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(54) Title: METHODS OF PREVENTING FLUID LEAKS FROM BODY CAVITIES DURING MEDICAL IMAGING PROCEDURES

(57) Abstract: One aspect of the invention relates to the use of an optionally purified inverse thermosensitive polymer to prevent fluid leak from a body cavity through natural or surgical orifices or conduits connected to that cavity. Another aspect of the invention relates to a method of medical imaging comprising administering into an orifice of a body cavity an optionally purified inverse thermosensitive polymer, and then instilling a fluid into that cavity to open up the cavity or enhance the image before or during imaging.



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***METHODS OF PREVENTING FLUID LEAKS FROM BODY
CAVITIES DURING MEDICAL IMAGING PROCEDURES***

Related Applications

5 This application claims the benefit of priority to United States Provisional Patent Application serial number 61/050,324, filed May 5, 2008.

Background of the Invention

Medical diagnostic imaging is widely used for the examination of body cavities. A prerequisite for the imaging of body cavities is the instillation of a fluid in order to obtain a
10 fluid-filled cavity. In these fluid-filled cavities, the fluid has two functions (1) to open up the cavity from its "collapsed" state (distension) and (2) to enhance the contrast of the image of the body cavity. Conventionally, water or watery fluids are used for distension and contrast imaging. Sometimes, this is combined with the generation of bubbles, to further increase contrast. For example, US 4,681,119 describes novel compositions and methods
15 for generating microbubbles in a liquid-filled cavity for enhancing ultrasonic images of such cavities. Since water easily leaks from the body cavity, it has to be replenished continuously during imaging.

This disadvantage may be solved partly by using more viscous or phase changing media, instead of water, to provide contrast enhancement. WO 03/094710 suggests a solid
20 or semi-solid phase-shifting medium of pH 7.4 for providing contrast enhancement and/or distention of the subject body or organ cavity during imaging, radiographic visualization or similar medical examinations. The medium is designed to have high, but undefined, viscosity initially and then to liquefy or lose viscosity after a period of time in order to facilitate easy removal of the medium from the body cavity. This phase-shifting medium
25 includes polymers, such as starches, and colloidal clays, such as bentonite and tragacanth, in order to achieve the phase shift. Disadvantage of such ingredients is that the additives, such as starches, will interfere with image formation. WO 92/00707 describes an ophthalmic gel suspension for dry eye application containing lightly cross-linked polymers of acrylic acid with a particle size of not more than 50 micrometers. These polymers are formulated
30 into gel suspensions with one or more ophthalmic demulgents, such as cellulose derivatives, polyvinyl alcohol or polyvinylpyrrolidone, or ophthalmic vasoconstrictors, and optionally with ophthalmic adjuvants or additives. The ophthalmic suspensions have a pH of about 6.6-8.0 and a viscosity of 500 to 4000 centipoise. Due to the acrylic acid polymers, these

compositions will not be the preferred choice for imaging body cavities. In addition, the particles in these ophthalmic gel suspension will interfere with image formation.

WO/2006/006861 suggests alternative contrast agents based on a clear gel comprising a cellulose derivative. However these alternative media are more expensive than saline, may
5 have side effects, and delivering them adds complexity to the procedure, while not fully avoiding the risk of leaks.

This disadvantage may be also be solved partly by using liquid instillation devices which reduce the leakage. For instance, a catheter equipped with an inflatable balloon may be used. However, this is not very convenient for the patient and the pressure required to
10 inflate the balloon may cause pain.

Hysteroscopy is a surgical procedure involving a small scope placed through the cervix into the uterine cavity. This allows for diagnostic as well as operative procedures to be performed. The procedure begins with or without cervical dilation. The scope is then introduced into the cervix. A distending medium such as saline or glycine is used to
15 separate the walls of the uterus as the scope is advanced into the uterine cavity. The uterine cavity can then be inspected for things such as fibroids, polyps, abnormal endometrium, and uterine anomalies.

Sonohysterography, or saline contrast hystero-graphy, is a diagnostic test involving the use of saline as a contrast agent inside the uterine cavity. This contrast is visualized by
20 vaginal ultrasound in the clinic. The contour of the endometrial cavity can be assessed using this technique. Other types of contrast media have been shown to be helpful in evaluation of the fallopian tubes.

The instillation of saline, and potentially air bubbles or other echogenic contrast agents, into the uterine cavity and fallopian tubes during sonography has been known by
25 many names including sonohysterography, hysterosonography, transvaginal sonography with fluid contrast augmentation, saline infused sonography, and saline infusion sonohysterography. These current diagnostic as well as operative procedures, and future procedures as they are developed, may involve filling the uterus with saline, contrast agent, or other liquids, as a distending media, for visualization or for some other purposes such as
30 irrigation.

In all the procedures involving instillation of a fluid into the uterine cavity, fluid may escape not only from the cervix, but also from the fallopian tubes into the peritoneal cavity, with reports of heated saline escaping through the fallopian tube and causing injury

to adjacent tissues. Therefore there is a need for temporary occlusion of the fallopian tubes to prevent leakage of fluid during the intrauterine procedure.

US Patent 4,834,091 describes an Intrauterine fallopian tube ostial plug that is inserted into the tubal ostia of each fallopian tube so that the saline does not flow through the fallopian tubes during the period of time in which a laser is used to treat the uterus. At the conclusion of the laser treatment, the retrievable ostial plugs are hysteroscopically retrieved and withdrawn. However the connection between the uterus and the fallopian tubes is a fragile area and one should avoid any unnecessary mechanical manipulation. Balloons could also be used but exert traumatic radial pressure on the fragile fallopian tube.

A number of methods are in use or have been attempted for permanent or temporary occlusion of the fallopian tubes for sterilization or contraception. Some of these methods involve polymers, such as the injection of a liquid silicone polymer that vulcanizes at body temperature. However these methods are meant to damage the fallopian tubes, or risk damaging them, and are not meant for short term (less than 24 hours) temporary occlusion to avoid fluid leakage.

Therefore there is a need for as simple, atraumatic, reversible method for short-term (less than 24 hours) temporary occlusion for preventing fluid leak from body cavities during medical imaging for diagnostic or operative purposes.

Summary of the Invention

In certain embodiments, the invention relates to a method of preventing fluid leak from a body cavity of a mammal, comprising the steps of: delivering a polymer composition to a site near an orifice of the body cavity or a site in a conduit connected to the body cavity; allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit; and placing a fluid into the body cavity.

In certain embodiments, the invention relates to a method of medical imaging of a body cavity of a mammal, comprising the steps of: delivering a polymer composition to a site near an orifice of the body cavity or a site in a conduit connected to the body cavity; allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit; placing a fluid into the body cavity; and imaging the body cavity.

