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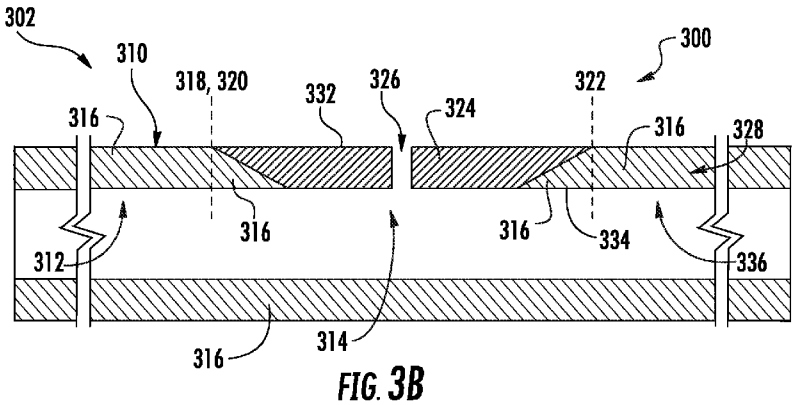

FIG. 3B

(57) Abstract: A drug delivery device is provided. In an embodiment, the device includes a polymeric wall structure which includes a first wall portion and an adjacent second wall portion, wherein the first and second wall portions have been co-extruded to define and bound a drug reservoir space. A drug is contained in the drug reservoir space. The device includes an aperture that is in fluid communication with the drug reservoir space. The first and second wall portions are impermeable to the drug. The first wall portion is water impermeable, and the second wall portion is water permeable and configured to permit water in vivo to diffuse into the drug reservoir space and produce an osmotic pressure for driving release of the drug through the aperture.

WO 2017/151983 A1

OSMOTIC DRUG DELIVERY DEVICES AND METHODS OF MAKING OSMOTIC DRUG DELIVERY DEVICES

Cross-Reference to Related Applications

This application claims priority to U.S. Provisional Patent Application No. 62/302,597, filed March 2, 2016, which is incorporated herein by reference.

Background

The present disclosure is generally in the field of medical devices, and more particularly relates to drug delivery devices for insertion into the body of patient for controlled release of drug, including but not limited to devices deployable in the urinary bladder for administration of drug into the bladder.

Intravesical drug delivery devices are known. Examples of such devices are described in U.S. Patent 8,679,094 to Cima et al., U.S. Patent 9,017,312 to Lee et al., U.S. Patent 9,107,816 to Lee et al., and U.S. Patent Application Publication No. 2012/0089121 A1 to Lee et al. In some embodiments, the intravesical devices include a water permeable housing defining a drug reservoir lumen which contains a solid or semi-solid drug formulation, and release of the drug *in vivo* occurs by water from the bladder diffusing into drug reservoir lumen to solubilize the drug, and then an osmotic pressure build-up in the drug reservoir lumen drives the solubilized drug out of the device through a release aperture. In these embodiments, the housing is primarily water permeable, and therefore many other variables or device specifications, such as the surface area of the housing, the thickness of the housing wall, and the shape, size, number and placement of the apertures, are considered for modifying the drug release kinetics in such a situation; however, changing these variables may undesirably alter mechanical tolerability, available drug payload volume, or other desired characteristics of the device.

In some cases, e.g., with certain drugs and therapeutic applications, it would be desirable to extend the period over which a therapeutic amount of the drug is released and/or to keep the drug from coming out too quickly. One way of accomplishing this is by retarding the rate at which the water can enter the drug reservoir. U.S. Patent Application Publication No. 2009/0149822 A1 to Cima et al. discloses adding a conformal coating or sheath over at least a portion of an outer surface of the housing to reduce the water-permeability of the housing. However, this approach complicates manufacturing. Furthermore, because the device housing of these intravesical devices typically are designed to be elastically deformable, maintaining an effective coating may be challenging, since the

coating may delaminate and/or crack during device deformation, which could undesirably alter the drug release kinetics and negatively impact reproducibility of results.

It therefore would be desirable to provide new designs of intravesical drug delivery devices, or other drug delivery devices, having greater flexibility and are capable of releasing drug in *vivo* at controlled and effective release rates over an extended, particularly those devices operable as osmotic pump systems.

Summary

In one aspect, drug delivery devices are provided. In an embodiment, the device includes a polymeric wall structure which includes a first wall portion and an adjacent second wall portion, wherein the first and second wall portions have been co-extruded to define and bound a drug reservoir space. A drug is contained in the drug reservoir space, and the device includes an aperture in fluid communication with the drug reservoir space, for releasing the drug from the device. The first and second wall portions are impermeable to the drug. The first wall portion is water impermeable, and the second wall portion is water permeable and configured to permit water *in vivo* to diffuse into the drug reservoir space and produce an osmotic pressure for driving release of the drug through the aperture.

In a preferred embodiment, the polymeric wall structure comprises an annular tube, the annulus of which is the drug reservoir space. In some cases, the first and second wall portions are adjacent one another over the full length of the annular tube. In some other cases, the second wall portion is adjacent to the first wall portion over only part of the full length of the annular tube.

In another aspect, methods are provided for administering a drug to a patient in need thereof. In an embodiment, the method includes the steps of (i) inserting into the patient a drug delivery device which includes a polymeric wall structure which includes first and second adjacent wall portions bounding a drug contained in a reservoir space, wherein the second wall portion, but not the first wall portion, is water permeable and configured to permit water *in vivo* to diffuse into the drug reservoir space and produce an osmotic pressure; and (ii) permitting water *in vivo* to diffuse into the drug reservoir space and produce an osmotic pressure to drive the drug from the device through an aperture for release into the patient.

In still another aspect, methods are provided for making a drug delivery device. In one embodiment, the method includes (i) introducing a first material into an extrusion stream of an extruder to form a first wall portion of a tubular structure; and (ii) introducing a second material into the extrusion stream in a manner to replace the first material in at least

one position and to form a second wall portion of the tubular structure, wherein the first wall portion is integrally connected to the second wall portion, and the first and second wall portions together define a drug reservoir space in the form of a drug reservoir lumen. In embodiments, the method further includes forming an aperture through a sidewall of the tubular structure, loading a drug into the drug reservoir lumen; and sealing the ends of the drug reservoir lumen.

Brief Description of the Drawings

The detailed description is set forth with reference to the accompanying drawings. The use of the same reference numerals may indicate similar or identical items. Various embodiments may utilize elements and/or components other than those illustrated in the drawings, and some elements and/or components may not be present in various embodiments. Elements and/or components in the figures are not necessarily drawn to scale.

FIG. 1A is a plan view of one embodiment of a drug delivery device in accordance with the present disclosure.

FIG. 1B is a traverse cross-sectional view of the drug delivery device of **FIG. 1A**, taken along line **1B-1B**.

FIG. 2A is a perspective view of a polymeric wall structure of another embodiment of a drug delivery device (with ends open and the drug and elastic retention frame omitted for clarity) in accordance with the present disclosure.

FIG. 2B is a longitudinal cross-sectional view of the polymeric wall structure shown in **FIG. 2A**, taken along line **2B-2B**.

FIG. 2C is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 2A**, taken along line **2C-2C**.

FIG. 2D is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 2A**, taken along line **2D-2D**.

FIG. 3A is top plan view of a polymeric wall structure of still another embodiment of a drug delivery device (with ends open and drug omitted for clarity) in accordance with the present disclosure.

FIG. 3B is a longitudinal cross-sectional view of the polymeric wall structure shown in **FIG. 3A**, taken along line **3B-3B**.

FIG. 3C is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 3A**, taken along line **3C-3C**.

FIG. 3D is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 3A**, taken along line **3D-3D**.

FIG. 3E is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 3A**, taken along line **3E-3E**.

FIG. 4A is a perspective view of a polymeric wall structure in still another embodiment of a drug delivery device (with ends open and the drug and elastic retention frame omitted for clarity) in accordance with the present disclosure.

FIG. 4B is a longitudinal cross-sectional view of the polymeric wall structure shown in **FIG. 4A**, taken along line **4B-4B**.

FIG. 4C is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 4A**, taken along line **4C-4C**.

FIG. 4D is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 4A**, taken along line **4D-4D**.

FIG. 5A is a perspective view of a polymeric wall structure in another embodiment of a drug delivery device (with ends open and the drug and elastic retention frame omitted for clarity) in accordance with the present disclosure.

FIG. 5B is a longitudinal cross-sectional view of the polymeric wall structure shown in **FIG. 5A**, taken along line **5B-5B**.

FIG. 5C is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 5A**, taken along line **5C-5C**.

FIG. 5D is a traverse cross-sectional view of the polymeric wall structure shown in **FIG. 5A**, taken along line **5D-5D**.

FIG. 5E is a traverse cross-sectional view of a polymeric wall structure showing an alternative placement of the aperture as compared to the aperture shown in **FIG. 5D**.

FIG. 6A is a perspective view of yet another embodiment of a drug delivery device (with the drug and elastic retention frame omitted for clarity) in accordance with the present disclosure.

FIG. 6B is a longitudinal cross-sectional view of the drug delivery device shown in **FIG. 6A**, taken along line **6B-6B**.

FIG. 6C is a traverse cross-sectional view of the drug delivery device shown in **FIG. 6A**, taken along line **6C-6C**.

FIG. 6D is a traverse cross-sectional view of the drug delivery device shown in **FIG. 6A**, taken along line **6D-6D**.

FIG. 7A is a perspective view of a polymeric wall structure of yet a further embodiment of a drug delivery device in accordance with the present disclosure.

FIG. 7B is a longitudinal cross-sectional view of the drug delivery device shown in **FIG. 7A**, taken along line **7B-7B**.

FIG. 7C is a traverse cross-sectional view of the drug delivery device shown in **FIG. 7A**, taken along line **7C-7C**.

FIG. 8A is a partial perspective view of another embodiment of a drug delivery device in accordance with the present disclosure

FIG. 8B is a longitudinal cross-sectional view of the drug delivery device shown in **FIG. 8A**, taken along line **8B-8B**.

Detailed Description

Improved drug delivery devices have been developed. In particular embodiments, the devices are configured for intravesical drug delivery. In embodiments, the devices have a housing containing a drug payload for controlled release by osmotic pumping, in which the housing is formed of a combination of a water permeable wall portion and a water impermeable wall portion. These two portions are formed by at least two different elastomeric materials, which preferably are co-extruded to form an annular housing that includes at least one water impermeable wall portion integrally formed and connected to at least one water permeable wall portion.

As used herein, the term "impermeable" with respect to the drug refers to the material(s) forming the tubular wall structure, being substantially impermeable to the solubilized drug, such that no substantial amount of the solubilized drug can diffuse therethrough over the therapeutic period in which the device is located *in vivo*. As used herein, the term "impermeable" with respect to water refers to the material(s) forming the particular portion of the tubular wall structure being substantially impermeable to water, such that no substantial amount of the water can diffuse therethrough over the therapeutic period in which the device is located *in vivo*. In context of these terms, the impermeability refers to transwall diffusion. It does not refer to passage through a drug release aperture that may be manufactured to extend through the wall structure.

It is known that the drug release rate from a delivery system that relies, at least in part, on diffusion of water through a tubular device wall can be controlled by the tube wall thickness for a given material. For an osmosis-based system, increased wall thickness means slower osmotic water imbibition through the wall leading to slower drug release. However, because such intravesical tubular drug delivery systems desirably are insertable

into the bladder through a deployment instrument placed in a patient's urethra, the available port size for insertion of the drug delivery system is limited by the column strength of the deployment instrument, human anatomy and patient discomfort associated with a larger size of the instrument. This limitation inevitably affects the maximum allowable cross-sectional size of the drug delivery system. Therefore, the approach of increasing the wall-thickness to slow down drug release cannot be taken beyond a certain point due to the size limitation of the device.

Furthermore, because the drug delivery device systems of intravesical devices are typically designed to be elastically deformable, the thickness of the wall may have a maximum limit, since increasing the thickness also increases the stiffness/hardness of the wall, thereby negatively impacting the overall elasticity of the systems.

Therefore, if material thickness cannot be increased, then an alternative approach to reduce the drug release rate (e.g., compared with that obtained with silicone annular tube) is to screen for alternative materials of construction having suitable water permeability. However, the alternative material with lower permeability also needs to satisfy the mechanical and biochemical property requirements of the device, including biocompatibility, suitable stiffness/hardness and elasticity to move between a bladder retentive shape and a linear insertion shape, in addition to being effective within the size limitations for device deployment. Such screening is not trivial.

In both approaches (increasing wall thickness and selecting alternative materials), the selected combination of material and wall thickness should impart a device body flexibility that satisfies the shape changing functionality and should not dominate/alter the shape that otherwise would be imparted by a retention frame, such as a nitinol wireform, if used.

The Drug Delivery Devices

Accordingly, new tubular osmotic drug delivery devices have been developed that are designed to reduce or control drug release rates without negatively altering the mechanical properties and suitable dimensions for device deployment and tolerability. In embodiments, the designs reduce drug release rates by incorporating both water permeable and water impermeable materials into the device housing so as the rate of osmotic water imbibition of the devices can be selected/controlled by the relative proportions of the water permeable and water impermeable portions. That is, in these devices, drug release is driven by osmotic pressure created by the influx of water into the device, and that influx of water is controlled by the permeability and size/area of the water permeable portion of the device

housing. In embodiments, the two materials are formed into a tubular housing structure by a continuous or discontinuous co-extrusion process.

The present osmotic systems provide advantages in both device performance and manufacturability. In one aspect, the device body or housing of the osmotic drug delivery system is constructed of two different biocompatible polymeric (e.g., elastomeric) materials, which are co-extruded, together, in a continuous or discontinuous manner. The first material, which typically forms the majority portion of the sidewall of a tubular (annular) device body, is practically water impermeable and drug impermeable. The second material, which typically forms a minority portion of the sidewall of the tubular device body (often in the form of a strip, or stripe), is also drug impermeable but is water permeable. In a preferred embodiment, the second material is not hydrophilic. Drug is released from the device driven by osmotic pressure, either through one or more apertures (through-holes) in the device (e.g., in the sidewall of the annular device body or in an end piece plugging one or both ends of the annulus of the annular device body) or through one or more microchannels transiently formed between the annular tube and a restraining plug inserted into one or both ends of the annulus of the annular device body. In this aspect of the device, one beneficially is able to easily modify the water flux by changing the stripe angle instead of changing the overall wall thickness. One of the advantages for this type of stripe extrusion is that the same tooling can create different angles, which means great cost saving for multiple variations. Considering all the difficulties involved with changing the wall thickness and/or the materials of construction, the present systems and methods therefore advantageously improve the development of osmotic release systems.

In embodiments, the device housing includes a first elastomeric material that is water permeable and a second elastomeric material that is water impermeable. Both materials are selected to be impermeable to the drug contained in the housing.

