225-260 degrees Fahrenheit. If necessary, a posterior scaffolding can be constructed of polymethylmethacrylate, a silicon polymethylmethacrylate polymer, polypropylene or hydrogel and joined to either posterior and/or anterior polymer films by heat impulse, compatible adhesive or the manufacturing process itself when mesh and/or film are in a precast state.

Example II

A concave lens to correct high myopia, thus gaining "minus" power can be similarly constructed. For example, a lens correcting relatively extreme myopia of -10.00 diopters, can be constructed. Assuming a cornea of average radius of 7.8 mm, choosing a refractive index for the lens of 1.366 equalling the index ascertained for a 20% solution of amylopectin, and a large optical zone of 7.0 mm diameter, the required anterior radius of the lens will be 9.9 mm. Given the basic stability and characteristics of this type of lens, it can be constructed with no significant center point thickness except for the thickness of the opposing membranes, thus attaining a maximum vertical height at its lateral thickest portion of 0.19 mm. The volume of this lens is 4.58 mm^3 and thus 1.1 mg of amylopectin will be added to the lens cavity. The osmotic pressure generated in the lenses is well below the burst strength of 30 pounds per square inch for a 1 mil film of polyvinylidene chloride.

Example III

A lens for incorporation within the corneal substance (keratophakia) can be similarly constructed. The following conditions are assumed: an example of aphakic hyperopia; the need to generate a total ocular power from the posterior corneal surface of 60 diopters; an average normal anterior corneal radius of 7.8 mm; and a posterior corneal radius of 6.5 mm. As an extreme

example, the lens may be made with a dilute solution of macromolecules such that the refractive index approaches that of water and aqueous humor and tears, namely 1.336, less than that of the cornea itself (1.376). A large optical zone of diameter of 7.0 mm is chosen and a new anterior corneal radius of 5.6 mm is necessary. To achieve this change in corneal configuration, a lenticule, with an anterior radius of 5.35 mm, a posterior radius of 7.55 mm, thus generating a central maximum thickness of 0.4 mm should be fabricated. Obviously, for increasing refractive index, a decreased thickness for any given diameter of optical zone can be achieved by requiring less of a change in the anterior convexity of the cornea. Reduction in corneal convexity, by incorporating minus concave lenses for the correction of myopia, can be similarly accomplished by fashioning such intrastromal lenticules as described for the contact lens. Support scaffolding can be incorporated into the anterior and/or posterior surfacs as needed. The periphery of this particular lens may be impulse sealed after incorporation of less than one-half mg of dextran (less than 5% solution), requiring a peripherally sealed zone of 1/2 to 1 mm for a total 8.0 to 9.0 mm diameter lenticule.

Example IV

An intraocular lens may be constructed in accordance with the invention. Assuming an average intraocular lens power of 20 diopters, a lens symmetrically biconvex, and 33-1/3% solution of dextran or amylopectin with a refractive index of 1.400, a generous optical zone for an intraocular lens of 6.0 mm diameter is chosen, thus requiring a radius anteriorly and posteriorly of 6.4 mm and creating a total thickness at the center maximum of 1.4 mm. The lens will have a volume of 11.92 mm^3 and thus require incorporation of 5.9 mg of dextran or amylopectin. This lens may be constructed so that it has a 1/2 mm wide circumferential seal which incorporates thin support haptics enabling the lens in its dehydrated state to be folded or rolled and maneuvered into the eye through an incision 3-1/2 to 4 mm long.

It will be understood that the above description of the present invention is susceptible to various modifications, changes and adaptations and the same are intended to be comprehended within the meaning and range of equivalents of the appended claims.

CLAIMS:

1. An osmotic device for immersion in a physiological fluid comprising:

a semipermeable sheath defining a fully enclosed cavity and being imperforate except for a plurality of pores for permitting the flow of the physiological fluid into said cavity; and

at least one macromolecule disposed within said cavity and having a size larger than the pores in said sheath so that said macromolecule is prevented from leaving said cavity when said device is immersed in the physiological fluid, such physiological fluid being caused to flow into said cavity through said pores under the influence of osmotic pressure;

wherein said cavity will always contain a molecular concentration greater than the molecular concentration of physiological fluid surrounding said sheath.

