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FILAMENT SYSTEM FOR DELIVERING
A MEDICAMENT AND METHOD

BACKGROUND OF THE INVENTION

The present invention relates to delivery of a medicament to the intestine. More particularly, the present invention relates to a system and method for delivering a medicament to the intestine which delivers that medicament to an animal for an extended period of time.

There have been a number of attempts to improve systems for delivering a medicament to the intestine of an animal. The benefits of such a system are summarized, for instance, in U.S. Patent Nos. 3,901,232, 4,627,851, and 4,642,230. These same references characterize the disadvantages of prior attempts to provide such systems, and the following summary of the pharmacokinetics of such systems and their disadvantages will provide an illustration of the motivation for the present invention.

Although the primary function of the small intestine is absorption, making that organ an ideal candidate for administration of a therapeutic agent, many factors combine to limit the use of that mode of delivery. For instance, the pH of the duodenal portion of the small intestine is about 4 to 5, but pH becomes more alkaline progressively farther down the intestine, and the effect of pH on the bioavailability of many medicaments is well documented. The flora of the gastrointestinal tract may inactivate certain medicaments or otherwise reduce their absorption or bioavailability, and digestive enzymes produced in the intestinal mucosa have the same effect. Further, although passage through the small intestine is slow compared to

passage through the mouth or stomach, an orally ingested medicament does eventually pass out of the intestine, making administration of the medicament over a sustained period of time problematical.

It is these problems, particularly the latter, with which the present invention is concerned. Several prior art patents describe systems which purport to address the problems of passage through the gastrointestinal tract and administration of a medicament over extended periods, but in less than satisfactory fashion. For instance, U.S. Patent Nos. 3,844,285 and 4,623,345 describe devices enclosing a medicament which, after ingestion, open to release the medicament, the open container acting to retain the device in the gastrointestinal tract by physical engagement of the mucosa. Such devices are retained in the gastrointestinal tract even after all the medicament has been released. As described in the above-referenced U.S. Patent No. 4,642,230, it is also known to use weights to retain the device in which the medicament is contained within the gastrointestinal tract. However, the weight is generally a heavy metal and, even if coated to prevent oxidation, sooner or later, the ingestion of heavy metals can have deleterious effects. Neither such consequence is generally considered acceptable in the case of human patients.

Another problem relating to absorption through the intestine is that it is often necessary to coat the medicament for passage through the stomach. Such "enteric" coatings are of particular use with medicaments which are destroyed or inactivated by the acidic contents of the stomach or which cause gastric irritation. However, many enteric-coated medicaments resist dissolution in the intestine as well as the stomach such that comparatively little of the medicament may be absorbed before it is passed. Other problems with such medicaments are characterized in L.Z. Benet and L.B. Sheiner, "Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination," in A.G. Gilman, et al. (Eds.),

Goodman & Gilman's The Pharmacological Basis of Therapeutics (7th Ed.), New York: MacMillan Publishing Co., pp. 3-34 (1985).

It is, therefore, an object of the present invention to provide a system and method for delivery of a medicament in the intestine which overcomes the above-described disadvantages and limitations of prior known systems. This object is achieved by providing a coiled elongate filament having a medicament contained therein, the composition of the filament and the medicament being selected so as to allow the filament to uncoil and release the medicament in the intestine after ingestion by an animal, and means integral with the filament for retarding the passage of the filament through the intestine after the filament uncoils. The passage retarding means may take the form of a bioadhesive either incorporated in the material comprising the filament or coating a portion of the filament. The system optionally includes a capsule in which the coiled filament is contained for preventing the uncoiling of the filament after ingestion and until the capsule reaches the intestine.