The length and width, e.g., wall portion formed of the water permeable material are selected to provide a desired rate of water flux into the reservoir defined by device housing. In one embodiment, the width of the water permeable wall portion may be quantified by the arc angle defining the wall when viewed in cross-section normal to the luminal axis. The water permeable region(s) of the device housing can be controlled to give a selected area of, and thus rate for, osmotic water imbibition, and yet advantageously maintain suitable overall dimensions and elasticity of the device, formed of suitable biocompatible elastomers. Advantageously by forming the device housing by a co-extrusion process, the structural variations of the water permeable region(s) can be created with conventional co-

extrusion equipment by selection of the processing parameters, thereby beneficially providing the ability to cost-effectively manufacture multiple structural device configurations.

In some embodiments, the length of the water permeable regions(s) runs along only a portion of the overall length of the device. In such an embodiment, larger arc angles of the water permeable region(s) can therefore be employed while keeping the rate of drug release at a desirable level over an extend period of time.

In a preferred embodiment, the drug is in a solid form and a portion of the tubular housing is water permeable to permit *in vivo* solubilization of the drug while in the drug reservoir lumen. For example, the solid form may be a plurality of tablets or granules.

In some preferred embodiments, the device includes one or more elastic structures configured to retain the drug delivery device within a natural lumen in a patient's body. For example, the lumen may be one of the genitourinary system, such as the renal pelvis or bladder. In some embodiments, the elastic structure is an elastic retention frame positioned in a retention frame lumen in the drug delivery device. In certain embodiments, the retention frame includes an elastic wire, such one made of a superelastic alloy. For example, in one case, the retention frame consists of a nitinol wire that has been set in a coiled configuration. In certain other embodiments, the retention frame is an elastic polymer. For example, a liquid polymer or precursor may be filled into a retention frame lumen and then cured or solidified, for example while the lumen is held in a coiled configuration, to produce a shape set elastomeric retention frame. In a preferred embodiment, the device is elastically deformable between a relatively straightened shape suited for insertion through the urethra of a patient and into the patient's bladder and a retention shape suited to retain the device within the bladder.

In some embodiments, the device does not include a retention frame lumen or a retention frame or wire. Instead, the materials of the tubular wall structure are configured to be elastically deformable between the straightened shape and the retention shape, in the absence of a retention frame or wire. Thus, in such embodiments, the design and manufacturing of the device is simplified, and the overall size of the device is minimized (or drug payload may be increased if the size of the device remains constant). Advantageously, in embodiments without a retention frame, the tubular wall structure serves the functions of (i) forming the drug reservoir lumen, (ii) controlling drug release, and (iii) retaining the device in the bladder upon deployment.

Illustrative Embodiments

In one aspect, as shown in **FIGS. 1A** and **1B**, a drug delivery device **100** is provided that includes a tubular housing having a closed drug reservoir lumen **106** bounded by a wall structure **104**, and having an aperture **124** extending through the wall structure **104** and in fluid communication with the drug reservoir lumen **106**, wherein (i) at least a portion of the wall structure **104** is water permeable, and (ii) at least a portion of the wall structure is impermeable to the drug (in solid drug units **108**) and impermeable to water, such that the drug is releasable *in vivo* through the aperture **124**, driven by osmotic pressure.

In one aspect, as shown in **FIGS. 2A-2D**, a drug delivery device **200** is provided that includes an elongated, elastic housing **202** having a drug reservoir lumen **204** extending between a first end **206** and a second end **208**. The elastic housing **202** is formed of a tubular wall structure **210** that is impermeable to a drug (not shown) disposed in the drug reservoir lumen **204**. In use, the drug contained in the drug reservoir lumen **204** is released from the housing **202** through aperture **226** driven by osmotic pressure. The elastic housing **202** of the device **200** further includes a retention frame lumen **242** and an elastic retention frame **244** positioned in the retention frame lumen **242**.

In this embodiment, the tubular wall structure **210** includes a first annular segment **212** and a second annular segment **214**. The first and second annular segments **212**, **214** may be formed together in an extrusion process. The first annular segment **212** is formed entirely of a first material **216** which is impermeable to water. The first annular segment **212** has a first end **218** which is integrally formed and connected with a first end **220** of the second annular segment **214**. The second annular segment **214** is formed of the first material **216** and a second material **224** which is water permeable, such that water *in vivo* diffuses into the drug reservoir lumen **204** and solubilizes the drug. This influx of water creates an osmotic pressure gradient within the drug reservoir lumen **204**, which drives the drug from the device **200** through an aperture **226** that is in communication with the drug reservoir lumen **204**.

In this embodiment, the aperture **226** extends through a sidewall **228** of the tubular wall structure **210** located within the second annular segment **214**, although the aperture could, in alternative embodiments, extend through the first annular segment or through an end piece (plug) sealing one of the ends of the annular housing. In alternative embodiments (not shown), the drug delivery device **200** may include more than one aperture **236**.

In the embodiment illustrated in **FIGS. 2A-2D**, the second annular segment **214** includes a central portion **230** that extends between an external surface **232** and an internal

surface **234** of the tubular wall structure **210**. The central portion **230** may be formed entirely of the second material **224**.

The particular material and arc angle (θ) of the second material **224** within the second annular segment **214** may be selected to achieve a particular drug release profile, which generally would correspond to a selected rate of water permeation. In one embodiment, the portion of the second annular segment **214** comprising the first material **216** forms a first arcuate portion and the portion of the second annular segment **214** comprising the second material **226** forms a second arcuate portion having an arc angle of from about 15 degrees to about 120 degrees of a circumference of the tubular wall structure. The first and second arcuate portions are integrally connected and together define the annulus of the second annular segment **214**. In one embodiment, the portion of the second annular segment **214** comprising the second material **226** has an arc angle of from about 30 degrees to about 90 degrees, e.g., from about 30 degrees to about 60 degrees. In certain embodiments, the portion of the second annular segment comprising the second material comprises less than about 25% of a cross sectional area of the tubular wall structure taken at the central portion. In one embodiment, the portion of the second annular segment **214** comprising the second material **224** has an arc angle of from about 15 degrees to about 120 degrees of a circumference of the tubular wall structure. In one embodiment, the portion of the second annular segment comprising the second material has an arc angle of about 30 degrees to about 90 degrees. As used herein, the phrase "about" with reference to the arc angles of the portion of the second annular segment comprising the second material refers to the arc angle plus or minus 3 degrees.

In certain embodiments, as illustrated in **FIGS. 2A-2D**, the tubular wall structure further includes a third annular segment **236**, which is integrally formed and connected with an opposed second end **222** of the second annular segment **214** at a first end **223** of the third annular segment **236**. In a preferred embodiment, the second and third annular segments **214**, **236** are formed together in an extrusion process. In one embodiment, the third annular segment **236** is formed entirely of the first material **216**.

By limiting the area/proportion of the wall structure bounding the drug reservoir space through which water diffuse into the drug reservoir space, one is able to limit/control (i) the rate at which the drug in the reservoir becomes solubilized, and therefore (ii) the rate at which osmotic pressure is generated in the reservoir, and ultimately (iii) the rate at which drug is released from the device *in vivo*. This advantageously can enable the device to provide continuous release of the drug over a longer period, while still using desired

materials of construction at desirable wall thicknesses and overall device dimensions (needed for device flexibility/softness, for deployment into/through lumen in the patient's body, and/or for patient tolerability) , without sacrificing drug payload volume and without needing to resort to more complex and difficult to manufacture systems for controlled release.

FIGS. 3A-3E illustrate a variation of the drug delivery device **200** shown in in **FIGS. 2A-2D**, with **FIG. 3B** showing only a partial longitudinal cross-sectional view of the device **300**, and **FIGS. 3C-3E** showing traverse cross-sectional views of the device **300** taken along lines **3C-3C**, **3D-3D**, and **3E-3E**, respectively. The drug delivery device **300** includes an elongated, elastic housing **302** formed of a tubular wall structure **310**. The tubular wall structure **310** includes a first annular segment **312**, a second annular segment **314**, and a third annular segment **336**. The first annular segment **312** is formed of a first material **316**, the second annular segment **314** is formed of the first material **316** and a second material **324**, and the third annular segment **336** is formed of the first material **316**. In this embodiment, the second annular segment **314** is shown to include a transition region leading to each of the first and third annular segments **312**, **336**. In this way, not all of the second material **324** within the second annular segment **314** extends from the external and internal surfaces **332**, **334** of the tubular wall structure **310**. The segments are integrally formed and connected, but for purposes of illustration, the first and second segments are shown to interface at the dashed line where end **318** of segment **312** is joined to end **320** of segment **314**, and the second and third segments are shown to interface at the dashed line at end **322** of the second segment. In this embodiment, the aperture **326** extends through a sidewall **328** of the tubular wall structure **310** located within the second annular segment **314**.

In other embodiments, the tubular wall structure includes one or more additional annular segments that comprise the first or second materials.

Another embodiment of a drug delivery device is shown in **FIGS. 4A-4D**. The drug delivery device **400** includes an elongated, elastic housing **402** having a drug reservoir lumen **404** extending between a first end **406** and a second end **408**. The elastic housing **402** is formed of a tubular wall structure **410** that is impermeable to the drug contained in the drug reservoir lumen **404**. (For clarity of housing structure, the drug is not shown in these figures.) The tubular wall structure **410** includes a first wall structure **412** and a second wall structure **414**. In a preferred embodiment, the first and second wall structures **412**, **414** are formed together in an extrusion process.

The first wall structure **412** is formed of a first material **416** that is impermeable to water. In an embodiment, the first wall structure is formed entirely of the first material. The first wall structure **412** is integrally formed and connected to the second wall structure **414**. The second wall structure **414** is formed primarily or exclusively of the second material **424** that is water permeable. When the device is placed *in vivo*, water (e.g., urine in the bladder or renal pelvis, interstitial fluid, etc.) diffuses through the second wall structure and into the drug reservoir lumen **404**. In embodiments in which the drug is in a solid form, the water entering the drug reservoir lumen solubilizes the drug. This influx of water creates an osmotic pressure gradient within the drug reservoir lumen **404**, which drives the drug from the device **400** through an aperture **426** that is in communication with the drug reservoir lumen **404**. In this embodiment, the aperture **426** extends through a sidewall **428** of the tubular wall structure **410** located within the first wall structure **412**. In an alternative embodiment (not shown), the drug delivery device **400** includes more than one aperture **436**.

In certain embodiments, as illustrated in **FIGS. 4A-4D**, the tubular wall structure **410** further includes a third wall structure **436**, which is integrally formed and connected with an opposed second end **422** of the second wall structure segment **414**. In one embodiment, the second and third wall structures **414**, **436** are formed together in an extrusion process. The segments are integrally formed and connected, but for purposes of illustration, the second and third wall structures **414**, **436** are shown to interface at the dashed line where end **422** of wall structure **414** is joined to end **423** of wall structure **436**. In one embodiment, the third wall structure **436** is formed entirely of the first material **416**. The segments are integrally formed and connected, but for purposes of illustration, the first and second segments are shown to interface at the dashed line where end **418** of segment **412** is joined to end **420** of segment **414**, and the second and third segments are shown to interface at the dashed line at end **422** of the second segment.

The elastic housing **402** of the device **400** further includes a retention frame lumen **442**. An elastic retention frame (not shown) may be positioned in the retention frame lumen **442**.

FIGS. 5A-5E illustrate an alternative embodiment to the device shown in **FIGS. 2A-2D**. In **FIGS. 5A-5E**, the drug delivery device **500** includes an elongated, elastic housing **502** having a drug reservoir lumen **504** extending between a first end **506** and a second end **508**. The elastic housing **502** is formed of a tubular wall structure **510** that includes a first wall structure **516** and a second wall structure **524** that are adjacent one

another and together form a tube defining the drug reservoir lumen **504**. The second wall structure **524** extends the entire length of the device housing, instead of only extending in the middle annular segment as shown in **FIGS. 2A-2D**. The embodiment of **FIGS. 5A-5E** may be made by a continuous co-extrusion process, whereas the embodiment shown in **FIG. 2A-2D** would be made by a discontinuous co-extrusion process.

FIG. 5E illustrates an alternative placement of the aperture as compared to the aperture placement shown in **FIGS. 5A-5D**. As shown in **FIGS. 5A-5D**, the aperture **526** may extend through the second wall structure **524**. In an alternative embodiment, as shown in **FIG. 5E**, the aperture **526** may extend through the first wall structure **516**.

In some embodiments, the second wall structure **524**, or both the first wall structure **516** and the second wall structure **524**, are permeable to water, and the first wall structure **516** and the second wall structure **524** are impermeable to the drug, such that the drug is releasable *in vivo* through aperture **526**, driven by osmotic pressure. In a preferred embodiment, the first and second wall structures **510**, **516** are formed together in an extrusion process.

The elastic housing **502** of the device **500** further includes a retention frame lumen **542**. An elastic retention frame (not shown) may be positioned in the retention frame lumen **542**.

In any of the foregoing illustrated embodiments, once the drug is loaded into the drug reservoir lumen, any suitable sealing substances and/or structures may be used to seal the first and second ends of the elastic housing. The sealing structure may be an end plug or closure. The end plug(s) or closure(s) may be formed of biocompatible material, including a metal such as stainless steel, a polymer such as silicone, a ceramic, or sapphire, or adhesive, among others or combinations thereof. In one embodiment, the first and second ends of the elastic housing are sealed with thermally formed seals. For example, a medical grade silicone adhesive or other adhesive may be loaded into the opening in a fluid or workable form and then cured within the housing opening to seal it.

In a variation of the foregoing illustrated embodiments, the drug release aperture, or apertures, may be provided through the first closed end, the second closed end, or both. In embodiments where the first and/or second closed ends include a sealing structure, e.g., an end plug or closure, the one or more apertures may extend through one or both sealing structures. In embodiments where the first and/or second closed ends are sealed with thermally sealed ends, the one or more apertures may extend through one or both thermally sealed ends. In certain embodiments, the first closed end includes an end plug and the

second closed end is sealed with a thermally formed seal, as illustrated in the embodiment of **FIGS. 6A-6D**, or vice versa, in which the one or more apertures extend through the end plug.

FIGS. 6A-6D illustrate a variation of the drug delivery device **400** shown in **FIGS. 4A-4D**. The drug delivery device **600** includes an elongated, elastic housing **602** having a drug reservoir lumen **604** extending between a first end **606** and a second end **608**, in which the first end **606** is closed with an end plug **638** and the second end **608** is closed with a seal **640**. Seal **640** may be thermally formed. The elastic housing **602** of the device **600** further includes a retention frame lumen **642**. In certain embodiments, the retention frame lumen includes a retention frame. The elastic housing **602** is formed of a tubular wall structure **610** that is impermeable to the drug disposed in the drug reservoir lumen **604**. The tubular wall structure **610** includes a first wall structure **612** that is impermeable to water and a second wall structure **614** that is water permeable. In this embodiment, an aperture **626** extends through the end plug **638**.

The aperture **626** provides a passageway for release of solubilized drug. It may be positioned through a sidewall or an end of the housing. In a preferred embodiment, as shown the aperture **626** is located at the end distal to the water permeable wall structure, in order to induce a flow of water through all of the drug reservoir lumen.