2. A system for the controlled delivery of a physiologically active agent to a fluid environment comprising the osmotic device of claim 1, and further including a physiologically active agent complexed to said macromolecule such that said physiologically active agent dissociates from said macromolecule over time, goes into solution with the fluid in said cavity and passes out of said cavity through said pores whereby said physiologically active agent is delivered from said semipermeable sheath exclusively through said plurality of pores.

3. The system of claim 1, wherein said sheath is transparent and said macromolecule is photostable.

4. The system of claim 1, wherein said macromolecule is inert.

5. The system of claim 1, wherein said macromolecule is selected from a group consisting of protein, cellulose carbohydrate, rubber or high polymer.

6. The system of claim 1, wherein said sheath has a thickness of less than 50 microns.

7. The system of claim 1, wherein the diameter of said pores is less than 1,000 Angstroms.

8. The system of claim 1, wherein said sheath has a pore density between 100 and 10^{10} pores per square cm.

9. An ocular lens system comprising the osmotic device as defined by claim 1, wherein said sheath is transparent and the physiological fluid which flows into said cavity through said pores under the influence of osmotic pressure constitutes an optical lens.

10. A lens comprising

a semipermeable transparent sheath having opposite anterior and posterior portions joined at their edge and forming a closed interior space between themselves;

a body of liquid within said sheath and filling said interior space, said body of liquid constituting an optical lens whose anterior and posterior surfaces are bounded by said anterior and posterior portions of said sheath, respectively, thus defining the anterior and posterior surfaces of the lens; and

means in said body of liquid for producing within said interior space a concentration which is greater than the concentration of a liquid medium in association with which the lens is to be used, in consequence of which when said lens is in contact with such medium, the interior space will be kept filled with liquid under the influence of osmosis which causes the flow of liquid from the exterior of the sheath to the interior thereof whenever the interior space is less than full thereby maintaining the shape of the lens.

11. The lens of claim 10, wherein said transparent sheath has a thickness of less than 50 microns.

12. The lens of claim 10, wherein said body of liquid and said medium in association with which the lens is to be used comprises a physiological solution.

13. The lens of claim 12, wherein said physiological solution comprises a physiological saline solution.

14. The lens of claim 12, wherein said body of liquid further includes a physiologically active agent.

15. The lens of claim 10, wherein said semipermeable transparent sheath comprises a transparent sheet having a plurality of pores.

16. The lens of claim 15, wherein the diameter of said pores is less than 1,000 Angstroms.

17. The lens of claim 15, wherein said transparent sheet has a pore density between 100 and 10^9 pores per square cm.

18. The lens of claim 10, wherein said means for producing within said interior space a concentration which is greater than the concentration of a liquid medium in association with which the lens is to be used comprises a macromolecule.

19. The lens of claim 10, wherein said pores are sufficiently small to prevent the passage therethrough of said macromolecule.

20. The lens of claim 18, wherein said macromolecule is photostable.

21. The lens of claim 18, wherein said macromolecule is inert.

22. The lens of claim 18, wherein said macromolecule is selected from a group consisting of protein, carbohydrate, rubber or high polymer.

23. A contact lens, comprising a concave semipermeable transparent element adapted to seat on a human cornea to form therewith a closed interior space which contains a body of physiological solution produced by the wearer of the element, said body of liquid constituting an optical lens whose anterior surface is bounded by said element and whose posterior surface is bounded by the cornea of the wearer; and means carried by said element at its interior for producing within said interior space, when the same contains said body of liquid, a concentration which is greater than the concentration of the physiological solution produced by the wearer of the contact lens, in consequence of which when said element is worn on the cornea, said interior space will be kept filled with liquid under the influence of osmosis

which causes the flow of liquid from the exterior of said space to the interior thereof whenever said interior space is less than full.

24. The lens of claim 23, wherein said body of liquid further includes a physiologically active agent.

25. The lens of claim 23, wherein said transparent sheath has a thickness of less than 50 microns.

26. The lens of claim 23, wherein said means for producing within said interior space a concentration which is greater than the concentration of a liquid medium in association with which the lens is to be used comprises a macromolecule.

27. The lens of claim 26, wherein said macromolecule is photostable.

28. The lens of claim 26, wherein said macromolecule is inert.

29. The lens of claim 26, wherein said macromolecule is selected from a group consisting of proteins, carbohydrate, rubber or high polymer.

30. The lens of claim 26, wherein said pores are sufficiently small to prevent the passage therethrough of said macromolecule.

