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(54) **Title:** PROTECTIVE COVERINGS FOR DRUG COATED BALLOONS

(57) **Abstract:** The present disclosure concerns protective layers covering drug-coated layers on the external surface of a balloon that offer protection to the drug-coating until the balloon is in positions and ready for inflation. In aspects, the protective layer is water-soluble, meaning that the protective layer starts to dissolve within a subject's circulatory system once introduced. The protective layer is of a sufficient thickness or density over the drug-coating to allow for the balloon to be positioned in situ before exposing completely the drug-coating. The protective layer allows for preservation of therapeutic on the balloon surface, thereby increasing the accuracy of site-specific delivery.

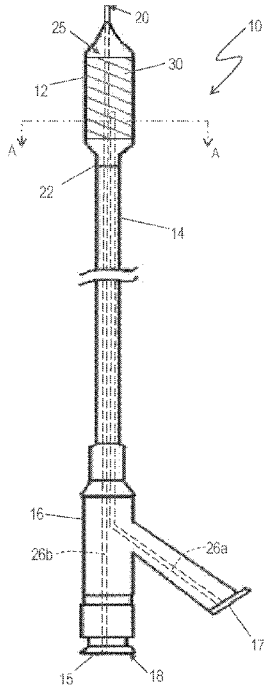


FIG. 1

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# Protective Coverings for Drug Coated Balloons

## BACKGROUND

**[0001]** Drug coated balloon catheters provide site specific delivery of one or more therapeutics to assist the mechanical force within a blood vessel to attempt to clear obstructions therein. The coatings on the balloon need to be carefully crafted to allow for accurate transfer of the therapeutic(s) during the short residency time of the inflated balloon within the vessel. TO that end, the coatings on these devices are typically crafted to allow for quick release from the exterior surface of the balloon. The physical properties of these coatings, however, renders them vulnerable to the turbulence and fluid forces present within the vasculature as a user maneuvers the balloon to a desired location. Factors such as the length of time, distance from insertion to inflation, as well as the type of vessel and width of the vessel can all attribute to wash off of the coating before the balloon is even able to be inflated. Accordingly, there is a need in the art for protective coverings that allow the balloon to be positioned with any coating thereon in tact and deliver the therapeutic at the desired location.

## SUMMARY

**[0002]** A 1st aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns a balloon catheter for delivering a therapeutic agent to a blood vessel, the balloon catheter comprising: an elongate member having a lumen and a distal end; an expandable balloon attached to the distal end of the elongate member and in fluid communication with the lumen; a coating layer overlying an exterior surface of the expandable balloon, the coating layer comprising a therapeutic agent or a polymer microparticle containing the therapeutic agent and an excipient; and a protective layer overlying the coating layer, the protective layer comprising a hydrophilic polymer.

**[0003]** A 2nd aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 1st aspect, wherein the hydrophilic polymer is selected from polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), polyacrylic acid (PAA), N-(2-hydroxypropyl) methacrylamide (HPMA), divinyl ether-maleic anhydride (DIVEMA), polyoxazoline, polyphosphate, polyphosphazene, xanthan gum, pectin,

chitosan derivatives, dextran, carrageenan, guar gum, cellulose ethers, sodium CMC, HPC, HPMC, hyaluronic acid (HA), albumin, starch, or a combination thereof.

**[0004]** A 3rd aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 1st aspect, wherein the hydrophilic polymer is PVA.

**[0005]** A 4th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 1st aspect, wherein the hydrophilic polymer is HA.

**[0006]** A 5th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 4th aspect, wherein the hydrophilic polymer has a molecular weight (MW) of from about 20 kDa to about 500 kDa.

**[0007]** A 6th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the hydrophilic polymer has a molecular weight (MW) of from 20 kDa to about 200 kDa.

**[0008]** A 7th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the protective layer has a thickness of of from about 2 μm to about 100 μm.

**[0009]** An 8th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the protective layer further includes an additive.

**[0010]** A 9th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 8th aspect, wherein the additive is a second excipient.

**[0011]** A 10th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 8th aspect, wherein the additive is kaolin.

**[0012]** An 11th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the excipient comprises a biodegradable polymer chosen from a fatty acid, a fatty acid ester, polylactic acid (PLLA,PDLA,PDLLA), polycaprolactone (PCL), sodium docusate, PLGA, PLGA-b-mPEG,

polyglutamic acid, polyacrilic acid, hyaluronic acid, alginate, PVA, PVP, Pluronic (PEO-PPO-PEO),cellulose, CMC, HPC, starch, chitosan, human serum albumin (HSA), phospholipids, fatty acid, fatty acid esters, triglycerides, beeswax, cyclodextrin, Tween 20, Tween 80, TPGS, SLS, butylated hydroxytoluene, vitamin E, vitamin E succinate, tannic acid, polyethylene glycol, N-isopropylacrylamide, and sorbitol esters.

**[0013]** A 12th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the coating layer further comprises a hydrophobic material containing the therapeutic agent embedded therein.

**[0014]** A 13th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 12th aspect, wherein the hydrophobic material comprises a hydrophobic material with a glass transition temperature of 37 °C or lower.

**[0015]** A 14th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 12th aspect, wherein the hydrophobic material is semi-synthetic glycerides, methyl stearate, hydrogenated coconut oil, coconut oil, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, hard fats, petroleum jelly/petrolatum, a PEG-fatty acid ester, or a combination thereof.

**[0016]** A 15th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 14th aspect, wherein the hydrophobic material is hydrogenated coconut oil, coconut oil, mineral oil, cetyl alcohol, petroleum jelly, decanol, tridecanol, dodecanol, long chain saturated fatty acids, long chain unsaturated fatty acid, fatty acid esters, fatty acid ethers, witepsol, solid lipids, methyl stearate, triglycerides, glyceryl monostearate, glyceryl palmitostearate, stearic acid, palmitic acid, decanoic acid, behenic acid, beeswax, carnauba wax, paraffin, a fatty acid triglycerides, a fatty acid alcohol, or a combination thereof.