In other embodiments, the aperture may be located about a middle region of the drug reservoir lumen or at other positions along the sidewall of the housing. In alternative embodiments, two or more apertures may be used. The size, number, and placement of the aperture(s) may be selected to further control the drug release rate. The aperture may be dimensioned to be small enough to reduce diffusion of the drug through the aperture, yet large enough to reduce the buildup of hydrostatic pressure in the housing. Within these constraints, the size and number of apertures in communication with one or more drug reservoir lumens of a single device can be varied to achieve a selected release rate.

In exemplary embodiments, the diameter of the aperture is between about 20 μm and about 500 μm, such as between about 25 μm and about 300 μm, and more particularly between about 30 μm and about 200 μm. In one particular example, the aperture has a diameter between about 100 μm and about 200 μm, such as about 150 μm. A single device may have apertures of two or more different sizes. The aperture may be circular, although other shapes are possible and envisioned, with the shape typically depending on manufacturing considerations. The aperture may slightly taper from an exterior to an interior of the device housing.

In one embodiment, the length of the second annular segment or wall structure is from about 5% to about 25% of the length of the elastic body. In another embodiment, the length of the second annular segment or wall structure is from about 10% to about 30% of the length of the elastic body. In one embodiment, the length ratio of the second annular segment or wall structure to the elastic body is less than about 0.1. In another embodiment, the length ratio of the second annular segment or wall structure to the elastic body is less than about 0.4. As used herein, the phrase "about" with reference to lengths refers to the length plus or minus 10 percent of the recited value.

Unless otherwise noted, as used herein, the length of a particular segment is the longitudinal distance such segment extends between its opposing ends. For example, in one embodiment, the length of each annular segment or wall structure is the longitudinal distance between its first and second opposing ends. For example, in one embodiment, the length of the elastic body is the length between its opposed first and second ends.

The material(s) for the annular segments or wall structures of the present devices can be selected from a variety of suitable materials, for example silicone, polyurethane, ethylene-vinyl acetate (EVA), thermoplastic silicone polyether polyurethane, aliphatic thermoplastic silicone polyether polyurethane, segmented polyether polyurethane, thermoplastic polyether polyurethane, thermoplastic polycarbonate polyurethane, Bionate®PCU, BioSpan® SPU, CarboSil®TSPCU, Elasthane™ TPU, PurSil®TSPU (DSM), other thermoplastic polyurethanes (TPUs), including aliphatic and aromatic, polycarbonate-based thermoplastic polyurethanes, such as Carbothane™ TPU, Tecothane™ TPU, Tecothane™ Soft TPU, Pellethane®TPU, and Tecophilic™ TPU, and combinations or blends thereof.

In certain embodiments, the first material and/or second material include at least one thermoplastic material. In certain embodiments, the first material, the second material, or both, comprise a polyurethane, such as a thermoplastic polyurethane.

In a preferred embodiment, the first material is Tecothane™ Soft TPU (e.g., AR-62A), and the second material is Tecoflex™ (e.g., EG-80A), Carbothane™ TPU (e.g., AC-4075A), or a combination or blend thereof.

In some embodiments, the first material has a Shore durometer value from about 50A to about 70A. In one embodiment, the first material has a Shore durometer value of less than 90A. In certain embodiments, the second material has a Shore durometer value from about 70A to about 65D.

In some preferred embodiments, the first and second materials each comprise a thermoplastic polyurethane, the tubular wall structure is elastically deformable from a retention shape suited to retain the device within the bladder to a relatively straightened shape suited for insertion through a lumen into the bladder, and the tubular wall structure is thermally shaped to have the retention shape.

In some embodiments, it is desirable for the portion of the housing wall that defines the retention frame lumen to be made of a different material from those materials forming the part of the housing that defines the drug reservoir. For example, the material forming the retention frame lumen desirably may be selected to be lubricious to facilitate loading of the elastic retention frame into the lumen. In particular, the first and second materials selected for forming the water impermeable and permeable wall portions bounding the drug reservoir lumen may be sticky and resist loading of the retention frame. Therefore, a third material, which is lubricious may be selected to form the retention frame lumen. As used herein, a "lubricious" material is a material which has a relatively low kinetic coefficient of friction, for example, a kinetic coefficient of friction of less than about 0.8. The kinetic coefficient of friction may be measured using methods known in the art, such as ASTM D1894.

In embodiments, these three materials can be co-extruded together to form the device housing, as illustrated in **FIGS. 7A-7C**, which provides one non-limiting example of a combination of materials that may be used. In a preferred embodiment, all three materials are biocompatible thermoplastic polyurethanes known in the art. **FIGS. 7A-7C** illustrate an alternative embodiment to the device shown in **FIGS. 2A-2D**. In **FIGS. 7A-7C**, the drug delivery device **700** includes an elongated, elastic housing **702** having a drug reservoir lumen **704** extending between a first end **706** and a second end **708**. The elastic housing **702** is formed of a tubular wall structure **710** that includes a first wall structure **716** made of a first material **717** and a second wall structure **724** made of a second material **725**. The first wall structure **716** and the second wall structure **724** are adjacent one another and together form a tube defining the drug reservoir lumen **704**. The second wall structure **724** extends the entire length of the device housing, instead of only extending in the middle annular segment as shown in **FIGS. 2A-2D**. The embodiment of **FIGS. 7A-7C** may be made by a continuous co-extrusion process, whereas the embodiment shown in **FIG. 2A-2D** would be made by a discontinuous co-extrusion process.

The elastic housing **702** of the device **700** further includes a retention frame lumen **742** made of a third material **743**. In some embodiments, the third material **743** is a

lubricious material, such as a lubricious thermoplastic polyurethane resin. An elastic retention frame (not shown) may be positioned in the retention frame lumen **742**.

In embodiments, the second wall structure **724**, or both the first wall structure **716** and the second wall structure **724**, are permeable to water, and the first wall structure **716** and the second wall structure **724** are impermeable to the drug, such that the drug is releasable *in vivo* through aperture **726**, driven by osmotic pressure. In a preferred embodiment, the first and second wall structures **710**, **716** are formed together in an extrusion process. In a preferred embodiment, the first material **717** comprises Tecoflex™ EG-80A, the second material **725** comprises Techothane™ soft AR-62A, and the third material **743** comprises EG-80A. In some embodiments, each of the first end **706** and a second end **708** may be closed by an end plug or closure.

In certain variations of the foregoing embodiments, the polymeric wall structure of the device still includes a first wall portion and an adjacent second wall portion, wherein the first and second wall portions have been co-extruded to define and bound a drug reservoir space, which contains a drug, wherein (i) the first and second wall portions are impermeable to the drug, (ii) the first wall portion is water impermeable, and (iii) the second wall portion is water permeable and configured to permit water to diffuse into the drug reservoir space and produce an osmotic pressure for driving release of the drug, however the drug is released through different structures. In one case, the drug delivery device does not have any pre-formed aperture for drug release. Instead, the drug delivery device in that case is configured to release drug, such that the osmotic pressure generated *in vivo* in the drug reservoir of the device is released by the transient formation of one or more microchannels between a restraining plug and the elastic wall of the annular housing in contact with the restraining plug, as described in U.S. Application Publication 2016/0008271, which is incorporated herein by reference. In another case, the drug delivery device is configured to release of the drug through the transient formation of one or more microchannels leading to a preformed release port or other opening, as described in U.S. Patent Application No. 62/453,333, which is incorporated herein by reference.

In one embodiment shown in **FIGS. 8A** and **8B**, the drug delivery device **800** has a first end **806** and a second end **808**, and includes (i) an elastomeric, annular wall structure **810** which comprises a first wall portion **812** and an adjacent second wall portion **814**, the first and second wall portions **812**, **814** being co-extruded to define and bound the annulus of the annular wall structure **810**, the annulus being a drug reservoir space **804**; (ii) a drug contained in the drug reservoir space **804**; and (iii) a restraining plug **838** inserted into the

second end **808** of the annulus and in engagement with an interior portion of the annular tube. The drug delivery device **800** further includes a retention frame lumen **842**. An elastic retention frame would be positioned in the retention frame lumen **842**. The first end **806** of the annulus is closed by a seal **840**. Seal **840** may be thermally formed. In this embodiment, the first and second wall portions **812**, **814** are impermeable to the drug, the first wall portion **812** is water impermeable, the second wall portion **814** is water permeable and configured to permit water *in vivo* to diffuse into the drug reservoir space **804** and produce an osmotic pressure, and the restraining plug **838** is configured to permit transient formation of one or more microchannels between the annular tube and the restraining plug **838**.

In other embodiments (not shown), the drug delivery device illustrated in **FIGS. 8A-8B** optionally includes two restraining plugs, one at each end of the annular body, and/or optionally includes a pre-formed aperture, along with the one or two restraining plugs. In such embodiments, two or three passageways are provided for drug release, which advantageously can mitigate the risk of aperture clogging and drug release failure.

Further Details of the Drug Delivery Devices

Drug

The drug contained in the drug reservoir space of the present drug delivery devices is generally provided in a payload amount needed to release a therapeutically effective amount of the drug over a predetermined treatment period. As used herein, the term "drug" refers to an active pharmaceutical ingredient (API) and with reference to any specific drug includes its alternative forms, such as salt forms, free acid forms, free base forms, and hydrates. The drug may be small molecule, macromolecule, biologic, or metabolite, among other forms/types of active ingredients.

The drug may be part of a drug formulation including one or more pharmaceutically acceptable excipients known in the art. A drug formulation may consist only of the API, or one or more excipients may be included. The term "excipient" is known in the art, and representative examples of excipients useful in the present drug units may include ingredients such as binders, lubricants, glidants, disintegrants, colors, fillers, diluents, coatings, or preservatives, as well as other non-active ingredients to facilitate manufacturing, stability, dispersibility, wettability, and/or release kinetics of the drug or administering the drug unit.

The drug or drug formulation can be provided in any suitable form. In one embodiment, the drug formulation is in a solid form. In another embodiment, the drug

formulation is in semi-solid form, such as an emulsion or suspension; a gel or a paste. For example, the drug formulation may be a highly viscous emulsion or suspension. In one embodiment, the drug formulation is in a liquid form. In some other embodiments, the drug is included in a granular or particulate form.

In some particular embodiments, a drug formulation is formed into solid drug units. Examples of solid drug units include tablets, capsules, pellets, or beads, although other configurations are possible. In some embodiments, the drug is included in a mini-tablet form, as described in U.S. Patent No. 8,343,516, which is incorporated herein by reference. The solid drug units may be made by a direct powder compaction or tabletting process, a molding process, or other processes known in the art.

In some embodiments, the drug and excipients are selected, and the solid drug unit formulated, to be water soluble, so that the solid drug units can be solubilized when the device is located in vivo, e.g., within the bladder, to release the solubilized drug.

The individual solid drug units may have essentially any selected shape and dimension that fits within the devices described herein. For example, the drug units may be substantially cylindrical in shape for positioning in a substantially cylindrical drug reservoir lumen. Once loaded, the solid drug units can, in some embodiments, substantially fill the drug reservoir lumens. In one embodiment, the solid drug units are shaped to align in a row when the device is in its deployment configuration. The drug delivery device may be relatively flexible or deformable despite being loaded with a solid drug, as each drug unit may be permitted to move with reference to adjacent drug units.

In some embodiments, the drug delivery device is configured to treat renal or urinary tract cancer, such as bladder cancer and prostate cancer. Drugs that may be used include antiproliferative agents, cytotoxic agents, chemotherapeutic agents, or combinations thereof. Representative examples of drugs which may be suitable for the treatment of urinary tract cancer include Bacillus Calmette Guerin (BCG) vaccine, docetaxel, cisplatin, doxorubicin, valrubicin, gemcitabine, mycobacterial cell wall-DNA complex (MCC), methotrexate, vinblastine, thiotepa, mitomycin (e.g., mitomycin C), fluorouracil, leuprolide, diethylstilbestrol, estramustine, megestrol acetate, cyproterone, flutamide, a selective estrogen receptor modulators (i.e. a SERM, such as tamoxifen), botulinum toxins, and cyclophosphamide. The drug may comprise a monoclonal antibody, a TNF inhibitor, an anti-leukin, or the like. The drug also may be an immunomodulator, such as a TLR agonist, including imiquimod or another TLR7 agonist. The drug also may be a kinase inhibitor, such as a fibroblast growth factor receptor-3 (FGFR3)-selective tyrosine kinase inhibitor, a

phosphatidylinositol 3 kinase (PI3K) inhibitor, or a mitogen-activated protein kinase (MAPK) inhibitor, among others or combinations thereof. Other examples include celecoxib, erolotinib, gefitinib, paclitaxel, polyphenon E, valrubicin, neocarzinostatin, apaziquone, Belinostat, Ingenolmebutate, Urocidin (MCC), Proxinium (VB 4845), BC 819 (BioCancell Therapeutics), Keyhole limpet haemocyanin, LOR 2040 (Lorus Therapeutics), urocanic acid, OGX 427 (OncoGenex), and SCH 721015 (Schering-Plough). The drug treatment may be coupled with a conventional radiation or surgical therapy targeted to the cancerous tissue.

In some other embodiments, the devices described herein are configured to release an anesthetic agent, analgesic agent, and combinations thereof. The anesthetic agent may be an aminoamide, an aminoester, or combinations thereof. Representative examples of aminoamides or amide-class anesthetics include articaine, bupivacaine, carticaine, cinchocaine, etidocaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and trimecaine. Representative examples of aminoesters or ester-class anesthetics include amylocaine, benzocaine, butacaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine, hexylcaine, larocaine, meprylcaine, metabutoxycaine, orthocaine, piperocaine, procaine, proparacaine, propoxycaine, proxymetacaine, risocaine, and tetracaine. These anesthetics typically are weak bases and may be formulated as a salt, such as a hydrochloride salt, to render them water-soluble, although the anesthetics also can be used in free base or hydrate form. Other anesthetics, such as lontocaine, also may be used. The drug also can be an antimuscarinic compound that exhibits an anesthetic effect, such as oxybutynin or propiverine. The drug also may include other drugs described herein, alone or in combination with a local anesthetic agent.

In certain embodiments, the analgesic agent includes an opioid. Representative examples of opioid agonists include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan,

phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof. Other opioid drugs, such as mu, kappa, delta, and nociception opioid receptor agonists, are contemplated.

Representative examples of other suitable pain relieving agents include such agents as salicyl alcohol, phenazopyridine hydrochloride, acetaminophen, acetylsalicylic acid, flufenisal, ibuprofen, indoprofen, indomethacin, and naproxen.