The present invention also provides a method of delivering a medicament to the intestine which comprises the steps of ingesting a coiled filament having a medicament contained therein to introduce the coiled filament into the intestine and then uncoiling the coiled filament in the intestine. The method additionally comprises retarding the passage of the uncoiled filament through the intestine to deliver the medicament over an extended period of time. The method may optionally include the step of encapsulating the coiled filament with an enteric material which dissolves, decomposes, disperses, or otherwise disintegrates in the intestine to allow the coiled filament contained therein to uncoil. Both the method and the delivery system of the present invention are better understood by reference to the following description of a presently preferred embodiment thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is schematic representation of a filament of the type contemplated for use with the present invention.

Figure 2 is a schematic representation of the filament of Fig. 1 after that filament has been coiled and encapsulated for ingestion by an animal.

Figure 3 is a schematic representation of the disintegration of the capsule of Fig. 2 in the intestine of the animal which ingested the capsule.

Figure 4 is a schematic representation of an animal with which the present invention may be advantageously utilized which provides, by the various lines extending therefrom to the other figures, a point of reference for discussion of the method of the present invention.

Figure 5 is a schematic representation of the uncoiled filament of Fig. 2 with reference to the intestine of the animal of Fig. 4.

Figure 6 is schematic representation (not to scale) of an isolated section of the intestine of the animal of Fig. 4 having the uncoiled filament of Fig. 5 contained therein.

DETAILED DESCRIPTION OF THE INVENTION

Referring to the figures, there is shown a schematic representation of a filament system for delivering a medicament to the intestine at reference number 10. As shown in Fig. 2 and indicated by the arrow 12 from Fig. 2 to the mouth 13 of patient 14 shown in Fig. 4, filament 10 is tightly coiled for ingestion by patient 14. After ingestion, the coiled filament 10 passes through the esophagus 16 of patient 14, through the stomach 18, and into the intestine, specifically the small intestine 20. As shown in Fig. 3 and indicated by arrow 22, once filament 10 reaches the small intestine 20, the filament 10 begins to uncoil, at which point the medicament contained in filament 10 is available for release from filament 10.

The material comprising filament 10, and the medicament contained in filament 10, are selected so as to allow the filament 10 to uncoil and release the medicament in the

intestine after ingestion by patient 14. The material comprising filament 10 may be any one, or a mixture, of many materials into which the medicament is incorporated for release over an extended period of time.

For purposes of convenience, materials which are appropriate for use as the filament 10 of the present invention are categorized as being water insoluble, semipermeable, enteric, or bioerodible depending upon the manner in which the medicament is released from the material in the intestine. For instance, a material having a medicament dispersed therein from which the medicament migrates without decomposition, dispersion, disintegration, or dissolution thereof is considered either water insoluble or semipermeable. Materials through which aqueous solutions penetrate to dissolve the medicament and cause the medicament to be dispersed therefrom are considered semipermeable. Enteric materials are those which do not dissolve, disperse, decompose, or disintegrate in the stomach during the time the filament 10 passes through the stomach as defined in column 6, beginning at line 5, of the above-noted U.S. Patent No. 4,627,851. Materials which dissolve, disperse, decompose, or disintegrate in the intestine to release the medicament are considered bioerodible; a more complete explanation of that term appears throughout U.S. Patent No. 3,901,232 and need not be repeated here. These categories are not mutually exclusive; many materials appropriate for use as the material comprising filament 10 may be both, for instance, bioerodible and semipermeable such as certain polyurethanes which can be formulated in uncrosslinked, partially crosslinked, or highly crosslinked form, or water insoluble and enteric, such as hydroxypropyl methylcellulose phthalate.

