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(54) Title: A NOVEL BIO-ERODIBLE INSERT FOR OPHTHALMIC APPLICATIONS AND A PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention provides a novel bio-erodible ophthalmic insert a process for the preparation of the said bio-erodible insert. In the said process collagen is treated with organic polar solvents, hydrophilic polymers and therapeutically active substances under controlled conditions. The resulting solution is air dried in a dust free chamber to make collagen film. This film is cut into shape to obtain insert, which is subjected to cross-linking with UV irradiation followed by conventional sterilization. The prepared inserts are very effective for temporary punctal occlusion in various corneal conditions and are very effective to treat dry eye syndrome due to occupational conditions.

"A NOVEL BIO-ERODIBLE INSERT FOR OPHTHALMIC APPLICATIONS AND A PROCESS FOR THE PREPARATION THEREOF"

FIELD OF INVENTION:

The present invention relates to a novel bio-erodible insert for ophthalmic applications and a process for the preparation thereof. More particularly the present invention provides a bio-erodible ophthalmic insert, which is biocompatible, having viscoelastic properties at physiological pH (4.5 - 9.0), for the medical treatment of eye diseases. The process of the present invention is envisaged to have enormous potential in ophthalmologic applications, like a protective insert to obstruct the tear drainage to treat dry eye syndrome and for the dry eye component of any of the ocular surface diseases (OSD) like conjunctivitis, corneal ulcer, pterygium, blepharitis, keratitis, red lid margins, recurrent chalazions, recurrent corneal erosions, filamentary keratitis and other external eye diseases.

BACKGROUND OF THE INVENTION:

A good ophthalmic insert should be biologically inert, soft, bio-erodible, viscoelastic, should not undergo changes during sterilization, and after exposure to therapeutic agents when used as an ophthalmic insert to treat dry eyes and other ocular surface diseases (OSD). It should be able to prevent infections from air borne bacteria, help in healing of wounds. Additionally it should be bio-erodible, biocompatible, viscoelastic than the normally used ophthalmic insert.

Macro Fabrizio et al (Advanced Drug Delivery Reviews 16, 95 -106, 1998) reported the use of different types of ocular inserts like Soluble Ophthalmic Drug Insert (SODI), which is a polymeric oval film that can be introduced in the upper conjuctival sac for drug delivery. OCUSERT® (Pilocarpine ocular therapeutic system) developed by Alza Corporation is made of ethylene vinyl acetate, which is an elliptical insert, gets twisted and results in discomfort and irritation in the eyes. OCUFIT® developed by Escalon Ophthalmics Inc. (Skillman, NS) is a rod shaped silicone elastomer and Lacrisert is rod shaped insert made of cellulose. New Ophthalmic Drug Delivery Systems (NODS) are made up of poly (vinyl

alcohol). The major drawback with these inserts is they are not biocompatible and bioerodible and are lost without being noticed.

Ophthalmic inserts are in use to treat dry eyes syndrome, but they are made of synthetic polymers. Bruno Fayet et al (American academy of Ophthalmology, 8, 2000) used silicone punctal plugs for the treatment of dry eye syndrome, although these polymeric plugs are widely used to provide reversible occlusion of the lacrimal drainage for treating the symptoms of dry eyes, the problem associated with these is the absence of biocompatibility which is likely to generate various physiological complications. The plug applies a degree of mechanical stress on the canalicular mucosa and results in corneal or conjuctival aberration by the exposed portion of a large plug. The major limitation with these plugs is plug extrusion and complications like instability of the small plugs usually resulting in loss of the prosthesis and intra canalicular migration of the plug.

Freeman et al (U.S Patent number 3,949,750) disclosed a punctal plug having a solid cone shaped tip or barb portion, a disc or dome shaped head portion and a cylindrical shaft, like a body or neck joining the barb and head portions, however the major drawback with these plugs is one end of the plug always sticks out of the lacrimal punctum, that will create irritation on the corneal surface and create foreign body sensation in the eye.

Herrick et al (U.S. Patent number 4,660,546) disclosed intra canicular implants having a shaft like body for being fully inserted into patients canaliculus, however the major limitations with these implants is they may increase the size of the lacrimal punctum on a long term use, as it has a larger diameter than the lacrimal punctum.

Margarita cologne (Survey of Ophthalmology, 45, 2, 2001) reported the use of silicone punctal plugs to treat dry eye syndrome, the major drawback of these plugs is the formation of pyogenic granuloma due to plug extrusion, this may lead to rupture of punctal ring, pruritis and discomfort.

The limitations associated with polymeric punctal plugs are the lack of biocompatibility and viscoelasticity, thereby rendering the materials unsuitable for ophthalmic applications. Silicone plugs are permanent inserts and are not bioerodible thereby the plugs are to be extruded out of the canaliculus that would further damage the punctum and lead to granuloma.

Yet other limitations associated with the polymeric punctal plugs is the discomfort caused by the exposed portion of the silicone plugs touching the corneal surface resulting in severe irritation and discomfort during blinking of the eye, thereby rendering the material unsuitable for ophthalmic applications.

This prompted the researchers to look for a biocompatible material that is bioerodible and soft to ensure better ophthalmic insert. Several attempts have therefore been made to explore the possibility of using a proteinecious source for this purpose. The most important and abundant animal protein is collagen, which constitutes nearly 30% of the vertebrate body protein. It is highly cross linked there by forming a consistency within the tissues. Collagen has already been recognized as an excellent naturally occurring biomaterial because of the following advantages-

1. Bio compatibility
2. High tensile strength
3. Low antigenicity
4. Bioerodibility

Use of collagenous material as ophthalmic insert in general is a better choice, due to its biocompatibility. The similarity of collagen and the proteins of the cornea make allergic and toxic reactions very unlikely.

Hamano et al (U.S Patent number 5,840,054) disclosed a liquid canalicular obstruct of a solution or a liquid dispersion containing gelling material collagen. This remains in the lacrimal puncta and block the flow of tears, but the major drawback of this method is it is difficult for aqueous material to sustain their efficacy for a long time.

Our co-pending patent application (313 del 2004) disclosed the process for the preparation of an ophthalmic shield by succinylation of collagen. The major limitation with the process is, collagen is oxidized during the preparation due to the absence of inert atmosphere resulting in air bubbles, which makes the solution unsuitable for ophthalmic applications.

