DOWNLOAD PDF BIOACTIVE POLYMERIC SYSTEMS

Chapter 1 : Charles G. Gebelein (Author of Bioactive Polymeric Systems)

The vast array of libraries in the world bear mute witness to the truth of the year-old observation of King Solomon who stated " of making many books there is no end, and much study is a wear.

The delivery systems of the present invention may be comprised of either biodegradable or nondegrading polymeric fibers. Bioactive compounds are included in the delivery system either by suspending the compound particles or dissolving the compound in the polymer solution used to produce the fibers. Patent 3,, describes a medicament repository consisting of a surgical element in the form of tubes, sheets, sponges, gauzes or prosthetic devices of polyglycolic acid having incorporated therein an effective amount of a medicament. Patent 4,, describes a method for producing a biodegradable prothesis or implant by encasing an effective amount of fibers of calcium phosphate or calcium aluminate in a matrix of polymer selected from the group consisting of polyglycolide , poly DL- lact ide , poly L- lactide , polycaprolactone , , polydioxanone , polyesteramides , copolyoxalates, polycarbonates, poly glutamic-co-leucine and blends, copolymers and terpolymers thereof to form a composite. Patent 4,, discloses a method for preparing a spherical microporous polymeric network with interconnecting channels having a drug distributed within the channels. Patent 5,, discloses a medical device and methods for manufacturing medical devices with a highly biocompatible surface wherein hydrophillic polymer is bonded onto the surface of the medical device covalently through a nitrogen atom. Patent 5,, discloses a composition and method for controlled release of water-soluble proteins comprising a surface-eroding polymer matrix and water-soluble bioactive growth factors. Patent 5,, discloses synthetic, biocompatible, biodegradable polymer fiber scaffolds for cell growth. Fibers are spaced apart by a distance of about to microns for diffusion and may comprise polyanhydrides, polyorthoesters, polyglycolic acid or polymethacrylate. The scaffolds may be coated withe materials such as agar, agarons, gelatin, gum arabic, basement membrane material, collagen type I, II, III, IV or V, fibronectin, laminin, glycosaminoglycans, and mixtures thereof. Patent 5,, discloses a polymeric article for use in drug delivery systems which comprises a polymeric substrate with a highly uniform microporous polymeric surface layer on at least part of the substrate. Encapsulation of a bioactive compound within a polymer matrix has also been described. Patent 5,, discloses a foam precursor comprising a crystalline thermoplastic polymer and solid crystalline additive for use in preparation of drug delivery systems. Recently, it has been shown that polymer fibers of nanometer diameter can be electrospun from sulfuric acid into a coagulation bath Reneker, D. In these studies more than 20 polymers including polyethylene oxide, nylon, polyimide, DNA, polyaramide and polyaniline were electrospun into electrically charged fibers which were then collected in sheets or other useful geometrical forms. Electrospinning techniques have also been applied to the production of high performance filters Doshi, J. Journal of Electrostatics AIChE Journal The present invention relates to delivery systems for the controlled release of bioactive compounds which comprise polymeric fibers and the bioactive compound. Another object of the present invention is to provide a method for delivering a bioactive compound to a patient for controlled release of the bioactive compound in the patient. In one embodiment of this method of the present invention, the bioactive compound is incorporated into a polymeric fiber matrix or linear assembly or a braided or woven structure and implanted into the patient. In another embodiment, the bioactive compound is incorporated into a polymeric fiber film used to coat implants, tissue engineering scaffolds and other devices such as pumps and pacemakers which are then implanted into the patient. In yet another embodiment, the bioactive compound is incorporated into a polymeric fiber film used to wrap organs, tissues or vessels in a patient. Another object of the present invention is to provide methods for modulating the rate of release of a bioactive compound from a delivery system for bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers. These methods include modulating loading of the bioactive compound incorporated with or between polymeric fiber, selecting polymers to produce the polymeric fibers which degrade at varying rates, varying polymeric concentration of the polymeric fibers and varying polymeric fiber diameter. Detailed Description of the Invention Electrospinning is a simple and low cost electrostatic self-assembly method capable of fabricating a large variety of long,

