A pressure responsive valve assembly suitable for use in a drug-infusing device is disclosed. The drug-infusing device with a pressure responsive valve is implanted into a body cavity such as a bladder. Fluid drug is introduced into an infuser device. The rate of fluid dispensed from an infuser can be controlled based upon the pressure differential between the internal pressure of the infuser and the pressure within a body cavity. Drug infusion can be accomplished utilizing a duckbill valve assembly disposed within an infuser device. A pressurized drug is introduced outside of the resilient lips of a duckbill valve and the lips are urged toward each other. The drug comes in contact with a compressible multi-channel flow membrane located between the resilient lips of the duckbill valve. The drug flows through the membrane and out through the throat of the duckbill valve, slowing the amount of drug being released over time.
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PRESSURE RESPONSIVE VALVE FOR USE WITH
AN INTRAVESICAL INFUSER

Background of the Invention

Field of the Invention

The present invention relates to flow controlling valves suitable for use in fluid delivery, such as in delivering pharmaceuticals to a patient from an infusion device, and also relates to infusion devices containing those valves, as well as methods of using the valves.

Description of the Related Art

Various types of drug delivery systems are well known in the prior art. Possibly the most common of these systems has been employed for the delivery of drugs to bedridden patients using an elevated container with a valve controlling the drip rate of the drug into a tube coupled with a needle inserted into the patient's body. With such a system, the flow rate may be controlled by means of a valve. This system presents a number of problems, not the least of which is their limitation for use only with non-ambulatory patients.

Other types of drug delivery systems are also known which employ various types of flow control devices. For example, a drug may be delivered by operation of a low volume pump. All of these systems as employed within the prior art have exhibited numerous shortcomings. For example, most systems employing pumps have been rather large and have required substantial amounts of power for proper operation. In addition, these devices are typically limited to use with bedridden patients.

Delivery of drugs into a body cavity is typically accomplished systemically. Systemic drug delivery through oral, intravenous, intramuscular, or transdermal administration methods carries with it the obvious drawbacks of any systemic treatment, such as side effects. The drug may also be metabolized or altered by physiological processes, and the ultimate quantity of active drug that reaches the body cavity may be reduced. In addition, because many drugs are not well tolerated systemically, the dosage must be limited, thereby reducing the total effective dose that reaches the targeted body cavity.

Numerous attempts have been made to optimize drug delivery to a targeted body cavity such as the brain, nasal cavity, lungs, heart, stomach, peritoneum, bladder, or uterus. For example, Domb et al., U.S. Patent No. 5,170,189 describe a biodegradable wafer soaked with a chemotherapeutic for implantation into the brain cavity to treat brain tumors. Pocknell, U.S. Patent No. 4,888,074 discloses therapeutic rings containing contraceptive medications for insertion into the vagina. Lowe et al., U.S. Patent No. 5,277,912 disclose a sustained release capsule adapted for insertion into the rumen of an animal for delivery of a biologically active composition over time.

Drug delivery to the bladder, for example, can be accomplished by retrograde injection of the drug into the bladder via catheter. Retrograde introduction of drug via a urethral catheter, however, is suitable only for limited situations and has inherent drawbacks. See for example, Bladder Tissue Pharmacokinetics of Intravesical Taxol, Song, D, Wientjes, MG, Au, JL, Cancer Chemotherapy and Pharmacology, 1997, 40(4): 285-92; The Pharmacokinetics of Intravesical and Oral Oxybutynin Chloride, Massad, CA, Kogan, BA, Trigo-Rocha, FE, Journal of Urology, 1992, Aug.,

Stephen et al., U.S. Patent No. 5,301,688, discloses a method for treating bladder cancers through electromotive administration of drugs into the bladder via a catheter. This type of treatment is suitable primarily for care administered on an in-patient or out-patient basis, not for chronic treatment.

Tskada, U.S. Patent No. 5,219,334 discloses an infuser for connection to a catheter that is suitable for long-term delivery of drug into a patient through the catheter. This device requires continuous catheterization in order to function adequately.

Pryor et al., U.S. Patent No. 5,062,829, discloses a helical device for insertion into a body cavity, e.g., the rumen of a bovine. The helical device includes a drug that can be released over time and further includes a biodegradable portion so that, upon exhaustion of the drug, the device can break up and be naturally eliminated.

Garay et al., U.S. Patent No. 4,925,446, discloses an infusion device having an annular shape that is suitable for delivering materials into the stomach over a prolonged period of time.

None of these prior art devices address the problem of intravesical drug delivery where drug delivery is intended to continue over a prolonged period of time while the patient maintains an active lifestyle.

Two of the major causes of urge incontinence are detrusor instability and hyperreflexia. Trospium chloride and oxybutynin has been used to treat urge incontinence. Oxybutynin is a pharmacological agent that has been used to treat urge incontinence with some success. This drug is an anticholinergic agent that blocks contraction to the bladder and has direct smooth muscle relaxant properties. Unfortunately, this drug is associated with significant side effects upon oral administration, including dry skin, dry mouth, blurred vision, constipation, and urinary retention. In patients with cardiovascular disease, oxybutynin may lead to tachycardia. Because of the side effects, the accepted oral dose of oxybutynin is limited to 10-15 mg per day.

Interstitial cystitis is a debilitating condition in which the lining of the bladder is irritated, creating a sense of urgency and pain. The condition results in extreme frequency of urination, sometimes as many as 40, 50, or more times per day and can lead to cystectomy. Sufferers of interstitial cystitis can be treated by administration of certain drugs, including pentosan polysulfate, manufactured by Bene of Munich, Germany and distributed by ALZA Corporation of Palo Alto, CA under the trademark ELMIRON. However, there is currently no satisfactory method for delivery of such drugs to a patient over a prolonged period of time while permitting the patient to enjoy a relatively normal lifestyle.

Superficial bladder cancer is likewise of great urological concern. Typically, treatment of superficial bladder cancer includes transurethral resection and chemotherapy. Chemotherapy for the treatment of bladder cancer is usually administered through a catheter to instill the medication directly into the bladder. The catheter is removed...
immediately after the medication has been instilled, and the patient must hold the medication in the patient’s bladder for at least two hours after treatment. Several different types of medications may be used for chemotherapy, such as mitomycin-C, thiopeta, and doxorubicin. Common side effects include bladder wall irritation, genital area skin rash, and bone marrow suppression. Choice of a specific agent is usually based on the stage of the tumor. As with many chemotherapeutics, these medicines often causes nausea, vomiting, and loss of appetite.

Pain management for bladder maladies is typically accomplished using analgesics. Analgesics are drugs that relieve pain and include opioids (opiates and similar synthetic compounds), which act on receptors in the brain to inhibit pain impulses, or nonopioids (nonsteroidal anti-inflammatory drugs, or NSAIDs, as well as acetaminophen and phenacetin), which inhibit the synthesis of prostaglandins. Most of the commonly used mild nonopiod analgesics are derived from salicylic acid, pyrazolone derivatives, or phenacetin and include ibuprofen, acetaminophen, and aspirin. As described above, systemic treatment with any drug, including an analgesic, has the risk of side effects. Analgesics typically cause nausea and stomach irritation if given in a high dose. Consequently, they are not always well tolerated systemically. The dosage often has to be limited, thereby reducing the total effective dose that reaches the targeted body cavity.

One of the problems associated with implantable infusion devices is flow control. It is desirable for the flow to be relatively constant for the entire period of drug delivery. It is also desirable to control the flow so that a modest dosage of drug can be infused over a period of several days at a relatively constant rate.

Summary of the Invention

The present invention relates to microflow valves, and also to their use in infusion devices. Although the valves or flow controllers are described in the context of one preferred infusion device, it should be noted that the invention also includes the valves themselves, with or without an infusion device, and that infusion devices of any kind, both external and internally-implantable, can be used with these valves.

In one aspect of the present invention, there is provided a pressure responsive valve assembly. One type of pressure responsive valve assembly includes a duckbill valve assembly with at least two resilient lips at one end of the body of the valve that define an outlet slit between the two lips. Preferably, a multi-channel flow member is positioned between the two resilient lips, extending in the fluid passageway, and through the outlet slit. In operation, the resilient lips tend to compress the multi-channel flow member, effectively varying the resistance and subsequent fluid flow through the valve.

Advantageously, the pressure responsive valve assembly can include numerous pressure responsive valves. For example, a dual duckbill valve assembly is contemplated by the present invention. A dual duckbill valve may include a first and second duckbill valve. In one aspect of the invention, the first duckbill valve includes a body member with an axial fluid passageway and at least two resilient lips at one end of valve assembly that define an outlet slit between the resilient lips. Additionally, the first duckbill valve may further comprise a multi-channel flow member located between the resilient lips. The multi-channel flow member may extend into the fluid passageway and
through the outlet slit such that the resilient lips compress the multi-channel flow member and vary resistance to fluid flow through the valve.