Many such materials are natural products such as keratin, salol, triglycerides, fatty acids, latexes and locust bean gum; derivatives of natural products such as modified collagen and formalized or regenerated proteins;

cellulose derivatives such as ethyl cellulose and cellulose acetate derivatives, especially cellulose acetate phthalates; or polymers such as polylactic acid, polyvinylpyrrolidone, polyvinyl acetates, and polyethylene oxide. It is particularly preferred that filament 10 be comprised of a material which is pH sensitive, e.g., which is stable in acid but which dissolves, disperses, decomposes, or otherwise disintegrates at a pH greater than about 5, and therefore may be utilized to achieve the delivery of the medicament to a specific location in the intestine due to the progressively increasing alkalinity of the intestine. For instance, certain polyvinyl acetate phthalates are available which are capable of releasing the medicament at a pH of 4.5 - 5.0, e.g., in the area of the intestine 20 immediately below the pyloric valve 24. A variety of pH sensitive polyacrylic acids are available, for instance those sold under the brand name EUDRAGITS (Rohm-Tech), which are capable of releasing the medicament at a pH ranging from about 5.5 (L-100-55) up to as high as 7.0 (S-100). Cellulose acetate trimellitate is also capable of releasing the medicament at a pH greater than about 5.5. When it is desired to deliver the medicament even farther down the intestine, a material such as shellac, which dissolves at a pH greater than about 7.4, is utilized. Other pH sensitive materials include hydroxypropyl methyl cellulose phthalate and cellulose acetate phthalate.

Many other water insoluble, semipermeable, enteric or bioerodible materials which are appropriate for use as the material comprising the filament 10 are known to those skilled in the art. They include, but are not limited to, polyethylene, polybutene and other polyalkenes; paraffin, natural, and microcrystalline waxes; hydrocarbon resins; mono- and diglycerides; cellulose derivatives such as cellulose acetyl, diacetyl and triacetyl phthalate, cellulose ester and ether phthalate, methylcellulose phthalate, hydroxypropyl cellulose phthalate, cellulose acetate and hydroxypropyl methylcellulose hexahydroxyphtha-

late, cellulose acylate, and cellulose di- and triacylate; salts of cellulose derivatives such as the sodium, calcium, alkali or alkaline earth salt of cellulose acetate phthalate and the ammonium salt of hydroxypropyl methylcellulose phthalate; polymers of acrylic acid and acrylic acid derivatives such as polymethacrylate esters, polyesters of acrylic and methacrylic acid, uncrosslinked hydroxyalkyl acrylates and methacrylates and other α, β -ethylenically unsaturated mono- and dicarboxylic acids and/or anhydrides; polyglycolic acid and derivatives of polyethylene glycol; polymers and co-polymers such as ethylene-vinyl acetate polymer and partial or completely hydrolyzed ethylene-vinyl acetate co-polymers, vinylidene chloride/acrylonitrile polymer, highly plasticized polyvinyl chloride, homo- and co-polymers of polyvinyl acetate, polyvinyl alkyl ethers, polyvinyl fluoride, silicone polycarbonates, silicone elastomers, polymeric epoxides, co-polymers of an alkylene oxide and alkyl glycidyl ether, derivatives of polystyrene such as poly(-sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride) and the so-called "block" polymers, polyimides, polybenzimidazoles, selectively permeable polymers formed by coprecipitation of a polycation and a polyanion as described in U.S. Patent Nos. 3,276,589, 3,541,006, 3,541,055, and 3,546,142, poly(anhydride) polymers as described in U.S. Patent Nos. 2,073,799, 2,668,162, and 2,676,945, and in Chapter 6 of Stille, J.K., Introduction to Polymer Chemistry, New York: John Wiley Publishing (1962), polyesters as described in U.S. Patent Nos. 2,668,162, 2,676,945, 2,703,316, and 3,297,033 and in 36 Industrial and Engineering Chemistry 223-228 (1964) and 75 Macromol. Chem. 211-214 (1964), co-polymers of acrylamide and methacrylamide including up to about 40% by weight of a cross-linker such as N-methylene bisacrylamide or N,N-dimethylurea, and polyethyleneimine; and materials such as starch, fatty alcohols, calcium alginate, calcium caseinate, calcium pectate, cross-linked gelatin of the type having a cross-linker that is reactive with the

hydroxyl, carboxyl, or amino groups of the gelatin molecule as described in 5 J. Polymer Science, Part A-1 (1967), 54 J. Polymer Science 321-335 (1961) and 41 Adv. Protein Chem., "Cross Linkage in Protein Chemistry", New York: Academic Press (1961), and the materials and mixtures listed at line 28 of column 6 of U.S. Patent No. 4,627,851, noted above; and proteins and hydrocolloids of animal and plant origin such as elastin, keratin, fibrin, algin, karaya, pectin, carrageenin, chitin, heparin, and locust bean gum.