**[0017]** A 16th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the polymer microparticle comprises poly(lactic-co-glycolic) acid (PLGA) and the therapeutic agent loaded therein.

**[0018]** A 17th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 16th aspect, wherein the therapeutic agent is loaded in the polymer microparticle at 30-50 % weight of the polymer microparticle.

**[0019]** An 18th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 17th aspect, wherein the polymer microparticles are of a first size grouping and a second size grouping, wherein the first size grouping has an average size of 10 μm and further wherein the second size grouping has an average size different from the first size grouping.

**[0020]** A 19th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 18th aspect, wherein the second size grouping has an average size of 30 μm, 35 μm, or 40 μm.

**[0021]** A 20th aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the therapeutic agent is crystalline particles.

**[0022]** A 21st aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 20th aspect, wherein the average size of the crystalline particles is of 0.1 μm to 100 μm.

**[0023]** A 22nd aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns the balloon catheter of the 2nd, 3rd, or 4th aspect, wherein the coating layer further comprises a hydrophilic material chosen from poly(ethylene glycol), polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polyacrylamides, N-(2-Hydroxypropyl) methacrylamide (HPMA), divinyl ether-maleic anhydride (DIVEMA), polyoxazoline, xanthan gum, pectins, chitosan derivatives, dextran, casein sodium, cellulose ethers, sodium carboxy methyl cellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hyaluronic acid (HA), albumin, or a combination thereof.

**[0024]** A 23rd aspect of the present disclosure, either alone or in combination with any other aspect herein, concerns a method for treating a blood vessel in a subject comprising introducing the balloon catheter of the 1st aspect into the blood vessel of the subject; maneuvering the balloon catheter to an atherosclerotic plaque in the blood vessel; and, expanding the

expandable balloon, wherein the protective coating dissolves prior to expanding the expandable balloon.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0025]** It is to be understood that both the foregoing general description and the following detailed description describe various aspects and are intended to provide an overview or framework for understanding the nature and character of the claimed subject matter. The accompanying drawings are included to provide a further understanding of the various aspects, and are incorporated into and constitute a part of this specification. The drawings illustrate the various aspects described herein, and together with the description serve to explain the principles and operations of the claimed subject matter.

**[0026]** FIG. 1 is a schematic of an exemplary aspect of a medical device, particularly a balloon catheter, according to the present disclosure.

**[0027]** FIG. 2A is a cross-section of some aspect of the distal portion of the balloon catheter of FIG. 1, taken along line A—A, including a drug coating layer on an exterior surface of a balloon.

**[0028]** FIG. 2B and is a cross-section of some aspect of the distal portion of the balloon catheter of FIG. 1, taken along line A—A, including an intermediate layer between a exterior surface of the balloon and a drug coating layer.

## DESCRIPTION

**[0029]** The present disclosure pertains to protective layer(s) that cover, at least in part, the drug coating on the exterior surface of a balloon. In some aspects, the presence of the protective layer shields the drug coating from the turbulence of a subjects circulatory system, as well as against abrasion along the vessel wall as the balloon is maneuvered within the subject to a desired location. It is an aspect of the present disclosure that once in place *in situ*, the balloon will inflate and release or transfer the drug coating at the site of inflation.

**[0030]** In aspects, the protective layer is of a water-soluble polymer. The protective layer is designed to dissolve or be absorbed in the circulating plasma and blood as the balloon is introduced into the lumen of a subject's vessel and shuttled into the desired location.

**[0031]** In aspects, the protective layer is therefore dissolved from the exterior surface of the balloon prior to inflation thereof such that the drug coating layer is exposed once the balloon expands within the lumen. In aspects, the protective layer is of a water-soluble polymer. In aspects, the protective layer is chosen from polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), polyacrylic acid (PAA), N-(2-hydroxypropyl) methacrylamide (HPMA), divinyl ether-maleic anhydride (DIVEMA), polyoxazoline, polyphosphate, polyphosphazene, xanthan gum, pectin, chitosan derivatives, dextran, carrageenan, guar gum, cellulose ethers, sodium CMC, HPC, HPMC, hyaluronic acid (HA), albumin, starch, or combinations thereof.

**[0032]** In aspects, the protective layer is of polyvinyl alcohol (PVA). It will be appreciated that the molecular weight and/or degree of cross-linking in PVA (as well as with other polymers described herein) can alter the rate of dissolution within the subject's circulatory system. It is understood in the art that polymers such as PVA are comprised of linked repeats of monomer units. For PVA, the repeated monomer unit is vinyl alcohol or $CH_2CHOH$ (which can tautomerize to $CH_3CHO$). In aspects, PVA can be expressed as $[CH_2CHOH]_n$ wherein n is an integer of the number of repeats in the polymer. In some aspects, n is from about 2 to about 50 to about 100 to about 200 to about 500 to about 1000 to about 5000 to about 10000 and upward. It will be appreciated that the PVA molecule need not be restricted by the number of repeats possible, as the polymer can continue to accept additional monomer units. It will be appreciated that the limitations to PVA can be controlled by the amount of monomer units provided, as well as restrictions on the cross-linking process itself such as concentration of alkaline catalyst and/or reaction duration and/or reactions conditions, such as temperature. In aspects, PVA (as well as some other polymers discussed herein) may be referred to based on the molecular weight (MW) of the formed molecule(s) or molecular weight range. As the MW increases, the PVA solubility decreases. Accordingly, the selection of the PVA MW can provide for faster dissolving protective layers and slower dissolving protective layers. The tenability of the protective layer therefore can accommodate high turbulence blood vessels and lengthier times from insertion to inflation, as well as short procedures.