In certain embodiments, the invention relates to a method of ultrasound imaging of a uterus of a mammal, comprising the steps of: delivering a polymer composition to a site

near an orifice of the uterus or a site in a conduit connected to the uterus; allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit; placing a fluid into the uterus; and imaging the uterus.

5 **Brief Description of the Figures**

Figure 1 depicts a hysterosonogram before (left) and after injection (right) of sterile saline into the uterine cavity. This patient had a normal result. Images were obtained with transvaginal ultrasound.

Detailed Description of the Invention

10 *Overview*

One aspect of the invention relates to use of an optionally purified inverse thermosensitive polymer to prevent fluid leak from a body cavity through natural or surgical orifices or conduits connected to that cavity. Another aspect of the invention relates to a method of medical imaging comprising administering into an orifice of a body

15 cavity an optionally purified inverse thermosensitive polymer, and then instilling a fluid into that cavity to open up the cavity or enhance the image before or during imaging. Another aspect of the invention relates to a method of medical imaging comprising instilling a fluid into that cavity to open up the cavity or enhance the image and then administering into an orifice of a body cavity an optionally purified inverse thermosensitive

20 polymer, and then proceed with imaging. Yet another aspect of the invention relates to a kit for use in occluding the orifice of a body cavity during medical imaging, comprising an optionally purified inverse thermosensitive polymer; a syringe, a catheter; and instructions for use thereof. Other aspects of the invention relate to the above inventions where the cavity is a uterus and the opening a fallopian tube. Yet another aspect of the invention

25 relates to the above inventions where the cavity is a uterus and the opening a cervix. Yet another aspect of the invention is medical imaging of a body cavity, comprising substantially filling a body cavity using a fluid having reverse thermosensitive properties, such a fluid increases in viscosity at body temperature after instillation in the body cavity to form a gel that prevents or reduces leaks from the body cavity during the procedure.

30 Yet another aspect of the invention relates to the above inventions where the occlusion is reversed by cooling or saline injection.

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples, and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements.

This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet

another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts
5 of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including
10 but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

When used with respect to a therapeutic agent or other material, the term “sustained release” is art-recognized. For example, a subject composition which releases a substance
15 over time may exhibit sustained release characteristics, in contrast to a bolus type administration in which the entire amount of the substance is made biologically available at one time.

The term “poloxamer” denotes a symmetrical block copolymer, consisting of a core of PPG polyoxyethylated to both its terminal hydroxyl groups, i.e., conforming to the
20 interchangeable generic formula $(\text{PEG})_X\text{-(PPG)}_Y\text{-(PEG)}_X$ and $(\text{PEO})_X\text{-(PPO)}_Y\text{-(PEO)}_X$. Each poloxamer name ends with an arbitrary code number, which is related to the average numerical values of the respective monomer units denoted by X and Y.

The term “poloxamine” denotes a polyalkoxylated symmetrical block copolymer of ethylene diamine conforming to the general type $[(\text{PEG})_X\text{-(PPG)}_Y]_2\text{-NCH}_2\text{CH}_2\text{N-}[(\text{PPG})_Y\text{-(PEG)}_X]_2$. Each Poloxamine name is followed by an arbitrary code number, which is
25 related to the average numerical values of the respective monomer units denoted by X and Y.

The term “reverse thermosensitive polymer” or “inverse thermosensitive polymer” as used herein refers to a polymer that is soluble in water at ambient temperature, but at
30 least partially phase-separates out of water at physiological temperature. Reverse thermosensitive polymers include, for example, poloxamer 407, poloxamer 188, Pluronic® F127, Pluronic® F68, poly(N-isopropylacrylamide), poly(methyl vinyl ether), poly(N-vinylcaprolactam); and certain poly(organophosphazenes). See: B. H. Lee, *et al.*

“Synthesis and Characterization of Thermosensitive Poly(organophosphazenes) with Methoxy-Poly(ethylene glycol) and Alkylamines as Side Groups,” *Bull. Korean Chem. Soc.* **2002**, 23, 549-554.

5 The terms “reversibly gelling” and “reverse thermosensitive” and “inverse thermosensitive” refer to the property of a polymer wherein gelation takes place upon an increase in temperature, rather than a decrease in temperature.

The term “transition temperature” refers to the temperature or temperature range at which gelation of a reverse thermosensitive polymer occurs.

10 The term “degradable”, as used herein, refers to having the property of breaking down or degrading under certain conditions, e.g., by dissolution.

The phrase “polydispersity index” refers to the ratio of the “weight average molecular weight” to the “number average molecular weight” for a particular polymer; it reflects the distribution of individual molecular weights in a polymer sample.

15 The phrase “weight average molecular weight” refers to a particular measure of the molecular weight of a polymer. The weight average molecular weight is calculated as follows: determine the molecular weight of a number of polymer molecules; add the squares of these weights; and then divide by the total weight of the molecules.

20 The phrase “number average molecular weight” refers to a particular measure of the molecular weight of a polymer. The number average molecular weight is the common average of the molecular weights of the individual polymer molecules. It is determined by measuring the molecular weight of n polymer molecules, summing the weights, and dividing by n.

25 The term “biocompatible”, as used herein, refers to having the property of being biologically compatible by not producing a toxic, injurious, or immunological response in living tissue.

30 As used herein “cold-packs” are two containers containing chemicals separated by a frangible seal. When the seal is broken, as the contents from the separate containers begin to react, energy is absorbed from the surroundings creating a cooling effect. An example of chemicals which can be mixed in a cold pack are ammonium nitrate and water. In certain embodiments the cold pack has two sealed bags, one inside the other. The outer bag is made of thick strong plastic. It contains a ammonium nitrate and the second plastic bag. The second (inner) bag is made of a thin weak plastic and contains water. When the bag is

squeezed the inner bag breaks and the water mixes with the powder creating the cooling effect.

The term “hemostasis” refers to the stoppage of blood flow through a blood vessel or organ of the body. Hemostasis generally refers to the arrest of bleeding, whether it be by
5 normal vasoconstriction (the vessel walls closing temporarily), by an abnormal obstruction (such as a plaque) or by coagulation or surgical means (such as ligation). As used herein, hemostasis is achieved by using a viscous polymer solution to create an obstruction.