The term "medicament" as used herein refers to any pharmacological agent which is advantageously delivered in the intestine, is capable of being dispersed or otherwise contained in the matrix of the material comprising filament 10, and which is compatible with the material comprising filament 10. The term "contained" is used in its general sense to describe the physical relationship between the material comprising filament 10 and the medicament in the case of materials into which the medicament is absorbed, materials in which the medicament is impregnated, materials in which the medicament is dispersed in the matrix comprising the material, materials in which the medicament is dissolved, and materials which surround, coat, and/or or encapsulate the medicament. In other words, the term contemplates any arrangement by which the material is capable of serving as a reservoir for the medicament and still be capable of being shaped into a filament.

Appropriate medicaments for use in connection with the present invention include, but are not limited to, antibiotics, antioxidants, biocides, hormones, steroids, fungicides, nutritional supplements, vitamins, co-factors, anti-inflammatories, decongestants, antivirals, analgesics-antipyretics, anesthetics, anti-cancer and/or anti-tumor agents, immunostimulants, immunodepressants, monoclonal antibodies and/or other immunological agents, muscle relaxants, central nervous system stimulants or depressants, enzymes, detoxicants, antihistamines, and anti-metabolites. Two or more compatible and/or synergistic medicaments may

also be contained in the same filament or in two or more filaments coiled together for ingestion or contained in the same capsule 28 as discussed below. The compounding of these medicaments, and their therapeutically effective dosage levels, are matters known in the art and, insofar as those matters are not considered part of the present invention, are not addressed in detail here.

Filament 10 is made by any number of methods known in the art for forming materials such as those listed above for containing the medicament. For instance, filament 10 can be made with a centrifugal extrusion device or by co-extrusion, both processes being known in the art, hence there is no need to describe them further here. Another process appropriate for manufacturing filament 10 is the process, known as an interfacial polymerization process, for making nylon. Production of filament 10 by extrusion processes also makes possible the changing of the amount of medicament contained in the filament 10, e.g., the concentration of the medicament, along the length of the filament, thereby allowing the control of the dosage delivered in the intestine for topical application or to maximize the bioavailability of the medicament. Extrusion methods also enable the containment of a first medicament in one portion of the filament and one or more additional medicaments, or alternate formulations of the same medicament, in other portions of the filament for the same purpose. Filament 10 may contain two or more incompatible medicaments in spatially distinct portions thereof. Two or more compatible medicaments may be contained in the matrix of the material comprising filament 10 in equal concentrations, or in overlapping, changing concentrations (e.g., a first medicament in increasing concentration from one end of filament 10 to the other and a second medicament in decreasing concentration from that end to the other). In the event the medicaments are not compatible, one or both can also be encapsulated in the material with an encapsulant

which does not alter their release characteristics from filament 10.

As shown in Figs. 2 and 3, the coiled filament 10 may be contained in a capsule 26 for ingestion. Capsule 28 is optional depending upon the composition of the filament 10. For instance, if the material comprising filament 10 is a semipermeable or bioerodible, it is advantageous to encapsulate such a filament to prevent uncoiling, and the release of the medicament, until the capsule 28, having the filament 10 coiled therein, reaches the intestine. Two or more filaments, each comprised of different materials or containing different medicaments, may be encapsulated in the same capsule 28.