31. The lens of claim 23, wherein said semipermeable transparent element comprises a transparent sheet having a plurality of pores.

32. The lens of claim 31, wherein said transparent sheet has a pore density of between 100 and 10^9 pores per square cm.

33. The lens of claim 31, wherein the diameter of said pores is less than 1,000 Angstroms.

34. The lens of claim 33, wherein the diameter of said pores is between 50 and 1,000 Angstroms,

35. A method of locating an intraocular lens into an eye or its cornea comprising the steps of:

(a) providing a lens forming device comprising a dehydrated semipermeable transparent sheath having opposite anterior and posterior portions joined at their edges and forming a closed interior space between themselves and means within said interior space for producing within said interior space a concentration which is greater than the concentration of the physiological solution produced by the wearerof the lens,in consequence of which when the sheath is worn by the wearer, the sheath will hydrate such that said interior space will be kept filled with liquid under the influence of osmosis and thereby form a lens;

(b) making an incision for insertion of the dehydrated semipermeable sheath into the eye; and

(c) inserting the dehydrated semipermeable sheath into the eye whereby the dehydrated semipermeable sheath will contact the physiological solution produced by the wearer and hydrate to form a lens.

36. The method of claim 35 wherein the dehydrated semipermeable sheath is folded prior to inserting it into the eye and further comprising the step of unfolding said dehydrated semipermeable sheath after insertion into the eye.

37. The method of claim 36 wherein the incision is made only large enough to permit the insertion of the folded dehydrated semipermeable sheath.

FIG. 1

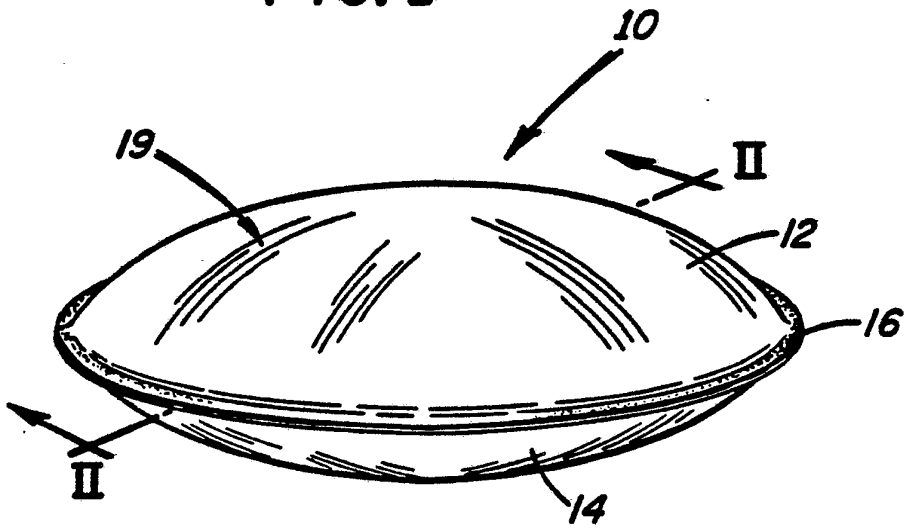
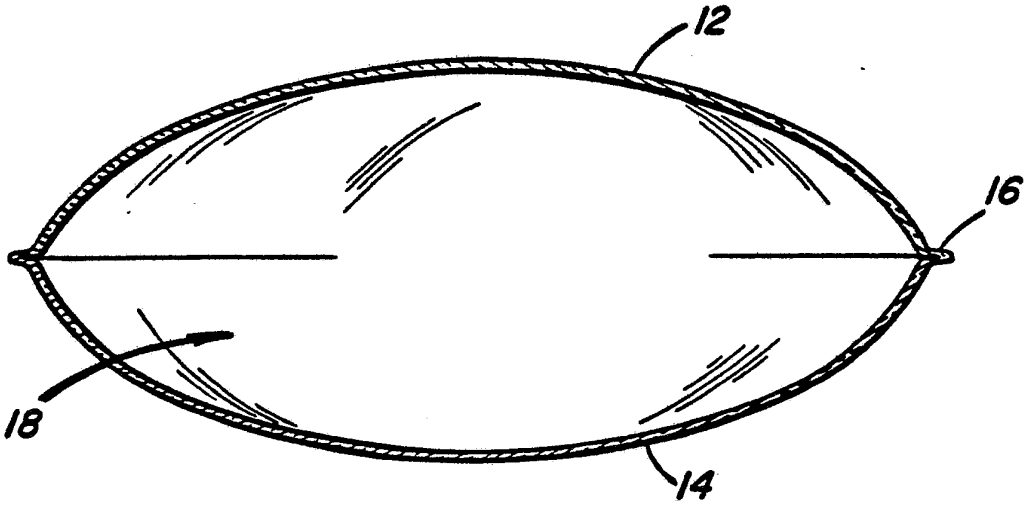