Contemplated equivalents of the polymers, subunits and other compositions described above include such materials which otherwise correspond thereto, and which
10 have the same general properties thereof (e.g., biocompatible), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of such molecule to achieve its intended purpose. In general, the compounds of the present invention may be prepared by, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures.
15 In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

Inverse Thermosensitive Polymers

In certain embodiments, the methods of the invention may be accomplished by the use of polymers that form a plug inside the body and then dissolve or are dissolved, such as
20 other inverse thermosensitive polymers and any polymer solution or combination of polymers that form a gel inside the body, being under the effect of temperature, pH, pressure, or as a result of a chemical or biological reaction. In other embodiment, the viscous polymer solutions used in a method of the invention are crosslinkable polymers. In certain embodiments, the viscous polymer solutions can be generated in situ. In certain
25 embodiments, the viscous polymer solutions can be non-tissue adhesive.

In certain embodiments, two solutions, a polymer solution and a crosslinker solution, are injected separately (e.g., through a dual lumen catheter) into a biological lumen wherein they gel, forming a viscous polymer solution. The polymer solution may comprise an anionic polymer, a cationic polymer or a non-ionically crosslinkable polymer.
30 Such polymers may comprise one or more of the following: alginic acid, sodium alginate, potassium alginate, sodium gellan, potassium gellan, carboxy methyl cellulose, hyaluronic acid, and polyvinyl alcohol. The cross-linking of the polymer to form a polymer gel may be achieved with anionic crosslinking ions, cationic crosslinking ions, or non-ionic

crosslinking agents. Crosslinking agents include, but are not limited to, one or more of the following: phosphate, citrate, borate, succinate, maleate, adipate, oxalate, calcium, magnesium, barium and strontium. Exemplary pairings of polymers and crosslinkers include anionic polymer monomers with cations, such as, for example, alginates with
5 calcium, barium or magnesium; gellans with calcium, magnesium or barium; or hyaluronic acid with calcium. An example of an exemplary pairing of a non-ionic polymer with a chemical crosslinking agent is a polyvinyl alcohol with borate (at a slightly alkaline pH).

In general, the polymers used in the methods of the invention, which become a gel at or about body temperature, can be administered to a patient in a liquid form. In general,
10 the polymers used in the methods of the invention, which become a gel at or about body temperature, can be administered to a patient in a soft gel form. In certain embodiments, the polymer composition of the invention may be a flexible or flowable material. By “flowable” is meant the ability to assume, over time, the shape of the space containing it at body temperature. This characteristic includes, for example, liquid compositions that are
15 suitable for: injection with a manually operated syringe fitted with, for example, a needle; or delivery through a catheter. Also encompassed by the term “flowable” are highly viscous, gel-like materials at room temperature that may be delivered to the desired site by pouring, squeezing from a tube, or being injected with any one of the commercially available power injection devices that provide injection pressures greater than would be
20 exerted by manual means alone. When the polymer used is itself flowable, the polymer composition of the invention, even when viscous, need not include a biocompatible solvent to be flowable, although trace or residual amounts of biocompatible solvents may be present. Once the injected material reaches body temperature, it undergoes a transition from a liquid or a soft gel to a hard gel.

25 In addition, in certain embodiments, the viscous polymer solution of the invention may be aqueous solution of one or more inverse thermosensitive polymers. These polymer solutions are liquids below body temperature and gel at about body temperature. In certain embodiments, the polymer solution is prepared external of the body, i.e., at a temperature below body temperature. The polymer solution may be further chilled to prolong the time
30 the solution stays in the liquid form upon introduction into the body. A preferred temperature is about 10 °C below the gelation temperature of the polymer solution. In certain embodiments, the viscous polymer solution used in connection with the methods of the invention may comprise a block copolymer with inverse thermal gelation properties. In

general, biocompatible, biodegradable block copolymers that exist as a gel at body temperature and a liquid at below body temperature may also be used according to the present invention. The block copolymer can further comprise a polyoxyethylene-polyoxypropylene block copolymer, such as a biodegradable, biocompatible copolymer of polyethylene oxide and polypropylene oxide. Also, the inverse thermosensitive polymer can include one or more additives; for example, therapeutic agents may be added to the inverse thermosensitive polymers.

In certain embodiments, the inverse thermosensitive polymers have molecular weights ranging from about 1,000 to about 1,000,000 Daltons, more particularly at least about 10,000 Daltons, and even more specifically at least about 25,000 Daltons or even at least about 50,000 Daltons. In certain embodiment, the block copolymers have a molecular weight between about 5,000 Daltons and about 30,000 Daltons. In certain embodiments, the molecular weight of the inverse thermosensitive polymer may be between about 1,000 and about 50,000 Daltons, or between about 5,000 and about 35,000 Daltons. In other embodiments, the molecular weight of a suitable inverse thermosensitive polymer (such as a poloxamer or poloxamine) may be, for example, between about 5,000 and about 25,000 Daltons, or between about 7,000 and about 20,000 Daltons. Number-average molecular weight (M_n) may also vary, but will generally fall in the range of about 1,000 to about 400,000 Daltons, in some embodiments from about 1,000 to about 100,000 Daltons and, in other embodiments, from about 1,000 to about 70,000 Daltons. In certain embodiments, M_n varies between about 5,000 and about 300,000 Daltons.

In certain embodiments, the polymer is in an aqueous solution. For example, typical aqueous solutions contain about 5% to about 30% polymer, preferably about 10% to about 25%. The pH of the inverse thermosensitive polymer formulation administered to a mammal is, generally, about 6.0 to about 7.8, which are suitable pH levels for injection into the mammalian body. The pH level may be adjusted by any suitable acid or base, such as hydrochloric acid or sodium hydroxide.

In certain embodiments, the inverse thermosensitive polymers of the invention are poloxamers or poloxamines. Pluronic® polymers have unique surfactant abilities and extremely low toxicity and immunogenic responses. These products have low acute oral and dermal toxicity and low potential for causing irritation or sensitization, and the general chronic and sub-chronic toxicity is low. In fact, Pluronic® polymers are among a small number of surfactants that have been approved by the FDA for direct use in medical

applications and as food additives. See: BASF (1990) Pluronic® & Tetronic® Surfactants, BASF Co., Mount Olive, N.J. Recently, several Pluronic® polymers have been found to enhance the therapeutic effect of drugs, and the gene transfer efficiency mediated by adenovirus. K. L. March, J. E. Madison, and B.C. Trapnell, "Pharmacokinetics of
5 adenoviral vector-mediated gene delivery to vascular smooth muscle cells: modulation by poloxamer 407 and implication for cardiovascular gene therapy," *Hum Gene Therapy* **1995**, 6, 41-53.