The second duckbill valve may have a body member with an axial fluid passageway and a first and second end. Similarly, the second duckbill valve may include resilient lips that define an outlet slit between the lips at the second end of the body member and a multi-channel flow member positioned between the resilient lips and extending in the fluid passageway and through the outlet slit such that the resilient lips tend to compress the multi-channel flow member thereby varying resistance to fluid flow through the valve. In one aspect of the invention, the first duckbill valve is coupled to the first end of an ante-chamber. The second end of the first duckbill valve protrudes into the chamber. The first end of the second duckbill valve is coupled to the second end of the ante-chamber such that the second end of the second duckbill valve protrudes from the ante-chamber. The second duckbill valve can be placed in communication with a pressurized fluid such that fluid is able to flow through the second duckbill valve, into the ante-chamber, and then through the first duckbill valve of the ante-chamber. The dual pressure-responsive valve assembly may further comprise a plurality of sub chambers.

In another aspect of the present invention, there is provided a method of using a pressure responsive valve. In one example, the utilization of a duckbill valve includes disposing a compressible multi-channel flow member between the lips of a duckbill valve and applying a pressurized agent outside of the resilient lips of the valve to urge the resilient lips towards each other. At the same time, the pressurized agent can be put in contact with the multi-channel flow member, thereby causing the pressurized agent to flow in through the resilient lips and out through the throat of the duckbill valve.

In still another aspect of the present invention, there is provided an implantable infusion device with a pressure-responsive valve. The device is comprised of a reservoir with a first shape that permits the reservoir to be passed into a body cavity. The reservoir may be expanded to a second shape to hold a substance under pressure. Additionally, the infusion device may contain a valve assembly configured to admit the pressurized substance into the reservoir while the reservoir is within the body cavity. An aspect of the infusion device includes a duckbill valve comprising a body member with an axial fluid passageway and a first end and a second end. Two resilient lips define an outlet slit between the lips at the second end of the body member. A multi-channel flow member is positioned between the two lips and extend through the outlet slit thereby causing the resilient lips to compress the multi-channel flow member and to vary the resistance of fluid flow through the valve. The first end of the duckbill valve preferably is coupled to an exit port of the reservoir and the second end of the duckbill valve protrudes into the reservoir.

Advantageously, the duckbill valve provides a flow path for the pressurized drug or substance to exit the reservoir.

Multiple duckbill valves are similarly contemplated for use within an infuser device. Like the infuser device described above, the infuser may have an additional, second duckbill valve. The first end of the first duckbill valve can be coupled to the first end of an ante-chamber such that the second end of the first duckbill valve protrudes into the ante-chamber. Advantageously, the first end of the second duckbill valve can be coupled to the second end of the second duckbill valve such that it protrudes away from the ante-chamber into the reservoir. In one aspect of the
invention, the dual duckbill valve assembly communicates with the pressurized substance in the reservoir such that the substance flows through the second duckbill valve into the ante-chamber, and through the first duckbill valve out of the ante-chamber. The reservoir resumes substantially the first shape as the pressurized substance is dispensed.

In yet another aspect, the infusion device is a capable of changing shape. The infusion device may assume a first shape during implantation and a second shape after implantation into a body cavity of the mammal. For example, the device may assume the first shape when empty and the second shape when filled. The first shape may be generally elongated and the second shape may be arcuate. Removal of the infusion device may cause a shape change of the device from the second shape to the first shape, and then directing the infusion device out of the urethra. More particularly, the change from the second shape to the first shape may be accomplished by allowing matter within the device to be depleted by the infusing step. Alternatively, the infuser can change from the second shape to the first shape by opening a passageway in the device, thereby allowing matter within the device to exit the device.

The infusion device may have a flow-restricted exit port that provides delivery of the drug over a period of at least 24 hours, 5 days, 10 or 15 days or 30 days or more. In one aspect of the invention, the infusion device comprises a plurality of pressure responsive valves. The first pressure-responsive valve can be configured to admit the agent into the ante-chamber. The second pressure-responsive valve can be configured to release the agent from the ante-chamber. In yet another aspect of the present invention, the agent to be released from the infuser is under pressure and the first and second pressure-responsive valves vary the area of a flow channel in inverse proportion to the pressure of the drug to control the flow into a body cavity.

The device may also have a coating to inhibit deposition of material on the device when implanted into a body cavity of a mammal. For example, the coating may inhibit deposition of materials present in the urinary tract. The coating may be sulfated polysaccharide such as pentosanpolysulfate. The coating may be a surface coating on surfaces of the device exposed to the body upon implantation. The coating may be impregnated into the device. In addition or alternatively, a coating may be applied to the device to increase its lubricity.

Another aspect of the present invention relates to a method for delivering a drug to a patient. Preferably, the method of drug delivery includes the step of delivering an infusion device into a body cavity of the patient. The body cavity may be a mammalian bladder. An elastomeric member of the infusion device may be pressurized by adding an agent to the elastomeric member. Optionally, the agent may be a drug. Alternatively, the agent may be a diagnostic tool. The drug may be in a liquid form and the device can preferably deliver the drug at a rate of less than about 400 μl/hour. The agent may be delivered at a rate of less than about 1 ml/hour. The agent may be a reconstitution agent which activates a drug within the device. The reconstitution agent may activate a second drug within the ante-chamber of the infuser device. Alternatively, the drug may be present in the infusion device in condensed form during the step of delivering the infusion device into the patient. The drug within the device may be effective to treat incontinence such as urge incontinence. For example, the drug may be oxybutynin. The drug may also be an anesthetic, analgesic, antibiotic, or anti-cancer agent. Additionally, the drug may be used to treat cystitis.
The method of delivering a drug to a patient may further include the step of releasing the infusion device into a body cavity such as a mammalian bladder. The agent within the infusion device can be infused in a controlled manner from the elastomeric member into an ante-chamber. Optionally, the step of infusing the agent from the elastomeric member into the ante-chamber results in a delay in the delivery of the agent into the body cavity. The agent is released into the body cavity in a controlled manner from the ante-chamber. The ante-chamber may have a subchamber containing a drug in condensed form when the infusion device is delivered into the patient and the drug may be infused into the body cavity during an initial treatment period.

Infusing a drug into a body cavity may additionally include the step of controlling the rate of flow of drug from the device into the body cavity. The infusing step may include infusing an agent into the bladder for at least about 5 days. Infusing an agent from the elastomeric member into the ante-chamber may cause a reduction in the delivery rate of the agent into the body cavity during the initial period of time when the agent or infuser is first introduced into the body cavity. By having a low delivery rate of drug, the side effects associated with high delivery rates of the drug can be reduced.

Flow of drug may be controlled by means of a pressure-responsive valve or valves. For example, the drug may be under pressure and the pressure-responsive valve may control the flow by varying the area of multiple flow channels in inverse proportion to the pressure of the drug.

The drug used with the method may be used to treat incontinence such as urge incontinence. For example, the drug may be oxybutynin. The drug may also be used to treat pain, neuralgia or cystitis. The drug may be an antibiotic or an anti-cancer drug.

In yet another aspect of the present invention, an implantable infusion device may be configured to permit the elongated pressure member to be passed through a mammalian urethra. The pressure member may be configured to expand to a second shape to hold a pressurized fluid substance. A valve assembly of the type disclosed herein may be disposed at a first end of the elongated reservoir and configured to admit the pressurized fluid substance into the elongated pressure member while the elongated pressure member is within a mammalian bladder. A flow-restricted exit port may be configured to dispense the pressurized fluid substance from the pressure member while the infuser is within the mammalian bladder. In addition, the device may comprise a tethering means for tethering the device to a bladder wall. The first shape of the device may have a linear configuration with at least one axis of symmetry and the second shape may have a curved configuration that has no axial symmetry.

The valve assembly located at the first end of the infuser and configured to admit the pressurized fluid substance may also be configured to provide a means of rapidly purging the pressurized fluid substance from the infuser device. The device may comprise a capture member which is incorporated into a release mechanism that is configured to allow the valve assembly to rapidly purge the pressurized fluid substance from the infuser. The pressurized fluid substance may be a diagnostic tool. The check valve assembly may comprise a disc which is biased to occlude an input channel. The device may comprise a means for tethering the device to the bladder wall. In addition, the device may comprise one or more of the features previously enumerated.
Brief Description of the Drawings

Figure 1 is a schematic representation of a pressure-responsive valve.

Figure 2A is an illustrative cross-sectional view of a pressure-responsive valve.

Figure 2B is an illustrative cross-sectional view of a pressure-responsive valve being exposed to an external pressure.

Figure 3A is an illustrative cross-sectional view of a pressure-responsive valve.

Figure 3B is an illustrative cross-sectional view of a pressure-responsive valve being exposed to an external pressure.

Figure 4A is a perspective view of a pressure-responsive valve.

Figure 4B is an illustrative cross-sectional view of a pressure-responsive valve.

Figure 4C is an illustrative cross-sectional view of a pressure-responsive valve being exposed to an external pressure.

Figure 5A is a top planar view of the tip of a pressure-responsive valve.

Figure 5B is a cross-sectional view of the pressure-responsive valve in Figure 5A.

Figure 6 is a perspective view of an intravesical infuser in uninflated form.

Figure 7 is a cross-sectional view of an infuser according to the present invention, wherein the infuser is pressurized or inflated with a fluid, causing it to undergo a shape change.