meter-length, organic polymer fibers with micron or submicron diameters, in linear, 2-D and 3-D architecture. In the electrospinning process, a high voltage electric field is generated between oppositely charged polymer fluid contained in a glass syringe with a capillary tip and a metallic collection screen. As the voltage is increased, the charged polymer solution is attracted to the screen. Once the voltage reaches a critical value, the charge overcomes the surface tension of the suspended polymer cone formed on the capillary tip of the syringe and a jet of ultrafine fibers is produced. As the charged fibers are splayed, the solvent quickly evaporates and the fibers are accumulated randomly on the surface of the collection screen. This results in a nonwoven mesh of nano and micron scale fibers. Varying the charge density applied voltage , polymer solution concentration, solvent used, and the duration of electrospinning can control the fiber diameter and mesh thickness. Other electrospinning parameters which may be varied routinely to effect the fiber matrix properties include distance between the needle and collection plate, the angle of syringe with respect to the collection plate, and the applied voltage. In the present invention, electrospinning is used to produce polymeric fiber matrices with the capability of releasing bioactive compounds in a controlled manner over a selected period of time. In one embodiment, the delivery system of the present invention is used to maintain delivery of a steady concentration of bioactive compound. In another embodiment, the delivery system is used in pulsed delivery of the bioactive compound wherein the compound is released in multiple phases in accordance with either rapid or slow degradation of the polymer fibers or diffusion of the bioactive compound from the polymer fibers. In yet another embodiment, the delivery system is used to obtain a delayed release of a bioactive compound. For example, the bioactive compound-containing fiber polymer matrix can be coated with a layer of nonwoven polymer fiber matrix with no bioactive compound. In this embodiment, different polymers with different degradation times can be used to obtain the desired time delays. The delivery systems of the present invention can be used to deliver a single bioactive compound, more than one bioactive compound at the same time, or more than one bioactive compound in sequence. Thus, as used herein, the phrases "a bioactive compound" and "the bioactive compound" , are meant to be inclusive of one or more bioactive compounds. For purposes of the present invention by "fiber" it is meant to include fibrils ranging in diameter from submicron, i. The bioactive compound is incorporated within the polymeric fibers either by suspension of compound particles or dissolution of the compound in the solvent used to dissolve the polymer prior to electrospinning of the polymeric fibers. For purposes of the present invention, by "incorporated within" it is meant to include embodiments wherein the bioactive compound is inside the fiber as well as embodiments wherein the bioactive compound is dispersed between the fibers. The polymeric fibers comprising the bioactive compound can be arranged as matrices, linear assemblies, or braided or woven structures. In addition, the fibers which release a bioactive compound can serve as film coatings for devices such as implants, tissue engineering scaffolds, pumps, pacemakers and other composites. These fiber assemblies can be spun from any polymer which can be dissolved in a solvent. The solvent can be either organic or aqueous depending upon the selected polymer. Examples of polymers which can be used in production of the polymeric fibers of the present invention include, but are not limited to, nondegradable polymers such as polyethylenes, polyurethanes, and EVA, and biodegradable polymers such as poly lactic acid-glycolic acid , poly lactic acid , poly glycolic acid , poly glaxanone , poly orthoesters , poly pyrolic acid and poly phosphazenes. Examples of bioactive compounds which can be incorporated into the polymeric fibers include any drug for which controlled release in a patient is desired. Some examples include, but are not limited to, steroids, antifungal agents, and anticancer agents. Other bioactive compounds of particular use in the present invention include tissue growth factors, angiogenesis factors, and anti-clotting factors. If the bioactive compound is to reside within or inside the polymer fiber, selection of the polymer should be based upon the solubility of the bioactive compound within the polymer solution. Water soluble polymers such as polyethylene oxide can be used if the bioactive compound also dissolves in water. Alternatively, hydrophobic bioactive compounds which are soluble in organic solvent such as steroids can be dissolved in an organic solvent together with a hydrophobic polymer such as polylactic glycolic acid PLAGA. If the bioactive compound is to reside between the polymer fibers, dissolution of the bioactive compound in the polymer solution is not required. Instead, the bioactive compound can be suspended in the polymer solution prior to