To accomplish that function, capsule 28 is comprised of an enteric material as defined above or a pH sensitive material which dissolves, disperses, decomposes, or otherwise disintegrates at the more alkaline (as compared to the pH of the stomach) pH of the intestine (note that many pH sensitive materials are "enteric materials"). A commercially available, two-part gelatin capsule is an example of such a material and is used to advantage. The method by which the capsule 28 is made depends upon the nature of the material comprising the capsule and can be accomplished in a number of commercially practiced methods. One such method, pan coating, is described at column 10, line 1 of the above-noted U.S. Patent No. 4,627,851. Other methods are summarized in, for instance, U.S. Patent No. 4,578,075. Because such methods are known in the art, no further description of them is necessary here.

Referring now to Fig. 5, there is shown a schematic representation of filament 10 after uncoiling in the intestine, the arrow 30 providing the point of reference to the intestine 20 of the patient 14. Although present while coiled (see Fig. 3), there is clearly visible in Fig. 5 a means integral with filament 10 for retarding the passage of filament 10 through intestine 20. This passage retarding means may take the form of a bioadhesive "head" 32 at one

end of filament 10 or is part of the filament 10 itself in the sense that many of the materials listed above as being appropriate for use as the material comprising filament 10 are tacky. In the case of filaments comprised of such materials, once filament 10 is uncoiled in the intestine 20, the filament 10 is at once both the container or delivery system for the medicament and the passage retarding means. In another embodiment, a bioadhesive is coated along the length of filament 10 by spraying or dipping filament 10 in a solution of the bioadhesive and then drying the coated filament before coiling or encapsulating. In describing this latter embodiment, one reason why the capsule 28 is optional for practicing the present invention is made clear: one function of capsule 28 is to prevent filament 10 from uncoiling until the capsule 28, having the filament 10 coiled therein, reaches the intestine 20. In the case of a filament 10 coated with bioadhesive, the filament 10 need only be coiled before drying (or when partially dry), or dried and then moistened slightly with water or other aqueous solution, to form a layer which effectively prevents filament 10 from uncoiling until reaching the intestine 20.

The bioadhesive may be selected from a number of known, synthetic, natural-occurring, or modified naturally-occurring substances which exhibit a measure of stickiness, or "tack". The term "bioadhesive" does not require that an adhesive be naturally-occurring; instead, that term refers to an adhesive which is bio-compatible, e.g., non-toxic and/or inert in the intended application. The adhesive must also be compatible with the material comprising filament 10 as well as the medicament contained therein. Substances appropriate for use as a bioadhesive include, but are not limited to, calcium polycarbophil, polymers of acrylic acid and its derivatives, gelatin, carboxymethyl and hydroxypropyl methyl cellulose, and other cellulose derivatives, karaya, tragacanth, locust bean and other synthetic and naturally occurring gums, algin, chitosan, starches, pectins, and naturally-occurring resins

such as balsam, mastic, and sandarac. Various mixtures of these substances are also utilized to advantage.

As shown schematically in Fig. 6, the passage retarding means, in the form of head 32, functions by adhering to the intestinal musosa, the remainder, or "tail", of the uncoiled filament 10 extending down intestine 20. A portion of the intestine 20 is shown in Fig. 6, with the arrow 34 providing a point of reference to the patient 14 shown in Fig. 4, and provides an illustration of how filament 10 is utilized to deliver a medicament to a specific location in the intestine 20. As noted above, the pH of the contents of the small intestine becomes increasingly more alkaline as the contents move through the intestine, e.g., in the direction of arrow 36 in Fig. 6. When filament 10 is comprised of a pH-sensitive material such as the cellulose acetate trimellitate available from Eastman-Kodak or the polyacrylic acids available from Rohm-Tech under the brand name "EUDRAGITS" (catalog/stock No. L-100-55), the medicament is released in the portion of the intestine 20 in which the pH is greater than about 5.5. The portion of filament 10 having the head 32 integral therewith initially adheres to the intestinal mucosa in an area of the intestine in which the pH is less than 5.5 to retard the passage of filament 10 through the intestine with the tail of filament 10 extending downwardly through intestine 20. In this manner, the period of time during which the medicament is delivered to the patient 14, or to the specific portion of the intestine 20 in which the pH is greater than 5.5, is extended because the reservoir of available medicament is continually replenished as the passage of the tail of filament 10 through the portion of intestine 20 in which the pH is less than 5.5 is slowed by the head 32. Filament 10 also functions to deliver larger total dosages of the medicament than can be achieved using previously known systems, if desired, because the passage retarding means retains the filament in the intestine for long periods of time.