Figure 8 is a longitudinal cross-section of the intravesical infuser of Figure 6, taken along the line 3-3.

Figure 9 is a detailed view of the proximal end of an infuser with a pressure-responsive valve.

Figure 10 is a detailed, cross-sectional view of the proximal end of an infuser with a duckbill valve assembly.

Figure 11 is a detailed view of the distal end of the infuser of Figure 3.

Figure 12 is a cross section of a pressure-responsive valve installed in an infuser.

Figure 13 is a cross section of a pressure-responsive valve disposed within an infuser.

Figure 14 is a cross section of a pressure-responsive valve installed in the infuser.

Figure 15 is a cross section of the distal end of an infuser with multiple pressure-responsive valves installed in the infuser.

Figure 16 is an illustration of relative drug delivery rates for an infuser with flow controlling valves.

Detailed Description of the Preferred Embodiment

The present invention relates to pressure-responsive microflow valves or flow controllers. It also includes the use of such flow controllers in infusion devices in general, as well as in a unique implantable intravesical infuser device suitable for delivery into a body cavity such as the bladder. In one embodiment, the infusion device with a microflow valve or flow controller is filled with a substance, which results in a reversible shape change to prevent voiding of the filled device or obstruction of the bladder neck. The microflow valves or flow controllers can be used with other implantable devices, external infusion devices, and other fluid delivery systems, such as in irrigation, manufacturing,
analytical instruments, electrodes, lubrication systems, and the like. Suitable infusion devices include, for example, osmotically pressurized devices, pumps that pressurize the drug with an elastomeric structure, spring driven pumps, syringe pumps, gas-pressurized drug delivery devices, devices pressurized by chemical reaction or electrolysis of a solid or liquid into a gas, electrically-driven pumps, and any other suitable structures.

The microflow valves or flow controllers of the present invention allow for the delivery of varying amounts of drug including drug delivery rates in the range of 1-10,000 microliter per hour (μl/hr). The term “drug” as used herein includes without limitation any pharmaceutical, therapeutic, medicament, or other substrate such as saline that is delivered into a body to achieve some efficacious effect. For example, drug may be delivered at a rate of 1, 10, 20, 40, 80, 100, 200, 400, 800, 1,000, 2,000, 4,000, 8,000 or 10,000 μl/hr. In particular preferred embodiments, the microflow valves or flow controllers allow for the delivery of varying amounts of drug over a period of a few hours to several weeks. For example, drug may be delivered over a period of 1 hour, 1 day, 5 days, 15 days, 30 days, or 60 days. In preferred embodiments, the drug is delivered over a period of not less than 5 days. In particularly preferred embodiments, the drug is delivered over a period of at least 15 days.

Further, it should be noted that the microflow valves of the present application have application in areas other than drug delivery such as industrial processes, delivery of pesticides, delivery of fertilizers or micronutrients in agricultural applications, irrigation, fragrance delivery, fluoridation or chlorination of water supplies, sterilization of liquids, and a large number of other uses that will be apparent to those of ordinary skill in the art.

The microflow valves of the present invention may advantageously be contained within an infusion device. The device with microflow valves provides controlled, site specific delivery of a drug into the bladder or other body cavity over an extended period of time by infusing a drug in a sufficiently low delivery rate so as to reduce side effects associated with high delivery rates of the drug. In preferred embodiments, the infusion device can contain as little as 1, 3, or 5 ml of drug or up to about 30, 50 or 100 ml or more.

One particularly preferred aspect of the present invention is a pressure-responsive valve assembly or flow controller suitable for use with an implantable infusion device, as well as for use in other implantable devices, external infusion devices, and other fluid delivery systems, such as in irrigation, manufacturing, analytical instruments, electrodes, lubrication systems, and the like. In one embodiment, such valve assemblies are used to control the flow of drug out of the infuser. The profile of a desired drug delivery rate can vary such as, for example, desiring a high initial delivery to stabilize a condition followed by a constant delivery rate; a low initial delivery rate to allow the patient to acclimate followed by a increase yet constant delivery rate; or a constant rate throughout the entire delivery period of the drug.

The delivery rate of a drug can be affected by the pressure profile within an infuser. For example, in an elastomeric infuser, the pressure in the infuser decreases over time, as the volume of drug inside the infuser decreases. Because it is advantageous to control the drug delivery rate in the presence of this varying pressure profile of the infuser, a pressure-responsive valving system is described below.
Embodiments of the invention will now be described with reference to the accompanying figures, wherein like numerals refer to like elements throughout. The terminology used in the description presented herein is not intended to be interpreted in any limited or restrictive manner simply because it is being utilized in conjunction with a detailed description of certain specific embodiments of the invention. Furthermore, embodiments of the invention may include several novel features, no single one of which is solely responsible for its desirable attributes or which is essential to practicing the inventions herein described.

The operation of one suitable type of pressure-responsive valve is illustrated in Figure 1. A pressure source P1 directs fluid from a fluid reservoir 72 into a valve assembly 74 through multiple flow channels 76. When the fluid reaches the valve assembly 74, the valve assembly 74 is subjected to an exterior and interior pressure differential that creates a flow resistance proportional to the differential pressure. Thus, with reference to Figure 1, the pressure P1 in the fluid reservoir 72 is also applied to the exterior of the valve assembly 74. The pressure P1 reduces the flow area of the portion of the flow of channels 76 extending through the valve assembly 74 or otherwise increases resistance to flow through the flow channel 76, dropping the pressure in the flow channel 76 to a lower pressure P3 as it exits the valve assembly 74. The fluid continues along the flow channels 84 to the exit 80.

Note that in this type of pressure-responsive valving, fluid flow can be maintained relatively constant despite variations in the pressure of the fluid reservoir as illustrated by the pressure P1. As illustrated, higher pressures, which would ordinarily facilitate higher flow rates, are counteracted by greater resistance of the flow channels 76 through the valve assembly 74. Conversely, as the pressure P1 in the fluid reservoir 72 decreases, the flow channel 76 through the valve assembly 74 is increased in size or cross-sectional area, thus compensating for the reduced pressure driving fluid through the flow channel 76.

One embodiment of a valve assembly 74 is shown in Figure 2. Figure 2A illustrates an embodiment of the valve assembly 74, taken in transverse cross section to the direction of the multiple flow channels 404. In this embodiment, a membrane 240 containing multiple flow channels 404 extends through the valve assembly 74, shown in Figure 1, leading to an exit (not shown). The membrane 240 is located between a fixed, stationary wall 400 and a movable wall 402. The movable wall 402 may be formed of any deformable material, preferably in the form of a sheet or a web, such as polyethylene, teflon, polyvinyl chloride, polytetrafluoroethylene, polyvinylidene chloride, thin stainless steel and the like.

As shown in Figure 2B, when an external pressure, indicated by arrows P1, impinges on the exterior of the movable wall 402, the movable wall 402 is pressed inwardly compressing the membrane 240 that contains the multiple flow channels 404. Compression of the membrane 240 constricts the multiple flow channels 404. In this manner, as the pressure P1 increases, the cross-sectional area of the flow channel 404 decreases, thereby constricting the flow of fluid through the valve assembly 74. It will be appreciated that a wide variety of configurations and materials can be used to construct movable walls that will compress against a flow channel upon the application of pressure to the movable wall. Any such pressure-responsive valve utilizing a movable wall, or other pressure-
responsive elements, such as those in which the flow pressure acts against a spring or the like, are considered to fall within the scope of the present invention.

Another embodiment of a valve assembly 74 is shown in Figure 3. Figure 3A illustrates an embodiment of the valve assembly 74, taken in transverse cross section to the direction of the multiple flow channels 404. In this embodiment, a membrane 240 containing multiple flow channels 404 extends through the valve assembly 74 leading to an exit (not shown). The membrane 240 is located between a first flexible wall 410, and a second flexible wall 412. The movable walls 410 and 412 may be formed of any deformable material, preferably in the form of a sheet or a web, such as polyethylene, teflon, polyvinyl chloride, polytetrafluoroethylene, polyvinylidene chloride, thin stainless steel and the like.

As shown in Figure 3B, when an external pressure, indicated by arrow P1, impinges on the exterior of the movable walls 410 and 412, the movable walls 410 and 412 are pressed inwardly compressing the membrane 240 that contains the multiple flow channels 404. Compression of the membrane 240 constricting the multiple flow channels 404. In this manner, as the internal pressure P2 increases, the cross-sectional area of the flow channel 404 decreases, thereby constricting the flow of fluid through the valve assembly 74. It will be appreciated that a wide variety of configurations and materials can be used to construct movable walls that will compress against a flow channel upon the application of pressure to the movable wall. Any such pressure-responsive valve utilizing a movable wall, or other pressure-responsive elements, such as those in which the flow pressure acts against a spring or the like, are considered to fall within the scope of the present invention.