electrospinning of the fibers. In one embodiment of the present invention, the bioactive compound-containing fibers can be splayed directly onto devices such as implants, tissue engineering scaffolds, pumps and pacemakers as a film coating. For implants and tissue engineering scaffolds, examples of preferred bioactive compounds include tissue growth factors and angiogenesis factors. For pumps or pacemakers, the bioactive compound may comprise an anti-clotting factor. The coated device is then implanted into a patient wherein the bioactive compound or compounds are released upon degradation of or by diffusion from, or combinations thereof, the polymeric fiber film. In another embodiment, a matrix or linear assembly of the bioactive compound-containing fibers is prepared. Alternatively, the matrix may comprise layers of fibers containing different bioactive compounds. The matrix or linear assembly is then implanted into a patient for controlled release of the bioactive compound as the polymeric fibers degrade or as the bioactive compound diffuses from the polymeric fibers. For purposes of the present invention, by "implanting" or "implanted" as used herein, it is meant to be inclusive of placement of the delivery systems of the present invention into a patient to achieve systemic delivery of the bioactive compound, as well as placement of the delivery system into a patient to achieve local delivery. For example, the delivery systems of the present invention may be placed on the wound of a patient to enhance healing via release of the bioactive compound. Delivery systems may also be placed on the surface or wrapped around an organ, tissue or vessel for delivery of the bioactive compound to the organ tissue or vessel. In another embodiment of the present invention, a braided, knitted or woven structure of bioactive compound- containing fibers is prepared. These structures are prepared using an extension of the traditional 2 -dimensional braiding technology in which fabric is constructed by the intertwining or orthogonal interlacing of yarns to form an integral structure through position displacement. A wide range of 3-dimensional structures comprising the bioactive compound- containing fibers can be fabricated in a circular or rectangular loom. In this embodiment, the structure may comprise only bioactive compound-containing fibers, bioactive compound-containing fibers sandwiched between polymeric fibers which contain no bioactive compound, or a mixtures of fibers containing different bioactive compounds. Like the matrix or linear assembly, this structure can be implanted into a patient for controlled release of the bioactive compound or compounds as the polymeric fibers degrade or as the bioactive compound diffuses from the polymeric fibers. Accordingly, the present invention also relates to methods for modulating the rate of release of a bioactive compound from a delivery system for bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers. By "modulate" or "modulating", it is meant that the rate or release of the bioactive compound incorporated within of between the polymeric fibers of the delivery system is increased or decreased. Varying one or more of these parameters can be performed routinely by those of skill in the art based upon teachings provided herein. The ability of systems of the present invention to release a bioactive compound in a controlled manner was demonstrated using polymeric fiber matrices containing fluorescently labeled bovine serum albumin FITC-BSA dispersed between the fibers of the matrix. To construct the bioactive compound-loaded matrices, various concentrations of finely ground FITC-BSA were suspended in biodegradable polymer polylactic glycolic acid in Suspensions contained in a glass syringe with a capillary tip were electrospun into approximately nm diameter fibers via an electrostatic based self-assembly process in which a high voltage electric field was generated between the oppositely charged polymer and a metallic collection screen. At a critical voltage the charge overcomes the surface tension of the deformed polymer drop at the needle tip, producing an ultrafine jet. The similarly charged fibers are splayed and during their passage to the screen, the solvent quickly evaporates so that dry fibers accumulate randomly on the screen forming a mesh matrix. The material properties of this mesh matrix of bioactive compound-containing fibers were examined via standard electron microscopy and tensile testing. It was found that tensile strength and the release profiles were a function of protein loading. This sink mimics in vivo conditions. While release in the first 24 hours after initiation was dominant, release to over hours was observed with an increase in release at the point where the fibers started to breakdown. The following nonlimiting examples are provided to further illustrate the present invention. The syringe was fitted with a 16G needle with the tip of the needle at a distance of 24 cm from the metallic collection screen. A piece of nonwoven mat was placed on the metallic screen. A voltage of 20 kV was applied between the collection screen and the needle tip which resulted in

fibers being sprayed into a nonwoven matrix on the metallic screen. The spraying was complete in about 4 hours. The buffer was exchanged at different points in time in order to mimic infinite sink conditions. The amount of protein released was measured in the form of fluorescence of the FITC-BSA on a spectrophotofluorometer at an excitation wavelength of nm and an emission wavelength of nm. Claims What is Claimed is; 1. A system for delivery of bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers. The system of claim 1 which is biodegradable. The system of claim 1 which is nondegradable. The system of claim 1 wherein the fibers are arranged as a matrix or linear assembly, a film coating on a device, or a braided or woven structure. The system of claim 1 wherein particles of the bioactive compound are suspended in a polymer solution prior to electrospinning of the polymeric fibers so that the bioactive compound is incorporated between the polymeric fibers. The system of claim 1 wherein the bioactive compound is dissolved into a polymer solution prior to electrospinning of the polymeric fibers so that the bioactive compound is incorporated within the polymeric fibers. The system of claim 1 comprising more than one bioactive compound incorporated into a single or multiple layers of polymeric fibers for delivery of the bioactive compounds sequentially or in concert.

Chapter 2 : Open Journal Systems

Bioactive polymeric systems would also include biologically active polymers, such as natural polymers, synthetic polypeptides, pseudoenzymes, pseudonucleic acids, and polymeric drugs. In addition, the area can include immobilized bioactive materials, such as immobilized enzymes, antibodies, and other bioactive agents.