**[0033]** In aspects, the protective layer is of hyaluronic acid (HA). It will be appreciated that the molecular weight and/or degree of cross-linking in HA (as well as with other polymers described herein) can alter the rate of dissolution within the subject's circulatory system. It is

understood in the art that polymers such as HA are comprised of linked repeats of monomer units. For HA, the repeated monomer unit is hyaluronate (an anionic glycosaminoglycan). In aspects, HA can be expressed as $[C_{14}H_{21}NO_{11}]_n$ wherein n is an integer of the number of repeats in the polymer. In some aspects, n is from about 2 to about 50 to about 100 to about 200 to about 500 to about 1000 to about 5000 to about 10000 and upward. It will be appreciated that the PVA molecule need not be restricted by the number of repeats possible, as the polymer can continue to accept additional monomer units. It will be appreciated that the limitations to HA can be controlled by the amount of monomer units provided, as well as restrictions on the cross-linking process itself such as concentration of alkaline catalyst and/or reaction duration and/or reactions conditions, such as temperature. In aspects, HA (as well as some other polymers discussed herein) may be referred to based on the molecular weight (MW) of the formed molecule(s) or molecular weight range. As the MW increases, the HA solubility decreases. Accordingly, the selection of the HA MW can provide for faster dissolving protective layers and slower dissolving protective layers. The tenability of the protective layer therefore can accommodate high turbulence blood vessels and lengthier times from insertion to inflation, as well as short procedures.

**[0034]** In aspects, the protective layer includes a polymer with a molecular weight of from about 25 kDa (kilo Daltons) to about 200 kDa, including about 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, and 195 kDa. In some aspects, the PVA/HA is of from about 25 to about 175 kDa, from about 25 to about 150 kDa, from about 25 to about 125 kDa, from about 25 to about 100 kDa, from about 25 to about 75 kDa, from about 25 to about 50 kDa, from about 50 to about 175 kDa, from about 50 to about 150 kDa, from about 50 to about 125 kDa, from about 50 to about 100 kDa, from about 50 to about 75 kDa, from about 75 to about 175 kDa, from about 75 to about 150 kDa, from about 75 to about 125 kDa, from about 75 to about 100 kDa, from about 100 to about 175 kDa, from about 100 to about 150 kDa, from about 100 to about 125 kDa, from about 125 to about 175 kDa, from about 125 to about 150 kDa, and from about 150 to about 175 kDa (including all numbers therebetween). In some aspects, the HA may be of a higher MW such as about 225, 250, 275,, 300, 325, 350, 375, 400, 425, 450, 475, and 500 kDa (and all numbers therebetween).

**[0035]** In aspects, the protective layer is of a sufficient thickness that the rate of dissolution of the same allows for the exposure of the underlying drug coating at a desired point where the

balloon is ready for inflation. By changing the thickness of the protective layer, another tunable parameter is presented that allows for the protective layer to dissolve at a desired rate.

**[0036]** In aspects, the protective layer is of from about 2 to about 100 μm in thickness, from about 2 to about 90 μm in thickness, from about 2 to about 80 μm in thickness, from about 2 to about 70 μm in thickness, from about 2 to about 60 μm in thickness, from about 2 to about 50 μm in thickness, from about 2 to about 40 μm in thickness, from about 2 to about 30 μm in thickness, from about 2 to about 20 μm in thickness, from about 2 to about 10 μm in thickness, from about 2 to about 5 μm in thickness, from about 5 to about 100 μm in thickness, from about 5 to about 90 μm in thickness, from about 5 to about 80 μm in thickness, from about 5 to about 70 μm in thickness, from about 5 to about 60 μm in thickness, from about 5 to about 50 μm in thickness, from about 5 to about 40 μm in thickness, from about 5 to about 30 μm in thickness, from about 5 to about 20 μm in thickness, from about 5to about 10 μm in thickness, from about 10 to about 100 μm in thickness, from about 10 to about 90 μm in thickness, from about 10 to about 80 μm in thickness, from about 10 to about 70 μm in thickness, from about 10 to about 60 μm in thickness, from about 10 to about 50 μm in thickness, from about 10 to about 40 μm in thickness, from about 10 to about 30 μm in thickness, from about 10 to about 20 μm in thickness, from about 20 to about 100 μm in thickness, from about 20 to about 90 μm in thickness, from about 20 to about 80 μm in thickness, from about 20 to about 70 μm in thickness, from about 20 to about 60 μm in thickness, from about 20 to about 50 μm in thickness, from about 20 to about 40 μm in thickness, from about 20 to about 30 μm in thickness, from about 30 to about 100 μm in thickness, from about 30 to about 90 μm in thickness, from about 30 to about 80 μm in thickness, from about 30 to about 70 μm in thickness, from about 30 to about 60 μm in thickness, from about 30 to about 50 μm in thickness, from about 30 to about 40 μm in thickness, from about 40 to about 100 μm in thickness, from about 40 to about 90 μm in thickness, from about 40 to about 80 μm in thickness, from about 40 to about 70 μm in thickness, from about 40 to about 60 μm in thickness, from about 40 to about 50 μm in thickness, from about 50 to about 100 μm in thickness, from about 50 to about 90 μm in thickness, from about 50 to about 80 μm in thickness, from about 50 to about 70 μm in thickness, from about 50 to about 60 μm in thickness, from about 60 to about 100 μm in thickness, from about 60 to about 90 μm in thickness, from about 60 to about 80 μm in thickness, from about 60 to about 70 μm in thickness, from about 70 to about 100 μm in thickness, from about 70 to about 90 μm in thickness, from about 70 to about 80 μm in thickness, from about

80 to about 100 μm in thickness, from about 80 to about 90 μm in thickness, and from about 90 to about 100 μm in thickness.