In some embodiments, the drug delivery device is configured to treat inflammatory conditions such as interstitial cystitis, radiation cystitis, painful bladder syndrome, prostatitis, urethritis, post-surgical pain, and kidney stones. Non-limiting examples of specific drugs for these conditions include lidocaine, glycosaminoglycans (e.g., chondroitin sulfate, sulodexide), pentosanpolysulfate sodium (PPS), dimethyl sulfoxide (DMSO), oxybutynin, mitomycin C, heparin, flavoxate, ketorolac, cyclosporine, or combinations thereof. For kidney stones, the drug(s) may be selected to treat pain and/or to promote dissolution of renal stones.

Other non-limiting examples of drugs that may be used in the treatment of IC include nerve growth factor monoclonal antibody (MAB) antagonists, such as Tanezumab, and calcium channel alpha-2-delta modulators, such as PD-299685 or gabepentin. Evidence suggests that the bladder expresses nerve growth factor (NGF) locally, since exogenously delivered NGF into the bladder induces bladder hyperactivity and increases the excitability of dissociated bladder afferent neurons (*Nature Rev Neurosci* 2008; 9:453-66). Accordingly, it would be advantageous to locally deliver a MAB or other agent against NGF using the described delivery devices, significantly reducing the total dose needed for therapeutic efficacy. Evidence also suggests that binding of the alpha-2-delta unit of voltage-sensitive calcium channels, such as with gabapentin, may be effective in the treatment of diseases of neuropathic pain such as fibromyalgia and that there may be common mechanisms between IC and diseases of neuropathic pain (See *Tech Urol.* 2001 Mar, 7(1):47-49). Accordingly, it would be advantageous to locally deliver a calcium channel alpha-2-delta modulator, such as PD-299685 or gabepentin, using the described delivery devices, minimizing does-related systemic toxicities in the treatment of IC.

Other intravesical cancer treatments include small molecules, such as Apaziquone, adriamycin, AD-32, doxorubicin, doxetaxel, epirubicin, gemcitabine, HTI-286 (hemiasterlin analogue), idarubicin, γ-linolenic acid, mitozantrone, meglumine, and thiotepa; large molecules, such as EGF-dextran, HPC-doxorubicin, IL-12, IFN-a2b, IFN-γ, α-lactalbumin,

p53adenovector, TNFα; combinations, such as Epirubicin + BCG, IFN + farmarubicin, Doxorubicin + 5-FU (oral), BCG + IFN, and Pertussis toxin + cystectomy; activated cells, such as macrophages and T cells; intravesical infusions such as IL-2 and Doxorubicin; chemosensitizers, such as BCG+antifirinolytics (paramethylbenzoic acid or aminocaproic acid) and Doxorubicin + verapimil; diagnostic/imaging agents, such as Hexylaminolevulinate, 5-aminolevulinic acid, Iododexyuridine, HMFG1Mab+Tc99m; and agents for the management of local toxicity, such as Formaline (hemorrhagic cystitis).

In some embodiments, the drug delivery devices described herein are configured to treat urinary incontinence, frequency, or urgency, including urge incontinence and neurogenic incontinence, as well as trigonitis. Drugs that may be used include anticholinergic agents, antispasmodic agents, anti-muscarinic agents, β-2 agonists, alpha adrenergics, anticonvulsants, norepinephrine uptake inhibitors, serotonin uptake inhibitors, calcium channel blockers, potassium channel openers, and muscle relaxants. Representative examples of suitable drugs for the treatment of incontinence include oxybutynin, S-oxybutytin, emepronium, verapamil, imipramine, flavoxate, atropine, propantheline, tolterodine, rociverine, clenbuterol, darifenacin, terodiline, trospium, hyoscyamin, propiverine, desmopressin, vamicamide, clidinium bromide, dicyclomineHCl, glycopyrrolateaminoalcohol ester, ipratropium bromide, mepenzolate bromide, methscopolamine bromide, scopolamine hydrobromide, iotropium bromide, fesoterodinefumarate, YM-46303 (Yamanouchi Co., Japan), lanperisone (Nippon Kayaku Co., Japan), inaperisone, NS-21 (Nippon Shinyaku Orion, Formenti, Japan/Italy), NC-1800 (Nippon Chemiphar Co., Japan), ZD-6169 (Zeneca Co., United Kingdom), and stilonium iodide.

In some embodiments, the drug delivery devices described herein are configured to treat infections involving the bladder, the prostate, the kidney, and the urethra. Antibiotics, antibacterial, antifungal, antiprotozoal, antiseptic, antiviral and other antiinfective agents can be administered for treatment of such infections. Representative examples of drugs for the treatment of infections include mitomycin, ciprofloxacin, norfloxacin, ofloxacin, methanamine, nitrofurantoin, ampicillin, amoxicillin, nafcillin, trimethoprim, sulfonamides trimethoprimsulfamethoxazole, erythromycin, doxycycline, metronidazole, tetracycline, kanamycin, penicillins, cephalosporins, and aminoglycosides.

In some embodiments, the drug delivery devices described herein are configured to treat fibrosis of a genitourinary site, such as the bladder or uterus. Representative examples of drugs for the treatment of fibroids include pentoxphylline (xanthine analogue), antiTNF,

antiTGF agents, GnRH analogues, exogenous progestins, antiprogestins, selective estrogen receptor modulators, danazol and NSAIDs.

In some embodiments, the drug delivery devices described herein are configured to treat spastic or flaccid neurogenic bladder. Representative examples of drugs for the treatment of neurogenic bladder include analgesics or anaesthetics, such as lidocaine, bupivacaine, mepivacaine, prilocaine, articaine, and ropivacaine; anticholinergics; antimuscarinics such as oxybutynin or propiverine; a vanilloid, such as capsaicin or resiniferatoxin; antimuscarinics such as ones that act on the M3 muscarinic acetylcholine receptor (mAChRs); antispasmodics including $GABA_B$ agonists such as baclofen; botulinum toxins; capsaicins; alpha-adrenergic antagonists; anticonvulsants; serotonin reuptake inhibitors such as amitriptyline; and nerve growth factor antagonists. In various embodiments, the drug may be one that acts on bladder afferents or one that acts on the efferent cholinergic transmission, as described in Reitz et al., *Spinal Cord* 42:267-72 (2004).

In some embodiments, the drug delivery devices described herein are configured to treat incontinence due to neurologic detrusor overactivity and/or low compliant detrusor. Examples of drugs for this include bladder relaxant drugs (e.g., oxybutynin (antimuscarinic agent with a pronounced muscle relaxant activity and local anesthetic activity), propiverine, impratroprium, tiotropium, trospium, terodiline, tolterodine, propantheline, oxyphencyclimine, flavoxate, and tricyclic antidepressants); drugs for blocking nerves innervating the bladder and urethra (e.g., vanilloids (capsaicin, resiniferatoxin), botulinum-A toxin); or drugs that modulate detrusor contraction strength, micturition reflex, detrusor sphincter dyssynergia (e.g., GABAb agonists (baclofen), benzodiazapines).

In some embodiments, the drug delivery devices described herein are configured to treat incontinence due to neurologic sphincter deficiency. Examples of drugs for this include alpha adrenergic agonists, estrogens, beta-adrenergic agonists, tricyclic antidepressants (imipramine, amitriptyline).

In another embodiment, the drug is selected from those known for facilitating bladder emptying (e.g., alpha adrenergic antagonists (phentolamine) or cholinergics). In yet another embodiment, the drug is selected from among anticholinergic drugs (e.g., dicyclomine), calcium channel blockers (e.g., verapamil) tropane alkaloids (e.g., atropine, scopolamine), nociceptin/orphaninFQ, and bethanechol (e.g., m3muscarinc agonist, choline ester). In some embodiments, the drug is a steroid, such as triamcinolone, budesonide, or prednisolone.

In some embodiments, the drug includes gemcitabine, docetaxel, carboplatin, cisplatin, oxaliplatin, trospium, tolterodine, oxybutynin, or mitomycin C.

Tolerability and Retention of the Device in a Body Cavity

In some embodiments, the drug delivery device is configured for intravesical insertion and tolerability to the patient. Such device characteristics are described in U.S. Patent 8,679,094, which is incorporated herein by reference.

The device also may be configured to facilitate buoyancy in urine within a patient's bladder. In some embodiments, this may be accomplished as described in U.S. Patent No. 9,457,176, which is incorporated herein by reference.

In certain embodiments, the devices are configured for intravesical insertion and retention in a patient. For example, the devices can be elastically deformable between a relatively straightened shape suited for insertion through a lumen into a body cavity of a patient and a retention shape suited to retain the device within the body cavity, such as shown in **FIGS. 1A-1B**. When in the retention shape after deployment in the bladder, for example, the devices may resist excretion in response to the forces of urination or other forces. In certain embodiments, the drug delivery device may naturally assume the retention shape and may be elastically deformed, either manually or with the aid of an external apparatus, into the relatively straightened shape for insertion into the body, and once deployed the device may elastically return to the initial, retention shape for retention in the body.

For the purposes of this disclosure, the term "retention shape" generally denotes any shape suited for retaining the device in the intended implantation location, including, but not limited to, a coiled or "pretzel" shape, such as shown in **FIG. 1A**, which is suited for retaining the device in the bladder. Similarly, the term "relatively straightened shape" generally denotes any shape suited for deploying the drug delivery device into the body, including, but not limited to, a linear or elongated shape, such as shown in **FIGS. 2A-2D**, **3A-3E**, **4A-4D**, **FIGS. 5A-5E**, **6A-6D**, **7A-7C**, and **8A-8B**, which is suited for deploying the device through the working channel of catheter, cystoscope, or other deployment instrument positioned in a lumen of the body, such as the urethra.

In some embodiments, the device further includes a retention lumen and an elastic retention frame positioned in the retention frame lumen. The retention frame and retention frame lumen may be configured as described in U.S. Patent No. 9,586,035 and U.S. Application Publication No. 2010/0331770, which are incorporated herein by reference.

In other embodiments, the device does not include a retention frame lumen or a retention frame or wire. Instead, the material(s) of the tubular wall structure is configured to be elastically deformable between the straightened shape and the retention shape, in the absence of a retention frame or wire, as described in U.S. Application Publication No. 2016/0310715, which is incorporated herein by reference.

In certain embodiments where the tubular body comprises first and second annular segments, the first and second annular segments each a thermoplastic polyurethane and the tubular body is thermally shaped to have the retention shape. In one embodiment, the tubular wall structure has a spring constant effective to impede the device from assuming the relatively straightened shape once implanted in the bladder. Thus, the properties of the tubular wall structure may cause the device to function as a spring, deforming in response to a compressive load but spontaneously returning to its initial shape once the load is removed.

In certain embodiments, the devices may exhibit the retention shape when not under load, may be elastically deformed into the relatively straightened shape, and may spontaneously return to the retention shape upon insertion into the body. The tubular wall structure in the retention shape may be shaped for retention in a body cavity, and in the relatively straightened shape may be shaped for insertion into the body through the working channel of a deployment instrument such as a catheter or cystoscope. To achieve such a result, the tubular wall structure may have an elastic limit, modulus, and/or spring constant selected to impede the device from assuming the relatively lower-profile shape once inserted into the patient's body. Such a configuration may limit or prevent accidental expulsion of the device from the body under expected forces. For example, the device may be retained in the bladder during urination or contraction of the detrusor muscle.

Advantageously, drug delivery devices utilizing thermally formed coextruded tubing with water permeable and water impermeable regions integrate three functional components (drug reservoir/housing, water permeation route, and retentive feature) into a single thermally shaped co-extruded tubing component, which simplifies the device design and the ability to control the drug release rate. As discussed herein, in such devices, the drug release rate can be relatively easily modified by controlling the angle and amount of the water permeable portion (e.g., a full or partial strip along the length) without changing whole tube housing material.

In vivo Detectability

The devices described herein may include a radio-opaque portion or structure to facilitate detection or viewing (e.g., by X-ray imaging or fluoroscopy) of the device by a

medical practitioner as part of the implantation or retrieval procedure. In one embodiment, the device body is constructed of a material that includes a radio-opaque filler material, such as barium sulfate or another radio-opaque material known in the art. Some device bodies may be made radio-opaque by blending radio-opaque fillers, such as barium sulfate or another suitable material, during the processing of the material from which the device body is formed. The radio-opaque material may be associated with the retention frame in those embodiments that include a retention frame. Ultrasound imaging or fluoroscopy may be used to image the device *in vivo*.

Retrieval Features

The drug delivery device may further include a retrieval feature, such as a string, a loop, or other structure that facilitates removal of the device from the body cavity, for example for removal of a non-resorbable device body following release of the drug formulation from the solid drug units. In one case, the device may be removed from the bladder by engaging the string to pull the device through the urethra. The device may be configured to assume a relatively narrow or linear shape when pulling the device by the retrieval feature into the lumen of a catheter or cystoscope or into the urethra.

Methods of Making the Drug Delivery Device

In embodiments, the drug delivery devices described herein are produced by (i) forming the device body, which includes a drug reservoir space; (ii) placing a drug payload in the drug reservoir space; and (iii) closing the opening(s) used to access the drug reservoir space during the step of placing the drug payload in the drug reservoir space. In embodiments in which the device includes a retention frame, step (i) may further include forming a retention frame lumen in the device body, and the method may further include placing a retention frame in the retention frame lumen. In embodiments in which the device includes one or more apertures in the device body, the method may further include forming the one or more apertures in a sidewall of the device body, either simultaneously with or after formation of the device body. Some steps or sub-steps of the method of making a drug delivery device may be performed in other orders or simultaneously.

The devices described herein generally are formed by using a co-extrusion process to form the elongated, elastic housing of the device. In some embodiments, the method of making the device includes (i) introducing a first material into an extrusion stream of an extruder to form a first wall portion of a tubular structure; and (ii) introducing a second material into the extrusion stream in an manner to replace the first material in at least one position and to form a second wall portion of the tubular structure, wherein the first wall

portion is integrally connected to the second wall portion, and the first and second wall portions together define the drug reservoir space in the form of a drug reservoir lumen.

In some embodiments, the process of forming/assembling the device also includes providing at least one aperture in the housing wall or in an end plug closing of the drug reservoir lumen. For example, the aperture may be formed within the device during the co-extrusion process, before or after drug loading, or before or after the closing off of the ends of the tubular housing. In embodiments, the method includes forming an aperture through a sidewall of the tubular structure. Examples of processes for forming the apertures include mechanical punching, laser drilling, laser ablation, extrusion, and molding. The aperture may be created either before or after the drug is loaded into the drug reservoir lumen or lumens.

In embodiments, the method further includes loading a drug into the drug reservoir lumen, and sealing the ends of the drug reservoir lumen. Optionally the drug may be formulated with one or more excipients. The drug reservoir space may further include an osmotic agent, which may be part of composition with the drug or which may be positioned in the drug reservoir space in a position separate from the drug. In some embodiments, the drug is loaded into the drug reservoir lumen in a solid form. For example, the drug may be in the form of tablets or granules. The ends of the drug reservoir lumen may sealed with an end piece that is non-permeable to drug or water. Optionally, such an end piece may have an aperture which extends through the end piece in fluid communication with the drug reservoir lumen.