Dosage levels and the location to which the medicament is delivered are controlled by manipulating the amount of medicament contained within filament 10 (e.g., the size of the reservoir), the length of filament 10, the permeability or bioerodibility of the material comprising filament 10, and the pH sensitivity of that material. Additional control is achieved by use of a capsule 28 and the nature of the substance comprising that capsule. For instance, if it is desired to deliver a medicament effective against ulcerative lesions located immediately below the pyloric valve 24 of patient 14, and high local dosage levels are indicated, the filament 10 is formulated from a material into which high concentrations of that medicament can be dispersed and which releases the medicament at a pH just slightly more alkaline than that of the stomach contents, and the filament is made fairly short, e.g., a few inches in length. If low, relatively constant levels over long periods of time are desired and the medicament is poorly absorbed at acidic pH, or hydrolyzed or denatured in acid, filament 10 is comprised of a semipermeable material having a relatively low concentration of the medicament dispersed therein and is several feet in length. The long filament is ingested in a capsule comprised of a pH sensitive substance which disperses, disintegrates, decomposes, or dissolves at a pH of, for instance, 6.8 so that the coiled, encapsulated filament does not even begin to uncoil until the capsule is well down the intestine. Once uncoiled, the long length of the filament provides a reservoir large enough to contain a fairly large total amount of the medicament so that the filament can be expected to contain enough medicament to maintain effective dosage levels for a long time, but the relatively low concentration of the medicament in the filament decreases the absorption rate therefrom to maintain the desired low dosage levels. The permeability of the filament can be changed, for instance by using a more highly cross-linked polymer, to provide an even greater degree of control over dosage levels.

Although described in terms of the above embodiments of the invention, changes can be made to those embodiments without departing from the manner in which the system functions to achieve the desired results. Such changes are included within the spirit of the invention and are intended to fall within the scope of the following claims.

What is claimed is:

1. A system for delivery of a medicament to the intestine comprising a coiled elongate filament having a medicament contained therein, the composition of said filament and said medicament being selected so as to allow said filament to uncoil and release said medicament in the intestine after ingestion of said coiled filament by an animal, and a bioadhesive integral with said filament for retarding the passage of said filament through the intestine after said filament uncoils.

2. The delivery system of claim 1 wherein said filament is comprised of a water insoluble, semipermeable, enteric, or bioerodible material having said medicament dispersed in the matrix thereof.

3. The delivery system of claim 1 additionally comprising a capsule in which said coiled filament is contained for preventing the uncoiling of said filament until said capsule, having said coiled filament contained therein, reaches the intestine.

4. The delivery system of claim 3 wherein said capsule is comprised of an enteric material.

5. The delivery system of claim 1 wherein said bioadhesive is selected from the group consisting of calcium polycarbophil, gelatin, polymers of acrylic acid and derivatives thereof, carboxymethyl and hydroxypropyl methyl cellulose and other cellulose derivatives, natural and synthetic gums, algin, chitosan, starches, pectins, and naturally-occurring resins, and mixtures thereof.

6. The delivery system of claim 1 wherein said bioadhesive is integral with only one end of said filament for adhering the end of the filament to the intestinal mucosa of the animal, the other end of said filament uncoiling to extend down the intestine of the animal.