FIG. 2



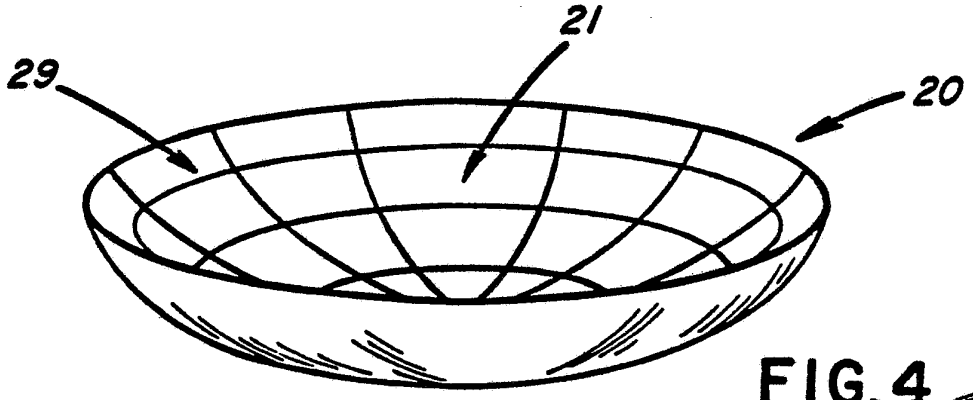


FIG. 4