**[0037]** In aspects, the protective layer is prepared with one or more additives to assist in providing the protective layer as an even coating on the drug layer. Such additives may include kaolin, a surfactant, or other additive or excipient as described herein.

**[0038]** In aspects, the protective layer is configured to have dissolved or be absorbed by the circulatory system of the subject by the time that a user is prepared to inflate the balloon *in situ* within the subject. In aspects, the choice of soluble or bioabsorbable polymer and the thickness of the protective layer can control when the protective layer is indifferent to the balloon being able to deliver the drug coating layer to the lumen of the vessel walls. Factors for consideration in selecting the protective layer include the length of time of travel, the distance that the balloon is expected to travel within the vasculature, the vessel within which the balloon is to travel and the expected turbulence therein from the subject's circulatory system, the vessel diameter, the salinity concentration of the subject's blood, obstructions that the balloon is expected to maneuver by, the blood flow rate in the vessel, the subject's blood pressure, therapeutics that the subject may be otherwise taking, and similar.

**[0039]** In aspects, the balloon is of a material that may include a polymer material, such as, for example only, polyvinyl chloride (PVC), polyethylene terephthalate (PET), polyethylene, polyamide (e.g. nylon), PEBAX (i.e. a copolymer of polyether and polyamide), polyurethane, polystyrene (PS), polyethleneterephthalate (PETP), or various other suitable materials with a similar elastic modulus.

**[0040]** Referring to the exemplary drawing of FIG. **1**, a balloon catheter **10** has a proximal end **18** and a distal end **20**. The balloon catheter **10** may be any suitable catheter for desired use, including conventional balloon catheters known to one of ordinary skill in the art. For example, the balloon catheter **10** may be a rapid exchange or over-the-wire catheter. In some specific examples, the balloon catheter may be a ClearStream™ Peripheral catheter available from BD Peripheral Intervention. The balloon catheter **10** may be made of any suitable biocompatible material. The balloon **12** of the balloon catheter may include a polymer material, such as, for example only, polyvinyl chloride (PVC), polyethylene terephthalate (PET), polyethylene,

polyamide, PEBAX (i.e. a copolymer of polyether and polyamide), polyurethane, polystyrene (PS), polyethleneterephthalate (PETP), or various other suitable materials as will be apparent to those of ordinary skill in the art.

**[0041]** Referring jointly to FIGS. **1**, **2A**, and **2B**, the balloon catheter **10** includes an expandable balloon **12** and an elongate member **14**. The elongate member **14** extends between the proximal end **18** and the distal end **20** of the balloon catheter **10**. The elongate member **14** has at least one lumen **26a**, **26b** and a distal end **20**. The elongate member **14** may be a flexible member which is a tube made of suitable biocompatible material. The elongate member **14** may have one lumen or, as shown in FIGS. **1**, **2A**, and **2B**, more than one lumen **26a**, **26b** therein. For example, the elongate member **14** may include a guide-wire lumen **26b** that extends to the distal end **20** of the balloon catheter **10** from a guide-wire port **15** at the proximal end **18** of the balloon catheter **10**. The elongate member **14** may also include an inflation lumen **26a** that extends from an inflation port **17** of the balloon catheter **10** to the inside of the expandable balloon **12** to enable inflation of the expandable balloon **12**. From the elements of FIGS. **1**, **2A**, and **2B**, even though the inflation lumen **26a** and the guide-wire lumen **26b** are shown as side-by-side lumens, it should be understood that the one or more lumens present in the elongate member **14** may be configured in any manner suited to the intended purposes of the lumens including, for example, introducing inflation media and/or introducing a guide-wire. Many such configurations are well known in the art.

**[0042]** The expandable balloon **12** is attached to the distal attachment end **22** of the elongate member **14**. The expandable balloon **12** has an exterior surface **25** and is inflatable. The expandable balloon **12** is in fluidic communication with a lumen of the elongate member **14**, (for example, with the inflation lumen **26a**). At least one lumen of the elongate member **14** is configured to receive inflation media and to pass such media to the expandable balloon **12** for its expansion. Examples of inflation media include air, saline, and contrast media.

**[0043]** Still referring to FIG. **1**, in one aspect, the balloon catheter **10** includes a handle assembly such as a hub **16**. The hub **16** may be attached to the balloon catheter **10** at the proximal end **18** of the balloon catheter **10**. The hub **16** may connect to and/or receive one or more suitable medical devices, such as a source of inflation media (e.g., air, saline, or contrast media) or a guide wire. For example, a source of inflation media (not shown) may connect to the inflation port **17**

of the hub **16** (for example, through the inflation lumen **26a**), and a guide wire (not shown) may be introduced to the guide-wire port **15** of the hub **16**, (for example through the guide-wire lumen **26b**).

**[0044]** In some examples, the cross section A—A of FIG. **1** may be as depicted according to FIG. **2A**, in which the drug coating layer **30** is applied directly onto an exterior surface **25** of the balloon **12**. The specific compositions of the drug coating layer **30** itself, according to various aspects, will also be described subsequently in greater detail. In other examples, the cross section A—A of FIG. **1** may be as depicted according to FIG. **2B**, in which the drug coating layer **30** is applied onto an intermediate layer **40** overlying the exterior surface **25** of the balloon **12**. In some aspects, the exterior surface **25** may undergo a surface modification. In some aspects where the exterior surface **25** is a modified exterior surface, the exterior surface **25** has been subjected to a surface modification, such as a fluorine plasma treatment, which decreases a surface free energy of the exterior surface **25** before application of the drug coating layer **30**. Subjecting the exterior surface to a surface modification may decreases the surface free energy of the exterior surface before application of the coating layer and affect the release kinetics of drug in the coating layer from the balloon, the crystallinity of the drug layer, the surface morphology of the coating and particle shape, or the particle size of drug of a therapeutic layer in the coating layer, drug distribution on the surface.