The document WO2006/031658 by Chang et al discloses the use of lacrimal canalicular inserts made of non-biodegradable and biodegradable polymers with therapeutic agents. The inserts consist of head portion and neck and a distal end having a greater diameter relative to the diameter of the neck. The major limitation includes the lack of biocompatibility and viscoelasticity as they are made of synthetic polymers, leading to side effects like discomfort, foreign body sensation in the eye. Yet another limitation is the shape of the distal end having larger diameter than the neck, which causes rupture of the punctum and the nasolacrimal duct during insertion, as the inserts are rigid material leading to pyogenic granuloma, discomfort and pain. The head portion of the insert always protrudes out causing discomfort and irritation during blinking and closure of eyelids. This also causes irritation to the cornea.

These limitations can be overcome by the present invention, where the major constituent of the inserts is collagen, a naturally occurring bio-erodible polymer compatible with the human cornea. This essentially eliminates the limitations of discomfort, foreign body sensation etc. The inserts of the present invention are soft and flexible (visco-elastic) and fits into the punctum without any discomfort.

OBJECTS OF THE INVENTION:

The main object of the present invention is thus to provide a process for the preparation of bio-erodible insert for ophthalmic applications, which obviates the limitations as stated above.

Another object of the present invention is to prepare ophthalmic insert, which is very much compatible with human eye.

Yet another object of the present invention is to prepare an ophthalmic insert which is bio-erodible at physiological pH (4.5 - 9.0).

Still another object of the present invention is to prepare ophthalmic insert which is soft having visco-elastic properties.

Another object of the present invention is to use the abundantly available collagenous material like Achilles tendons and Foetal Calf-skin for preparing the said novel ophthalmic insert.

SUMMARY OF THE INVENTION:

Accordingly the present invention provides a novel bio-erodible insert for ophthalmic applications comprising a visco-elastic collagenous membrane along with a therapeutic agent.

The invention further provides a process for the preparation of the said insert for ophthalmic applications, wherein the process comprises:

a) treating the succinylated collagen solution, with an organic polar solvent in the range of 25 to 50% v/v at a temperature in the range of 18 to 27^{0}C for a period of 20 to 24 hrs to get a homogenous solution;

b) treating the homogenous solution as obtained in step (a), with 5 to 10%v/v of a biodegradable hydrophilic polymer under stirring condition at a temperature in the range of 16 to 27^0 C for a period of 1 to 4 hr to get a visco-elastic solution;

c) treating the solution as obtained in step (b), with 0.3 to 0.5% v/v of a therapeutic agent for a period of 1 to 4 hrs;

d) subjecting the solution as obtained in step (c) to drying in a dust free chamber at a temperature in the range of 15 to 25^0 C for a period of 25 to 40 hrs to obtain dry film;

e) casting the dry film as formed in step (d) in desired shape and subsequent exposure to UV irradiation for about 2 to 8 hours followed by sterilization to get the desired bio-erodible insert.

In an embodiment of the present invention the organic polar solvent used may be selected from ethanol, isopropyl alcohol, n-propanol, n-butanol either individually or in any combination.

In another embodiment of the present invention the said insert has a length between 1.5mm to 4 mm, preferably 1.5mm to 2.75mm and a diameter in the range of 0.2mm to 0.5.5mm.

In yet another embodiment of the present invention the said insert has water content of 50% -65%.

In still another embodiment of the present invention the said insert is bio-erodible, bio-compatible and visco-elastic with high tensile strength and low antigenicity.

In a further embodiment of the present invention the said insert is compatible with the human corneal layer at physiological pH, leaving no residual matter in the intra canalicular duct.

In another embodiment of the present invention the said insert is very soft and flexible and easily inserted into the punctum without causing any rupture of the punctum.

In still another embodiment of the present invention the said insert dissolves automatically in the punctum and hence does not require removal.

In yet another embodiment of the present invention the said insert is very effective for temporary punctal occlusion in various corneal conditions and is very effective to treat dry eye syndrome due to occupational conditions

In a further embodiment of the present invention, the biodegradable hydrophilic polymer used may be selected from poly vinyl alcohol (PVA), polyvinyl pyrollidone (PVP), poly ethylene glycol (PEG), PLA (poly lactic acid), PGA (poly glycolic acid), PLGA (poly lactic-co-glycolic acid) either individually or in any combination.

In yet another embodiment of the present invention therapeutic agent used may be selected from steroids like dexamethasone, prednisole, antiviral agents like trifluthymidine idoxuridine, antibiotic agents like sulfacetamide, erythromycin, Ciprofloxacin, ofloxacin, non-steroidal, anti-inflammatory agents like diclofenec, ketorolac, flarbiprofen, Mydriatic agents, growth factors like Epithelial Growth Factors (EGF), Platelet derived growth factors (PDGF), Fibroblast Derived Growth Factors (FGF), Transforming growth factors (TGF-β), (TGF-γ), Anaesthetic agents like oxymetazoline, Analgesic agents like natromycin, geramycin either individually or in any combination.

In still another embodiment of the present invention, the known method of sterilization used may be such as γ irradiation, ethylene oxide treatment.

DETAILED DESCRIPTION OF THE INVENTION:

The succinylated collagen solution used in this invention is prepared in the following manner. A source of collagenous tissue is washed well in water and chopped into smaller pieces, which are minced at 10 - 20^{0}C. The minced tissue is then scoured using minimum 0.2% w/w of a surfactant, on the weights of the minced collagenous tissue, at a temperature of max 40^{0}C. The scoured mass is then slimed with minimum 0.2% of sliming agent at 30 - 40^{0}C. The slimed mass is then washed thoroughly to make the same free from non-collagenous particles, fat and other chemicals. The resulting stock is treated with minimum 0.5 - 2% w/w of a proteolytic enzyme on the weight of the minced tissue at 2 - 8^0 C for12 - 48 hrs, the pH of the bath is adjusted in the range of 2 - 4. The enzyme treated stock is homogenised at a temperature of maximum of 35^0 C and diluted with 100 - 300 v/v, water to form a collagen solution. The viscous solution thus formed is treated with 4 - 6% of precipitant with continuous stirring. The resulting suspension is separated conventionally by centrifugation in the range of 10000 - 15000 rpm at 4 - 7^0 C, the precipitated collagen is dissolved in 200 - 400% v/v of an acid at a pH in the range of 2 - 4 to obtain a clear viscous solution. The solution obtained is dialysed against 0.02 M di sodium hydrogen phosphate. The mass is centrifuged at 10000 rpm and precipitate is re dissolved in 400 - 500 ml of 0.5 M of an acid and dialysed against distilled water to get a pure collagen solution. The pure collagen solution, thus prepared from a collagenous solvent, is treated with minimum 0.2% w/v of surfactant under agitating conditions for a period of at least 5 minutes to form frothy mass the pH of the frothy collagen mass was found to be 6, which is adjusted to 9.0 by adding 10% NaOH. This frothy mass is reacted with 10% NaOH, 2.5 - 4.0% w/v of succinic anhydride, dissolved in acetone, was added with continuous stirring, maintaining the pH constantly at 9.0 using 10% NaOH solution. The suspension thus formed is subjected to separation by centrifugation at 10000 to 20000 rpm to get the precipitate, which is dissolved in 100-300% water to get pure succinylated collagen solution.

The pure succinylated collagen solution thus obtained is treated with organic polar solvent in the range of 25 - 50% under constant stirring for a minimum period of 24 hrs to get a homogenous solution. The resulting homogenous solution is then treated with 5 - 10% v/v of biodegradable hydrophilic polymers for a period of 1 to 2 hrs, under constant stirring at a temperature in the range of 15 - 25^0 C to get a visco-elastic collagen solution. The resulting solution is then treated with 0.3 - 0.5% v/v of the therapeutic agent under constant stirring for a period of 1 to 2 hrs, which is then subjected to drying by a known method in a dust free atmosphere at a temperature in the range of 15 - 25^0 C for a period of 20 - 45 hrs. The dried film is subject to inserts and cross-linked conventionally by exposure to UV irradiation for 2 - 8 hrs to control the bio-erodibility, which are then subjected to sterilization by known method to get bio-erodible insert for ophthalmic applications.

The inventive step of the present invention lies in the treatment of succinylated collagen with organic polar solvents to get a homogenous solution, resulting in the preparation of bio-erodible insert for ophthalmic applications.

The following examples are given by way of illustration and therefore should not be construed to limit the scope of the present invention.

Example 1

100 gm of Achilles tendons of a freshly slaughtered cow, collected from slaughter house, was thoroughly washed in plain water to free it from extraneous materials like the surrounding tissues. The washed stock was then chopped into small pieces of 2 cm^3 and the cut pieces were minced in Hobart meat grinder. The temperature was maintained at 15^0 C by mixing crushed ice cubes along with the tendon pieces. The minced mass was taken in a path containing the scouring solutions, which was prepared by dissolving 300 mg of sodium laurel sulphate in 300 ml water with vigorous stirring. The temperature in the bath was maintained at 40^0 C and the stirring was continued for 3 hrs. 200 mg of potassium peroxide was dissolved in 300 ml of water taken in a beaker and the pH of the solution

was adjusted to 10 for preparing sliming solution. The scoured stock was then added to this sliming solution and stirring was continued for 4 hrs at a temperature of 40^0C. The stock was then washed thoroughly with 4 changes of plain water to remove all non-collagenous materials. 3 gm of crystalline pepsin was added to 150 ml of water taken in a beaker at 5^0 C with constant stirring. The washed slime was put in to above enzyme bath with rigorous stirring. The pH of the bath was adjusted to 2.5 by adding HCl, After 24 hrs the enzyme treated mass was fed into a polytron homogeniser maintained at 30^0 C and the homogenization was done at 3000 rpm for 15 minutes till a viscous solution of collagenous tissue was obtained. The homogenate thus formed was taken in a beaker and was diluted with 100 ml of distilled water 5 gm of sodium chloride was then added to the beaker with stirring. When a precipitate of collagen tissue was formed at the bottom of the beaker, the precipitated collagen was centrifuged at 5^0C and 15,000 rpm, and the precipitate was then re solubilised in 400 ml of acetic acid at pH 2.5, while continuously stirring the solution for 60 minutes, till a viscous solution of collagen was obtained. The homogenous solution, thus obtained was dialysed against 4 litres of 0.02 M disodium hydrogen phosphate solution. The dialysate was centrifuged at 15000 rpm and the precipitate was re dissolved in 400 ml of 0.5 M acetic acid and dialyzed against 4 litres of distilled for 12 hrs. to get a pure collagen solution.

500 ml of pure collagen solution was taken in a round bottomed flask and was subjected to homogenization to get a frothy collagen solution with a pH found to be 6.0, which was adjusted to 9.0 by adding 10% NaOH solution to the flask.10 gm of succnic anhydride dissolved in 500ml of acetone was then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution.

After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0., 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 15000 rpm, and the supernatant was decanted. The precipitate collected was

there by washed with water and dialyzed against one liter of distilled water for 10 hrs to get pure succinylated collagen solution.

500 ml of pure succinylated collagen solution, prepared above was taken in a beaker, 25 ml of ethanol was added to the succinylated collagen solution in the beaker under constant stirring conditions and was continued for a period of 24 hrs at a temperature of 25^0 C. The resulting homogenous solution was treated with 6ml of poly ethylene glycol under constant stirring conditions and kept for 1 hr at a temperature of 15^0 C. 0.4 gm of dexamethasone was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications.

The solution was air dried in Teflon sheets in a dust free atmosphere at a temperature of 15^0C and made into ophthalmic inserts with a diameter of 0.2mm - 0.5mm and length of 1.5mm - 2.5mm. The inserts were cross-linked by exposure to UV irradiation for a period of 4 hrs. The inserts were packed in sterile polythene sachets and sterilized by ethylene oxide fumigation for 4 hrs and doubly packed for better protection.