In some embodiments, the drug is loaded into the drug reservoir space in a workable form and may cure therein. For example, in embodiments in which the drug formulation is configured to be melted and solidified, the drug formulation can be melted, injected into the drug reservoir space in melted form and then solidified. The drug formulation also may be extruded with the drug reservoir space and cured within the drug reservoir space.

In one embodiment, the method of making the device includes forming the first annular segment by an extrusion process which comprises introducing the first material into an extrusion stream; and forming the second annular segment by intermittently introducing the second material into the extrusion stream with the first material at preselected positions, in a manner effective to form a tubular structure comprising two or more first annular segments integrally connected to two or more second annular segments. In particular, the first and second materials are located in the extrusion stream such that, in the second annular segment, the first material forms a first arcuate portion and the second material

forms a second arcuate portion, wherein the first and second arcuate portions are integrally connected and together defining the annulus of the second annular segment. The method further may include cutting the tubular structure at one or more positions to form the elongated, elastic housing; loading a drug into the drug reservoir lumen; and sealing the first and second ends of the drug reservoir lumen. The method further includes forming at least one drug-release aperture in the device housing. With this method, the resulting device may have a tubular wall structure as illustrated in **FIGS. 2A-2D** or **FIGS. 3A-3E**.

In another embodiment, the method of making the device includes forming the first wall structure by an extrusion process which comprises introducing the first material into an extrusion stream; and forming the second wall structure by intermittently introducing the second material into the extrusion stream to replace the first material along a selected length of the extrusion stream, in a manner effective to form a tubular structure comprising two or more first wall structures integrally connected to two or more second wall structures. In particular, the first wall structure is formed entirely of a first material which is impermeable to water, and the second wall structure is formed primarily of a second material which is water permeable. The tubular structure configured to define the drug reservoir lumen and an aperture is provided in communication with the drug reservoir lumen. The term "primarily" is used to denote that any transition regions are, for purposes of description, included in the second wall structure. The method further includes cutting the tubular structure at one or more positions to form the elongated, elastic housing; loading a drug into the drug reservoir lumen; and sealing the first and second ends of the housing. With this method, the resulting device may have a tubular wall structure as illustrated in **FIGS. 4A-4D** or **5A-5E**.

In some embodiments, the tubular wall structure may include a retention lumen extending through the structure. The retention lumen optionally may be loaded with an elastic retention frame, such as a nitinol wire or other superelastic wire, and then sealed to keep the frame inside the lumen and/or optionally may be filled with a gas (e.g., air) and then sealed at its ends prior or subsequent to drug loading of the device. The retention frame and retention frame lumen may be configured as described in U.S. Patent No. 9,586,035 and U.S. Application Publication No. 2010/0331770, which are incorporated herein by reference. In another embodiment, the retention lumen may be filled with high durometer silicone, prior to drug loading of the device, which is then cured into a solid, elastic form effective to bias the tubular wall structure in the coiled bladder retention shape, as described for example in PCT Publication WO 2016/172704, which is incorporated

herein by reference.

The drug delivery device may be sterilized before being inserted into a patient. In one embodiment, the device is sterilized using a suitable process such as gamma irradiation or ethylene oxide sterilization, although other sterilization processes may be used.

Methods of Use/Drug Delivery

The devices and methods disclosed herein may be adapted for use in humans, whether male or female, adult or child, or for use in animals, such as for veterinary or livestock applications. Accordingly, the term "patient" may refer to a human or other mammalian subject.

In embodiments, a method of administering a drug to a patient includes inserting a drug delivery device as described herein into the patient and permitting a drug to be released from the device. In particular embodiments, the drug is released from the drug reservoir through an aperture, driven by osmotic pressure in the reservoir, wherein the aperture is in communication with the reservoir. In some embodiments, release of the drug from the device occurs following dissolution of a solid form of the drug within the device. For example, a biological fluid, such as urine or interstitial fluid, enters the drug reservoir space of the device, contacts the drug therein and solubilizes it. Because water diffuses through a portion of the housing wall structure bounding into the drug reservoir, but the drug solution therein cannot diffuse back out through those the housing wall structure, an osmotic pressure is developed. This pressure drives the drug solution out of the device through the drug release aperture, releasing the drug into the patient.

Insertion/Deployment

The drug delivery device may be inserted into the patient by any suitable means or route. In preferred embodiments, the device is inserted through natural anatomical lumen. In certain embodiments, the inserting comprises deploying the device through the patient's urethra and into the patient's urinary bladder.

In some embodiments, inserting the device into a body cavity or lumen of the patient is done via a deployment instrument. For example, the device may be deployed through a deployment instrument, such as a catheter or cystoscope, positioned in a natural lumen of the body, such as the urethra, or into a body cavity, such as the bladder. The deployment instrument may be a commercially available device or a device specially adapted for the present drug delivery devices. The drug delivery device may be passed through the deployment instrument, driven by a stylet or flow of lubricant or other fluid, for example, until the drug delivery device exits a lumen of the instrument, for example as the device

passes into the bladder. The deployment instrument typically is removed from the body lumen while the drug delivery device remains in the bladder or other body cavity for a prescribed treatment period.

Examples of suitable insertion tools and methods for intravesical insertion are described in U.S. Patent 8,721,621, which is incorporated herein by reference.

In cases in which the device is deployed into a body cavity such as the bladder, the device may assume a retention shape once the device emerges from the deployment instrument into the cavity. In one embodiment, deploying the drug delivery device in the patient includes (i) elastically deforming the device into the relatively straightened shape; (ii) inserting the device through the patient's urethra; and (iii) releasing the device into the patient's bladder such that it assumes the retention shape.

Treatments

The drug delivery devices described herein may be used to treat a wide variety of conditions and diseases, depending on the drug or drug combination administered from the devices.

For example, the device may be configured to release drug locally to the bladder, for treatment of the bladder or genitourinary tissues/organs near the bladder. Non limiting examples of conditions and diseases that may be treated include interstitial cystitis, radiation cystitis, pelvic pain, bladder inflammation, overactive bladder syndrome, bladder cancer, neurogenic bladder, neuropathic or non-neuropathic bladder-sphincter dysfunction, infection, post-surgical pain or other diseases, disorders, and conditions treated with drugs delivered to the bladder. The device may deliver drugs that improve bladder function, such as bladder capacity, compliance, and/or frequency of uninhibited contractions, that reduce pain and discomfort in the bladder or other nearby areas, or that have other effects, or combinations thereof.

In another embodiment, the device may be configured to release drug locally to the renal pelvis, for treatment of the kidneys, ureters, or other tissues/organs. Non limiting examples of conditions and diseases that may be treated include cancer of the kidney or ureters, kidney stones or fibrosis, and pelvis pain.

Following *in vivo* deployment of the drug delivery devices, the devices may release device may release the drug continuously for several days, weeks, months, depending on the particular device design, drug payload, therapeutic need, and other factors. The rate of delivery and dosage of the drug can be selected depending upon the drug being delivered and the disease or condition being treated. In embodiments, the device releases a

therapeutically effective amount of the drug continuously into the body over a desired predetermined period. In embodiments, the device can deliver the desired dose of drug over an extended period, such as 24 hours, 5 days, 7 days, 10 days, 14 days, or 20, 25, 30, 45, 60, or 90 days, or more. In certain embodiments, the device resides in the bladder releasing the drug over a predetermined period, such as two weeks, three weeks, four weeks, a month, or more. In some embodiments, a rate of release of the drug from the drug delivery device is essentially zero order over at least 36 hours, at least 48 hours, at least 3 days, at least 7 days, or at least 14 days.

In some embodiments, the device is configured to release a therapeutically effective amount of the drug over a period from 3 days to 90 days, e.g., from 7 days to 30 days, or from 7 days to 14 days. Desirably, the rate of the release of the drug from the drug delivery device is zero order over at least 7 days, e.g., from 7 to 14 days, or longer.

Removal

Following the end of the treatment period, or earlier if necessary, the device may be retrieved or otherwise removed from the patient.

In some cases, such as when the device is non-resorbable, the device may be retrieved via the route through which the device was initially inserted. For example, a device residing in the bladder (or renal pelvis) may be retrieved via catheter or cystoscope through the urethra (or through the ureter, bladder, and then urethra). As another example, the device may include a retrieval string that extends through the urethra, and the retrieval string can be used to manually pull the device from the bladder or renal pelvis. See, e.g., U.S. Application Publication 2015/0088150.

In some other cases, the device may be at least partially bioerodible, resorbable, or biodegradable, such that retrieval is unnecessary. For example, as described in U.S. Patent 8,690,840, the device may include degradable links that provide loss of a bladder retention shape following release of drug, which permits the device to be expelled from the bladder during urination.

Many modifications and other implementations of the disclosure set forth herein will be apparent having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the disclosure is not to be limited to the specific implementations disclosed and that modifications and other implementations are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

CLAIMS

I claim:

1. A drug delivery device comprising:

a polymeric wall structure which comprises a first wall portion and an adjacent second wall portion, the first and second wall portions being co-extruded to define and bound a drug reservoir space;

a drug contained in the drug reservoir space; and

an aperture in fluid communication with the drug reservoir space for release of the drug from the device;

wherein:

the first and second wall portions are impermeable to the drug,

the first wall portion is water impermeable, and

the second wall portion is water permeable and configured to permit water to diffuse into the drug reservoir space and produce an osmotic pressure for driving release of the drug through the aperture.

2. The device of claim 1, wherein the aperture extends through the first wall portion.

3. The device of claim 1, wherein the aperture extends through the second wall portion.

4. The device of any one of claims 1 to 3, wherein the polymeric wall structure comprises an annular tube, the annulus of which is the drug reservoir space.

5. The device of claim 4, wherein the first and second wall portions are adjacent one another over the full length of the annular tube.

6. The device of claim 4, wherein the second wall portion is adjacent to the first wall portion over only part of the full length of the annular tube.

7. The device of claim 4, wherein at least one end of the annulus is closed off by a restraining plug inserted therein in engagement with an interior portion of the annular tube, and wherein the restraining plug is configured to permit transient formation of one or more microchannels between the annular tube and the restraining plug.

8. The device of claim 7, wherein the restraining plug is formed of a thermoplastic polyurethane.

9. The device of claim 7, wherein the restraining plug is thermally bonded around part of, and not all of, its circumference to the interior portion of the annulus.

10. The device of claim 7, wherein the restraining plug has an outer diameter that exceeds the diameter of annulus by from 3% to 25%, such that the annular tube is elastically stretched about the restraining plug.

11. The device of claim 4, wherein the aperture extends through an end piece which closes off one end of the annulus of the annular tube.

12. The device of claim 4, wherein the annular tube comprises:

a first annular segment which consists of at least part of the first wall portion, and

a second annular segment which comprises at least part of the second wall portion,

wherein the first annular segment has a first end which is integrally formed and connected with a first end of the second annular segment.

13. The device of claim 12, wherein the annular tube further comprises a third annular segment which consists of another part of the first wall portion and which is integrally formed and connected with an opposed second end of the second annular segment.

14. The device of claim 12, wherein:

the second annular segment comprises a first arcuate portion and a second arcuate portion,

the first and second arcuate portions are integrally connected and together define the annulus of the second annular segment,

the first arcuate portion comprises part of the first wall portion, and

the second arcuate portion comprises part or all of the second wall portion.

15. The device of claim 14, wherein the second arcuate portion has an arc angle from 15 degrees to 120 degrees.

16. The device of claim 14, wherein the second arcuate portion has an arc angle from 30 degrees to 90 degrees.

17. The device of claim 12, wherein:

the first annular segment consists of all of the first wall portion, and

the second annular segment consists of all of the second wall portion,

18. The device of claim 17, wherein the aperture extends through an end piece secured to the first annular segment at a second end of the first annular segment distal to the second annular segment.

19. The device of claim 5, wherein:

the first wall portion is in the form of a first arcuate portion, and

the second wall portion is in the form of a second arcuate portion,

the first and second arcuate portions are integrally connected and together define the annulus of the annular tube.

20. The device of claim 19, wherein the second arcuate portion has an arc angle from 15 degrees to 120 degrees.

21. The device of claim 19, wherein the second arcuate portion has an arc angle from 30 degrees to 90 degrees.

22. The device of any one of claims 1 to 21, wherein the second wall portion comprises a thermoplastic polyurethane.

23. The device of claim 22, wherein the second wall portion is formed of a Tecoflex™ aliphatic polyether-based thermoplastic polyurethane.

24. The device of claim 23, wherein the Tecoflex™ aliphatic polyether-based thermoplastic polyurethane has a Shore hardness of 72A.

25. The device of claim 22, wherein the second wall portion is formed of a Carbothane™ aromatic, polycarbonate-based thermoplastic polyurethane.

26. The device of claim 25, wherein the Carbothane™ aromatic, polycarbonate-based thermoplastic polyurethane has a Shore hardness of 77A.

27. The device of any one of claims 22 to 26, wherein the first wall portion comprises a thermoplastic polyurethane.

28. The device of claim 27, wherein the first wall portion is formed of a Tecothane™ polyether-based thermoplastic polyurethane.

29. The device of claim 28, wherein the Tecothane™ polyether-based thermoplastic polyurethane has a Shore hardness of 62A.

30. The device of claim 1, wherein the second wall portion comprises a thermoplastic polyurethane.

31. The device of claim 30, wherein the second wall portion is formed of a Tecoflex™ aliphatic polyether-based thermoplastic polyurethane.

32. The device of claim 31, wherein the Tecoflex™ aliphatic polyether-based thermoplastic polyurethane has a Shore hardness of 72A.

33. The device of claim 30, wherein the second wall portion is formed of a Carbothane™ aromatic, polycarbonate-based thermoplastic polyurethane.

34. The device of claim 33, wherein the Carbothane™ aromatic, polycarbonate-based thermoplastic polyurethane has a Shore hardness of 77A.

35. The device of any one of claims 30 to 34, wherein the first wall portion comprises a thermoplastic polyurethane.

36. The device of claim 35, wherein the first wall portion is formed of a Tecothane™ polyether-based thermoplastic polyurethane.

37. The device of claim 36, wherein the Tecothane™ polyether-based thermoplastic polyurethane has a Shore hardness of 62A.

38. The device of any one of claims 1 to 37, wherein the polymeric wall structure further comprises:

a retention frame lumen, and

an elastic retention frame disposed in the retention frame lumen.

39. The device of claim 38, wherein the retention frame lumen is defined and bounded by a lubricious thermoplastic polyurethane which is different from the polymeric materials forming first and second wall portions.

40. The device of any one of claims 1 to 39, wherein the device is elastically deformable between a relatively straightened shape suited for insertion through a lumen into the bladder of a patient and a coiled retention shape suited to retain the device within the bladder.

41. A method of administering a drug to a patient in need thereof, comprising:

inserting into the patient the device of any one of claims 1 to 40; and

permitting water in vivo to diffuse into the drug reservoir space and produce an osmotic pressure to drive the drug from the device through the aperture for release into the patient.

42. The method of claim 41, wherein the inserting comprises deploying the device through the patient's urethra and into the patient's urinary bladder or renal pelvis.