Yet another embodiment of a valve assembly 74 is shown in Figure 4. Figure 4A illustrates an embodiment of the valve assembly 74, in a perspective view. In this embodiment, a base material 500 contains an entrance port 550, and an exit port 560. Additionally the base material has multiple tortuous flow channels 510 within it. These multiple tortuous flow channels may be formed in the base material 500 through various methods such as, for example, photore sist etching or machining. The multiple tortuous flow channels 510 are enclosed by a movable, compressive material 502. The compressive material may be bonded using any suitable method for bonding, including adhesives, solvent welding, mechanical fasteners, RF welding, ultrasonic welding, and the like.

Figure 4B illustrates the embodiment of the valve assembly 74 of Figure 4A, taken in transverse cross section to the direction of the multiple tortuous flow channels 510. As illustrated in Figure 4B, the number and width of the multiple tortuous flow channels 510 formed between the base material 500 and the flexible, compressive material 502 determines the degree of constriction of the multiple tortuous flow channels 510. As illustrated in Figure 4C, an external pressure, indicated by arrow P1, acting on the valve 74 causes the compressive material 502 to extrude into the multiple tortuous flow channels 510 formed in the base material 500. The extrusion of the compressive material 502 decreases the cross sectional area of the multiple tortuous flow channels 510 and increases the constriction of the multiple tortuous flow channels 510. Increasing the pressure causes the compressive material 502 to continue to extend and further occlude the multiple tortuous flow channels 510 and thus acts to reduce the flow through the flow channel 510. As the pressure is decreased, the compressive material 502 will recede from the
multiple tortuous flow channels. The recession of the compressive material 502 increases the cross sectional area of the multiple tortuous flow channels 510 and thus provides a less restrictive flow path. It will be appreciated that a wide variety of configurations and materials can be used to construct the compressive material 502 that will extend to partially occlude the multiple tortuous flow channel 510 upon the application of pressure to the compressive material 502. Any such pressure-responsive valve utilizing a compressive material, or other pressure-responsive elements, such as those in which the flow pressure acts against a spring or the like, are considered to fall within the scope of the present invention.

In a preferred embodiment, the pressure responsive valve is a duckbill valve as illustrated in Figures 5A and 5B. In the prior art, a duckbill valve has been typically used as one-way, on/off flow valve which allows free flow in a first direction while preventing flow through the valve in a second opposite direction. See, e.g., U.S. Patent No. 4,535,819 (disclosing a duckbill valve assembly). In typical operation, the valve is positioned in line with a fluid conducting conduit. The outer perimeter of a first cylindrical end of the valve is sealed with the inner wall of the conduit. The body of the valve tapers down to a pair of resilient lips at a second end of the valve which form an outlet slit. When pressure on the first end of the valve exceeds the pressure on the second end of the valve, fluid can flow through the throat of the valve, push apart the resilient lips, open the outlet slit, and flow through the outlet slit. If the pressure on the second end exceeds the pressure on the first, the pair of resilient lips are forced against each other, closing the outlet slit and preventing, or at least reducing, the flow of the fluid in through the resilient lips and out through the throat of the duckbill valve.

Figure 5A is a view of a duckbill valve assembly suitable for use in the present invention. The valve assembly comprises a body 200 having two body members 202 and 204. The body members 202 and 204 smoothly taper down to form a pair of resilient lips 208 and 210. Between the pair of resilient lips 208 and 210, an outlet slit 212 is formed. Duckbill valves of this general type are commercially available from such sources as Vernay Laboratories, Inc. and DaiPro Rubber Inc. of Tulsa, Oklahoma. The duckbill valve is preferably made of a resilient material, such as a thermoplastic or an elastomer. Silicone valves are particularly preferred.

With reference to Figure 5B, the body 200 has a first end 220 and a second end 222. A piece of membrane 240 or other material that contains multiple flow channels is inserted in the outlet slit 212 (not shown) between the pair of resilient lips 208 and 210. In this embodiment, if the pressure on the second end 222 exceeds the pressure on the first end 220, the pair of resilient lips 208 and 210 will be forced towards each other compressing the membrane 240. As the membrane 240 is compressed, the multiple flow channel cross-sectional area will be decreased, restricting fluid flow through the multiple flow channels from the second end 222 to the first end 220. The rate of flow through the membrane 240 will be controlled by the pressure differential between the second end 222 and the first end 220. The higher the pressure differential between the second end 222 and the first end 220, the more force that will be exerted by the pair of resilient lips 208 and 210 onto the membrane 240 or other material 240. The increased pressure will decrease the cross-sectional area of the multiple path flow channels and therefore decrease the flow through the membrane 240. As the pressure differential between the second end 222 and the first end 220
decreases, the force exerted on the multiple flow channel membrane 240 by the pair of resilient lips 208 and 210 will decrease. The decreased force on the membrane 240 will allow the cross-sectional area of the flow channels to expand providing a less restrictive path for the fluid to flow and thereby increasing the flow rate of the fluid out through the pair of resilient lips 208 and 210.

It should be appreciated that numerous infusion devices can house the pressure responsive valve embodiments as described throughout the specification. Infusion devices facilitate the delivery of drugs into a body cavity over an extended period of time. However, in the preferred embodiments, the microflow valves or flow controllers are contained within an intravesical infuser such as the infuser described in the co-pending U.S. Patent Application No. 09/041,475 entitled INTRAVESICAL INFUSER, filed on March 11, 1998, which claims priority to the Provisional Application No. 60/063,985 entitled INTRAVESICAL INFUSER filed on November 6, 1997. In a preferred embodiment, the pressure responsive valve is contained within an intravesical infuser as illustrated in Figure 6.

Figure 6 is a perspective view of an intravesical infuser suitable for use in the present invention in uninflated form. The infuser 10 has a proximal end 12 and a distal end 14. In general, for the infuser 10 to be appropriate for use in a human bladder, the uninflated length of the infuser 10 should be about 4 inches and may be in a range of about 3 to 6 inches long. The uninflated diameter of the infuser 10 is preferably about 0.25 inches. Extending between the proximal end 12 and the distal end 14, in one preferred embodiment, is an elastomeric pressure member 18 suitable for containing and pressurizing a liquid or fluid drug. The elastomeric pressure member 16 may be made of any suitable elastic medical grade polymer and is preferably made of medical grade dimethyl siloxane (silicone). For example, the elastomeric pressure member 16 may be USP class VI silicone tubing, 60 +/-10 Shore A with a peroxide cure, having approximately a 3/16 inch inner diameter and approximately a 1/4 inch outer diameter. In a particularly preferred embodiment, the pressure member 16 is comprised of a silicone tubing with a durometer of 45. The elastomeric pressure member 16 can also be made of other elastic materials such as coated or uncoated polyurethanes, polystyrenes, butyl rubbers, latex rubber or other natural or synthetic elastomers. The elastomeric pressure member 16 may be about half an inch shorter than the infuser 10. A proximal end cap 20 is provided at the proximal end 12. The proximal end cap 20 may be about 0.44 inches long and about 0.25 inches in diameter. A distal end cap 22 is similarly provided at the distal end 14 of the infuser 10. The distal end cap 22 is about 0.57 inches long and 0.25 inches in diameter.

A proximal collar 24 may be used to secure the pressure member 16 to the proximal end cap 20. Similarly, a distal collar 26 may be used to secure the pressure member 16 to the distal end cap 22 of the infuser 10. The proximal end cap 20, proximal collar 24, distal end cap 22, and distal collar 26 may be formed of any relatively rigid thermoplastic polymer, having long-term biocompatibility in vivo, such as G.E. Ultem 1000 from General Electric of Pittsfield, MA. The infuser 10 may be assembled using a variety of adhesive compounds, such as an epoxy.

A proximal opening 30 is provided at the proximal end 12 of the infuser 10, for introduction of fluid into the pressure member 16. The diameter of the proximal opening 30 may be about 0.1 inches. A distal opening 32 is provided at the distal end 14 of the infuser 10, through which drug pressurized by the pressure member 16 exits the
infuser 10 at a controlled rate. The diameter of the distal opening 32 may be about 0.07 inches. Of course, modifications and adaptations of the device are contemplated wherein both openings 30, 32 are at one end, or wherein one opening serves the purpose of filling, delivery and purging.

Figure 7 illustrates the infuser 10 in its filled or inflated state. Whereas the empty infuser of Figure 6 is relatively straight in profile and the pressure member 16 may be somewhat flaccid, the filled infuser 10 illustrated in Figure 7 is stretched causing the pressure member 16 to be relatively rigid. The embodiment illustrated in Figure 7 includes a tensile member 34 connecting the proximal end 12 and the distal end 14. The tensile member 34 may be made from a variety of generally inextensible materials, including wire, fabric or polymer. For example, the tensile member 34 can be a polyester ribbon approximately 0.006 inches thick by 0.085 inches wide as supplied Berwick Industries, Inc. of Berwick, PA. When the pressure member 16 is inflated or filled with a substance, the tendency is for the pressure member to extend both radially and axially. However, axial extension is inhibited by the tensile member 34. As a result, the infuser assumes a non-linear profile. In the embodiment illustrated in Figure 7, the infuser 10 assumes a crescent or annular shape as a result of the tension induced by the tensile member 34. When the device is used as an intravesical infuser 10, the non-linear shape may advantageously inhibit undesirable spontaneous or accidental voiding of the filled or inflated infuser 10. In general, for the infuser 10 to be appropriate for use in a human bladder, the inflated volume of the infuser 10 may be about 30 cc to about 40 cc. However, in some cases, it may be advantageous to increase the inflated volume above 60 cc or decrease it below 10 cc. Although the shape illustrated in Figure 2 is a crescent, it will be understood that other shapes, including sinusoidal, helical, supercoiled, and random folded shapes are also within the scope of the present invention. From another perspective, it should be understood that the shape change that prevents accidental voiding of the device is a change in profile. Thus, if the device when implanted has a cylindrical shape with a diameter of 6 mm, for example, allowing it to readily traverse the urethra, it may well have a crescent shape with an annular diameter of 150 mm, 200 mm, or more when filled in the bladder. This change in profile itself can reduce the chance of accidental voiding.