Example 2

100 gm of Achilles tendons of a freshly slaughtered cow, collected from a slaughtered house, was thoroughly washed in plain water to free it from extraneous materials like the surrounding tissues. The washed stock was then chopped into small pieces of $2cm^3$ and the cut pieces were minced in Hobart meat grinder The temperature was maintained at 18^0 C by mixing crushed ice cubes along with the tendon pieces. The minced mass was taken in a path containing the scouring solutions, which was prepared by dissolving 320 mg of sodium laurel sulphate in 320 ml water with vigorous stirring. The temperature in the bath was maintained at 35^0 C and the stirring was continued for 2 hrs. 210 mg of potassium peroxide was dissolved in 310 ml of water taken in a beaker and the pH of the solution was adjusted to 9 for preparing sliming solution. The scoured stock was then added to this sliming solution and stirring was continued for 3 hrs at a temperature of 35^0C. The stock was then washed thoroughly with 5

changes of plain water to remove all non-collagenous materials. 2.8 gms of crystalline pepsin were added to 140 ml of water taken in a beaker at 4^0 C with constant stirring. The washed slime was put in to above enzyme bath with rigorous stirring. The pH of the bath was adjusted to 2.5 by adding HCl, After 24 hrs the enzyme treated mass was fed into a polytron homogeniser maintained at 30^0 C and the homogenization was done at 3000 rpm for 15 minutes till a viscous solution of collagenous tissue was obtained. The homogenate thus formed was taken in a beaker and was diluted with 100 ml of distilled water 5 gm of sodium chloride was then added to the beaker with stirring. When a precipitate of collagen tissue was formed at the bottom of the beaker, the precipitate collagen was centrifuged at 4^0 C and 18000 rpm and the precipitate was then re solubilised in 400 ml of acetic acid at pH 3.0, while continuously stirring the solution 60 minutes, till a viscous solution of collagen was obtained. The homogenous solution, thus obtained was dialysed against 3 litres of 0.02 M disodium hydrogen phosphate solution. The dialysate was centrifuged at 15000 rpm and the precipitate was re - dissolved in 500 ml of 0.5 M acetic acid and dialyzed against 3 liters of distilled for 12 hrs to get a pure collagen solution 600 ml of pure collagen solution was taken in a round bottomed flask and was subjected to homogenization to get a frothy collagen solution with a pH found to be 6.0, which was adjusted to 9.0 by adding 10% NaOH solution to the flask.13 gm of succnic anhydride dissolved in 250 ml of acetone was then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution.

After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0. 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 15000 rpm, and the supernatant was decanted. The precipitate collected was there by washed with water and dialyzed against one liter of distilled water for 8 hrs to get pure succinylated collagen solution.

500 ml of pure succinylated collagen solution, prepared above was taken in a beaker. To that, 30 ml of isopropyl alcohol was added to the beaker under

constant stirring conditions and was continued for a period of 24 hrs at a temperature of 25^0 C. The resulting homogenous solution was treated with 8 ml of polyvinyl alcohol under constant stirring conditions and kept for 1 hr at a temperature of 15^0 C. 0.4 gm of ofloxacin was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications. The solution was poured into Teflon trays and air- dried in a dust free atmosphere at a temperature of 15^0 C and cut into cylindrical inserts having a diameter of 0.3mm - 0.5mm and length of 1.6mm - 2.5mm cross-linked by exposure to UV irradiation for a period of 3 hrs. The inserts were packed individually in sterile polythene sachets and sterilized by ethylene oxide fumigation for 3 hrs and doubly packed for better protection

Example 3

100 gm of foetal calfskin collected from a slaughterhouse was dehaired, cleaned by shaving, cut into smaller pieces and ground in homogeniser. The ground mass was solubilised in 0.5 M acetic acid overnight. Then the concentration of the solution was adjusted to about 4% by adding NaCl and the precipitate mass was collected by centrifugation. The process was repeated two times to get pure precipitated tissues. The tissues were re - dissolved in 0.5 M acetic acid, dialysed against 0.02 M $Na_2H\ PO_4$ followed by dialysis against 0.05 M acetic acid. The dialyzed solution was centrifuged to get a clear solution of collagen. All of the above experiments were carried out at a temperature at 15^0C.

500 ml of this pure collagen solution was taken in a round bottomed flask and the pH was found to be 3.0. The pH was slowly raised to 9.0 by adding 10% NaOH solution to the flask. 16 gm of succnic anhydride, dissolved in 400ml of acetone were then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution. After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0, 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 12,000 rpm and the supernatant was decanted. The precipitate collected thereby was washed with water and

dialyzed against 1 liter of distilled water for 12 hrs to get pure succinylated collagen solution.

100ml of the pure succinylated collagen solution was taken in a beaker. 25ml of ethanol was added under constant stirring conditions for a period at 25° C. 10 ml of polyvinyl pyrollidone (PVP) solution was taken in a beaker and was added to the succinylated collagen solution under stirring conditions and stirring was continued for a period of 2 hrs at a temperature of 15° C, and the stirring was continued for a period of 4 hrs to get a visco-elastic solution for ophthalmic applications. 0.3 gm of sulfacetamide was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications. The solution was poured into Teflon trays and air-dried in a dust free chamber at 27°C and made into inserts with a length of 1.5 mm - 4 mm and a diameter of 0.2 mm - 0.4 mm and cross-linked with UV irradiation for 3 hrs to control the erodibility of the inserts. The dry inserts were packed in sterile sachets and exposed to γ irradiation for 30 sec to sterilize the material.

Example 4

100 gm of foetal calfskin collected from a slaughterhouse was de haired, cleaned by shaving, cut into smaller pieces and ground in homogeniser. The ground mass was solubilised in 0.5 M acetic acid overnight. Then the concentration of the solution was adjusted to about 5% by adding NaCl and the precipitate mass was collected by centrifugation. The process was repeated two times to get pure precipitated tissues. The tissues were re-dissolved in 0.5 M acetic acid, dialysed against 0.02 M $Na_2H\ PO_4$ followed by dialysis against 0.05 M acetic acid. The dialyzed solution was centrifuged to get a clear solution of collagen. All of the above experiments were carried out at a temperature at 20°C. 500 ml of this pure collagen solution was taken in a round bottomed flask and the pH was found to be 2.5. The pH was slowly raised to 9.0 by adding 10% NaOH solution to the flask. 17 gm of succnic anhydride, dissolved in 400ml of acetone was then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution.