**[0045]** In aspects in which the cross section A—A of FIG. **1** is as depicted according to FIG. **2A**, the balloon catheter **10** includes a drug coating layer **30** applied over an exterior surface **25** of the balloon **12**. The drug coating layer **30** itself includes a therapeutic agent and an additive. In one particular aspect, the drug coating layer **30** comprises a kinase inhibitor, tyrosine kinase inhibitor, a PDE inhibitor, or an anti-fibrotic therapeutic agent, the polymer, and one or more additional additives. In further aspects, the drug coating layer **30** does not include a polymer.

**[0046]** In other aspects, two or more therapeutic agents are used in combination in the drug coating layer. In other aspects, the device may include a top layer (not shown) overlying the drug coating layer **30**. In some aspects, a protective layer **55** may be advantageous in order to prevent premature drug loss during the device delivery process before deployment at the target site.

**[0047]** In aspects, the protective layer covers at least in part a coating layer on the exterior surface of the balloon. In aspects, the coating layer includes one or more therapeutic agents. In some aspects, the therapeutic agent is chosen from paclitaxel, rapamycin, daunorubicin, 5-fluorouracil, doxorubicin, sunitinib, sorafenib, irinotecan, bevasizumab, cetuxamab, biolimus (biolimus A9), everolimus, sirolimus, zotarolimus, tacrolimus, dexamethasone, prednisolone, corticosterone, cisplatin, vinblastine, lidocaine, bupivacaine, or a combination thereof.

**[0048]** In some aspects, the coating layer may include microparticles of therapeutic agent(s) and a bioabsorbable polymer. Microparticles may be prepared the evaporation of a solvent with a bioabsorbable/biodegradable polymer and at least one therapeutic therein. In some aspects, the solvent is of dichloromethane (DCM) or ethyl acetate (EtOAc). Polymers may include a network of a poly-glycolic acid (PGA) and a poly-L-lactic acid (PLLA). Other bioabsorbable polymers that can be utilized in combination or alone for the microparticles include polycaprolactone (PCL), poly-DL-lactic acid (PDLLA), poly(trimethylene carbonate) (PTMC), poly (ester amine)s (PEA), poly(para-dioxanone) (PPDO), poly-2-hydroxy butyrate (PHB), and co-polymers with various ratios thereof. In some aspects, the bioabsorbable polymer may include, either alone or in combination with other bioabsorbable polymers, a polymer combination of lactic acid and glycolic acid, poly-lactic-co-glycolic acid (PLGA). Those skilled in the art will appreciate that PLGA can be of varying percentages of lactic acid and glycolic acid, wherein the higher the amount of lactide units, the longer the polymer can last *in situ* before degrading. Additional tunable properties with PLGA concern the molecular weight, with higher weights showing increased mechanical strength. In some aspects, the polymer microparticle is also loaded or embedded with an antioxidant, such as BHT.

**[0049]** In some aspects, the coating layer may include a polymer coating, such as a bioabsorbable polymer as set forth herein. In some aspects, the density of the therapeutic or polymer microparticle within the polymer coating is of from about 0.1 to 10 $\mu g/mm^2$. In certain aspects, the theapeutic or polymer microparticle is provided on the device in the polymer coating at a density of from about 0.5 to about 5 $\mu g/mm^2$. In some aspects, the dose density of the therapeutic in the coating and/or within each polymer microparticle can vary from about 0.1 to about 10 $\mu g/mm^2$, including about 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8., 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9,

6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, and 9.9 $\mu g/mm^2$. In some aspects, the therapeutic dose density is of about 0.5 to about 5 $\mu g/mm^2$.

**[0050]** In some aspects, the concentration density of the therapeutic agent in the coating layer or within the polymer microparticle may be from 0.1 $\mu g/mm^2$ to 10 $\mu g/mm^2$, from 0.1 $\mu g/mm^2$ to 8 $\mu g/mm^2$, from 0.1 $\mu g/mm^2$ to 6 $\mu g/mm^2$, from 0.1 $\mu g/mm^2$ to 4 $\mu g/mm^2$, from 0.1 $\mu g/mm^2$ to 2 $\mu g/mm^2$, from 0.1 $\mu g/mm^2$ to 1 $\mu g/mm^2$, from 1 $\mu g/mm^2$ to 10 $\mu g/mm^2$, from 1 $\mu g/mm^2$ to 8 $\mu g/mm^2$, from 1 $\mu g/mm^2$ to 6 $\mu g/mm^2$, from 1 $\mu g/mm^2$ to 4 $\mu g/mm^2$, from 1 $\mu g/mm^2$ to 2 $\mu g/mm^2$, from 2 $\mu g/mm^2$ to 10 $\mu g/mm^2$, from 2 $\mu g/mm^2$ to 8 $\mu g/mm^2$, from 2 $\mu g/mm^2$ to 6 $\mu g/mm^2$, from 2 $\mu g/mm^2$ to 4 $\mu g/mm^2$, from 4 $\mu g/mm^2$ to 10 $\mu g/mm^2$, from 4 $\mu g/mm^2$ to 8 $\mu g/mm^2$, from 4 $\mu g/mm^2$ to 6 $\mu g/mm^2$, from 6 $\mu g/mm^2$ to 10 $\mu g/mm^2$, from 6 $\mu g/mm^2$ to 8 $\mu g/mm^2$, or from 8 $\mu g/mm^2$ to 10 $\mu g/mm^2$. In some aspects the concentration density of therapeutic agent in the coating layer or polymer microparticle may be from 0.5 $\mu g/mm^2$ to 5 $\mu g/mm^2$.