One feature of the shape-changing is that a first shape facilitates the placement of the infuser in the bladder through the urethra and a second shape prevents spontaneous voiding of the infuser. Preferably, the second shape also facilitates micturition by retaining a shape which does not occlude the bladder neck. For example, in the embodiment described above, the cylindrical first shape has a diameter that is less than the diameter of the urethra so that it may be placed into the bladder through the urethra. Once inserted, the infuser in the annular second shape does not pass out the urethra nor does it block the bladder neck and prevent the patient from micturating.

As the contents of the device are dispensed into the bladder, the device may experience at least a partial shape change reversal. The shape change reversal may facilitate removal of the device. In one embodiment, the device has shape memory so that the device does not return to its original shape simply by dispensing its contents. In this way, even after dispensing some or all of the contents of the device, the device retains a shape which does not pass out the urethra or block the bladder neck.
Figure 8 illustrates the infuser 10 in longitudinal cross-section in a flaccid state. The infuser 10 includes the distal end 14, the distal end cap 22 with the distal opening 32 through which the controlled flow of drug exits the elastomeric pressure member 16. The proximal end 12 includes a proximal end cap 20 and the proximal opening 30 through which a capture member 36 protrudes out the proximal end cap 20. The capture member 36 may be a loop of suture material such as suture 2.0, thermoplastic polymer, silicone, polytetrafluoroethylene, or any other suitable configuration capable of being attached or grasped by a retrieval device may be used. Such configurations would include molded handles or latching mechanisms in the infuser device 10 itself.

As seen in more detail in Figure 9, the proximal end 12 of the infuser is comprised of the proximal end cap 20. The proximal end cap 20 has one end which has a reduced diameter over which the inner diameter of the elastomeric pressure member 16 extends. The proximal end cap 20 is attached to the elastomeric pressure member 16 with an adhesive 48 as well as the proximal collar 24. The adhesive may be a biocompatible adhesive, such as Loctite 4001. Located internal to the proximal end cap 20 is a check valve assembly which comprises a retainer cap 40 against which a sealing disk 42 sits. The sealing disk 42 is maintained in the proper position by a retainer sleeve 44. In its normal position, the sealing disk 42 is pressed against the retainer cap 40 by a spring 46. The force exerted against the sealing disk 42 by the spring 46 provides a pressure causing the sealing disk 42 to occlude an entrance into the pressure member through the retainer cap 40. When the sealing disk 42 is pressed against the retainer cap 40, occluding the opening in the retaining cap 40, a seal between the sealing disk 42 and retaining cap 40 is formed. The seal between the sealing disk 42 and the retainer cap 40 prevents fluids from flowing either into or out of the elastomeric pressure chamber 16. Attached to the sealing disk 42, on the opposite side from the retainer cap 40, is the capture member 36. The capture member 36 is secured to the sealing disk 42 with a biocompatible adhesive 48, such as Loctite 4001. Applying a force relative to the proximal end cap 20 to the capture member 36 to cause it to pull the sealing disk 42 against the spring 46 unseats the sealing disk 42 from the retainer cap 40. The unseating of the sealing disk 42 from the retainer cap 40 provides an opening into the elastomeric pressure chamber 58 to allow fluid to flow into or out of the elastomeric pressure chamber 58. The capture member 36 may be made of material such as a 2.0 suture. It is advantageous to have the capture member 36 connected from the center of the sealing disk 42 so that the infuser 10 aligns itself when a pulling force is applied to the capture member 36.

Figure 10 illustrates an alternative embodiment of the present invention where the infuser 10 contains a duckbill valve assembly 50 at the proximal end 12. Figure 10 is a detailed view of the longitudinal cross section of proximal end 12 of the infuser 10 as illustrated in Figure 8 wherein like numerals reflect like parts. Located internal to the proximal end cap 20 is a duckbill valve assembly 50 which comprises a first duckbill lip 208 and a second duckbill lip 210. A duckbill sleeve 54 envelopes the duck bill valve assembly 50 and secures the duckbill valve assembly 50 in place. Located within the duckbill valve assembly 50 is a draining rod 52. The draining rod is secured to the proximal end cap 20 with a biocompatible adhesive 48 such as Loctite 4001. The duckbill valve assembly 50 is further comprised of an attachment mechanism 56. The attachment mechanism is glued or otherwise affixed to the inside of
the duckbill valve. The attachment mechanism 56 is similarly secured to a capture member 36 with a biocompatible adhesive 48 such as Loctite 4001. The capture member 36 may be made of material such as 2-0 suture.

As illustrated in Figure 10, the infuser 10 is configured to enable the rapid purging of pressurized fluid. In its normal position, the duckbill valve assembly 50 prevents pressurized fluid from being released from the pressure chamber 58 through the proximal opening 30 of the infuser 10. When the infuser 10 is filled with pressurized fluid, the duckbill lips 210 and 208 are forced towards each other and fluid is prevented from exiting the elastomeric pressure chamber 58 of the infuser 10. However, in its draining or purging position, the duckbill lips 210 and 208 are be forced open to allow for the rapid release of fluid from within the pressure chamber 58 to the proximal opening 30. A pulling force relative to the proximal end cap 20 can be applied to the capture member 36. As the force is exerted against the capture member 36, the attachment mechanism 56 is pulled in the direction of the force, thereby causing the compression of the spring 46. The duckbill valve 50, secured to the attachment mechanism 56, is similarly pulled in the direction of the force being exerted on the capture member 36. The movement of the duckbill valve 50 forces the lips 208 and 210 to open as the valve 50 comes into increasing contact with the draining rod 52. The compression of the spring 46 and subsequent movement of the duckbill valve assembly 50 against the draining rod 52 provides an opening into the elastomeric pressure chamber 58 to allow fluid to flow into or out of the elastomeric pressure chamber 58.

The distal end of an infuser with a pressure responsive valve assembly is shown in Figure 11. As seen in Figure 11, the distal end 14 of the infuser 10 is comprised of a distal end cap 22. The distal end cap 22 has one end which has a reduced diameter over which the inner diameter of the elastomeric pressure member 16 extends. The distal end cap 22 is attached to the elastomeric pressure member with adhesive 48 as well as the distal collar 26. The adhesive is preferably a biocompatible adhesive. Located internal to the distal end cap 22 is a flow controlling valve 60 that meters the flow of fluid from the pressure member 16 through a distal opening 32. In a particularly preferred embodiment, the flow controlling valve 60 is a duckbill valve as described with reference to Figures 5A and 5B. The flow controlling valve 60 is contained within the distal end cap 22 by a support sleeve 62. The flow controlling valve 60 is configured to control the rate of drug delivery in the presence of pressure fluctuation in the elastomeric pressure chamber 16.

Still with reference to Figure 11, one sees a cross sectional view of the duckbill valve assembly mounted in the infuser 10. The first end of the valve 220 is sealed against the inner circumference of the distal end cap 22. The valve is secured in position by a support sleeve 62. The distal end cap 22 is secured to the end of the elastomeric pressure member 16 with a biocompatible adhesive such as Loctite 4001.

In operation, the infuser 10 is inflated. Pressure inside the infuser 10 is increased over the external pressure due to the force of the elastomeric pressure member 16 against the drug. The increased pressure inside the infuser will force the pair of resilient lips 208 and 210 down upon the multi-flow channel membrane 240. The amount of force the resilient lips 208, 210 exert against the multi-path flow channel membrane 240 is proportional to the pressure differential between the pressure inside the infuser 10 and the outside ambient pressure. This pressure
differential will cause the drug within the infuser to flow through the multiple flow channels within the membrane 240 through the resilient lips 208 and 210 of the duckbill valve through to the first end of the duckbill valve 220 and out through the distal opening 32. As the drug is dispensed, the pressure inside the elastomeric pressure chamber 18 will decrease. This decrease in pressure will cause the lips of the duckbill valve 208 and 210 to exert less force on membrane 240. The decrease in compressive force against the membrane will allow the cross-section of the multiple flow channels through the membrane to increase thereby providing lesser resistance to the flow.