The delivery systems of the present invention may be comprised of either biodegradable or nondegrading polymeric fibers. Bioactive compounds are included in the delivery system either by suspending the compound particles or dissolving the compound in the polymer solution used to produce the fibers. Fibers are spaced apart by a distance of about to microns for diffusion and may comprise polyanhydrides, polyorthoesters, polyglycolic acid or polymethacrylate. The scaffolds may be coated withe materials such as agar, agarons, gelatin, gum arabic, basement membrane material, collagen type I, II, III, IV or V, fibronectin, laminin, glycosaminoglycans, and mixtures thereof. Encapsulation of a bioactive compound within a polymer matrix has also been described. Recently, it has been shown that polymer fibers of nanometer diameter can be electrospun from sulfuric acid into a coagulation bath Reneker, D. In these studies more than 20 polymers including polyethylene oxide, nylon, polyimide, DNA, polyaramide and polyaniline were electrospun into electrically charged fibers which were then collected in sheets or other useful geometrical forms. Electrospinning techniques have also been applied to the production of high performance filters Doshi, J. Journal of Electrostatics AIChE Journal The present invention relates to delivery systems for the controlled release of bioactive compounds which comprise polymeric fibers and the bioactive compound. Another object of the present invention is to provide a method for delivering a bioactive compound to a patient for controlled release of the bioactive compound in the patient. In one embodiment of this method of the present invention, the bioactive compound is incorporated into a polymeric fiber matrix or linear assembly or a braided or woven structure and implanted into the patient. In another embodiment, the bioactive compound is incorporated into a polymeric fiber film used to coat implants, tissue engineering scaffolds and other devices such as pumps and pacemakers which are then implanted into the patient. In yet another embodiment, the bioactive compound is incorporated into a polymeric fiber film used to wrap organs, tissues or vessels in a patient. Another object of the present invention is to provide methods for modulating the rate of release of a bioactive compound from a delivery system for bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers. These methods include modulating loading of the bioactive compound incorporated with or between polymeric fiber, selecting polymers to produce the polymeric fibers which degrade at varying rates, varying polymeric concentration of the polymeric fibers and varying polymeric fiber diameter. In the electrospinning process, a high voltage electric field is generated between oppositely charged polymer fluid contained in a glass syringe with a capillary tip and a metallic collection screen. As the voltage is increased, the charged polymer solution is attracted to the screen. Once the voltage reaches a critical value, the charge overcomes the surface tension of the suspended polymer cone formed on the capillary tip of the syringe and a jet of ultrafine fibers is produced. As the charged fibers are splayed, the solvent quickly evaporates and the fibers are accumulated randomly on the surface of the collection screen. This results in a nonwoven mesh of nano and micron scale fibers. Varying the charge density applied voltage , polymer solution concentration, solvent used, and the duration of electrospinning can control the fiber diameter and mesh thickness. Other electrospinning parameters which may be varied routinely to effect the fiber matrix properties include distance between the needle and collection plate, the angle of syringe with respect to the collection plate, and the applied voltage. In the present invention, electrospinning is used to produce polymeric fiber matrices with the capability of releasing bioactive compounds in a controlled manner over a selected period of time. In one embodiment, the delivery system of the present invention is used to maintain delivery of a steady concentration of bioactive compound. In another embodiment, the delivery system is used in pulsed delivery of the bioactive compound wherein the compound is released in multiple phases in accordance with either rapid or slow degradation of the polymer fibers or diffusion of the bioactive compound from the polymer fibers. In yet another embodiment, the delivery system is used to obtain a delayed release of a bioactive

compound. For example, the bioactive compound-containing fiber polymer matrix can be coated with a layer of nonwoven polymer fiber matrix with no bioactive compound. In this embodiment, different polymers with different degradation times can be used to obtain the desired time delays. The delivery systems of the present invention can be used to deliver a single bioactive compound, more than one Ibioactive compound at the same time, or more than one bioactive compound in sequence. The bioactive compound is incorporated within the polymeric fibers either by suspension of compound particles or dissolution of the compound in the solvent used to dissolve the polymer prior to electrospinning of the polymeric fibers. The polymeric fibers comprising the bioactive compound can be arranged as matrices, linear assemblies, or braided or woven structures. In addition, the fibers which release a bioactive compound can serve as film coatings for devices such as implants, tissue engineering scaffolds, pumps, pacemakers and other composites. These fiber assemblies can be spun from any polymer which can be dissolved in a solvent. The solvent can be either organic or aqueous depending upon the selected polymer. Examples of polymers which can be used in production of the polymeric fibers of the present invention include, but are not limited to, nondegradable polymers such as polyethylenes, polyurethanes, and EVA, and biodegradable polymers such as poly lactic acid-glycolic acid , poly lactic acid , poly glycolic acid , poly glaxanone , poly orthoesters , poly pyrolic acid and poly phosphazenes. Examples of bioactive compounds which can be incorporated into the polymeric fibers include any drug for which controlled release in a patient is desired. 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A wide range of 3-dimensional structures comprising the bioactive compound-containing fibers can be fabricated in a circular or rectangular loom. In this embodiment, the structure may comprise only bioactive compound-containing fibers, bioactive compound-containing fibers sandwiched between polymeric fibers which contain no bioactive compound, or a mixtures of fibers containing different bioactive compounds. Like the matrix or linear assembly, this structure can be implanted into a patient for controlled release of the bioactive compound or compounds as the polymeric fibers degrade or as the bioactive compound diffuses from the polymeric