Interestingly, poloxamers (or Pluronics), as nonionic surfactants, are widely used in diverse industrial applications. See, for example, Nonionic Surfactants: polyoxyalkylene
10 block copolymers, Vol. 60. Nace VM, Dekker M (editors), New York, 1996. 280 pp. Their surfactant properties have been useful in detergency, dispersion, stabilization, foaming, and emulsification. A. Cabana, A. K. Abdellatif, and J. Juhasz, "Study of the gelation process of polyethylene oxide. polypropylene oxide-polyethylene oxide copolymer (poloxamer 407) aqueous solutions." *Journal of Colloid and Interface Science* **1997**, 190, 307-312.
15 Certain poloxamines, e.g., poloxamine 1307 and 1107, also display inverse thermosensitivity.

Importantly, several members of this class of polymer, poloxamer 188, poloxamer 407, poloxamer 338, poloxamine 1107 and poloxamine 1307 show inverse thermosensitivity within the physiological temperature range. Y. Qiu, and K. Park,
20 "Environment-sensitive hydrogels for drug delivery." *Adv Drug Deliv Rev* **2001**, 53(3), 321-339; and E. S. Ron, and L. E. Bromberg, "Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery," *Adv Drug Deliv Rev* **1998**, 31(3), 197-221. In other words, these polymers are members of a class that are soluble in aqueous solutions at low temperature, but gel at higher temperatures. Poloxamer
25 407 is a biocompatible polyoxypropylene-polyoxyethylene block copolymer having an average molecular weight of about 12,500 and a polyoxypropylene fraction of about 30%; poloxamer 188 has an average molecular weight of about 8400 and a polyoxypropylene fraction of about 20%; poloxamer 338 has an average molecular weight of about 14,600 and a polyoxypropylene fraction of about 20 %; poloxamine 1107 has an average molecular
30 weight of about 14,000, poloxamine 1307 has an average molecular weight of about 18,000. Polymers of this type are also referred to as reversibly gelling because their viscosity increases and decreases with an increase and decrease in temperature, respectively. Such reversibly gelling systems are useful wherever it is desirable to handle a

material in a fluid state, but performance is preferably in a gelled or more viscous state. As noted above, certain poly(ethyleneoxide)/poly(propyleneoxide) block copolymers have these properties; they are available commercially as Pluronic® poloxamers and Tetronic® poloxamines (BASF, Ludwigshafen, Germany) and generically known as poloxamers and poloxamines, respectively. See U.S. Pat. Nos. 4,188,373, 4,478,822 and 4,474,751; all of which are hereby incorporated by reference.

The average molecular weights of commercially available poloxamers and poloxamines range from about 1,000 to greater than 16,000 Daltons. Because the poloxamers are products of a sequential series of reactions, the molecular weights of the individual poloxamer molecules form a statistical distribution about the average molecular weight. In addition, commercially available poloxamers contain substantial amounts of poly(oxyethylene) homopolymer and poly(oxyethylene)/poly(oxypropylene diblock polymers. The relative amounts of these byproducts increase as the molecular weights of the component blocks of the poloxamer increase. Depending upon the manufacturer, these byproducts may constitute from about 15% to about 50% of the total mass of the commercial polymer.

The inverse thermosensitive polymers may be purified using a process for the fractionation of water-soluble polymers, comprising the steps of dissolving a known amount of the polymer in water, adding a soluble extraction salt to the polymer solution, maintaining the solution at a constant optimal temperature for a period of time adequate for two distinct phases to appear, and separating physically the phases. Additionally, the phase containing the polymer fraction of the preferred molecular weight may be diluted to the original volume with water, extraction salt may be added to achieve the original concentration, and the separation process repeated as needed until a polymer having a narrower molecular weight distribution than the starting material and optimal physical characteristics can be recovered.

In certain embodiments, a purified poloxamer or poloxamine has a polydispersity index from about 1.5 to about 1.0. In certain embodiments, a purified poloxamer or poloxamine has a polydispersity index from about 1.2 to about 1.0.

The aforementioned process consists of forming an aqueous two-phase system composed of the polymer and an appropriate salt in water. In such a system, a soluble salt can be added to a single phase polymer-water system to induce phase separation to yield a high salt, low polymer bottom phase, and a low salt, high polymer upper phase. Lower

molecular weight polymers partition preferentially into the high salt, low polymer phase.

Polymers that can be fractionated using this process include polyethers, glycols such as poly(ethylene glycol) and poly(ethylene oxide)s, polyoxyalkylene block copolymers such as poloxamers, poloxamines, and polyoxypropylene/ polyoxybutylene copolymers, and
5 other polyols, such as polyvinyl alcohol. The average molecular weight of these polymers may range from about 800 to greater than 100,000 Daltons. See U.S. Patent 6,761,824 (hereby incorporated by reference). The aforementioned purification process inherently exploits the differences in size and polarity, and therefore solubility, among the poloxamer molecules, the poly(oxyethylene) homopolymer and the

10 poly(oxyethylene)/poly(oxypropylene) diblock byproducts. The polar fraction of the poloxamer, which generally includes the lower molecular weight fraction and the byproducts, is removed allowing the higher molecular weight fraction of poloxamer to be recovered. The larger molecular weight poloxamer recovered by this method has physical characteristics substantially different from the starting material or commercially available
15 poloxamer including a higher average molecular weight, lower polydispersity and a higher viscosity in aqueous solution.

Other purification methods may be used to achieve the desired outcome. For example, WO 92/16484 (hereby incorporated by reference) discloses the use of gel permeation chromatography to isolate a fraction of poloxamer 188 that exhibits beneficial
20 biological effects, without causing potentially deleterious side effects. The copolymer thus obtained had a polydispersity index of 1.07 or less, and was substantially saturated. The potentially harmful side effects were shown to be associated with the low molecular weight, unsaturated portion of the polymer, while the medically beneficial effects resided in the uniform higher molecular weight material. Other similarly improved copolymers were
25 obtained by purifying either the polyoxypropylene center block during synthesis of the copolymer, or the copolymer product itself (e.g., U.S. Pat. No. 5,523,492 and U.S. Pat. No. 5,696,298; both of which are hereby incorporated by reference).

Further, a supercritical fluid extraction technique has been used to fractionate a polyoxyalkylene block copolymer as disclosed in U.S. Pat. No. 5,567,859 (hereby
30 incorporated by reference). A purified fraction was obtained, which was composed of a fairly uniform polyoxyalkylene block copolymer having a polydispersity of less than 1.17. According to this method, the lower molecular weight fraction was removed in a stream of

carbon dioxide maintained at a pressure of 2200 pounds per square inch (psi) and a temperature of 40 °C.