**[0051]** The methods to apply the coating layer include to a medical device may include dip coating, metering coating, spray coating, electrostatic spray coating, roller coating, spin coating, ink-jet printing, 3D printing, or combinations thereof. A preferred method is metering coating and spray coating. After the solvent has evaporated, the coating layer is left on the surface.

**[0052]** In some aspects, the coating layer may include crystalline therapeutic agent and/or an amorphous therapeutic agent of a particular size range or ranges. In some aspects, the crystalline and/or amorphous therapeutic agent can be embedded within the coating layer. In other aspects, the crystalline and/or amorphous therapeutic agent is loaded within a polymer microparticle embedded in the coating layer. In further aspects, the crystalline and/or amorphous therapeutic agent adheres to the surface of the medical device through the evaporation of a solvent. In some aspects, the crystalline and/or amorphous therapeutic agent microparticle size can vary from about 0.1 μm to about 100 μm, including about 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 99 μm and any size or number therein. In some aspects, the particle size is of from about 1 μm to about 20 μm. In other aspects, the particle size of from about 10 μm to about 100 μm. Size selection can be achieved through methods understood in the art, such as by passing through mesh of a pre-determined pore or hole size. The desired

particle size can be achieved by dry grind or wet grinding. The grinding method may include techniques such as use of a jaw crusher, ultra-centrifugal mill, cyclone mill, cross beater mill, rotor beater mill, cutting mill, knife mill, mortar grinder, disc mill, mixer mill, cryomill, planetary ball mill, drum mill, and/or fine grinding rod mill. In some aspects, the particle size may be achieved with use of a ball mill. The ground drug particles and polymer mix may be combined with a solvent (or a mixture of solvents) and form a slurry coating solution. The methods may also include application of the slurry coating solution to a medical device surface. Such techniques for application may include dip coating, metering coating, spray coating, electrostatic spray coating, roller coating, spin coating, ink-jet printing, and 3D printing. In certain aspects, the method includes metering coating.

**[0053]** In aspects, the coating layer includes a hydrophobic polymer with the therapeutic dispersed throughout. In some aspects, the biodegradable polymer chosen from a fatty acid, a fatty acid ester, polylactic acid (PLLA,PDLA,PDLLA), polycaprolactone (PCL), sodium docusate, PLGA, PLGA-b-mPEG, polyglutamic acid, polyacrilic acid, hyaluronic acid, alginate, PVA, PVP, Pluronic (PEO-PPO-PEO),cellulose, CMC, HPC, starch, chitosan, human serum albumin (HSA), phospholipids, fatty acid, fatty acid esters, triglycerides, beeswax, cyclodextrin, Tween 20, Tween 80, TPGS, SLS, butylated hydroxytoluene, vitamin E, vitamin E succinate, tannic acid, polyethylene glycol, N-isopropylacrylamide, and sorbitol esters.. In further aspects, the polymer is a bioabsorbable polymer of a hydrophobic or hydrophilic nature. By way of example and not limitation, examples of bioabsorbable hydrophobic materials may include semi-synthetic glycerides (e.g. Suppocire AIML, AML, BML, BS2, BS2X, NBL, NAIS 10, CS2X), lecithin, hydrogenated coconut oil, coconut oil, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, hard fats, mineral oil, cetyl alcohol, petrolatum, petroleum jelly, decanol, soft paraffin, tridecanol, dodecanol, long chain saturated fatty acids, long chain unsaturated fatty acids, fatty acid esters, fatty acid ethers, witepsol, solid lipids, methyl stearate, triglycerides, glyceryl monostearate, glyceryl palmitostearate, stearic acid, palmitic acid, decanoic acid, behenic acid, beeswax, carnauba wax, paraffin, fatty acid triglycerides, fatty acid alcohols, PEG-fatty acid esters (with hydrophilic-lipophilic balance (HLB) below 13), PEG-surfactants with an HLB below 13, or combinations thereof.

**[0054]** In some aspects, the coating layer includes one or more excipients. Suitable excipients that can be used in some aspects of the present disclosure include, without limitation,

organic and inorganic pharmaceutical excipients, natural products and derivatives thereof (such as sugars, vitamins, amino acids, peptides, proteins, and fatty acids), surfactants (anionic, cationic, non-ionic, and ionic), and mixtures thereof. The following list of excipients useful in the present disclosure is provided for exemplary purposes only and is not intended to be comprehensive. Many other excipients may be useful for purposes of the present disclosure, such as polyglutamic acid, polyacrilic acid, hyaluronic acid, alginate, PVA,PVP, Pluronic (PEO-PPO-PEO),cellulose, CMC, HPC, starch, chitosan, human serum albumin (HSA), phospholipids, fatty acid, fatty acid esters, triglycerides, beeswax, cyclodextrin, polysorbates, polyethylene glycol, polyvinylpyrrolidone (PVP) and aliphatic polyesters.

**[0055]** In some aspects, the excipients may feature a drug affinity part. The excipients of the present disclosure may feature a hydrophilic part. As is understood in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as an excipient in some aspects of the present disclosure, the excipient is a compound that includes polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties. The hydrophilic part can accelerate diffusion and increase permeation of the therapeutic agent into tissue. The hydrophilic part of the excipient may facilitate rapid movement of therapeutic agent off the expandable medical device during deployment at the target site by preventing hydrophobic drug molecules from clumping to each other and to the device, increasing drug solubility in interstitial spaces, and/or accelerating drug passage through polar head groups to the lipid bilayer of cell membranes of target tissues.

**[0056]** Exemplary excipients for application in the present disclosure may include chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties. Hydrophilic chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties having a molecular weight less than 5,000 to 10,000 are preferred in certain aspects. In other aspects, molecular weight of the excipient with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide, or ester moieties is preferably less than 1000 to 5,000, or more preferably less than 750 to 1,000, or most preferably less than 750. In these aspects, the molecular weight of the excipient is less than that of the therapeutic agent to be delivered.