After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0, 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 14,000 rpm and the supernatant was decanted. The precipitate collected thereby was washed with water and dialyzed against 1 liter of distilled water for 12 hrs to get pure succinylated collagen solution

100ml of the pure succinylated collagen solution was taken in a beaker. 15ml of isopropyl alcohol was taken in a beaker and 15ml of ethanol was added to it under constant stirring conditions for a period of 5 minutes. This mixture was then added to the succinylated collagen solution under stirring conditions and stirring was continued for a period of 24 hrs at a temperature of 20°C to get a homogenous solution.10 ml of polyvinyl pyrollidone (PVP) solution was taken in a beaker and was added to the homogenous solution under stirring conditions and stirring was continued for a period of 2 hrs at a temperature of 15° C. 0.3 gm of Ciprofloxacin solution is added to the above solution at a temperature of 15° C under constant conditions, and the stirring was continued for a period of 2 hrs to get a visco-elastic solution for ophthalmic applications. The solution was poured into polymeric trays, air-dried in a dust free chamber at 25° C to make films. The dry films were made into inserts having a length of 1.4 mm-3.4 mm with a diameter of 0.2 - 0.3.5 mm in the shape of a cylinder. The air-dried inserts were cross-linked with UV irradiation for 5 hrs to control the erodibility of the inserts. The dry inserts were packed in sterile sachets and exposed to γ irradiation for 20 sec to sterilize the material.

Example 5

100 gm of Achilles tendons of a freshly slaughtered cow, collected from a slaughtered house, was thoroughly washed in plain water to free it from extraneous materials like the surrounding tissues. The washed stock was then chopped into small pieces of 2 cm^3 and the cut pieces were minced in Hobart meat grinder The temperature was maintained at 18^0 C by mixing crushed ice cubes along with the tendon pieces. The minced mass was taken in a path containing the scouring solutions, which was prepared by dissolving 280 mg of

sodium laurel sulphate in 280 ml water with vigorous stirring. The temperature in the bath was maintained at 35^0C and the stirring was continued for 2 hrs. 170 mg of potassium peroxide was dissolved in 170 ml of water taken in a beaker and the pH of the solution was adjusted to 9 for preparing sliming solution. The scoured stock was then added to this sliming solution and stirring was continued for 5 hrs at a temperature of 35^0 C. The stock was then washed thoroughly with 3 changes of plain water to remove all non-collagenous materials. 3 gms of crystalline pepsin was added to 150 ml of water taken in a beaker at 4^0 C with constant stirring. The washed slime is put in to above enzyme bath with rigorous stirring. The pH of the bath was adjusted to 3.0 by adding HCl, After 20 hrs the enzyme treated mass was fed into a polytron homogeniser maintained 30^0 C and the homogenization was done at 4000 rpm for 10 minutes till a viscous solution of collagenous tissue is obtained.

The homogenate thus formed was taken in a beaker and was diluted with 100 ml of distilled water 4 gm of sodium chloride was then added to the beaker with stirring. When a precipitate of collagen tissue was formed at the bottom of the beaker, the precipitate collagen was centrifuged at 4^0 C and 18000 rpm and the precipitate was then re solubilised in 400 ml of acetic acid at pH 3.0 while continuously stirring the solution for 60 minutes, till a viscous solution of collagen was obtained. The homogenous solution, thus obtained was dialysed against 3 litres of 0.02 M disodium hydrogen phosphate solution. The dialysate was centrifuged at 15000 rpm and the precipitate was re dissolved in 500 ml of 0.5 M acetic acid and dialyzed against 3 litres of distilled water for 12 hrs to get a pure collagen solution 500 ml of pure collagen solution was taken in a round bottomed flask and is subjected to homogenization to get a frothy collagen solution with a pH found to be 6.0, which was adjusted to 9.0 by adding 10% NaOH solution to the flask.12 gm of succnic anhydride dissolved in 500ml of acetone was then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution.

After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0., 2 N HCl was added to the flask with

stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 15000 rpm, and the supernatant was decanted. The precipitate collected was there by washed with water and dialyzed against one litre of distilled water for 8 hrs to get pure succinylated collagen solution. 500 ml of pure succinylated collagen solution, prepared above was taken in a beaker. To that, 50 ml of ethanol was added under constant stirring conditions for 24 hrs at 25° C. 8 ml of polyvinyl alcohol and 6ml of polyvinyl pyrollidone was added to the beaker under constant stirring conditions and was continued for a period of 2 hrs at a temperature of 15^0 C. 0.4 gm of dexamethasone was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications. The solution was poured into Teflon trays and air-dried in a dust free atmosphere at a temperature of 15^0C and cut into cylindrical inserts with a diameter of 0.75 mm- 2 mm and length of 1.75 - 3 mm and they were cross-linked by exposure to UV irradiation for a period of 3 hrs. The inserts were packed in sterile polythene sachets and sterilized by ethylene oxide fumigation for 3 hrs and doubly packed for better protection.

Example 6

100 gm of fetal calfskin collected from a slaughterhouse was dehaired, cleaned by shaving, cut into smaller pieces and ground in homogenizer. The ground mass was solubilized in 0.5 M acetic acid overnight. Then the concentration of the solution was adjusted to about 4% by adding NaCl and the precipitate mass was collected by centrifugation. The process was repeated two times to get pure precipitated tissues. The tissues were re - dissolved in 0.5 M acetic acid, dialyzed against 0.02 M $Na_2H\ PO_4$ followed by dialysis against 0.05 M acetic acid. The dialyzed solution was centrifuged to get a clear solution of collagen. All the above experiments were carried out at a temperature at 15^0C.

500 ml of this pure collagen solution was taken in a round bottomed flask and the pH was found to be 3.0, the pH was raised slowly raised to 9.0 by adding 10% NaOH solution to the flask. 15 gm of succinic anhydride, dissolved in 380ml of acetone were then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution. After completion of succinylation,

which was ascertained by the fact that the pH of the solution remained constant at 9.0, 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 13,000 rpm and the supernatant was decanted. The precipitate collected thereby was washed with water and dialyzed against 1 liter of distilled water for 12 hrs to get pure succinylated collagen solution.