fibers. Accordingly, the present invention also relates to methods for modulating the rate of release of a bioactive compound from a delivery system for bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers. The ability of systems of the present invention to release a bioactive compound in a controlled manner was demonstrated using polymeric fiber matrices containing fluorescently labeled bovine serum albumin FITC-BSA dispersed between the fibers of the matrix. To construct the bioactive compound-loaded matrices, various concentrations of finely ground FITC-BSA were suspended in biodegradable polymer polylactic glycolic acid in Suspensions contained in a glass syringe with a capillary tip were electrospun into approximately nm diameter fibers via an electrostatic based self-assembly process in which a high voltage electric field was generated between the oppositely charged polymer and a metallic collection screen. At a critical voltage the charge overcomes the surface tension of the deformed polymer drop at the needle tip, producing an ultrafine jet. The similarly charged fibers are splayed and during their passage to the screen, the solvent quickly evaporates so that dry fibers accumulate randomly on the screen forming a mesh matrix. The material properties of this mesh matrix of bioactive compound-containing fibers were examined via standard electron microscopy and tensile testing. It was found that tensile strength and the release profiles were a function of protein loading. This sink mimics in vivo conditions. While release in the first 24 hours after initiation was dominant, release to over hours was observed with an increase in release at the point where the fibers started to breakdown. The following nonlimiting examples are provided to further illustrate the present invention. The syringe was fitted with a 16G needle with the tip of the needle at a distance of 24 cm from the metallic collection screen. A piece of nonwoven mat was placed on the metallic screen. A voltage of 20 kV was applied between the collection screen and the needle tip which resulted in fibers being sprayed into a nonwoven matrix on the metallic screen. The spraying was complete in about 4 hours. The buffer was exchanged at different points in time in order to mimic infinite sink conditions. The amount of protein released was measured in the form of fluorescence of the FITC-BSA on a spectrophotofluorometer at an excitation wavelength of nm and an emission wavelength of nm. A system for delivery of bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers.

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The vast array of libraries in the world bear mute witness to the truth of the year-old observation of King Solomon who stated " of making many books there is no end, and much study is a weariness of the flesh." Yet books are an essential written record of our lives and the progress of.

Bioactive borate glasses have been shown to promote angiogenesis. There is a need to investigate the biofabrication of polymer composites by incorporating borate glass to increase the angiogenic capacity of the fabricated scaffolds. ASCs suspended in Matrigel were ejected as droplets using a second syringe. Degradation of the scaffolds in cell culture medium showed a controlled release of bioactive glass for up to two weeks. The viability of ASCs printed on the scaffold was investigated during the same time period. Keywords bioprinting; biofabrication; human adipose-derived stem cell; MSCs; bioactive glass; polycaprolactone; scaffold; tissue engineering Full Text: Complications and functional assessment. Clinical Orthophopedics and Related Research, Journal of Materials Science: Materials in Medicine, vol. Journal of Mechanical Behaviour of Biomedical Materials, vol. Annals Biomedical Engineering, vol. Ozbolat I T and Hospodiuk M, , Current advances and future perspectives in extrusion-based bioprinting. Inexpensive, easy-to-use cotton candy-like glass fibers appear to speed healing in initial venous stasis wound trial. The American Ceramic Society Bulletin, vol. Cells Tissues Organs, vol. Journal of Cellular Biochemistry, vol. Superiority of synovium as a cell source. A new tool for regenerative medicine and tissue banking. Tissue Engineering Part C Methods, vol. Progress in Polymer Science, vol. Materials Science and Engineering:

Chapter 4 : JFB | Free Full-Text | Bioactive Polymeric Materials for Tissue Repair

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Chapter 5 : - Bioactive Polymeric Systems: An Overview by CHARLES G. GEBELEIN

Additional resources for Bioactive Polymeric Systems: An Overview Example text The cornea is convenient to view and implanted polymers can be observed without sacrificing the animal.