**[0057]** In some aspects, the one or more excipients may be selected from amino alcohols, alcohols, amines, acids, amides and hydroxyl acids in both cyclo- and linear- aliphatic and

aromatic groups. Examples include L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, sodium docusate, urea, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sorbitol, glucitol, sugar phosphates, glucopyranose phosphate, sugar sulphates, sugar alcohols, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, xylitol, 2-ethoxyethanol, sugars, galactose, glucose, ribose, mannose, xylose, sucrose, lactose, maltose, arabinose, lyxose, fructose, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine described above, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), and combinations thereof. Some of the chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, amide or ester moieties described herein are very stable under heating, survive an ethylene oxide sterilization process, and/or do not react with the therapeutic agent during sterilization.

**[0058]** In some aspects, the one or more excipients may be selected from amino acids and salts thereof. For example, the excipient may be one or more of alanine, arginine, asparagines, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, histidine, proline, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine, and derivatives thereof are. Certain amino acids, in their zwitterionic form and/or in a salt form with a monovalent or multivalent ion, have polar groups, relatively high octanol-water partition coefficients, and are useful in some facets of the present disclosure. In the context of the present disclosure “low-solubility amino acid” refers to amino acid having a solubility in unbuffered water of less than about 4% (40 mg/ml). These include cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine.

**[0059]** Amino acid dimers, sugar-conjugates, and other derivatives may also be considered for excipients. Through simple reactions well known in the art hydrophilic molecules may be joined to hydrophobic amino acids, or hydrophobic molecules to hydrophilic amino acids,

to make additional excipients useful in aspects of the present disclosure. Catecholamines, such as dopamine, levodopa, carbidopa, and DOPA, are also useful as excipients.

**[0060]** In some aspects, the excipient may be of a material that is at a glass transition temperature at 37 °C or higher. As identified herein, providing a material on the medical device that transitions to a sticky or tacky state *in situ* within the vessel of the subject allows for adhering the coating to the vessel wall. Such materials may include hydrogenated coconut oil, coconut oil, mineral oil, cetyl alcohol, petrolatum, petroleum jelly, decanol, soft paraffin, tridecanol, dodecanol, long chain saturated fatty acids, long chain unsaturated fatty acids, fatty acid esters, fatty acid ethers, witepsol, solid lipids, methyl stearate, triglycerides, glyceryl monostearate, glyceryl palmitostearate, stearic acid, palmitic acid, decanoic acid, behenic acid, beeswax, carnauba wax, paraffin, fatty acid triglycerides, fatty acid alcohols or combinations thereof.

**[0061]** In some aspects, the excipients may be liquid additives. One or more liquid excipients may be can be used in the medical device coating to improve the integrity of the coating. Without being bound by theory, a liquid excipient can improve the compatibility of the therapeutic agent in the coating mixture. The liquid excipients used in aspects of the present disclosure is not a solvent. The solvents such as ethanol, methanol, dimethylsulfoxide, and acetone, will be evaporated after the coating is dried. In other words, the solvent will not stay in the coating after the coating is dried. In contrast, the liquid excipients in aspects of the present disclosure will stay in the coating after the coating is dried. The liquid excipient is liquid or semi-liquid at room temperature and one atmosphere pressure. The liquid excipient may form a gel at room temperature. In some aspects, the liquid excipient may be a non-ionic surfactant. Examples of liquid excipients include PEG-fatty acids and esters, PEG-oil transesterification products, polyglyceryl fatty acids and esters, Propylene glycol fatty acid esters, PEG sorbitan fatty acid esters, and PEG alkyl ethers as mentioned above. Some examples of a liquid excipient are Tween 80, Tween 81, Tween 20, Tween 40, Tween 60, Solutol HS 15, Cremophor RH40, and Cremophor EL&ELP.

**[0062]** In some aspects, the excipient may be a surfactant; a chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, amides or ester moieties; or both. Exemplary surfactants may be chosen from PEG fatty esters, PEG omega-3 fatty esters and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty

esters, PEG sugar esters, Tween 20, Tween 40, Tween 60, p-isononylphenoxypolyglycidol, PEG laurate, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, polyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, polyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate , PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, Tween 20, Tween 40, Tween 60, Tween 80, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside and their derivatives. In some aspects, the excipients may include one of sodium docusate sorbitol, urea, BHT, BHA, PEG-sorbitan monolaureate, petrolatum, methyl stearate or a combination thereof.

**[0063]** In some aspects, one or more of a surfactant or a small water-soluble molecule (the chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, amides or ester moieties) with the therapeutic agent are in certain cases superior to only utilizing the therapeutic agent and a single excipient. By incorporating the one or more additional excipients, the drug coating may have increased stability during transit and rapid drug release when pressed against tissues of the lumen wall at the target site of therapeutic intervention when compared to some formulations comprising the therapeutic agent and only one excipient. Furthermore, the miscibility and compatibility of the therapeutic agent with the excipient or the drug coating with the medical device, generally, is improved by the presence of the one or more additional excipients. For example, a surfactant may allow for improved coating uniformity and integrity.