43. A method of making the device of claim 1, comprising:

introducing a first material into an extrusion stream of an extruder to form a first wall portion of a tubular structure; and

introducing a second material into the extrusion stream in an manner to replace the first material in at least one position and to form a second wall portion of the tubular structure,

wherein the first wall portion is integrally connected to the second wall portion, and the first and second wall portions together define the drug reservoir space in the form of a drug reservoir lumen.

44. The method of claim 43, further comprising forming an aperture through a sidewall of the tubular structure.

45. The method of claim 43 or 44, further comprising:

loading a drug into the drug reservoir lumen; and

sealing the ends of the drug reservoir lumen.

46. The method of claim 45, wherein the drug loaded into the drug reservoir lumen is in a solid form.

47. The method of claim 45 or 46, wherein one of the ends of the drug reservoir lumen is sealed with an end piece having an aperture which extends through the end piece in fluid communication with the drug reservoir lumen.

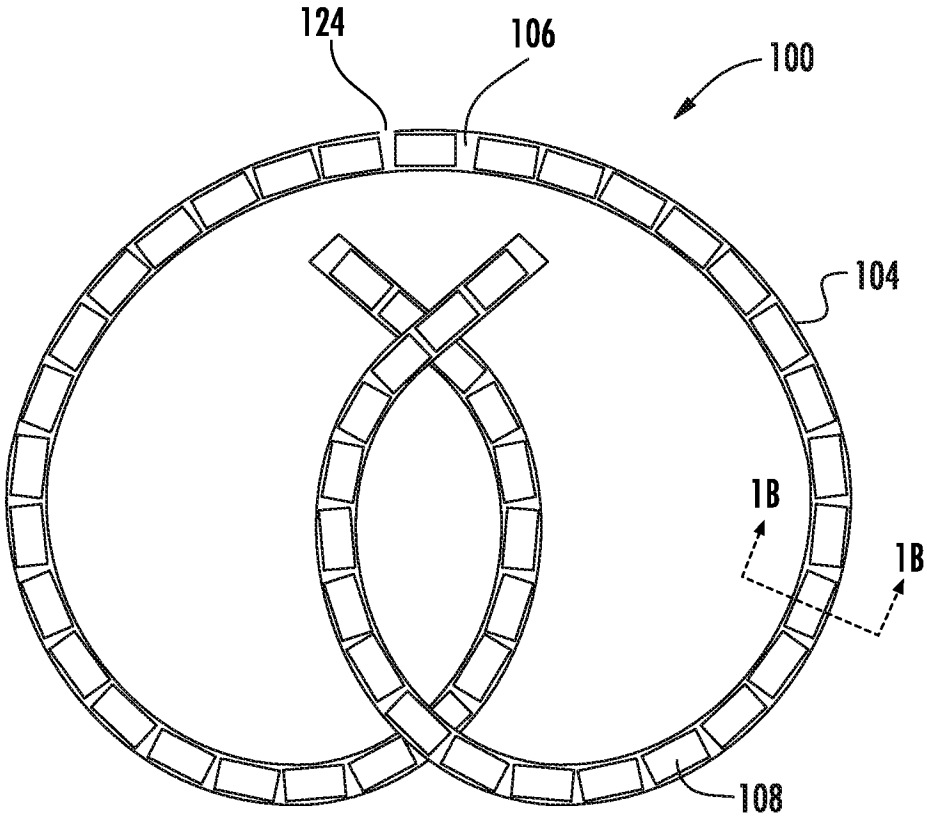

FIG. 1A

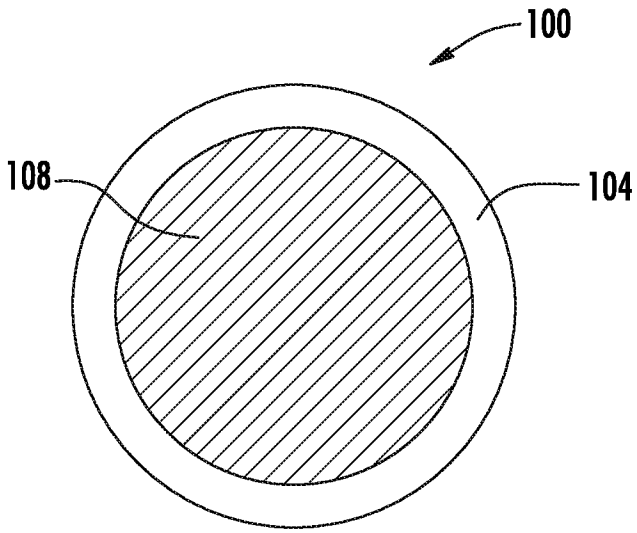

FIG. 1B

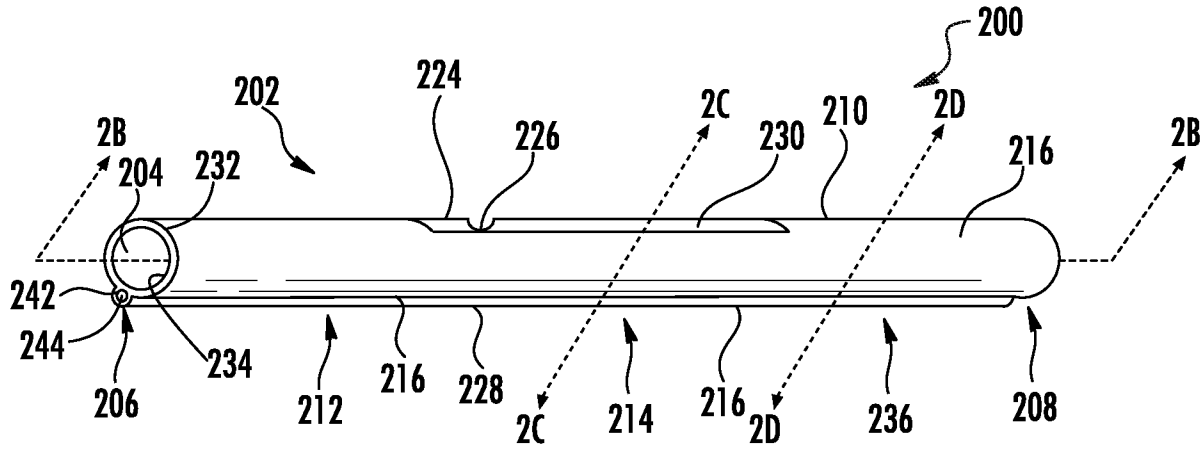

FIG. 2A

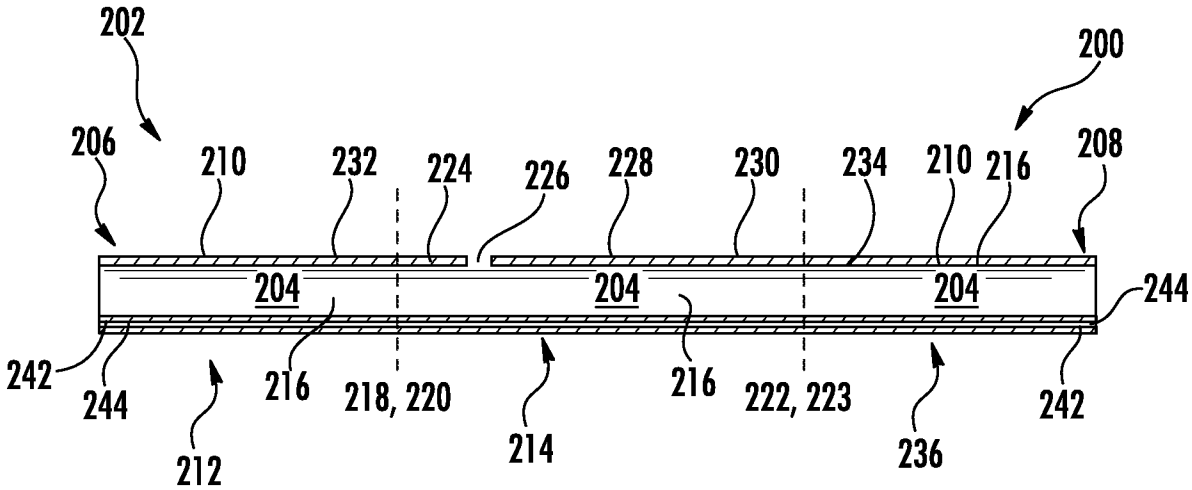

FIG. 2B

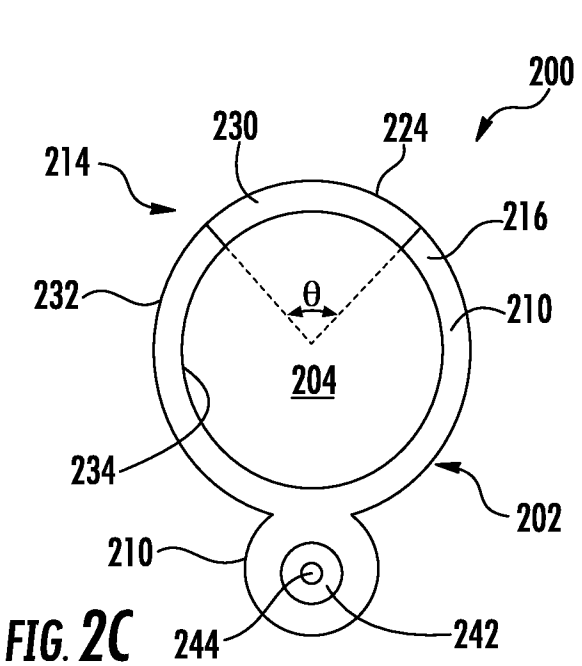

FIG. 2C

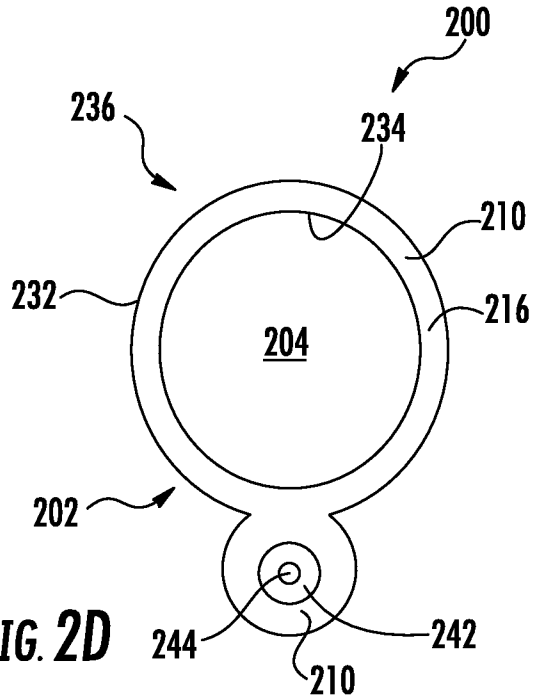

FIG. 2D

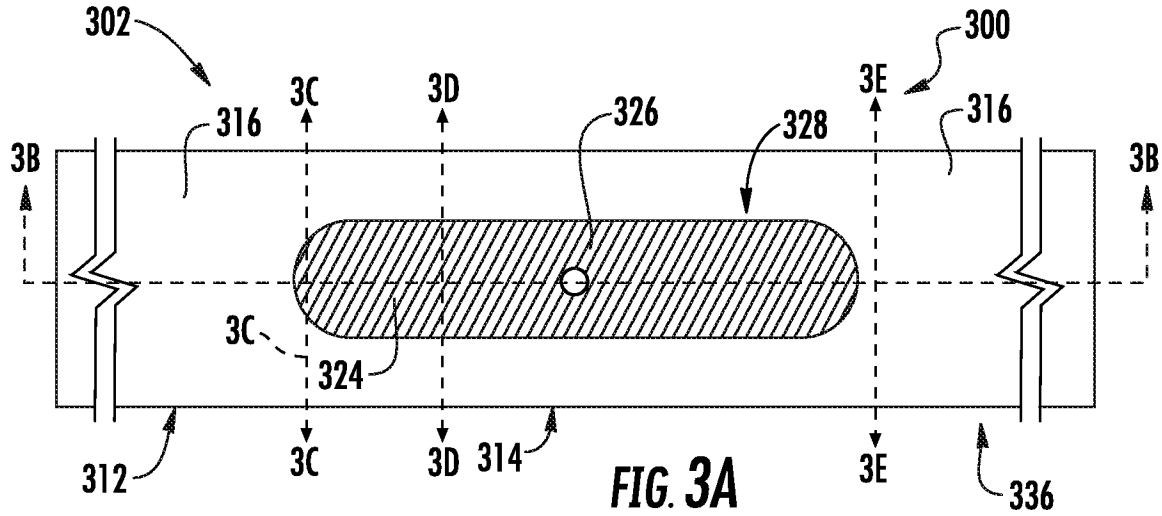

FIG. 3A

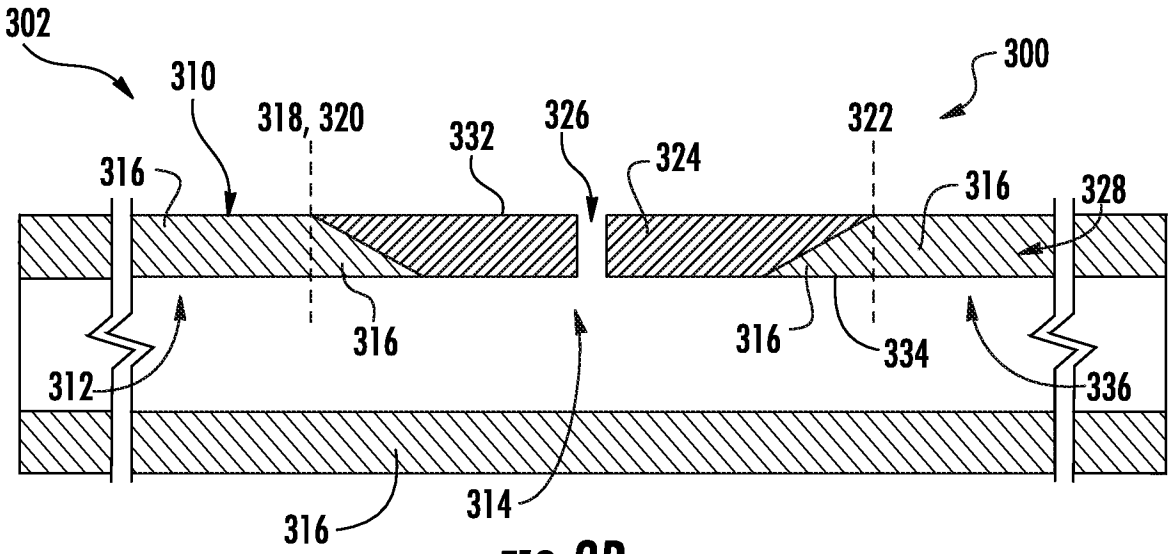

FIG. 3B

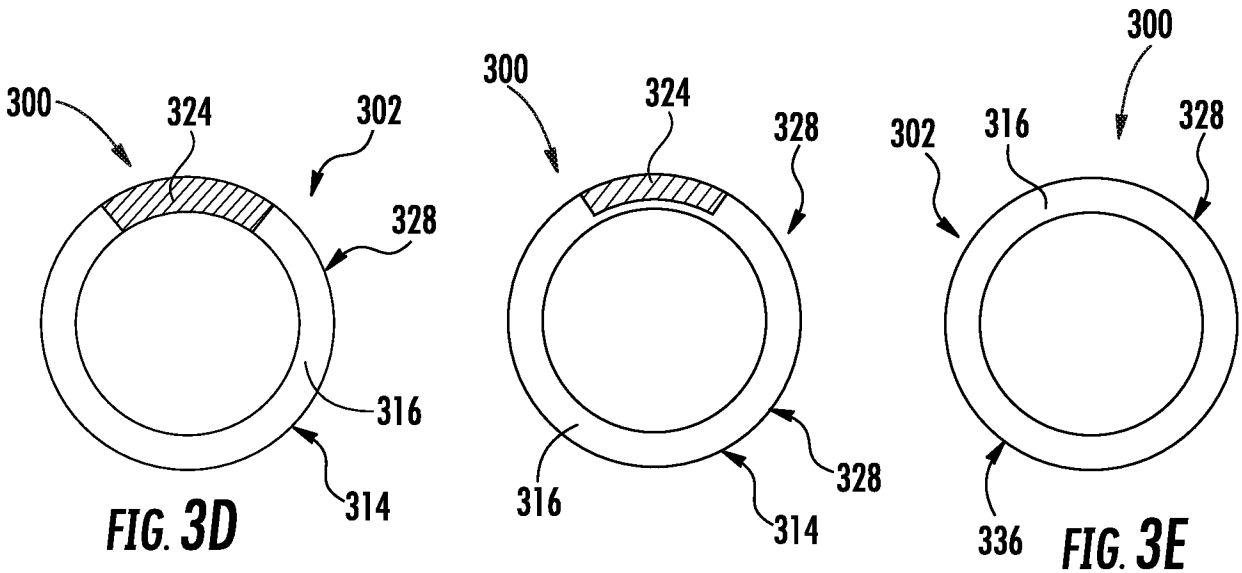

FIG. 3D

FIG. 3C

FIG. 3E

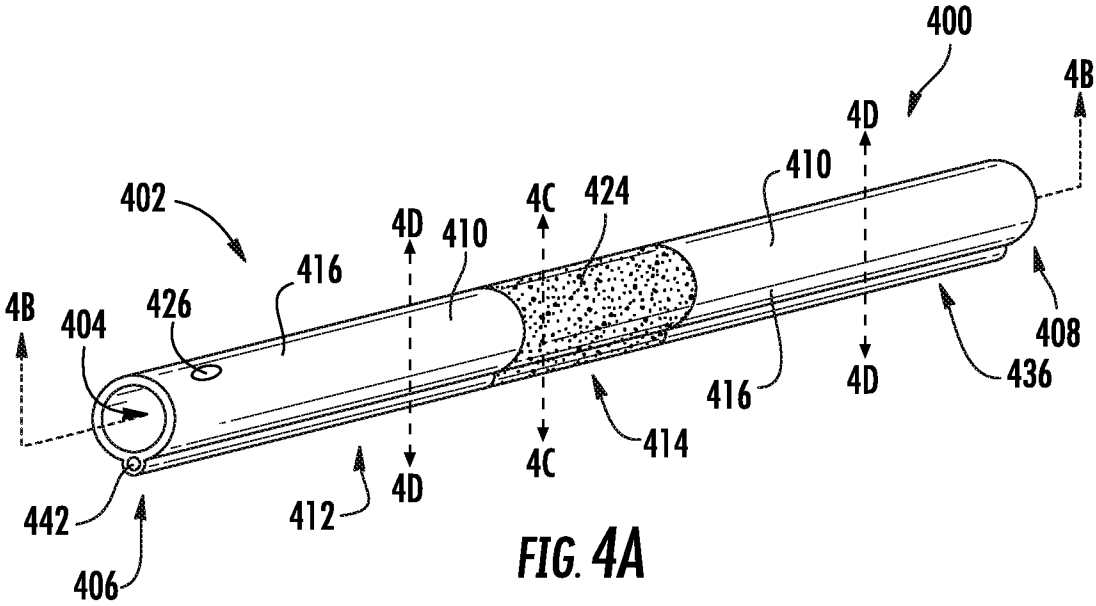
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FIG. 4A

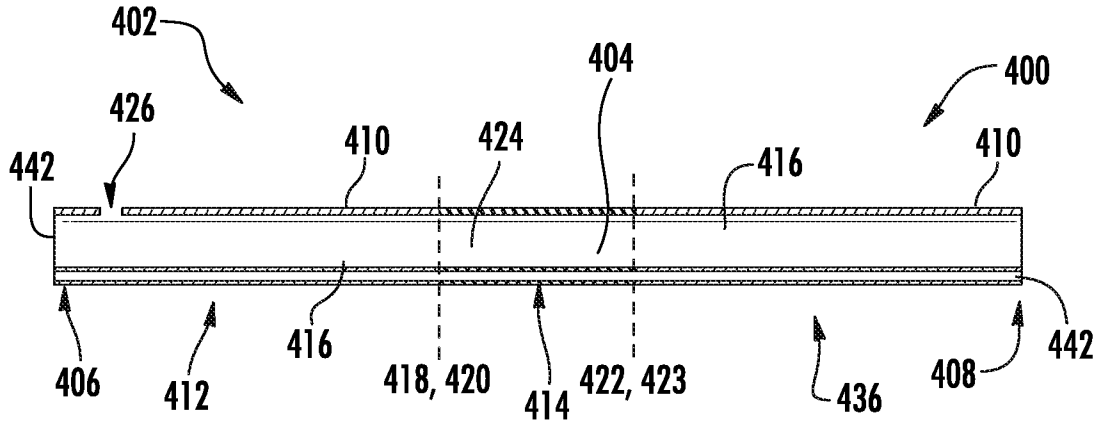
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FIG. 4B