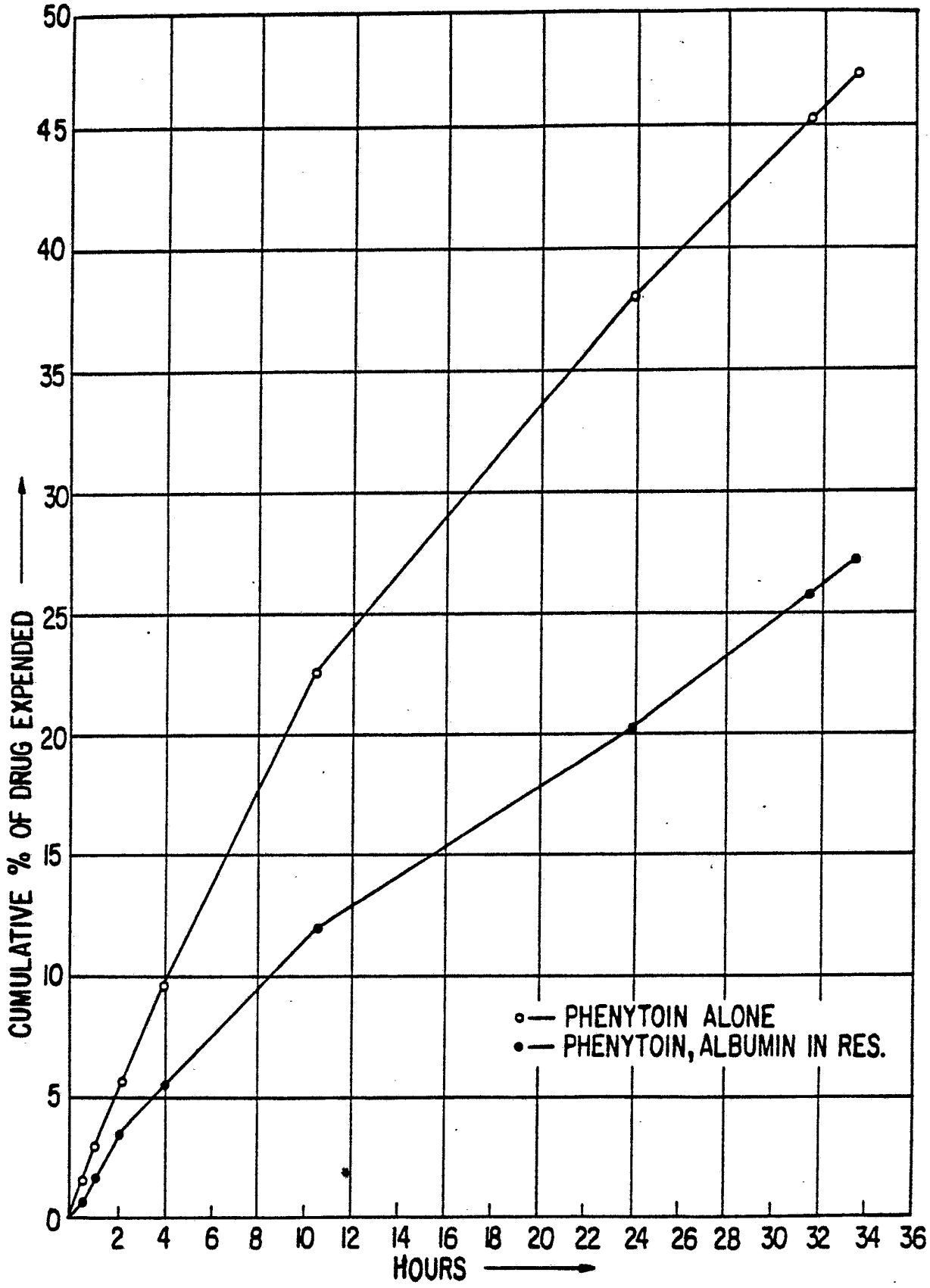
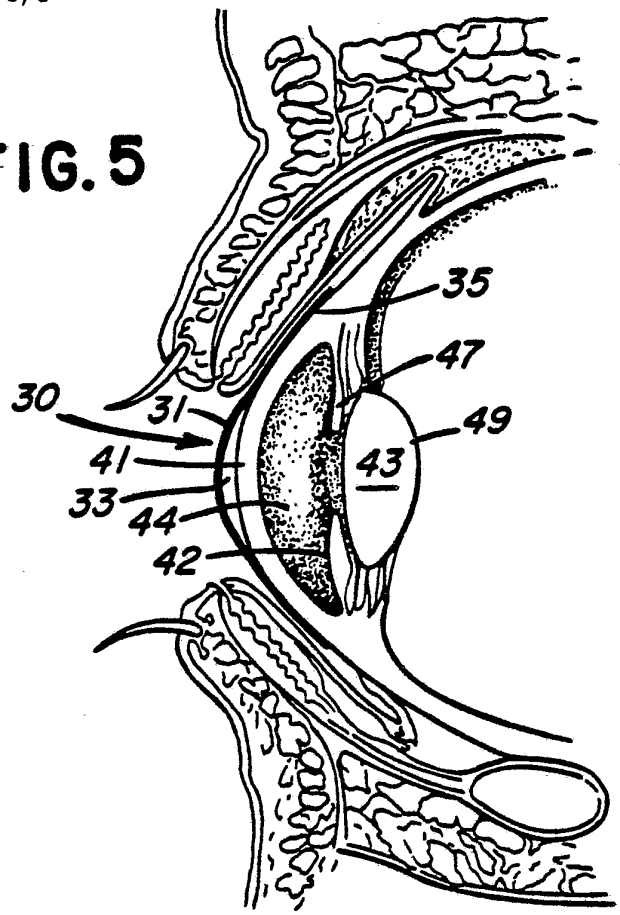