7. A delivery system according to any one of claims 1 to 5 for use in a method of delivering a medicament to an intestine, which method comprises ingesting a coiled

filament having a medicament contained therein to introduce the coiled filament into the intestine, uncoiling the coiled filament in the intestine, the material comprising the coiled filament and the medicament being selected so that, as the filament uncoils, the medicament is released therefrom, and retarding the passage of the uncoiled filament through the intestine, thereby causing the medicament to be released in the intestine over an extended period of time.

8. A method of delivering a medicament to the intestine comprising the steps of:

ingesting a coiled filament having a medicament contained therein to introduce the coiled filament into the intestine;

uncoiling the coiled filament in the intestine, the material comprising the coiled filament and the medicament being selected so that, as the filament uncoils, the medicament is released therefrom; and

retarding the passage of the uncoiled filament through the intestine, thereby causing the medicament to be released in the intestine over an extended period of time.

9. The method of claim 8 additionally comprising preventing the uncoiling of the filament until the filament reaches the intestine.

10. The method of claim 8 additionally comprising encapsulating the coiled filament in an enteric material to prevent the uncoiling of the filament until the capsule reaches the intestine.

11. The method of claim 8 wherein the medicament is released from the filament at a specific location in the intestine, the material comprising the filament being selected so as to release the medicament therefrom when exposed to a selected pH, the selected pH corresponding to the pH of the specific location in the intestine at which it is desired to release the medicament.

12. The method of claim 11 wherein the reservoir of medicament to be released at the specific location in the intestine is continually replenished by the retarded passage of the uncoiled filament through the intestine.

13. The method of claim 8 wherein passage of the uncoiled filament is retarded by adhering the uncoiled filament to the wall of the intestine.