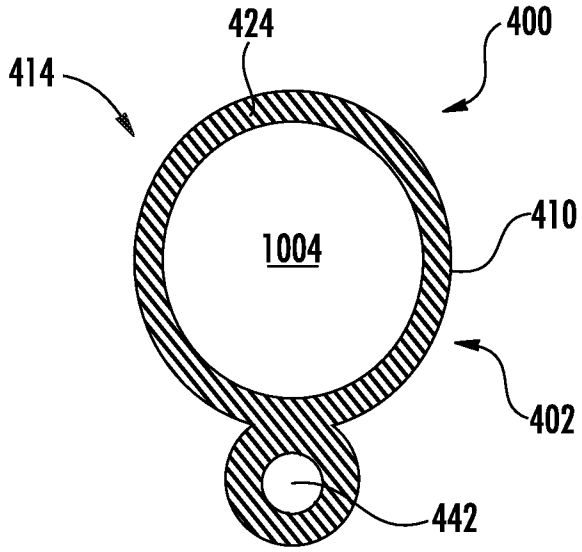

FIG. 4C

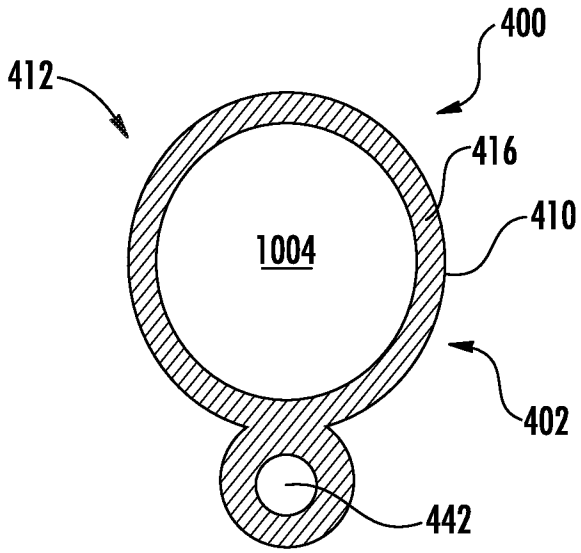

FIG. 4D

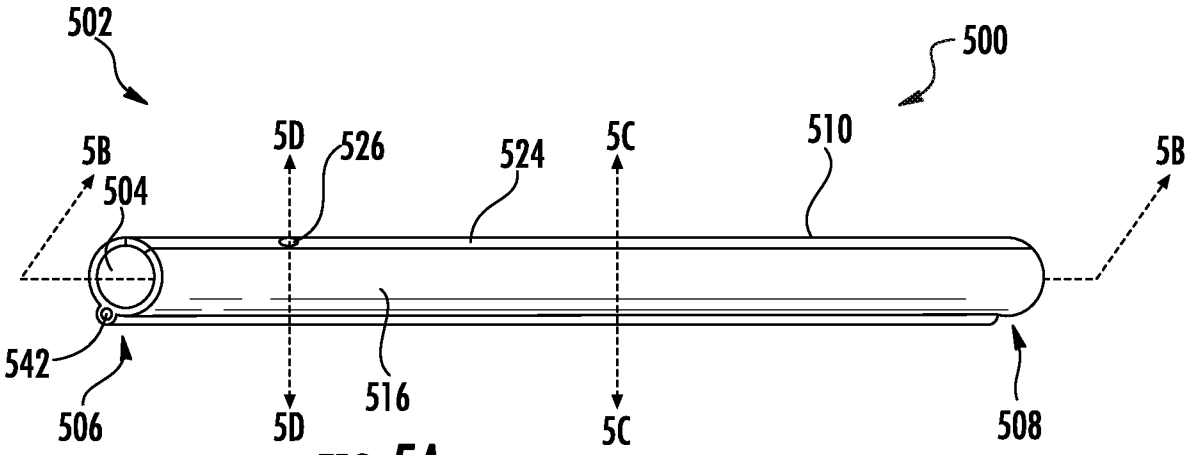

FIG. 5A

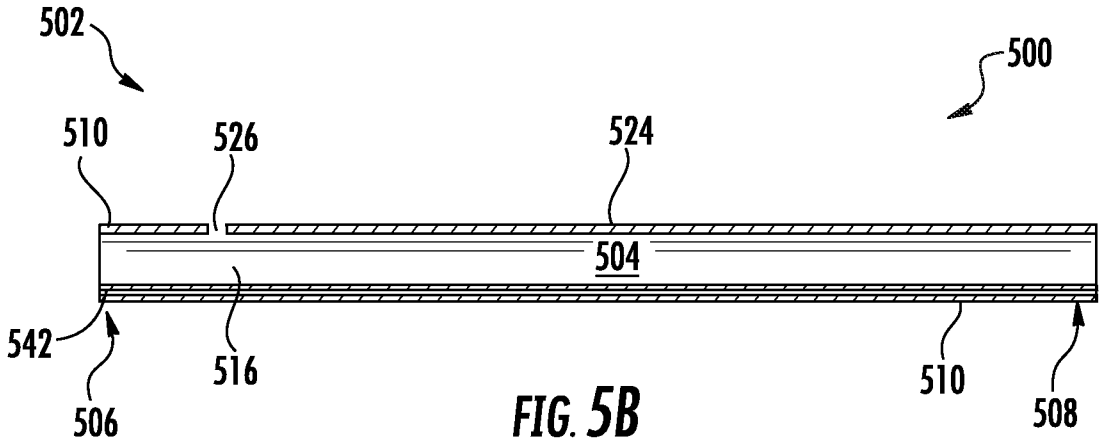

FIG. 5B

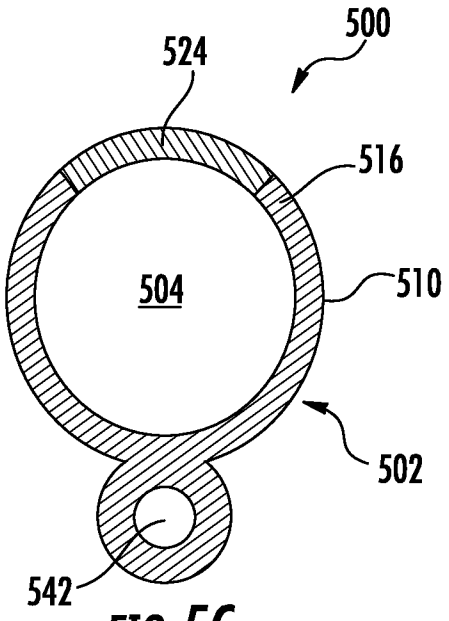

FIG. 5C

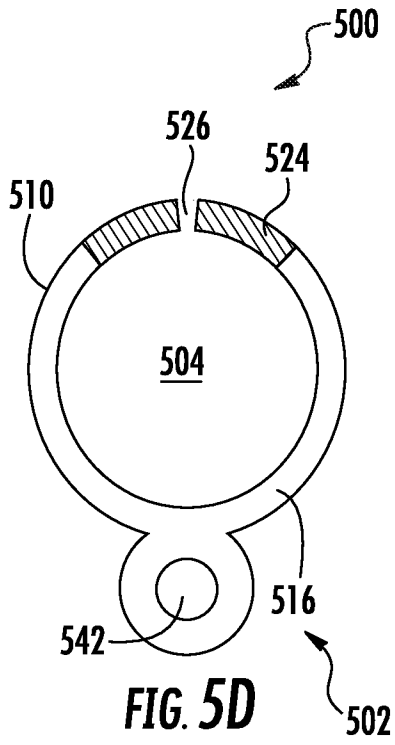

FIG. 5D

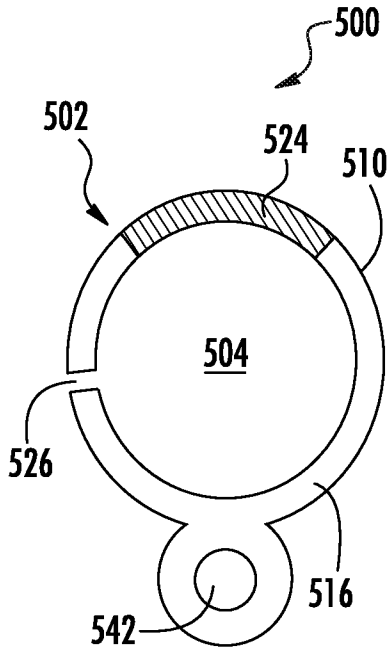

FIG. 5E

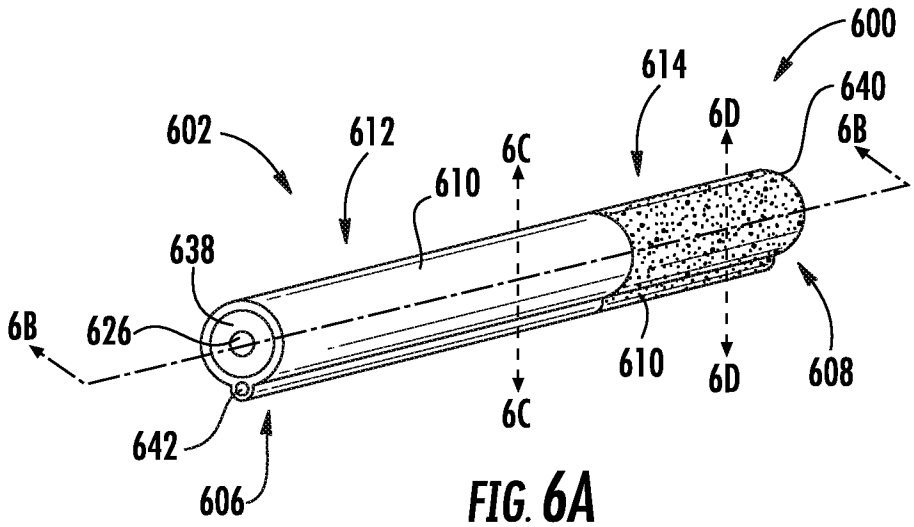

FIG. 6A

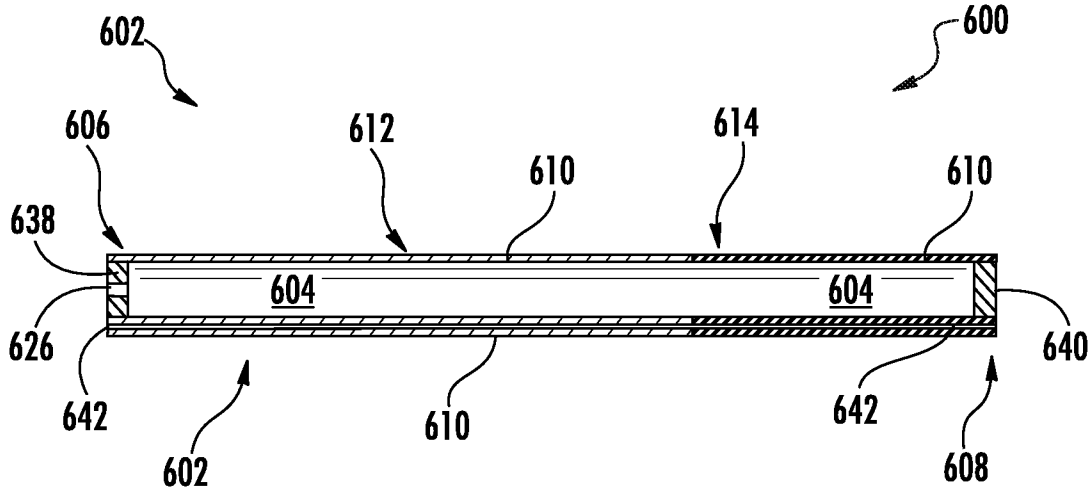

FIG. 6B

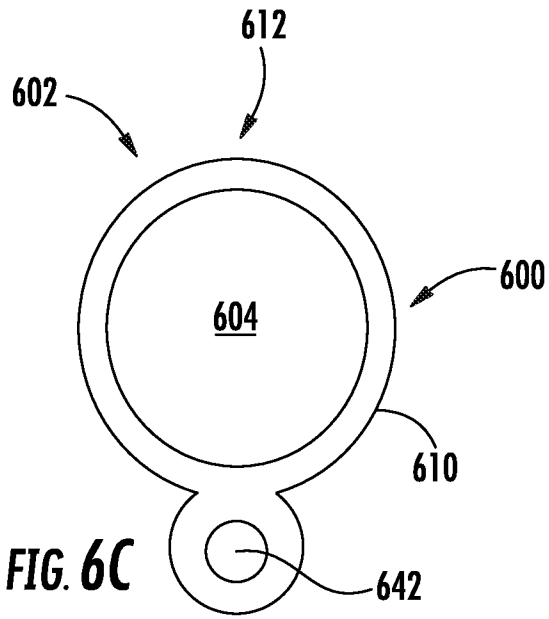

FIG. 6C

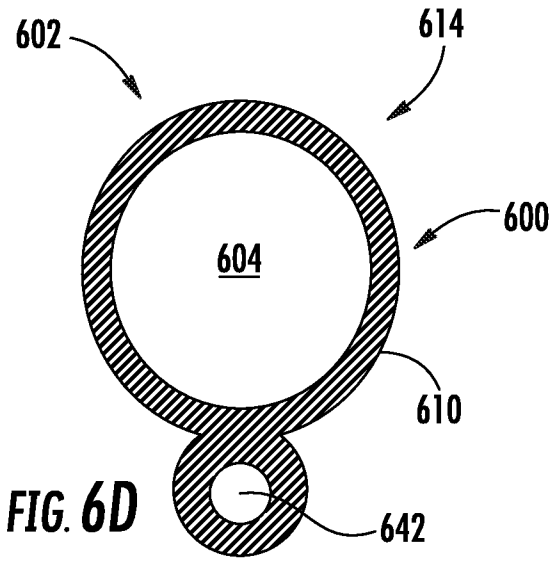

FIG. 6D

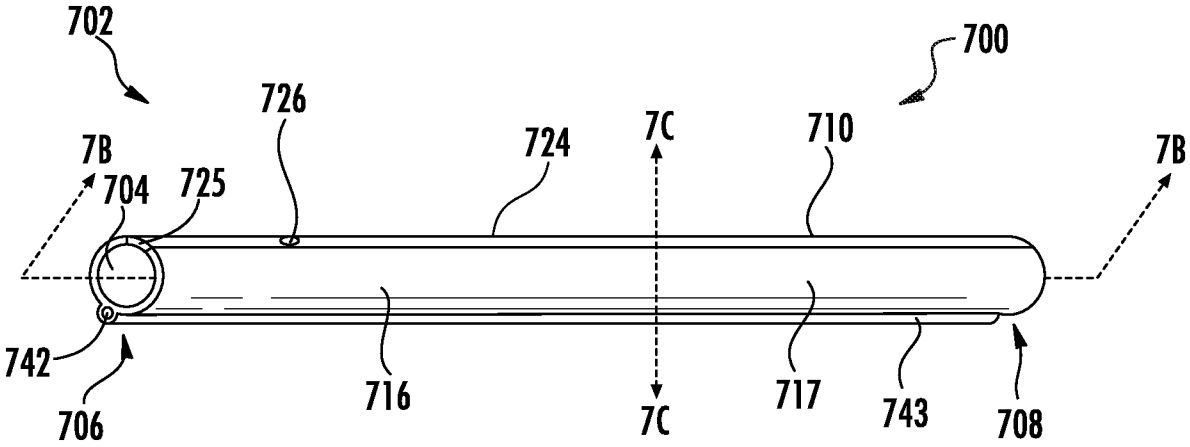

FIG. 7A

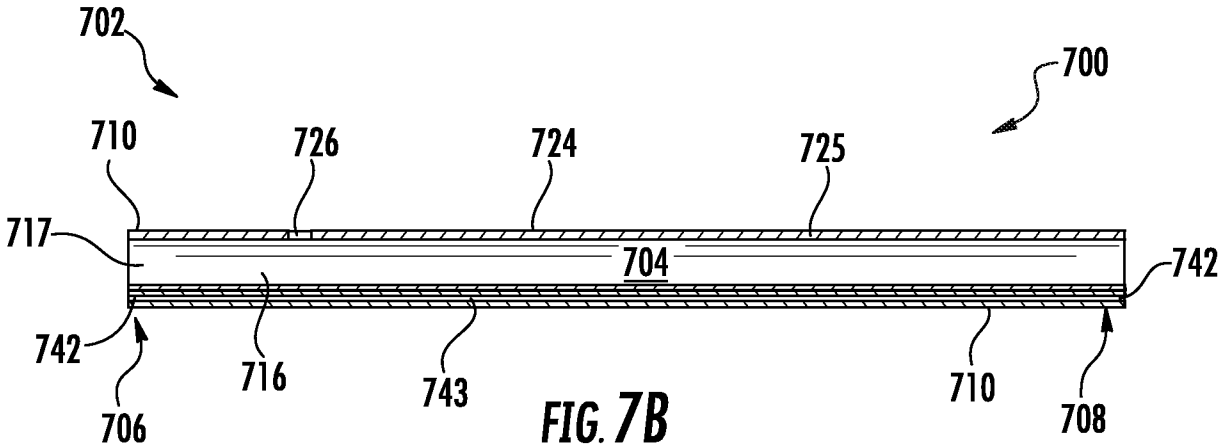

FIG. 7B

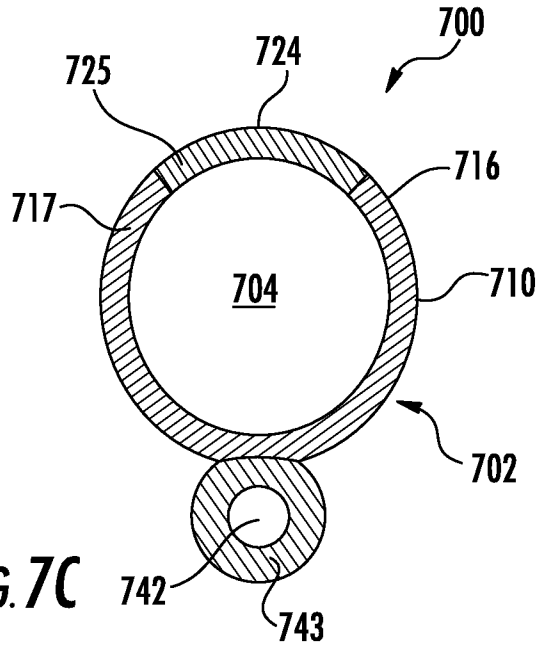

FIG. 7C

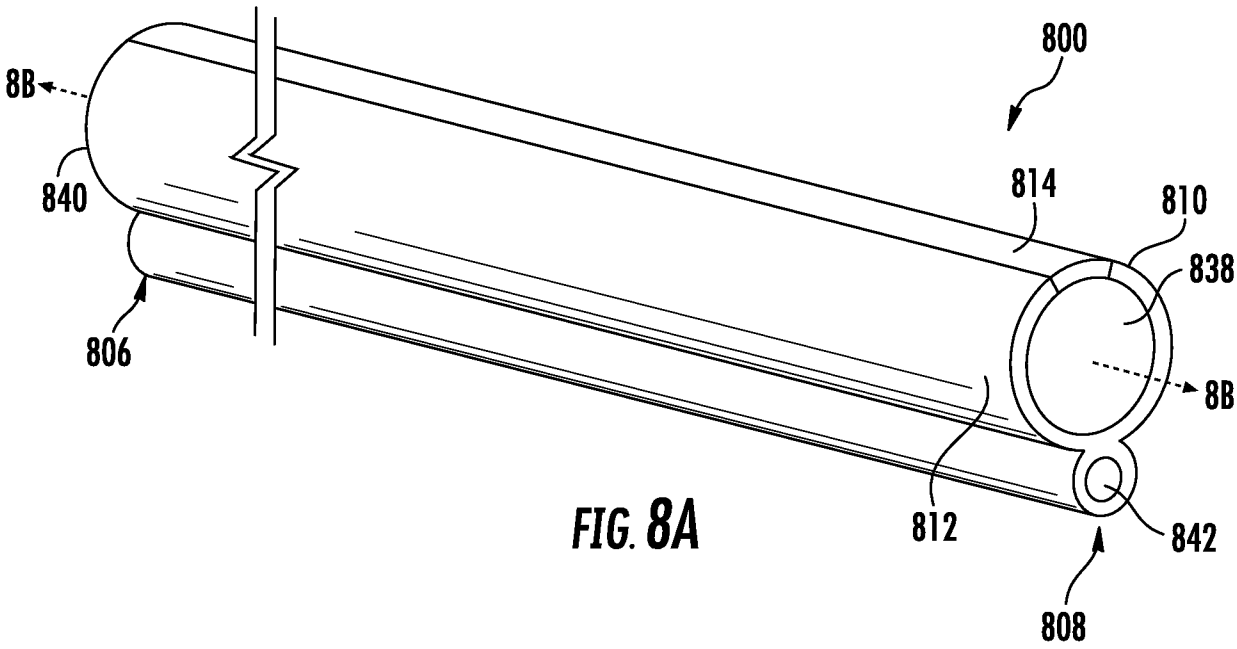
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FIG. 8A

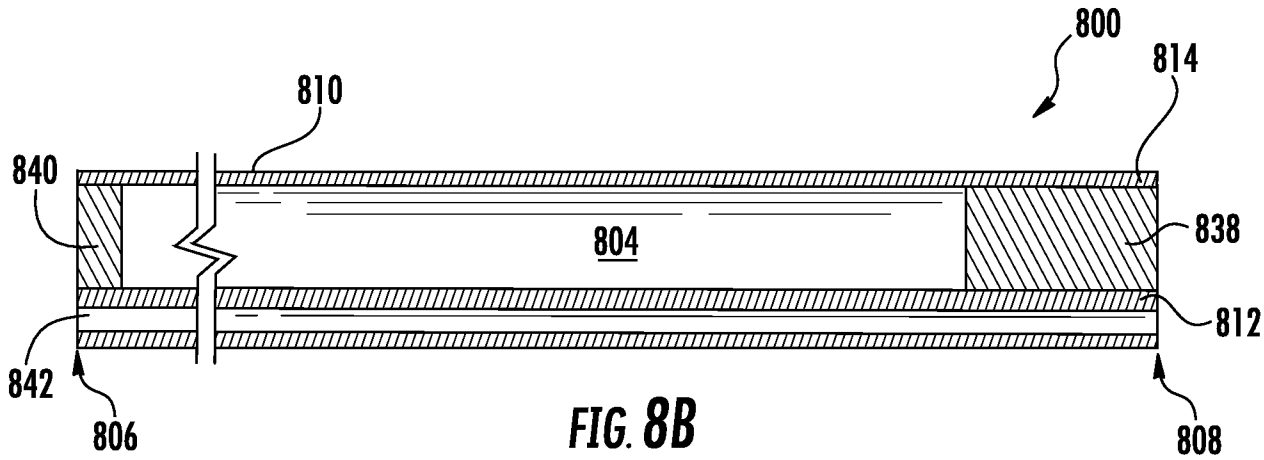
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FIG. 8B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/020536

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61M31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/026813 A1 (TARIS BIOMEDICAL LLC [US]) 26 February 2015 (2015-02-26) paragraphs [0031], [0059], [0062] figures 15A,15B,18 claims 1-10,20,21,25,32	1-47
X	US 2012/089122 A1 (LEE HEEJIN [US] ET AL) 12 April 2012 (2012-04-12) paragraphs [0055] - [0057], [0061], [0180] figures 1,2 claims 1,9	1-47
A	WO 92/13521 A1 (ALZA CORP [US]) 20 August 1992 (1992-08-20) page 6, lines 10-25 example 1 claim 1	1-47

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2017	15/05/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hedegaard, Anette

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/020536

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