Another embodiment of a pressure responsive valve for use in an infuser is shown in Figure 12. The valve consists of a diaphragm 300 and a valve stem 302. Inserted circumferentially around the valve stem 302 is a multiple flow channel membrane 306 positioned between the diaphragm 300 and the valve seat 304. The valve is installed inside the infuser 10 such that the valve seat 304 seals off the end of the elastomeric pressure chamber 312. The valve stem 302 extending through the valve seat protrudes inside the elastomeric pressure chamber 312. An exit port 308 is located adjacent to the diaphragm 300. Adjoining the exit port 308 is a filter 310. When the infuser 310 is filled, a high pressure drug will flow around the valve stem 302, through the valve seat 304, through the multiple flow channels within the membrane 306, around the diaphragm 300, through the exit port 308, through the filter 310 to the exterior of the infuser 10. The rate of this flow is controlled by the pressure differential between the high pressure drug inside the infuser and the ambient pressure.

This compressive force will decrease the cross-sectional area of multiple flow channels within the membrane, restricting the flow of the drug through the membrane. As the drug is dispensed and the pressure differential decreases, the compressive force against the flow channel membrane will decrease which will increase the cross-sectional area of the individual flow channels. This increase in cross-sectional area will decrease the resistance against flow. Changes in flow channel cross-sectional area in response to pressure differential regulate the flow to produce a constant flow rate of the drug.

Another embodiment is shown in Figure 13. In this embodiment, a piston valve is installed in the infuser 10 at the proximal end 12. This valve consists of a piston seal 410 bonded to the interior of the proximal end cap 20. A piston 400 which has a bore through the center of it. The end of the piston 404 is in contact with the multi-flow channel membrane 402. There is an exit hole 406 in the end of the proximal end cap 20. When the infuser is filled with the drug, a high pressure is exerted on the piston 400 which applies a force the piston end 404 exerting a compressive force between the piston end 404 and the interior of the proximal end 12. The high pressure exerted on the piston 400 and, more particularly, on the piston end 404 compresses the multi-flow channel membrane 402. Fluid flows through the bore in the center of the piston through the multi-flow channel membrane 402, through an exit hole 406 in the end of the proximal end cap 20, and through the distal opening 30. The amount of compressive force against the multi-flow channel membrane 402 is proportional to the pressure differential between the high pressure drug inside the infuser and the ambient pressure. When the pressure differential is high, a large compressive force is exerted against the membrane 402 reducing the cross-sectional area of the multiple flow channels. As the drug is dispensed and the pressure inside the infuser decreases, the pressure differential also decreases. This decreased
pressure differential exerts less force against the membrane 402 and increases the cross-sectional area of the multiple flow channels within the membrane. The increase in cross-sectional area provides a less restrictive flow channel for the drug. Therefore, this variation in cross-sectional area of the multiple flow channels regulates the rate at which the drug is dispensed.

Another embodiment of a pressure responsive valve in an infuser device is shown in Figure 14. In this embodiment, the distal end cap 14 protrudes into the elastomeric pressure chamber 18. A portion of the distal end cap 14 is of a reduced diameter 514. Within this region of reduced diameter, there is an exit hole 512. Around the reduced diameter 514 of the distal end cap 14, a multiple flow channel membrane 516 is wrapped circumferentially around the cylindrical section. A piece of soft silicone tubing 520 is inserted over the flow channel membrane 516. The diameter of the silicone tubing 520 is less than the inner diameter of the elastomeric pressure member 16. This allows a region 522 where the drug will flow between the inner diameter of the elastomeric pressure member 16 of the infuser and the silicone tubing 520. When the infuser 10 is filled with the high pressure drug, the drug will flow in the region between the inner wall of the elastomeric pressure member 16 and the external circumference of the silicone tubing 520, tending to compress the silicone tubing 520, thereby exerting a compressive force on the flow channel membrane 516. This compressive force will cause the cross-sectional area of the multiple flow channels in the membrane 516 to decrease in the cross-sectional area. The decrease in cross-sectional area offers a higher resistive flow path for the drug as it flows through the membrane 516 through the exit hole 512 and through the distal end hole 32. As the drug is dispensed and the pressure inside the infuser decreases, the compressive force against the silicone tubing 520 will decrease and, therefore, the compression of the membrane 516 will decrease. The decrease in compression of the membrane 516 increases the cross-sectional area of the flow channels within the membrane, offering a less restrictive path for the drug to flow through the membrane 516, through the exit hole 512, and out through the distal end opening 32.

In other embodiments, the pressure responsive valves within an infuser can be used in multi-valve configurations with the intent of modifying the flow characteristics. An example of one embodiment is shown in Figure 15. In this embodiment, a dual valve chamber 600 is installed in the distal end 14 of the infuser 10. The dual valve chamber 600 is comprised of a first duckbill valve 604, a second duckbill valve 602, a piece of tubing, either flexible or rigid, extending from the second end 612 of the second duckbill valve 602 to the first end 616 of the first duckbill valve 604 enclosing a volume between the two valves forming an ante-chamber 606. The dual valve chamber 600 is installed inside the distal end 14 of the infuser 10. The dual valve chamber 600 is retained in relative position in relationship to the diffuser 10 by the distal collar 20. The second duckbill valve 602 acts as a first stage regulator, and the first duckbill valve 604 acts as a second stage regulator. When the infuser is initially filled with the pressurized drug, the pressure inside the elastomeric pressure member 16 will be higher than inside the ante-chamber 606. This pressure differential will cause the drug to flow from the infuser through a multi-flow path channel membrane 620 in the second duckbill valve 602 and into the ante-chamber 606. This flow will continue as the ante-chamber fills and the pressure inside the ante-chamber approaches the pressure inside the infuser 10. When the
pressure in the ante-chamber 606 exceeds the external pressure, the drug flows through the first duckbill valve 604 at the distal end cap opening 32 into the bladder. The addition of the ante-chamber 606 introduces a delay in delivery of the drug to the patient following the initial filling of the infuser 10.

Figure 16 is a graph of a delivery rate curve 702 for a single duckbill valve, as shown in Figure 11, and a delivery rate curve 704 for a dual duckbill valve, as shown in Figure 15. The drug delivery rate curve 702 for the single duckbill valve shown in Figure 16 illustrates that during the initial period 706 after filling the infuser 10, the initial delivery rate 724 for the single duckbill valve is high relative to the steady state rate 720 achieved later in time. Following this high initial delivery rate 724, the delivery rate curve 702 for the single duckbill valve decays until a steady state delivery rate 720 is achieved during time steady state period 712. The expulsion of some of the drug into the patient contributes to the reduced drug delivery rate by decreasing the pressure in the infuser 10. Also, the elastomeric pressure chamber 16 wall material undergoes relaxation after filling thereby reducing the force the chamber walls exert on the drug and decreasing the pressure in the infuser 10. The high initial delivery rate 724 of the single duckbill valve may be undesirable because it causes too much drug to be delivered to the patient during the initial delivery period 706.

The delivery rate curve 704 of the dual duckbill valve shown in Figure 16 illustrates that with this embodiment, there is little or no drug delivered into the patient during the initial period 706 as the ante-chamber 606 (shown in Figure 15) fills. The delay in drug delivery rate into the patient during the initial period 706 after filling the infuser allows for relaxation of the elastomeric pressure member 16. After the ante-chamber 606 fills sufficiently so that the pressure in the ante-chamber 606 exceeds the external pressure in the patient's bladder, the drug will begin to flow through the first duckbill valve 604, through the distal end cap opening 32, and into the bladder. During the period following initial drug delivery 708 from the dual duckbill valve, the drug delivery rate 704 for the dual duckbill valve will increase as the drug flows into and increases the pressure in the ante-chamber 606. During the period following initial drug delivery 708, the pressure inside the infuser 10 will decrease due to some drug exiting the infuser 10 and entering the ante-chamber 606. Also, the relaxation of the wall of the elastomeric pressure member 16 contributes to the decrease in pressure. At the end of the initial drug delivery period 708, the drug delivery rate 702 for the single duckbill valve and the drug delivery rate 704 for the dual duckbill valve approach the same rate 722. During the stabilization period 710, the drug delivery rate 702 of the single duckbill valve and the drug delivery rate 704 of the dual duckbill valve are approximately the same. During post stabilization period 712, the drug delivery rate 702 of the single duckbill valve and the drug delivery rate 704 of the dual duckbill valve approach a steady state rate 720. The drug delivery rate of the infuser 10 remains at this steady state rate 720 until the infuser 10 is retrieved from the patient or until most or all of the drug is expelled.

Returning to Figure 15, the delay in drug delivery into the patient can be varied, for example, by increasing the volume of the ante-chamber 606 or varying the flow rates through the dual valve chamber 600. Through the selection of the multi-flow channel membrane 620 of the second duckbill valve 602 and the multi-channel flow membrane 622 of the first duckbill valve 604 the resistance to flow through the two valves can be adjusted. During
the initial period, while the ante-chamber is filling, if the resistance to flow through the second duckbill valve 602 is low, the valve will have a high flow rate. The higher flow rate will fill the ante-chamber faster and decrease the delay in delivery to the patient. If the resistance to flow through the second duckbill valve 602 is high, the valve flow rate will be lower. The lower flow rate will fill the ante-chamber slower leading to a longer delay in delivery of drug into the patient.

