days, these anti-VEGF drugs clear from the eye after standard intravitreal injection, necessitating monthly super-threshold bolus doses in attempt to prolong therapeutically effective periods.

A sustained and controlled release drug delivery device capable of delivering drugs including protein therapeutics to the anterior and/or posterior segments of the eye while minimizing the number of intraocular injections required for treatment and maintaining a therapeutic concentration of drug within the eye is of interest.

SUMMARY

Multilayer thin film medical devices that include a bioactive agent for elution to the surrounding tissue upon administration to a subject are provided. Also provided are methods and kits for localized delivery of a bioactive agent to a tissue of a subject, and methods of preparing the subject devices. The multilayer thin film medical device includes a first layer, a bioactive agent and a second layer. The first and the second layers may be porous or non-porous. The devices have a furled structure, suitable for administration to a subject via needle or a catheter.

Multilayer thin film devices that include a bioactive agent for elution to the surrounding tissue upon administration to a subject are provided. The devices are useful as medical devices for drug delivery, including ocular devices for delivery of bioactive proteins and small molecules. Also provided are methods of localized delivery of a bioactive agent to a tissue of a subject, and methods of preparing the subject multilayer thin film medical devices.

In one aspect of the present disclosure, there is provided a multilayer thin film medical device, comprising:

a first layer comprising a biodegradable polymer;

a bioactive agent; and

a second layer comprising a biodegradable polymer,

wherein the second layer is in contact with the bioactive agent;

wherein the bioactive agent is positioned only between the first layer and the second layer,

wherein the first and the second layers are sealed together at an area surrounding the area where the bioactive agent is disposed thereby sealing the bioactive agent inside the edges of the multilayer thin film medical device,

wherein the bioactive agent is not positioned between the first and the second layers at the edges of the multilayer thin film medical device,

wherein the multilayer thin film medical device has an area between 1 mm^2 and 36 mm^2,

wherein the device has a thickness between 10 μm and 500 μm, wherein

(a) the first layer is non-porous and the second layer is non-porous, or

(b) the first layer is non-porous and the second layer is nanoporous, or

(c) the first layer is non-porous and the second layer is microporous, and

wherein the device provides a zero order release of the bioactive agent over at least 10 days following administration.

In certain examples, the multilayer thin film medical devices include a first thin film layer, bioactive agent and a second thin film layer, where the bioactive agent is positioned between the first and second layers. The first layer may include a polymer and a pore forming agent. The second layer may be porous or non-porous. The first and second layers may be biodegradable or non-biodegradable. Following administration to a subject, the pore forming agent dissolves to produce a porous first layer and provides for elution of the bioactive agent (e.g., a protein therapeutic) to the surrounding tissue. In some examples, the device further includes a third nanostructured porous layer positioned between the first layer and the reservoir of bioactive agent.

In certain examples, the multilayer thin film medical devices include a first non-porous thin film layer, a bioactive agent, and a second non-porous thin film layer, where the bioactive agent is positioned in between the first and second layers.

In certain examples, the device has a furled structure, where the structure unfurls *in vivo* in the presence of a hydrating liquid. In certain cases, the device having a furled structure may be administered to a subject by injection into a target tissue.

These devices and methods find use in a variety of applications in which delivery of bioactive agents to subjects is desired.

BRIEF DESCRIPTION OF THE DRAWINGS

The embodiments described in this disclosure are best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

FIGURES 1A-F show scanning electron micrograph (SEM) images and corresponding pore size histograms of polycaprolactone (PCL)/gelatin thin films after five days incubation in PBS.

FIGURES 2A-B show graphs of the porosity and mass loss of PCL/gelatin thin films after incubation in PBS.

FIGURES 3A-C illustrate the fabrication of a multilayer thin film device. (A) Fabrication; (B) a finished device of ~2 mm in diameter; and (C) profile of the device edge.

FIGURES 4A-B show the fractional elution profile of proteins ((A) BSA; (B) IgG) from PCL/gelatin and PCL-only thin film devices.

FIGURE 5 shows a comparison of the rates of elution of BSA and IgG from a PCL/gelatin thin film device.

FIGURE 6A illustrates that the bioactivity of IgG eluted from a PCL/gelatin thin film device is maintained over time, as determined by ELISA and BCA assays. **FIGURE 6B** illustrates *in vivo* activity of IgG eluted from PCL/gelatin thin film device 6 weeks-post administration.

FIGURES 7A-C show a furled thin film device (A), and an unfurled device (B), that has a thin form factor (C).

FIGURES 8A-E illustrate thin film fabrication procedure. **FIGURES 8F-G** show scanning electron microscope (SEM) images of a typical nanostructured PCL film.