FIG. 3

FIG. 5



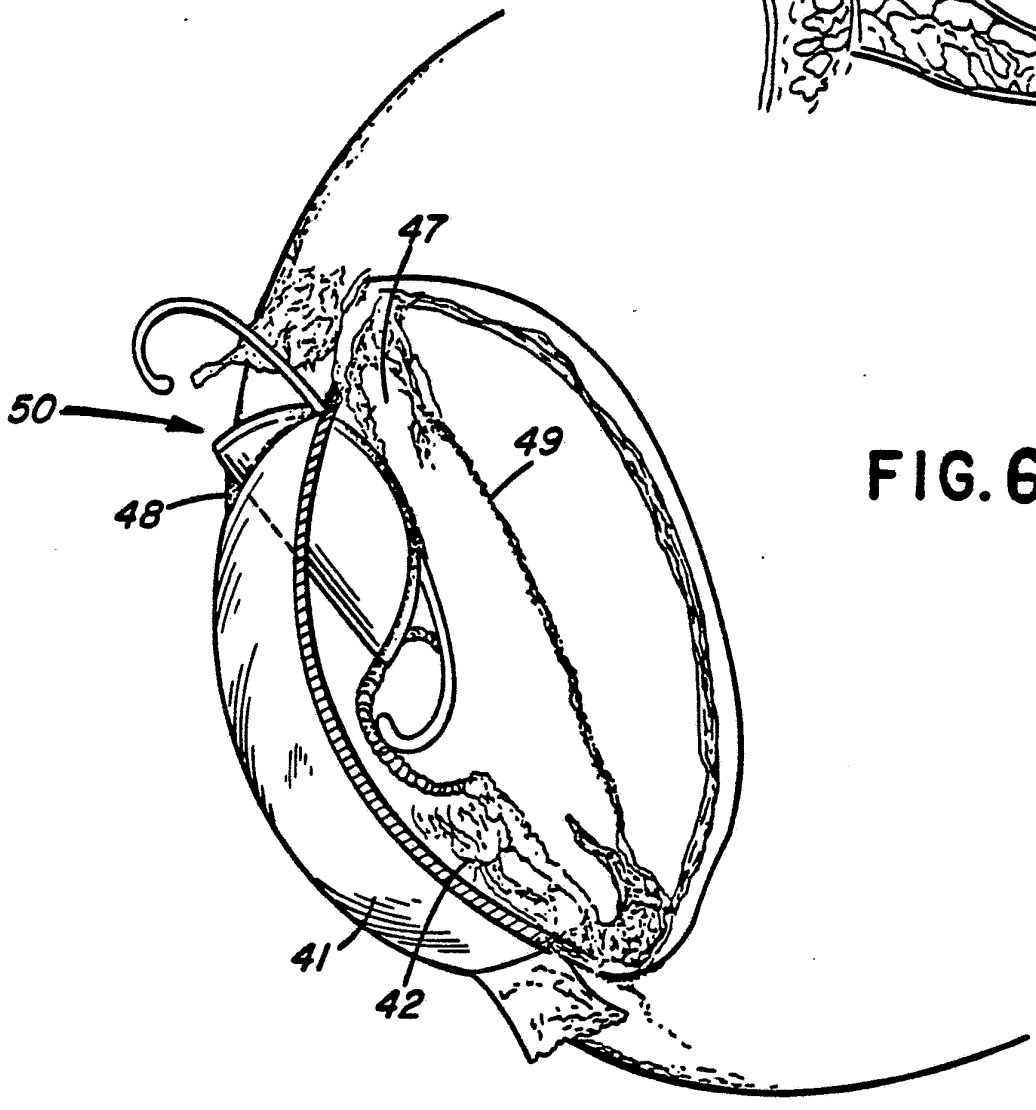


FIG. 6

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01531

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

US: 604/890;351/160;350/418; 3/13.
IPC3A61M 31/00;G03B 21/46; A61F 1/16.

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	604/890-900;424/18-25;128/127-132; 3/13 350/418,419, 351/160.R-162

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 2,952,023, Published 13 Sept. 1960, Rosen	1-37
Y	US, A, 3,641,237, Published 08 Feb. 1972, Gould et al.	1-37
Y	US, A, 3,854,480, Published 17 Dec. 1974, Zaffaroni	1-37
Y	US, A, 3,952,741, Published 27 Apr. 1976, Baker	1-37
Y	US, A, 3,967,618, Published 06 July 1976, Zaffaroni	1-37
Y	US, A, 3,995,631, Published 07 Dec 1976	1-37
Y	US, A, 4,016,880, Published 12 Apr. 1977, Theeuwes et al.	1-37
Y	US, A, 4,163,608, Published 07 Aug. 1979, Neefe	1-37

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
22 Nov. 1983	02 DEC 1983
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	T. J. Wallen

BENJAMIN R. PADGETT
EXAMINER
GROUP ART UNIT 223

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US, A, 4,235,236, Published 25 Nov. 1980, Theeuwes	1-37
Y	US, A, 4,326,525, Published 27 Apr. 1982, Swanson et al.	1-37
Y	US, A, 4,340,054, Published 20 July 1982, Micheals	1-37
X	CA, A, 990,164, Published June 1976, Ness	1-37
Y	US, A, 4,174,156, Published 13 Nov. 1979, Glorienx	1-37 1-37

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

See PCT/ISA/206

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☒ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.