In one embodiment, the ante-chamber 606 comprises a single chamber. In another embodiment, the ante-chamber 606 may comprise multiple sub-chambers (not shown). Additionally, there may be duckbill valves coupling adjacent sub-chambers. Sub-chambers may provide features such as, for example, additional control of the drug delivery rate and delay period of drug delivery. In addition, the sub-chambers may contain compounds such as, for example, a drug in condensed form which becomes activated by the pressurized agent introduced into the infuser. In one embodiment, the device itself contains a first drug in condensed form or the pressurized agent is a first drug, or both, and the sub-chamber contains a second drug. As the pressurized agent enters the sub-chamber, it activates the second drug, and the second drug as well as the first drug is delivered to the patient. When the second drug is depleted, the first drug continues to be delivered to the patient. For example, the second drug may be an antibiotic which is delivered to the patient only during an initial period of drug infusion, such as, for example, during the first 24-hours of treatment.

Also, the use of multiple sub-chambers allows sequential presentation of compounds in the individual sub-chambers. As the pressurized agent enters a preceding sub-chamber it may be presented to a compound contained therein. As the pressurized agent passes into a subsequent chamber after exposure to the compound in the preceding sub-chamber, the pressurized agent may then be presented to a compound contained in the subsequent sub-chamber. Thus, the pressurized agent is presented to each compound in sequence and the compounds in the sub-chambers remain isolated from one another before the introduction of the pressurized agent.

In yet another embodiment, there may be a plurality of preceding sub-chambers providing multiple parallel flow paths for the pressurized agent. The plurality of parallel preceding sub-chambers may contain different compounds, such as, a drug in condensed form which becomes activated by the pressurized agent. In addition, varying the delay period associated with the parallel preceding sub-chambers allows the patient to be exposed to different compounds, at different times, throughout the delivery period. In such a case, the preceding sub-chamber may be any combination of sub-chambers providing sequential, simultaneous, and/or parallel flow paths through the infusion device.

In one embodiment, the reservoir in uninflated state initially contains a drug in condensed form and the agent introduced to inflate the reservoir reconstitutes the drug. For example, the reconstitution agent may be a phase buffer, a viscosity enhancing agent, an osmotic agent or a sterile saline solution.

In one important aspect of the invention, the entire infuser 10 or appropriate portions thereof can be coated with a biocompatible coating to promote lubricity. A major problem that has been experienced with most devices that are left in the bladder for more than a few days is encrustation and infection. Various salts, proteins, and other
materials in the urine can rapidly build up on foreign objects left within the bladder. This, in turn, leads to irritation and difficulty in removing the device without injuring the patient. In one embodiment, the entire infuser 10 can be coated. In another embodiment, only appropriate portions of the infuser 10 are coated such as the proximal end cap 20 and distal end cap 22.

The infuser 10 can be coated with certain polysaccharide coatings can reduce or even prevent encrustation. These coatings include pentosanpolysulfate, heparin and other sulfonated polysaccharides or drugs. In preferred embodiments, the infuser 10 is surface pretreated by any number of surface modification techniques known by one of skill in the art including corona discharge, ionic discharge, chemical etching such as by treatment with a strong base, and plasma treatment. One technique is disclosed in U.S. Patent Application Serial Number 08/942,972, filed October 3, 1997, entitled "PENTOSANPOLYSULFATE COATING FOR MEDICAL DEVICES".

The infuser with pressure responsive valves or flow controllers according to the invention can be used as a self contained means of delivering therapeutic agents to a variety of functioning organs within a living organism. The infuser can be introduced into the functioning organ through a natural orifice or created orifice. Details of the introduction and removal of the infusion device from a body cavity are described in the co-pending U.S. Application No. 09/041,475 entitled INTRAVESICAL INFUSER, filed on March 11, 1998, which claims priority to the Provisional Application No. 60/053985 entitled INTRAVESICAL INFUSER filed on November 6, 1997.

The device may be used to treat urge incontinence, pain, neuralgia, cystitis or cancer. The drug can be oxybutynin, an antibiotic, a diagnostic agent, or anticancer drug among others.

In one embodiment, the device is inserted into the patient containing a therapeutic or diagnostic agent in condensed form. When the device is within the bladder, it is filled with a reconstitution agent which causes a shape change in the device and activates the agent within the device. For example, the device can be filled with a saline solution which activates a drug in powder form within the device.

A wide variety of drugs or other substances, including contrast agents can be administered into a body cavity such as the bladder by employing the methods and devices set forth in the present application. These drugs or other substances can be provided in a variety of forms, including liquids andhydratable powders. These drugs and other materials can be used for a variety of purposes, including the treatment of urinary incontinence, urinary tract cancer, urinary tract infections, inflammatory conditions of the urinary tract, and to provide pain relief.

Specifically, in one embodiment of the present invention, urinary incontinence, including urge incontinence and neurogenic incontinence, are treated using the device of the present invention. Preferably, anticholinergic and/or antispasmodic agents are used. In addition, antimuscarinic agents, 8.2 agonists, norepinephrine uptake inhibitors, serotonin uptake inhibitors, calcium channel blockers, potassium channel openers, and muscle relaxants can also be used. Suitable drugs for the treatment of incontinence include oxybutynin, S-oxbutynin, eproprionium, verapamil, imipramine, flavoxate, atropine, propantheline, tolterodine, racicline, clenbuterol, darifenac (Pfizer, Europe, USA, Japan), terodiline, trospium, hyoscymine, propiverine, desmopressin, vamicamide (Fujikawa Co., Japan), 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 stilimon iodide. Similarly, anticholinergic agents and anticholinergic salts such as scopolamine, hyoscyamine, glycopyrrolate, methantheline, oxybutynin hydrochloride, dicyclomine hydrochloride and flavoxate hydrochloride may be incorporated into the infuser device with pressure responsive valves to treat urge incontinence. Other suitable agents for treating urge incontinence include, without limitation, calcium antagonists such as nifedipine, potassium channel openers, beta-adrenergic agonists such as terbutaline, tricyclic antidepressants such as doxepin, dimethyl sulfoxide (DMSO), nitric oxide, capsaicin, and alpha adrenergic antagonists and agonists. The agent may be used alone or in combination with other drugs. It will be appreciated that other suitable agents for treating urge incontinence will be known to those skilled in the art. In addition, the substance released from the device can be used for diagnostic purposes.

In a particularly preferred embodiment, the microflow valves or flow controllers are used in concert with an infusion device to treat urinary tract cancer, such as bladder cancer and prostate cancer with antiproliferative agents, cytotoxic agents, and/or chemotherapeutics. Suitable drugs for the treatment of urinary tract cancer include Bacillus Calmette Guerin (BCG) vaccine, wild type vaccinia virus, cisplatin, anthracylines, doxorubicin, methotrexate, vinblastine, thiopeta, mitomycin C, etogolucid, taxol, fluorouracil, leuprolide, flutamide, diethylstilbestrol, estramustine, megestrol acetate, cyproterone, fluramite, cyclophosphamide, and other agents known to those of skill in the art. The drugs may be used alone or in combination with other drugs. Treatment of urinary tract cancer with an infuser as described above can be effected in conjunction with other conventional cancer treatment techniques, including surgical excision, and radiation therapy.

In a similar manner, infections involving the bladder, the prostate, and the urethra, can be treated using the device with microvalves or flow controllers of the present invention. Antibiotics, antibacterial, antifungal, antiprotozoal, antiviral and other antiinfective agents can be administered for treatment of such infections. Suitable drugs for the treatment of such infections include mitomycin, ciprofloxacin, norfloxacin, ofloxacin, methanamine, nitrofurantoin, ampicillin, amoxicillin, nafcilin, trimethoprim, sulfa, trimethoprim-sulfamethoxazole, erythromycin, doxycycline, metronidazole, tetracycline, kanamycin, penicillins, cephalosporins, and aminoglycosides.

In yet another aspect, the infuser device with pressure responsive valves is used to treat inflammatory conditions such as interstitial cystitis, prostatitis, and urethritis. Drugs having an anti-inflammatory and/or coating effect are useful in this regard. Suitable drugs include DMSO, heparin, pentosanpolysulfate sodium, and flavoxate.

In another embodiment, a device containing a pressure responsive valve or valves of the present invention is used to provide pain relief to a patient. In this regard, a variety of anesthetic and/or analgesic agents are infused through the device of the present invention, including lidocaine hydrochloride, procaine hydrochloride, salicyl alcohol, tetracaine hydrochloride, phenazopyridine hydrochloride, acetaminophen, acetylsalicylic acid, flufenisal, ibuprofen, indoprofen, indomethacin, naproxen, codeine, oxycodeone, and fentanyl citrate.