Additionally, U.S. Pat. No. 5,800,711 (hereby incorporated by reference) discloses a process for the fractionation of polyoxyalkylene block copolymers by the batchwise
5 removal of low molecular weight species using a salt extraction and liquid phase separation technique. Poloxamer 407 and poloxamer 188 were fractionated by this method. In each case, a copolymer fraction was obtained which had a higher average molecular weight and a lower polydispersity index as compared to the starting material. However, the changes in polydispersity index were modest and analysis by gel permeation chromatography indicated
10 that some low-molecular-weight material remained. The viscosity of aqueous solutions of the fractionated polymers was significantly greater than the viscosity of the commercially available polymers at temperatures between 10 °C and 37 °C, an important property for some medical and drug delivery applications. Nevertheless, some of the low molecular weight contaminants of these polymers are thought to cause deleterious side effects when
15 used inside the body, making it especially important that they be removed in the fractionation process. As a consequence, polyoxyalkylene block copolymers fractionated by this process are not appropriate for all medical uses.

Modification of the transition temperature of a inverse thermosensitive polymer can be obtained in a number of ways. For example, the transition temperature can be modified
20 either through the addition of transition temperature modifying additive or through the development of a modified polymer. The transition temperature can be influenced by a number of additives, e.g., the addition of pharmaceutical fatty acid excipients such as sodium oleate, sodium laurate or sodium caprate. Other possible pharmaceutical excipients may be solvents such as water, alcohols, especially C₁-C₅ alcohols such as ethanol, n-
25 propanol, 2-propanol, isopropanol, t-butyl alcohol; ethers such as MTBE; ketones such as acetone, methyl ethyl ketone; humectants such as glycerol; glycols such as ethylene glycol, propylene glycol; emulsifiers such as lower, optionally polyhydric C₁-C₅ alcohols partially esterified with long-chain (C₁₂-C₂₄) fatty acids such as glycerol monostearate, isopropyl myristate, fatty acid ester of sugar alcohols such as sorbitan mono-fatty acid ester,
30 polyethoxylated derivatives of such compounds, polyethoxyethylene fatty acid ester and fatty alcohol ether, cholesterol, cetyl stearyl alcohol, wool wax alcohols and synthetic surfactants with a low HLB value; solubilisers such as carbopol; low-viscosity paraffins, triglycerides; lipophilic substances such as isopropyl myristate; pH regulators such as TEA,

carbonates and phosphates; chelating agents such as EDTA and salts thereof; as well as preservatives. Furthermore, the addition of other poloxamers to form mixtures of poloxamers is known to influence the transition temperature.

In certain embodiments, to aid in visualization, a contrast-enhancing agent can be added to the viscous polymer compositions of the invention. Exemplarily contrast-enhancing agents are radiopaque materials, paramagnetic materials, heavy atoms, transition metals, lanthanides, actinides, dyes (such as methylene blue), and radionuclide-containing materials.

Selected Therapeutic Agents

The reversibly gelling polymers used in the methods of the invention have physico-chemical characteristics that make them suitable delivery vehicles for conventional small-molecule drugs, as well as macromolecular (e.g., peptides) drugs or other therapeutic products. Therefore, the composition comprising the thermosensitive polymer may further comprise a pharmaceutical agent selected to provide a pre-selected pharmaceutical effect. A pharmaceutical effect is one which seeks to prevent or treat the source or symptom of a disease or physical disorder. Pharmaceuticals include those products subject to regulation under the FDA pharmaceutical guidelines. Importantly, the compositions used in methods of the invention are capable of solubilizing and releasing bioactive materials. Solubilization is expected to occur as a result of dissolution in the bulk aqueous phase or by incorporation of the solute in micelles created by the hydrophobic domains of the poloxamer. Release of the drug would occur through diffusion or network erosion mechanisms.

Those skilled in the art will appreciate that the compositions used in the methods of the invention may simultaneously be utilized to deliver a wide variety of pharmaceuticals to a wound site. To prepare a pharmaceutical composition, an effective amount of pharmaceutically active agent(s), which imparts the desirable pharmaceutical effect is incorporated into the reversibly gelling composition used in the methods of the invention. Preferably, the selected agent is water soluble, which will readily lend itself to a homogeneous dispersion throughout the reversibly gelling composition. It is also preferred that the agent(s) is non-reactive with the composition. For materials, which are not water soluble, it is also within the scope of the methods of the invention to disperse or suspend lipophilic material throughout the composition. Myriad bioactive materials may be delivered using the methods of the present invention; the delivered bioactive material

includes anti-angiogenic agents, anesthetics, antimicrobial agents (antibacterial, antifungal, antiviral), anti-inflammatory agents, diagnostic agents, and wound-healing agents.

Because the reversibly gelling composition used in the methods of the present invention are suited for application under a variety of environmental conditions, a wide
5 variety of pharmaceutically active agents may be incorporated into and administered via the composition. The pharmaceutical agent loaded into the polymer networks of the thermosensitive polymer may be any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

10 A vast number of therapeutic agents may be incorporated in the polymers used in the methods of the present invention. In general, therapeutic agents which may be administered via the methods of the invention include, without limitation: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelmintics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants;
15 antidiuretic agents; antidiarrheals; antihistamines; anti-inflammatory agents; antimigraine preparations; anti-nauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics, antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators
20 including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers; and naturally derived or genetically engineered proteins, polysaccharides, glycoproteins, or lipoproteins. Suitable
25 pharmaceuticals for parenteral administration are well known as is exemplified by the Handbook on Injectable Drugs, 6th Edition, by Lawrence A. Trissel, American Society of Hospital Pharmacists, Bethesda, Md., 1990 (hereby incorporated by reference).

The pharmaceutically active compound may be any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides,
30 glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotrophic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules. The pharmaceutical agents may be selected from insulin, antigens selected from the group consisting of MMR (mumps, measles and rubella) vaccine, typhoid vaccine, hepatitis A vaccine, hepatitis B vaccine, herpes simplex virus, bacterial toxoids, cholera toxin B-subunit, influenza vaccine virus, bordetella pertussis virus, vaccinia virus, adenovirus, canary pox, polio vaccine virus, plasmodium falciparum, bacillus calmette geurin (BCG), klebsiella pneumoniae, HIV envelop glycoproteins and cytokins and other agents selected from the group consisting of bovine somatropine (sometimes referred to as BST), estrogens, androgens, insulin growth factors (sometimes referred to as IGF), interleukin I, interleukin II and cytokins. Three such cytokins are interferon- β , interferon- γ and tuftsin.

Examples of bacterial toxoids that may be incorporated in the compositions used in the methods of the invention are tetanus, diphtheria, pseudomonas A, mycobacterium tuberculosis. Examples of that may be incorporated in the compositions used in the occlusion methods of the invention are HIV envelope glycoproteins, e.g., gp 120 or gp 160, for AIDS vaccines. Examples of anti-ulcer H₂ receptor antagonists that may be included are ranitidine, cimetidine and famotidine, and other anti-ulcer drugs are omeprazole, cefepime and misoprostol. An example of a hypoglycaemic agent is glipizide.