100ml of the pure succinylated collagen solution was taken in a beaker. 25ml of n-propanol was added under constant stirring conditions for a period at 25° C. 10 ml of polyvinyl pyrollidone (PVP) solution was taken in a beaker and was added to the succinylated collagen solution under stirring conditions and stirring was continued for a period of 2 hrs at a temperature of 15° C, and the stirring was continued for a period of 4 hrs to get a visco-elastic solution for ophthalmic applications. 0.3 gm of sulfacetamide was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications. The solution was poured into Teflon trays and air-dried in a dust free chamber at 27°C and made into inserts with a length of 1.5 mm - 4.5 mm and a diameter of 0.2 mm - 0.3.5 mm and cross-linked with UV irradiation for 3 hrs to control the erodibility of the inserts. The dry inserts were packed in sterile sachets and exposed to γ irradiation for 30 sec to sterilize the material.

Example 7

100 gm of Achilles tendons of a freshly slaughtered cow, collected from a slaughtered house, was thoroughly washed in plain water to free it from extraneous materials like the surrounding tissues. The washed stock was then chopped into small pieces of $2cm^3$ and the cut pieces were minced in Hobart meat grinder The temperature was maintained at 17^0 C by mixing crushed ice cubes along with the tendon pieces. The minced mass was taken in a path containing the scouring solutions, which was prepared by dissolving 300 mg of sodium laurel sulphate in 300 ml water with vigorous stirring. The temperature in the bath was maintained at 35^0 C and the stirring was continued for 3 hrs. 200 mg of potassium peroxide was dissolved in 300 ml of water taken in a beaker and the pH of the solution was adjusted to 9 for preparing sliming solution. The

scoured stock was then added to this sliming solution and stirring was continued for 3 hrs at a temperature of 35^{0}C. The stock was then washed thoroughly with 5 changes of plain water to remove all non-collagenous materials. 2.8 g of crystalline pepsin were added to 140 ml of water taken in a beaker at 4^0 C with constant stirring. The washed slime was put in to above enzyme bath with rigorous stirring. The pH of the bath was adjusted to 2.5 by adding HCl, After 24 hrs the enzyme treated mass was fed into a polytron homogeniser maintained 30^0 C and the homogenization was done at 3000 rpm for 15 minutes till a viscous solution of collagenous tissue was obtained. The homogenate thus formed was taken in a beaker and was diluted with 100 ml of distilled water 5 gm of sodium chloride was then added to the beaker with stirring. When a precipitate of collagen tissue was formed at the bottom of the beaker, the precipitate collagen was centrifuged at 4^0 C and 17000 rpm and the precipitate was then re solubilized in 400 ml of acetic acid at pH 3.0 while continuously stirring the solution 60 minutes, till a viscous solution of collagen was obtained. The homogenous solution, thus obtained was dialysed against 3 litres of 0.02 M disodium hydrogen phosphate solution. The dialysate was centrifuged at 16000 rpm and the precipitate was re - dissolved in 500 ml of 0.5 M acetic acid and dialyzed against 4 liters of distilled for 10 hrs to get a pure collagen solution 500 ml of pure collagen solution was taken in a round bottomed flask and was subjected to homogenization to get a frothy collagen solution with a pH found to be 6.0, which was adjusted to 9.0 by adding 10% NaOH solution to the flask.12 gm of succinic anhydride dissolved in 250 ml of acetone was then added to the flask with continuous stirring, maintaining the pH constantly at 9.0 by using 10% NaOH solution.

After completion of succinylation, which was ascertained by the fact that the pH of the solution remained constant at 9.0. 2 N HCl was added to the flask with stirring to bring down the pH to 4.2. The resulting suspension was centrifuged at 16000 rpm, and the supernatant was decanted. The precipitate collected was there by washed with water and dialyzed against one liter of distilled water for 10 hrs to get pure succinylated collagen solution.

500 ml of pure succinylated collagen solution, prepared above was taken in a beaker to that, 30 ml of n-butanol was added to the beaker under constant stirring conditions and was continued for a period of 24 hrs at a temperature of 25^0 C. The resulting homogenous solution was treated with 6 ml of polyvinyl alcohol under constant stirring conditions and kept for 1 hr at a temperature of 15^0 C. 0.3 gm of ciprofloxacin was added to the resulting solution under constant stirring conditions for 1 hr to get a visco-elastic solution for ophthalmic applications. The solution was poured into Teflon trays and air- dried in a dust free atmosphere at a temperature of 15^0 C and cut into cylindrical inserts having a diameter of 0.2mm - 0.5mm and length of 1.5mm - 2.5mm cross-linked by exposure to UV irradiation for a period of 4 hrs. The inserts were packed individually in sterile polythene sachets and sterilized by ethylene oxide fumigation for 3 hrs and doubly packed for better protection.

Example 8

Elaborate data on the product characteristics viz., the comparability with the prior art, durability in terms of shelf-life and stability and physicochemical characteristics.

Parameters	Prior Art	Present Invention
Material	Synthetic polymers [silicone]	Natural polymer [collagen]
Properties of the insert	*Made with synthetic polymers, cause physiological complications like foreign body sensation, discomfort.	*The major constituent of the insert is Collagen, which is biocompatible, bioerodible with high tensile strength and low antigenicity. The inserts do not cause any reactions to the eye as inserts are prepared with Succinylated collagen pH (7.4) which is similar to the collagen in the cornea.
	*The synthetic plugs are rigid materials, hence insertion is	*The inserts are soft and flexible hence insertion in the

	difficult and cause mechanical stress on the canalicular mucosa leading to conjuctival aberration (rupture of the punctum) and pyogenic granuloma. Plug extrusion is very high due to the instability of the plug because of its rigid shape and does not properly fit in the punctum. One end of the plug sticks outside the punctum causing irritation to the cornea, foreign body sensation in the eye, plug loss etc.	puncutm of the eye is very easy and will not cause any rupture to the punctum. Collagen inserts swell inside the punctum, and block the punctum (complete punctal occlusion); there will not be any loss of insert or migration of the insert in the duct. It will not protrude outside the punctum, hence no foreign body sensation or irritation to the cornea.
	*Intracanicular migration of the plug is present leading to obstruction in the duct, which can be removed only through irrigation causing pain and damage to the punctum and nasolacrimal duct. In temporary punctal occlusion, the removal of the plug should be performed by surgery, which will cause damage to the punctum.	*The bioerodibility of collagen inserts dissolve the inserts in 12-14 days and do not require removal in the insert. It is very effective for temporary punctal occlusion in various corneal conditions and is very effective to treat dry eye syndrome due to occupational conditions.
	*The plugs may undergo physico chemical changes in longer use as they are made of synthetic polymers, and may affect the eye.	*Collagen is a naturally occurring protein hence it will not cause any side effects. It dissolves automatically in the punctum and hence does not require removal.