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FIGURE 1

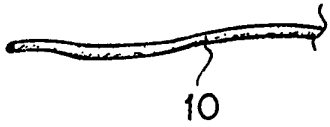


FIGURE 2

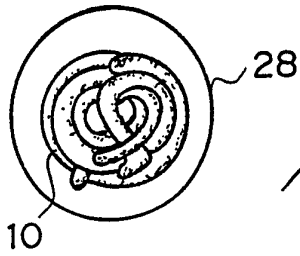


FIGURE 4

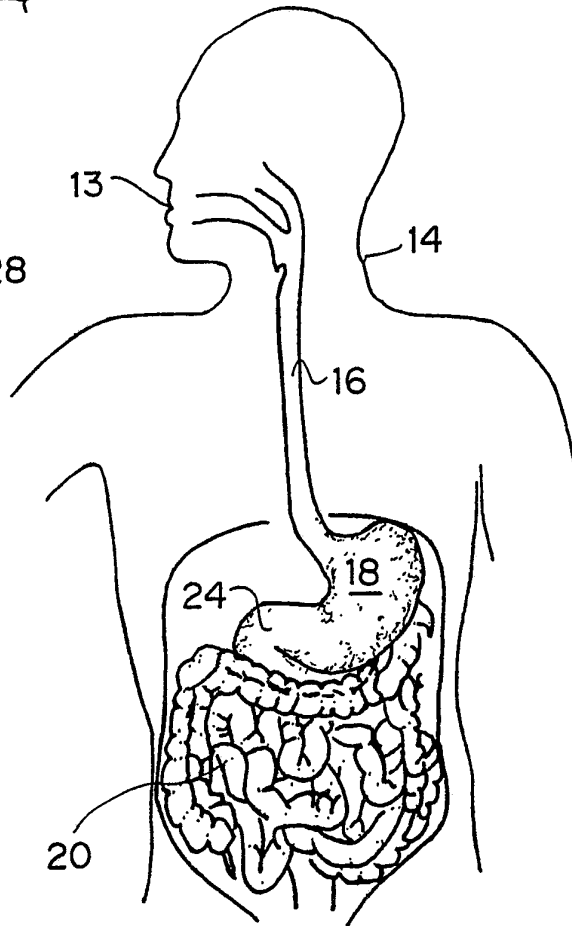


FIGURE 5

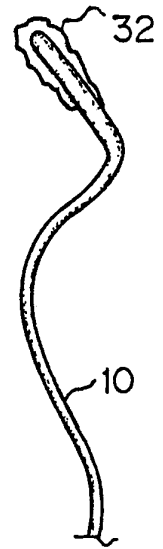


FIGURE 3

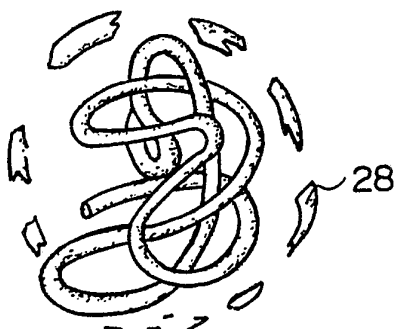
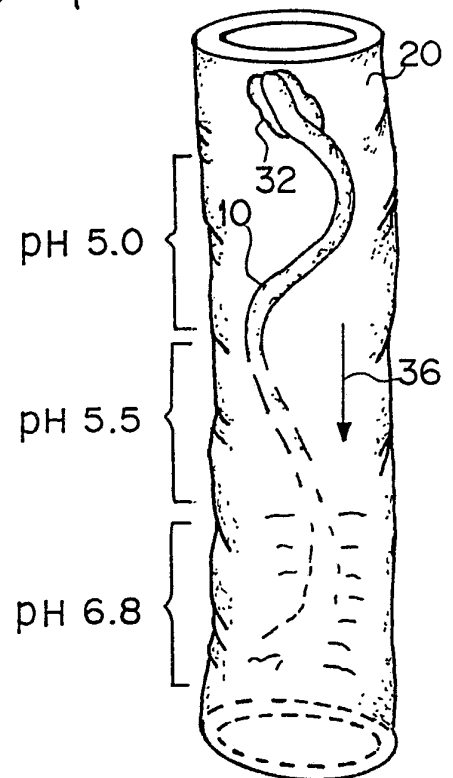


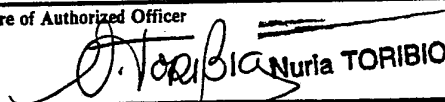
FIGURE 6



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/03595

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 9/22 A 61 K 9/70				
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
Int.C1.5	A 61 K			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹				
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
A	US,A,4878905 (K.G. BLASS) 7 November 1989, see claims; figures; column 2, lines 21-24,37-43,48-53; column 3, lines 28-33 ---	1,3,7		
A	US,A,3625214 (T. HIGUCHI) 7 December 1971, see claims 1,3,9,13; column 2, lines 21-26; column 3, lines 12-30,55-60 ---	1-2,7		
A	EP,A,0253554 (PFIZER) 20 January 1988, see claims 1-9; page 4, lines 1-16,32-35; page 6, lines 14-16,41-42 -----	1-2,7		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> ¹⁰ Special categories of cited documents : "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			¹⁰ Special categories of cited documents : "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
¹⁰ Special categories of cited documents : "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	Date of Mailing of this International Search Report			
28-08-1991	08. 10. 91			
International Searching Authority	Signature of Authorized Officer			
EUROPEAN PATENT OFFICE	 Nuria TORIBIO			

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

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 8-13 because they relate to subject matter not required to be searched by this Authority, namely:
see PCT-Rule 39.1(iv)
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, specifically:
3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

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.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9103595
SA 47940

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/09/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4878905	07-11-89	None	
US-A- 3625214	07-12-71	None	
EP-A- 0253554	20-01-88	AU-B- 574955	14-07-88
		AU-A- 7562687	21-01-88
		JP-A- 63023815	01-02-88