Classes of pharmaceutically active compounds which can be loaded into that may be incorporated in the compositions used in the occlusion methods of the invention include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g., cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NTHes, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic

substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

Exemplary pharmaceutical agents considered to be particularly suitable for incorporation in the compositions used in the methods of the invention include but are not limited to imidazoles, such as miconazole, econazole, terconazole, saperconazole, itraconazole, metronidazole, fluconazole, ketoconazole, and clotrimazole, luteinizing-hormone-releasing hormone (LHRH) and its analogues, nonoxynol-9, a GnRH agonist or antagonist, natural or synthetic progestin, such as selected progesterone, 17-hydroxyprogesterone derivatives such as medroxyprogesterone acetate, and 19-nortestosterone analogues such as norethindrone, natural or synthetic estrogens, conjugated estrogens, estradiol, estropipate, and ethinyl estradiol, bisphosphonates including etidronate, alendronate, tiludronate, resedronate, clodronate, and pamidronate, calcitonin, parathyroid hormones, carbonic anhydrase inhibitor such as felbamate and dorzolamide, a mast cell stabilizer such as xesterbergsterol-A, lodoxamine, and cromolyn, a prostaglandin inhibitor such as diclofenac and ketorolac, a steroid such as prednisolone, dexamethasone, fluromethylone, rimexolone, and lotepednol, an antihistamine such as antazoline, pheniramine, and histaminase, pilocarpine nitrate, a beta-blocker such as levobunolol and timolol maleate. As will be understood by those skilled in the art, two or more pharmaceutical agents may be combined for specific effects. The necessary amounts of active ingredient can be determined by simple experimentation.

By way of example only, any of a number of antibiotics and antimicrobials may be included in the thermosensitive polymers used in the methods of the invention. Antimicrobial drugs preferred for inclusion in compositions used in the occlusion methods of the invention include salts of lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amanfadine and the like. By way of example only, in the case of anti-inflammation, non-steroidal anti-inflammatory agents (NTHES) may be incorporated in the compositions used in the occlusion methods of the invention, such as propionic acid derivatives, acetic acid, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams, including but not limited to aspirin, acetaminophen, ibuprofen,

naproxen, benoxaprofen, flurbiprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, and bucloxic acid and the like.

Imaging Methodology

In certain embodiments, the invention related to a method of medical imaging. In
5 certain embodiments, the methods of the present invention relate to a noninvasive medical test that helps physicians diagnose or treat medical conditions.

In certain embodiments, the invention relates to a method of ultrasound imaging. Ultrasound imaging, also called ultrasound scanning or sonography, involves exposing part of the body to high-frequency sound waves to produce pictures of the inside of the body.
10 Ultrasound exams do not use ionizing radiation (as used in x-rays). Because ultrasound images are captured in real-time, they can show the structure and movement of the body's internal organs, as well as blood flowing through blood vessels.

Ultrasound imaging is a desirable diagnostic and operative technique for many reasons. In certain embodiments, ultrasound scanning is noninvasive (i.e., requires no
15 needles or injections) and is usually painless. In certain embodiments, ultrasound is widely available, easy-to-use and less expensive than other imaging methods. In certain embodiments, ultrasound imaging uses no ionizing radiation. In certain embodiments, ultrasound scanning gives a clear picture of soft tissues that do not show up well on x-ray images. In certain embodiments, ultrasound causes no health problems and may be
20 repeated as often as is necessary.

In certain embodiments, the invention relates to a method of hysterosonography. Hysterosonography, also known as sonohysterography or saline infusion sonography, is a special, minimally invasive ultrasound technique. It provides pictures of the inside of a woman's uterus. In certain embodiments, many uterine abnormalities that may not be seen
25 adequately with routine transvaginal ultrasound may be viewed in detail with hysterosonography. In general, hysterosonography is a valuable technique for evaluating unexplained vaginal bleeding that may be the result of uterine abnormalities such as polyps, fibroids, atrophy, adhesions (or scarring), masses, or congenital defects. Hysterosonography may also be used to investigate uterine abnormalities in women who
30 experience infertility or multiple miscarriages.

Hysterosonography is a valuable tool for physicians. In certain embodiments, it is a simple, minimally invasive procedure that is well tolerated by patients and has very few complications. In certain embodiments, hysterosonography is a relatively short procedure

that provides an excellent view of the uterus and endometrial lining. In certain embodiments, hysterosonography can prevent unnecessary surgery, and it can ensure that all polyps and fibroids are removed at surgery.

5 In certain embodiments, a hysterosonography may be performed about one week after menstruation to avoid the risk of infection. At this time in the menstrual cycle, the endometrium is at its thinnest, which is a good time to determine if the endometrium is normal. The timing of the exam may vary, however, depending on the symptoms and their suspected origins.

10 In certain embodiments, the invention relates to a method of ultrasound wherein the transducer may be inserted into the body. In these instances, the device may be covered or lubricated.

In certain embodiments, the invention relates to a method of hysterosonography wherein sterile fluid is injected into the cavity of the uterus, distending or enlarging it. In certain embodiments, the fluid is saline solution. In certain embodiments, the fluid is
15 infused into the uterus by using a small, lightweight catheter. The fluid outlines the endometrium (the lining of the uterine cavity) and allows for easy visualization and measurement. It also allows for identification of any polyps or masses within the cavity. In certain embodiments, fluid and air may also be injected into the uterus so that the physician can look for air bubbles passing through the fallopian tubes, which would indicate patency
20 of the fallopian tubes. In certain embodiments, the fluid may further comprise an additional agent, such as a contrast agent or a therapeutic agent.

In certain embodiments, a Doppler ultrasound study may be part of a hysterosonography examination. Doppler ultrasound is a special ultrasound technique that evaluates blood as it flows through a blood vessel by measuring the direction and speed of
25 the blood cells as they move. The movement of blood cells causes a change in pitch of the reflected sound waves (called the Doppler effect). In certain embodiments, a computer collects and processes the sounds and creates graphs or color pictures that represent the flow of blood through the blood vessels. In certain embodiments, Doppler ultrasound images can help the physician to see and evaluate blockages to blood flow (such as clots),
30 tumors, or congenital malformation.

In certain embodiments, the invention relates to a method of preventing fluid leak from a body cavity of a patient in need thereof. In certain embodiments, the invention relates to a method of medical imaging of a body cavity of a patient in need thereof. In

certain embodiments, the patient is a vertebrate, such as a bird or a mammal. In certain embodiments, the vertebrate is a human.