In still another embodiment, the present invention can also be used to administer drugs and other materials for a variety of other purposes. For example, the device can be used to administer glycine for purposes such as bladder irrigation.
The treatment method of the present invention provides for slow, continuous, intermittent or periodic release of a desired quantity of drug over a desired period of time. In one preferred embodiment, the volume of the infuser is such that it can deliver the desired dose of drug over an extended period of time, for example, 24 hours, 5 days, 10 days, 15 days or even 20, 25, 30, 60, 90 days or more. The rate of delivery in order to accomplish this result is relatively slow. Thus, the present invention contemplates the drug delivery rates within the range of 0.1, 1, 5, 10, 25, 50, 75, 100, 150, or 200 μl/hr. Of course, slower or faster delivery rates can be selected depending upon the drug being delivered and the disease being treated. In any particular situation, and for any particular disease state, the concentration of the drug and the rate of delivery can be selected by the physician based on conventional methodologies.

The foregoing description details certain embodiments of the invention. It will be appreciated, however that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways. Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. As is also stated above, it should be noted that the use of particular terminology when describing certain features or aspects of the invention should not be taken to imply that the terminology is being re-defined herein to be restricted to including any specific characteristics of the features or aspects of the invention with which that terminology is associated. Accordingly, the scope of the invention should therefore be construed in accordance with the appended claims and any equivalents thereof.
WHAT IS CLAIMED IS:

1. Use of an infusion device in preparation of a system for delivery of medication into a patient, wherein the infusion device is delivered into a body cavity of a patient, an elastomeric member of the infusion device is pressurized by the addition of an agent to the elastomeric member, the infusion device is released into the body, the agent is infused in a controlled manner from the elastomeric member into an ante-chamber, and the agent is infused in a controlled manner into the body cavity from the ante-chamber.

2. The use of Claim 1, wherein the agent is infused in a controlled manner from the elastomeric member into an ante-chamber to cause a delay in the delivery of the agent to the body cavity.

3. The use of Claim 1, wherein the infusion device is released into the body cavity and allowed to float freely in the body cavity.

4. The use of Claim 1, wherein the body cavity is a mammalian bladder.

5. The use of Claim 1, wherein the agent is infused in a controlled manner from the elastomeric member into the ante-chamber to cause a reduction in the delivery rate of the agent to the body cavity during an initial period of time.

6. The use of Claim 1, wherein the agent is infused in a controlled manner from the elastomeric member into the ante-chamber to provide for delivery of the agent in a sufficiently low delivery rate so as to reduce side effects associated with high delivery rates of the agent.

7. The use of Claim 1, wherein the agent is a reconstitution agent which activates a drug within the device.

8. The use of Claim 7, wherein the reconstitution agent activates a second drug within the ante-chamber.

9. The use of Claim 7, wherein the drug in condensed form is present in the infusion device when the infusion device is delivered into the patient.

10. The use of Claim 7, wherein the drug is an incontinence-treating drug.

11. The use of Claim 7, wherein the drug is used to treat urge incontinence.

12. The use of Claim 7, wherein the drug is oxybutynin.

13. The use of Claim 7, wherein the oxybutynin is released at a controlled rate in the body cavity for a period exceeding 24 hours.

14. The use of Claim 7, wherein the drug is used to treat pain or neuralgia.

15. The use of Claim 7, wherein the drug is an antibiotic.

16. The use of Claim 7, wherein the drug is used to treat cystitis.

17. The use of Claim 7, wherein the drug is an anti-cancer drug.

18. The use of Claim 1, wherein the agent is infused into the body cavity for at least about 5 days.

19. The use of Claim 1, wherein the infusion device assumes a first shape when empty and a second shape when filled, and wherein the removing step comprises changing the shape of the infusion device from the second shape to the first shape, and then directing the infusion device out of the urethra.
20. The use of Claim 19, wherein the change from the second shape to the first shape is accomplished by allowing matter within the device to be depleted by the infusing step.

21. The use of Claim 19, wherein the change from the second shape to the first shape is accomplished by opening a passageway in the device to allow matter within the device to exit the device.

22. The use of Claim 1, wherein the infusion device further comprises a first pressure-responsive valve configured to admit the agent into the ante-chamber and a second pressure responsive valve configured to release the agent from the ante-chamber.

23. The use of Claim 22, wherein the agent is under pressure and the first and second pressure-responsive valves control the flow by varying the area of a flow channel in inverse proportion to pressure of the drug.

24. The use of Claim 1, wherein the agent is infused into the body cavity at a rate of less than about 400 μl/hour.

25. The use of Claim 1, wherein the agent is infused into the body cavity at a rate of less than about 1 ml/hour.

26. The use of Claim 1, wherein the ante-chamber comprises a subchamber, wherein the subchamber contains a first drug in condensed form when the infusion device is delivered into the patient, and wherein the first drug is infused into the body cavity during an initial treatment period.

27. A method of using a duckbill valve, comprising the steps of:
   - disposing a compressible multi-channel flow member between resilient lips of a duckbill valve; and
   - applying a pressurized agent outside of the resilient lips of the duckbill valve to urge the resilient lips toward each other, and substantially simultaneously contacting the pressurized agent with the multi-channel flow member, thereby causing the pressurized agent to flow in through the resilient lips and out through the throat of the duckbill valve.

28. A duckbill valve comprising:
   - a body member having an axial fluid passageway and a first end and a second end;
   - at least two resilient lips at the second end of the body member defining an outlet slit therebetween, the axial fluid passageway having a cross section that progressively narrows from the first end to the second end; and
   - a multi-channel flow member positioned between the at least two resilient lips and extending in the fluid passageway and through the outlet slit such that the resilient lips tend to compress the multi-channel flow member thereby varying resistance to fluid flow through the valve.

29. A dual duckbill valve assembly comprising:
   - a first duckbill valve as set forth in Claim 28;
   - a second duckbill valve comprising:
     - a body member having an axial fluid passageway and a first end and a second end;
at least two resilient lips defining an outlet slit therebetween at the second end of the body member; and

a multi-channel flow member positioned between the at least two resilient lips and extending in the fluid passageway and through the outlet slit such that the resilient lips tend to compress the multi-channel flow member thereby varying resistance to fluid flow through the valve;

an ante-chamber having a first end and a second end;

wherein the first end of the first duckbill valve is coupled to the first end of the ante-chamber such that the second end of the first duckbill valve protrudes into the chamber,

wherein the first end of the second duckbill valve is coupled to the second end of the ante-chamber such that the second end of the second duckbill valve protrudes from the ante-chamber;

wherein, when the second duckbill valve of the dual duckbill valve assembly is placed in communication with a pressurized fluid, the fluid flows through the second duckbill valve into the ante-chamber, and then through the first duckbill valve out of the ante-chamber.

30. The dual duckbill valve assembly of Claim 29, wherein the ante-chamber comprises a plurality of sub chambers.

31. An implantable infusion device, comprising:

a reservoir having a first shape wherein a cross-sectional diameter of the reservoir permits the reservoir to be passed into a body cavity, the reservoir configured to expand to a second shape to hold a pressurized substance;

a valve assembly configured to admit the pressurized substance into the reservoir while the reservoir is within the body cavity;

a first duckbill valve comprising:

a body member having an axial fluid passageway and a first end and a second end;

at least two resilient lips defining an outlet slit therebetween at the second end of the body member; and

a multi-channel flow member positioned between the at least two resilient lips and extending through the outlet slit such that the resilient lips tend to compress the multi-channel flow member thereby varying resistance to fluid flow through the valve;

wherein the first end of the first duckbill valve is coupled to an exit port of the reservoir and the second end of the first duckbill valve protrudes into the reservoir; and

wherein the duckbill valve provides a flow path for the pressurized substance to exit the reservoir.

32. The implantable infusion device of Claim 31, further comprising:

a second duckbill valve comprising:

a body member having an axial fluid passageway and a first end and a second end;
at least two resilient lips defining an outlet slit therebetween at the second end of the body
member; and

a multi-channel flow member positioned between the at least two resilient lips and extending
through the outlet slit such that the resilient lips tend to compress the multi-channel flow member thereby
varying resistance to fluid flow through the valve;

an ante-chamber having a first end and a second end;

wherein the first end of the first duckbill valve is coupled to the first end of the ante-chamber such
that the second end of the first duckbill valve protrudes into the ante-chamber;

wherein the first end of the second duckbill valve is coupled to the second end of the ante-chamber
such that the second end of the second duckbill valve protrudes away from the ante-chamber into the
reservoir; and

wherein the dual duckbill valve assembly is in communication with the pressurized substance in the
reservoir such that the substance flows through the second duckbill valve into the ante-chamber, and through
the first duckbill valve out of the ante-chamber.

33. The device of Claim 32, wherein the pressurized substance is in a liquid form and the device delivers the
pressurized substance at a rate of less than about 400 μl/hour.

34. The device of Claim 32, wherein the pressurized substance is a drug.

35. The device of Claim 32, wherein the body cavity is a mammalian bladder.

36. A method for delivering a drug to a patient, comprising the steps of:

   delivering an infusion device into a body cavity of the patient;

   pressurizing an elastomeric member of the infusion device by the addition of an agent to the
elastomeric member;

   releasing the infusion device into the body cavity;

   infusion the agent in a controlled manner from the elastomeric member into an ante-chamber; and

   infusing the agent in a controlled manner into the body cavity from the ante-chamber.
A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/168 A61M39/22 A61M31/00 F16K15/14

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)
IPC 7 A61M F16K A61F

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 practical, search terms used)
EPO—Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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