WHAT IS CLAIMED IS:

1. A multilayer thin film medical device, comprising:

a first layer comprising a biodegradable polymer;

a bioactive agent; and

a second layer comprising a biodegradable polymer,

wherein the second layer is in contact with the bioactive agent;

wherein the bioactive agent is positioned only between the first layer and the second layer,

wherein the first and the second layers are sealed together at an area surrounding the area where the bioactive agent is disposed thereby sealing the bioactive agent inside the edges of the multilayer thin film medical device,

wherein the bioactive agent is not positioned between the first and the second layers at the edges of the multilayer thin film medical device,

wherein the multilayer thin film medical device has an area between 1 mm^2 and 36 mm^2,

wherein the device has a thickness between 10 μm and 500 μm, wherein

(a) the first layer is non-porous and the second layer is non-porous, or

(b) the first layer is non-porous and the second layer is nanoporous, or

(c) the first layer is non-porous and the second layer is microporous, and

wherein the device provides a zero order release of the bioactive agent over at least 10 days following administration.

2. The multilayer thin film medical device of claim 1, wherein the device comprises a furled structure.

3. The multilayer thin film medical device of claim 2, wherein the furled structure is substantially cylindrical.

4. The multilayer thin film medical device of claim 2, wherein the furled structure is substantially frusto-conical.

5. The multilayer thin film medical device of claim 1, wherein the device comprises an unfurled structure.

6. The multilayer thin film medical device of claim 5, wherein the unfurled structure comprises a substantially circular peripheral edge.

7. The multilayer thin film medical device of any one of claims 1 to 6, further comprising a third nanostructured porous layer positioned between the first layer and the bioactive agent.

8. The multilayer thin film medical device of claim 7, wherein the third nanostructured porous layer has an average pore size of between about 1 nm and about 100 nm.

9. The multilayer thin film medical device of any one of claims 1-8, wherein the biodegradable polymer is PLA, PGA, PCL, PLGA, PLCL, or a combination thereof..

10. The multilayer thin film medical device of claim 1, wherein the bioactive agent is disposed in a plurality of reservoirs located across one surface of the second layer.

11. The multilayer thin film medical of claim 1, wherein the second layer comprises a plurality of reservoirs located across one surface of the second layer, wherein a first reservoir of the plurality of reservoirs comprises the bioactive agent and a second reservoir of the plurality of reservoirs comprises another bioactive agent.

12. The multilayer thin film medical device of any one of claims 1-11, wherein the bioactive agent is present in a lyophilized form.

13. The multilayer thin film medical device of any one of claims 1-11, wherein the bioactive agent is disposed as a thin film and is in a lyophilized form.

14. The multilayer thin film medical device of claim 7, comprising a fourth non-porous layer in contact with the second layer, a fifth layer comprising a reservoir comprising another bioactive agent in contact with the fourth non-porous layer, a sixth nanostructured layer

in contact with the fifth layer, and a seventh layer, comprising a polymer and a pore forming agent, in contact with sixth nanostructured layer.

15. The multilayer thin film medical device of claim 7, wherein the bioactive agent is disposed in a plurality of reservoirs located across one surface of the second layer.

16. The multilayer thin film medical of claim 7, wherein the second layer comprises a plurality of reservoirs located across one surface of the second layer, wherein a first reservoir of the plurality of reservoirs comprises the bioactive agent and a second reservoir of the plurality of reservoirs comprises another bioactive agent.

17. The multilayer thin film medical device of any one of claims 1 to 16, wherein the bioactive agent is a protein therapeutic, a small molecule drug, a large molecule drug or an aptamer.

18. The multilayer thin film medical device of claim 17, wherein the bioactive agent is a protein therapeutic selected from ranibizumab, bevacizumab, trastuzumab, rituximab, gentuzumab ozogamicin and cetuximab.

19. The multilayer thin film medical device of claim 17, wherein the bioactive agent is a small molecule therapeutic selected from steroids, rapamycin, and prostaglandin.

20. The multilayer thin film medical device of claim 1, wherein the device is circular and has a diameter between 1 mm and 50 mm.

21. The multilayer thin film medical device of claim 1, wherein the first layer and the second layer are non-porous and wherein the bioactive agent is a small molecule drug.

22. The multilayer thin film medical device of claim 1, wherein the first layer is non-porous and the second layer is nanoporous.

23. The multilayer thin film medical device of claim 1, wherein the first layer is non-porous and the second layer is microporous.

24. The multilayer thin film medical device of claim 22 or 23, wherein the bioactive agent is a large molecule.

25. The multilayer thin film medical device of claim 24, wherein the large molecule is a protein therapeutic.

26. The multilayer thin film medical device of claim 25, wherein the protein therapeutic is selected from ranibizumab, bevacizumab, trastuzumab, rituximab, gentuzumab ozogamicin and cetuximab.