Imaged Objects

In certain embodiments, the invention relates to a method of preventing fluid leaks
5 from a body cavity or a method of medical imaging of a body cavity. The body cavity may be any organ which comprises an internal void. The heart, arteries, veins, stomach, intestines, lungs, colon, bladder, and organs rich in blood, such as liver and kidneys can be ultrasonically imaged with this technique.

In certain embodiments, the body cavity is a uterus. The uterine cavity resembles an
10 inverted triangle and the fallopian tubes open into the cavity, one in each of the upper regions of the triangle. 3D sonography can improve visualization of the uterus in patients with normal anatomy and especially in those with uterine anomalies, e.g., bicomuate uterus.

It is not essential that the subject being imaged be an organic tissue. Rather, the method of the present invention can be used to image anything containing spaces into
15 which the fluid can be introduced.

Exemplary Methods

In certain embodiments, the invention relates to a method of medical imaging of a body cavity of a mammal, comprising the steps of:

delivering a polymer composition to a site near an orifice of the body cavity or a site
20 in a conduit connected to the body cavity;
allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit;
placing a fluid into the body cavity; and
25 imaging the body cavity.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition is delivered by injection.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein delivery of the polymer composition comprises
30 injecting a first composition at the site; and
injecting a second composition at the site, wherein the first composition contacts the second composition, thereby forming the polymer composition in situ.

In certain embodiments, the invention relates to any one of the aforementioned methods, further comprising the step of reversing the temporary occlusion of the orifice or the conduit.

5 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the step of reversing the temporary occlusion of the orifice or the conduit comprises injecting in the vicinity of the polymer plug a second fluid at less than about 37 °C or lowering the temperature in the vicinity of the polymer plug.

10 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the temporary polymer plug is formed by temperature changes, pH changes, or ionic interactions.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises at least one optionally purified inverse thermosensitive polymer.

15 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the at least one optionally purified inverse thermosensitive polymer is a polyoxyalkylene block copolymer.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the at least one optionally purified inverse thermosensitive polymer is selected from the group consisting of poloxamers and poloxamines.

20 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the at least one optionally purified inverse thermosensitive polymer is poloxamer 407.

25 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the at least one optionally purified inverse thermosensitive polymer is selected from the group consisting of purified poloxamers and purified poloxamines.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the at least one optionally purified inverse thermosensitive polymer is purified poloxamer 407.

30 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises an anionic, cationic, or non-ionically crosslinkable polymer.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises a polymer selected from the group

consisting of alginic acid, sodium alginate, potassium alginate, sodium gellan, potassium gellan, carboxy methyl cellulose, hyaluronic acid and polyvinyl alcohol.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises phosphate, citrate, borate, succinate,
5 maleate, adipate, oxalate, calcium, magnesium, barium, or strontium.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises a protein selected from the group consisting of collagen, gelatin, elastin, albumin, protamine, fibrin, fibrinogen, keratin, reelin, and caseine.

10 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises hyaluronic acid, or chitosan.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises alginate, pectin, methylcellulose, or carboxymethylcellulose.

15 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition comprises a crosslinkable polymer.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the body cavity of the mammal is a uterus.

In certain embodiments, the invention relates to any one of the aforementioned
20 methods, wherein the body cavity of the mammal is a uterus; the temporary polymer plug is formed in a conduit connected to the uterus; and the conduit connected to the uterus is a fallopian tube.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the body cavity of the mammal is a uterus; the temporary polymer plug is
25 formed in an orifice of the uterus; and the orifice of the uterus is a cervix.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the fluid placed into the body cavity comprises saline.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the fluid placed into the body cavity comprises saline and air.

30 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the fluid placed into the body cavity comprises saline and a contrast agent or a therapeutic agent.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the temporary polymer plug substantially dissolves or degrades in less than about 24 hours.

5 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the temporary polymer plug substantially dissolves or degrades in less than about 16 hours.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the temporary polymer plug substantially dissolves or degrades in less than about 12 hours.

10 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the polymer composition is delivered using a syringe, cannula, catheter or percutaneous access device.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the body cavity is imaged by ultrasound imaging.

15 In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the body cavity is imaged by transvaginal ultrasound imaging.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the method is a diagnostic method.

20 In certain embodiments, the invention relates to a method of ultrasound imaging of a uterus of a mammal, comprising the steps of:

delivering a polymer composition to a site near an orifice of the uterus or a site in a conduit connected to the uterus;

allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit;

25 placing a fluid into the uterus; and
imaging the uterus.

Injection Systems

30 A delivery system may be used to facilitate and control injection of the inverse thermosensitive polymer composition. Ideally, the injection system would minimize the need for invasion of the orifice, conduit, or body cavity. Further, in constructing an optimal injection system it may be helpful to determine the thumb pressure required to inject the polymer in liquid form through various diameter needles while maintaining a flow rate of

about 0.5 mL per second. A tensile testing apparatus (e.g., Instron®) can be used measure the force needed and resulting rate of compression to depress the plunger.

In certain embodiments, use of a cannula that can be detected in the orifice or conduit using standard non-invasive systems in the operating room (e.g., a handheld
5 ultrasound) will aid in verifying that the cannula is correctly placed. The catheter may be a dilatation catheter. In one embodiment, the catheter is 3-10 French in size, and more preferably 3-6 French. In another embodiment, a catheter can be used to dispense one or more fluids other than, or in addition to, the polymer solution. In the embodiment the catheter may be a multiple lumen catheter with one lumen for the delivery of the polymer
10 solution, other lumen for the delivery of other fluids such as a contrast agent solution.

In another embodiment, the syringe or other mechanism may be used to inject the polymer solution into the body can be, for example, a 1-100 cc syringe, a 1-50 cc syringe or a 1-5 cc. Pressure applied to the syringe can be applied by hand or by an automated syringe pusher. In certain embodiments, a system to provide auxiliary power to a syringe for
15 injection of a viscous material (e.g., a spring loaded plunger assisted device) may be used.

Kits

This invention also provides kits for conveniently and effectively implementing the methods of this invention. Such kits comprise any of the polymers of the present invention or a combination thereof, and a means for facilitating their use consistent with methods of
20 this invention. Such kits may also include ice, a cold pack, or other means of cooling. Such kits provide a convenient and effective means for assuring that the methods are practiced in an effective manner. The compliance means of such kits includes any means which facilitates practicing a method of this invention. Such compliance means include instructions, packaging, and dispensing means, and combinations thereof. Kit components
25 may be packaged for either manual or partially or wholly automated practice of the foregoing methods. In other embodiments, this invention contemplates a kit including block copolymers of the present invention, and optionally instructions for their use. In certain embodiments, the inverse thermosensitive copolymers of such a kit of the present invention are contained in one or more syringes.