Cost reduction	High cost	Cost reduction may be to the tune of almost 50%

Example 9

Product characterization

The inserts were prepared with Succinylated Collagen, which gives a clear solution at physiological pH (7.4). The Succinylatecd Collagen was characterized with Fourier Transform Infrared Spectroscopy Studies (FTIR), Differential Scanning Calorimetric Studies (DSC) and Nuclear Magnetic Resonance Spectroscopy Studies (NMR).

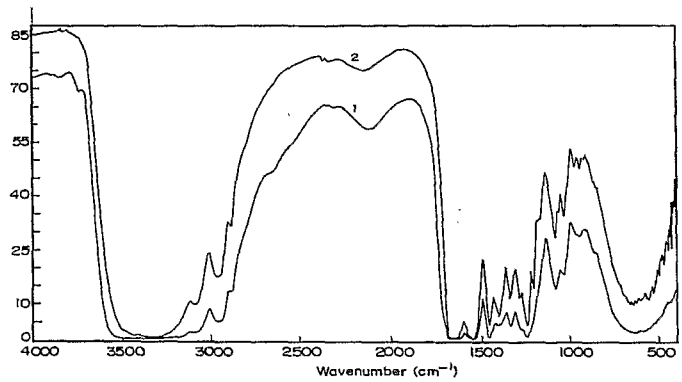

Figure 1.FTIR spectra

(1) Unmodified Collagen (2) Succinylated Collagen

In the FTIR spectra (Figure1) of unmodified Collagen (1) and Succinylated Collagen (2), the IR absorption ratio of (1250 / 1458) for Succinylated Collagen showed a value of almost 1 (numerical value) indicating triple helical nature of Succinylated Collagen.

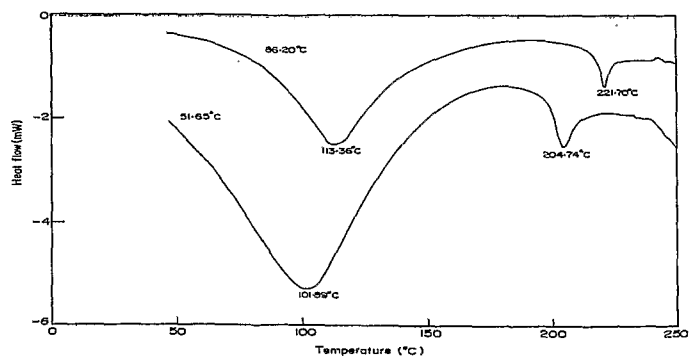

Figure (2) Comparative Thermogram of

(a) Unmodified Collagen and (b) Succinylated Collagen

DSC analysis characterizes both the water bounded to the collagen film and their thermal stability (Figure 2). Three temperatures were measured, the onset temperature (T_1), the maximum temperature of peak (T_{max}) and the recovery temperature (T_2), at which the curve returns to base line. They are similar in both Unmodified Collagen and Succinylated Collagen confirming the retention of the triple helical nature of Collagen.

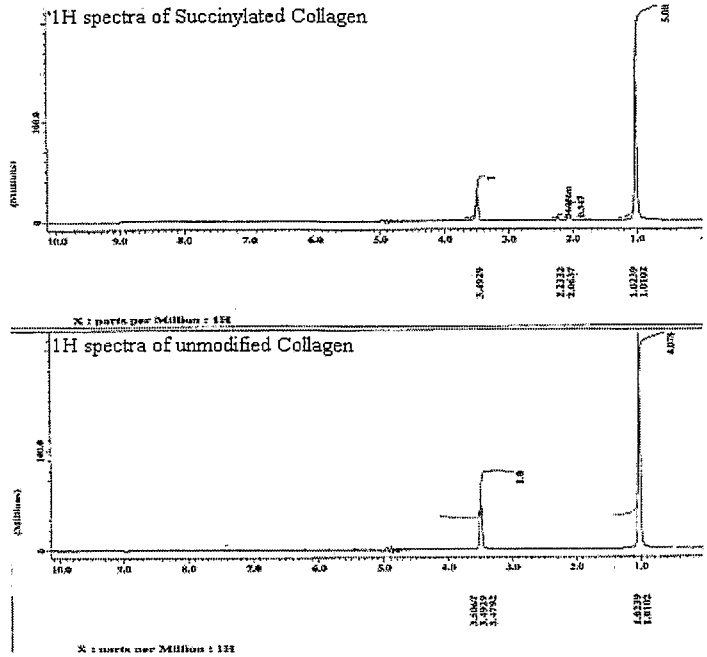

Figure (3) ^1H spectra of both unmodified and Succinylated Collagen

The spectra in Figure 3, shows ^1H FT NMR spectra of both unmodified collagen and Succinylated Collagen. The main proton peaks at two different chemical shift values indicate the two distinct chemical shifts of 1.0 ppm and 3.5 ppm. These chemical shifts are seen in the spectra of unmodified collagen. The two chemical shifts of 1.0 ppm and 3.5 ppm are also present in the spectra of Succinylated collagen.

The clinical benefits of the inserts of the present invention include temporary lacrimal occlusion i,e Short - term treatment of dry eye or the dry eye component of ocular surface disease (OSD), to enhance the efficacy of ocular medications, in the prevention of complication due to dry eye after eye surgery, as an adjunctive aid in the treatment of other external eye diseases and for short term

treatment of dry eye related contact lens problems. Use of collagenous material as ophthalmic insert in general is a better choice, due to its biocompatibility. The similarity of collagen inserts and collagen of the cornea do not cause any allergic and toxic reactions.

Example 10

Product evaluation and comparison with the related substance

The inserts of the present invention were prepared with appropriate dimensions of the punctum with length between 1.5 mm and 2.5 mm and a diameter in the range of 0.2 mm - 0.5 mm, that will not cause any discomfort during insertion as they are soft and flexible. Collagen inserts swell inside the punctum and blocks the punctum (complete punctal occlusion) hence there will not be any loss of insert or migration of the insert in the duct. It will not protrude outside the punctum, and there is no foreign body sensation or irritation to the cornea.