30 In certain embodiments, the present invention relates to a kit for conveniently and effectively implementing the method of this invention, comprising instructions for use thereof; and a first container comprising a volume of a composition, wherein the composition forms a viscous polymer composition at mammalian physiological

temperature. In certain embodiments, the present invention relates to the aforementioned kit and any of the attendant limitations, further comprising a cold pack. In certain embodiments, the present invention relates to the aforementioned kit and any of the attendant limitations, further comprising a syringe or cannula. In certain embodiments, the present invention relates to the aforementioned kit and any of the attendant limitations, wherein the viscous polymer composition comprises at least one optionally purified inverse thermosensitive polymer, such as those described above.

Exemplification

The invention, having been generally described, may be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way. All headings are for the convenience of the reader and should not be used to limit the meaning of the text that follows the heading, unless so specified.

Prophetic Examples

We intend to perform the following experiments on rabbits or other small or large animals:

- Occlusion of the fallopian tubes with an optionally purified inverse thermosensitive polymer, filling with marked fluid, perform hysteroscopy – Verify the lack of leakage – Verify by histopathology that the procedure was not traumatic to the lining of the fallopian tube
- Occlusion of the cervix with an optionally purified inverse thermosensitive polymer after filling with fluid while the hysteroscopy probe is in place.
- Compare purified inverse thermosensitive polymer with non-purified inverse thermosensitive polymer in the above experiment, to show that a purified inverse thermosensitive polymer may be needed to provide at the same time easy injectibility as the polymer is injected through a catheter which is inside a warm body, AND mechanical resistance at body temperature sufficient for a successful occlusion
- Reverse occlusion in above experiments by cooling, saline injection or natural erosion of the plugs.

INCORPORATION BY REFERENCE

All of the U.S. patents and U.S. published patent applications cited herein are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following

5 claims.

We claim:

1. A method of medical imaging of a body cavity of a mammal, comprising the steps of:
delivering a polymer composition to a site near an orifice of the body cavity or a site in a conduit connected to the body cavity;
allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit;
placing a fluid into the body cavity; and
imaging the body cavity.
2. The method of claim 1, wherein the polymer composition is delivered by injection.
3. The method of claim 1, wherein delivery of the polymer composition comprises injecting a first composition at the site; and
injecting a second composition at the site, wherein the first composition contacts the second composition, thereby forming the polymer composition in situ.
4. The method of claim 1, further comprising the step of reversing the temporary occlusion of the orifice or the conduit.
5. The method of claim 4, wherein the step of reversing the temporary occlusion of the orifice or the conduit comprises injecting in the vicinity of the polymer plug a second fluid at less than about 37 °C or lowering the temperature in the vicinity of the polymer plug.
6. The method of claim 1, wherein the temporary polymer plug is formed by temperature changes, pH changes, or ionic interactions.
7. The method of any one of claims 1-6, wherein the polymer composition comprises at least one optionally purified inverse thermosensitive polymer.
8. The method of claim 7, wherein the at least one optionally purified inverse thermosensitive polymer is a polyoxyalkylene block copolymer.
9. The method of claim 7, wherein the at least one optionally purified inverse thermosensitive polymer is selected from the group consisting of poloxamers and poloxamines.
10. The method of claim 7, wherein the at least one optionally purified inverse thermosensitive polymer is poloxamer 407.

11. The method of claim 7, wherein the at least one optionally purified inverse thermosensitive polymer is selected from the group consisting of purified poloxamers and purified poloxamines.
12. The method of claim 7, wherein the at least one optionally purified inverse thermosensitive polymer is purified poloxamer 407.
13. The method of any one of claims 1-12, wherein the polymer composition comprises an anionic, cationic, or non-ionically crosslinkable polymer.
14. The method of any one of claims 1-12, wherein the polymer composition comprises a polymer selected from the group consisting of alginic acid, sodium alginate, potassium alginate, sodium gellan, potassium gellan, carboxy methyl cellulose, hyaluronic acid and polyvinyl alcohol.
15. The method of any one of claims 1-12, wherein the polymer composition comprises phosphate, citrate, borate, succinate, maleate, adipate, oxalate, calcium, magnesium, barium, or strontium.
16. The method of any one of claims 1-12, wherein the polymer composition comprises a protein selected from the group consisting of collagen, gelatin, elastin, albumin, protamine, fibrin, fibrinogen, keratin, reelin, and caseine.
17. The method of any one of claims 1-12, wherein the polymer composition comprises hyaluronic acid, or chitosan.
18. The method of any one of claims 1-12, wherein the polymer composition comprises alginate, pectin, methylcellulose, or carboxymethylcellulose.
19. The method of any one of claims 1-12, wherein the polymer composition comprises a crosslinkable polymer.
20. The method of any one of claims 1-19, wherein the body cavity of the mammal is a uterus.
21. The method of any one of claims 1-19, wherein the body cavity of the mammal is a uterus; the temporary polymer plug is formed in a conduit connected to the uterus; and the conduit connected to the uterus is a fallopian tube.
22. The method of any one of claims 1-19, wherein the body cavity of the mammal is a uterus; the temporary polymer plug is formed in an orifice of the uterus; and the orifice of the uterus is a cervix.
23. The method of any one of claims 1-22, wherein the fluid placed into the body cavity comprises saline.

24. The method of any one of claims 1-22, wherein the fluid placed into the body cavity comprises saline and air.
25. The method of any one of claims 1-22, wherein the fluid placed into the body cavity comprises saline and a contrast agent or a therapeutic agent.
26. The method of any one of claims 1-3 or 6-25, wherein the temporary polymer plug substantially dissolves or degrades in less than about 24 hours.
27. The method of any one of claims 1-3 or 6-25, wherein the temporary polymer plug substantially dissolves or degrades in less than about 16 hours.
28. The method of any one of claims 1-3 or 6-25, wherein the temporary polymer plug substantially dissolves or degrades in less than about 12 hours.
29. The method of claim 1, wherein the polymer composition is delivered using a syringe, cannula, catheter or percutaneous access device.
30. The method of any one of claims 1-29, wherein the body cavity is imaged by ultrasound imaging.
31. The method of claim 20, wherein the body cavity is imaged by transvaginal ultrasound imaging.
32. The method of any one of claims 1-31, wherein the method is a diagnostic method.
33. A method of ultrasound imaging of a uterus of a mammal, comprising the steps of:
delivering a polymer composition to a site near an orifice of the uterus or a site in a conduit connected to the uterus;
allowing the polymer composition to substantially solidify at the site, thereby forming a temporary polymer plug that substantially occludes the orifice or the conduit;
placing a fluid into the uterus; and
imaging the uterus.

Figure 1