On the other hand, the conventional silicone plugs are very rigid, cause mechanical stress on the canalicular mucosa leading to conjuctival aberration (rupture of the punctum) and pyogenic granuloma. Plug extrusion is very high due to the instability of the rigid plug, as it does not properly fit in the punctum. One end of the plug sticks outside the punctum causing irritation to the cornea, foreign body sensation in the eye, plug loss etc. Intracanicular migration of the plug is present leading to obstruction in the duct, which can be removed only through irrigation or surgery causing further damage to the punctum, nasolacrimal duct and pain to the patient.

Clinical evaluation of the collagenous inserts of the present invention in dry eye syndrome patients showed increase in tear fluid level after punctal occlusion. The water content of collagen inserts is 50% - 55%, it swells and completely blocks the punctum (Complete Punctal Occlusion) compared to partial blockage with silicone plugs due to their rigidity and shape. The collagen inserts do not require removal of the insert after its use as it dissolves in 12-14 days. It is very effective for temporary punctal occlusion in various corneal conditions and to treat dry eye syndrome due to occupational conditions. This was confirmed with

the decrease in the tear fluid levels on 14th day resulting in the dissolution of the insert and the reoccurrence of dry eye symptoms. The inserts of the present invention show greater efficacy in the treatment of dry eye syndrome and the clinical evaluation confirms its biocompatibility as a punctal plug for temporary lacrimal occlusion.

In temporary punctal occlusion, the removal of the silicone plug requires surgery, which is likely to cause damage to the punctum. The plugs may undergo physico chemical changes in longer use as they are made of synthetic polymers, and may affect the eye.

Advantages :

1. The organic polar solvent, used in the present invention, interferes with the solvent air interfacial tensions and helps the air bubbles to migrate to the surface and finally to escape in the atmosphere leaving behind bubble free homogenous solution suitable for ophthalmic applications.
2. The hydrophilic polymer used in the present invention helps in bringing visco-elasticity to the solution, there by the ophthalmic insert is soft when placed in the punctum.
3. The ophthalmic insert is bio-erodible at physiological pH (4.5 - 9.0) leaving no residual matter in the intra canalicular duct, the degree of cross-linking thereby undermine the bio-erodibility property.
4. The insert containing the therapeutic agent is gradually solubilized by the tear fluid and the viscosity of the tear film increases, thereby prolonging the effect of the drug and maintaining higher concentration levels at the site of application.
5. Collagen applied to the cornea or injected into the punctum in the form of drops or ointments is washed relatively rapidly from the eye by tear flow. However, the collagen inserted as a shaped article is maintained in the punctum of the eye for longer periods thereby extending the desirable effects.
6. The inserts are very soft and flexible hence can be easily inserted into the punctum without causing any rupture of the punctum.
7. The ophthalmic insert of the present invention is very much compatible with human corneal layer at physiological pH (4.5 - 9.0) conditions.

WE CLAIM:

1. A novel bio-erodible insert for ophthalmic applications comprising a visco-elastic collagenous membrane along with a therapeutic agent.
2. An insert according to claim 1, wherein the said insert has a length between 1.5mm and 2.75mm and a diameter in the range of 0.2mm to 0.5.5mm.
3. An insert according to claim 1, wherein the said insert has water content of 50% -65%.
4. An insert according to claim 1, wherein the said insert is bio-erodible, bio-compatible and visco-elastic with high tensile strength and low antigenicity.
5. An insert according to claim 1, wherein the said insert is compatible with the human corneal layer at physiological pH, leaving no residual matter in the intra canalicular duct.
6. An insert according to claim 1, wherein the said insert is very soft and flexible and easily inserted into the punctum without causing any rupture of the punctum.
7. An insert according to claim 1, wherein the said insert dissolves automatically in the punctum and hence does not require removal.
8. An insert according to claim 1, wherein it is very effective for temporary punctal occlusion in various corneal conditions and is very effective to treat dry eye syndrome due to occupational conditions.
9. A process for the preparation of a novel bio-erodible insert for ophthalmic applications, wherein the process comprises:
   a) treating the succinylated collagen solution, with an organic polar solvent in the range of 25 to 50% v/v at a temperature in the range of 18 to 27^0C for a period of 20 to 24 hrs to get a homogenous solution;
   b) treating the homogenous solution as obtained in step (a), with 5 to 10%v/v of a biodegradable hydrophilic polymer under stirring condition at a temperature in the range of 16 to 27^0 C for a period of 1to 4 hr to get a visco-elastic solution;

c) treating the solution as obtained in step (b), with 0.3 to 0.5% v/v of a therapeutic agent for a period of 1to 4 hrs;

d) subjecting the solution as obtained in step (c) to drying in a dust free chamber at a temperature in the range of 15 to 25^0 C for a period of 25 to 40 hrs to obtain dry film;

e) casting the dry film as formed in step (d) in desired shape and subsequent exposure to UV irradiation for about 2 to 8 hours followed by sterilization to get the desired bio-erodible insert.

10. A process according to claim 9, wherein the organic polar solvent is selected from ethanol, isopropyl alcohol n-propanol, n-butanol either individually or in any combination.

11. A process according to claim 9, wherein the biodegradable hydrophilic polymer used is selected from poly vinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), poly ethylene glycol (PEG), poly lactic acid (PLA), poly glycolic acid (PGA), poly lactic-co-glycolic acid (PLGA) either individually or in any combination.

12. A process according to claim 9, wherein the therapeutic agent used is selected from steroids like dexamethasone, prednisole, antiviral agents like trifluthymidine idoxuridine, antibiotic agents like sulfacetamide, erythromycin, ciprofloxacin, ofloxacin, non-steroidal, anti-inflammatory agents like diclofenec, ketorolac, flarbiprofen, mydriatic agents, growth factors like Epithelial Growth Factors (EGF), Platelet derived growth factors (PDGF), Fibroblast Derived Growth Factors (FGF), Transforming growth factors (TGF-β), (TGF-γ), aesthetic agents like oxymetazoline, analgesic agents like natromycin, geramycin either individually or in any combination.

13. A process according to claim 9, wherein the method of sterilization used is preferably γ-irradiation, ethylene oxide treatment.