**[0064]** In some aspects, the coating layer(s) may include multiple excipients, and one excipient is more hydrophilic than one or more of the other excipients. In another embodiment, the coating layer multiple excipients, and one excipient has a different structure from that of one or more of the other excipients. In yet another aspect, the coating layer includes multiple excipients. Some aspects of the present disclosure may include a mixture of at least two additional

excipients, for example, a combination of one or more surfactants and one or more chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, amides or ester moieties. For example, therapeutic agents may bind to extremely water-soluble small molecules more poorly than surfactants, which can lead to suboptimal coating uniformity and integrity. Some surfactants may adhere so strongly to the therapeutic agents and the surface of the medical device that the therapeutic agent is not able to rapidly release from the surface of the medical device at the target site. On the other hand, some water-soluble small molecules (with one or more hydroxyl, amine, carbonyl, carboxyl, amides or ester moieties) adhere so poorly to the medical device that they release therapeutic agents before it reaches the target site, for example, into serum during the transit of a coated balloon catheter to the site targeted for intervention. By incorporating a mixture of multiple excipients, the coating layer may have improved properties over a formulation with only one excipient or no excipient.

**[0065]** In some aspects, the one or more additional excipients may include an antioxidant. An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation reactions can produce free radicals and/or peroxides, which start chain reactions and may cause degradation of therapeutic agents. Antioxidants terminate these chain reactions by removing free radicals and inhibiting oxidation of the active agent by being oxidized themselves. Antioxidants are used as the one or more additional excipients in certain aspects to prevent or slow the oxidation of the therapeutic agents in the coatings for medical devices. Antioxidants are a type of free radical scavengers. The antioxidant may be used alone or in combination with other additional excipients in certain aspects and may prevent degradation of the active therapeutic agent during sterilization or storage prior to use. Some representative examples of antioxidants that may be used in the drug coatings of the present disclosure include, without limitation, oligomeric or polymeric proanthocyanidins, polyphenols, polyphosphates, polyazomethine, high sulfate agar oligomers, chitooligosaccharides obtained by partial chitosan hydrolysis, polyfunctional oligomeric thioethers with sterically hindered phenols, hindered amines such as, without limitation, p-phenylene diamine, trimethyl dihydroquinolones, and alkylated diphenyl amines, substituted phenolic compounds with one or more bulky functional groups (hindered phenols) such as tertiary butyl, arylamines, phosphites, hydroxylamines, and benzofuranones. Also, aromatic amines such as p-phenylenediamine, diphenylamine, and N,N' disubstituted p-phenylene diamines may be utilized as free radical scavengers. Other examples include, without

limitation, butylated hydroxytoluene ("BHT"), butylated hydroxyanisole ("BHA"), L-ascorbate (Vitamin C), Vitamin E, herbal rosemary, sage extracts, glutathione, resveratrol, ethoxyquin, rosmanol, isorosmanol, rosmaridiphenol, propyl gallate, gallic acid, caffeic acid, p-coumeric acid, p-hydroxy benzoic acid, astaxanthin, ferulic acid, dehydrozingerone, chlorogenic acid, ellagic acid, propyl paraben, sinapic acid, daidzin, glycitin, genistin, daidzein, glycitein, genistein, isoflavones, and tertbutylhydroquinone. Examples of some phosphites include di(stearyl)pentaerythritol diphosphite, tris(2,4-di-tert.butyl phenyl)phosphite, dilauryl thiodipropionate and bis(2,4-di-tert.butyl phenyl)pentaerythritol diphosphite. Some examples, without limitation, of hindered phenols include octadecyl-3,5,di-tert.butyl-4-hydroxy cinnamate, tetrakis-methylene-3-(3',5'-di-tert.butyl-4-hydroxyphenyl)propionate methane 2,5-di-tert-butylhydroquinone, ionol, pyrogallol, retinol, and octadecyl-3-(3,5-di-tert.butyl-4-hydroxyphenyl)propionate. An antioxidant may include glutathione, lipoic acid, melatonin, tocopherols, tocotrienols, thiols, Beta- carotene, retinoic acid, cryptoxanthin, 2,6-di-tert-butylphenol, propyl gallate, catechin, catechin gallate, and quercetin. Preferable antioxidants are butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).

**[0066]** While particular aspects have been illustrated and described herein, it should be understood that various other changes and modifications may be made without departing from the spirit and scope of the claimed subject matter. Moreover, although various aspects of the claimed subject matter have been described herein, such aspects need not be utilized in combination. It is therefore intended that the appended claims cover all such changes and modifications that are within the scope of the claimed subject matter.

**[0067]** It is appreciated that all reagents are obtainable by sources known in the art unless otherwise specified.

**[0068]** It is also to be understood that this disclosure is not limited to the specific aspects and methods described herein, as specific components and/or conditions may, of course, vary. Furthermore, the terminology used herein is used only for the purpose of describing particular aspects of the present disclosure and is not intended to be limiting in any way. It will be also understood that, although the terms “first,” “second,” “third” etc. may be used herein to describe various elements, components, regions, layers, and/or sections, these elements, components, regions, layers, and/or sections should not be limited by these terms. These terms are only used to

distinguish one element, component, region, layer, or section from another element, component, region, layer, or section. Thus, "a first element," "component," "region," "layer," or "section" discussed below could be termed a second (or other) element, component, region, layer, or section without departing from the teachings herein. Similarly, as used herein, the singular forms "a," "an," and "the" are intended to include the plural forms, including "at least one," unless the content clearly indicates otherwise. "Or" means "and/or." As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. It will be further understood that the terms "comprises" and/or "comprising," or "includes" and/or "including" when used in this specification, specify the presence of stated features, regions, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, regions, integers, steps, operations, elements, components, and/or groups thereof. The term "or a combination thereof" means a combination including at least one of the foregoing elements.

**[0069]** Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. It will be further understood that terms such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the relevant art and the present disclosure, and will not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

**[0070]** Reference is made in detail to exemplary compositions, aspects and methods of the present disclosure, which constitute the best modes of practicing the disclosure presently known to the inventors. The Figures are not necessarily to scale. However, it is to be understood that the disclosed aspects are merely exemplary of the disclosure that may be embodied in various and alternative forms. Therefore, specific details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for any aspect of the disclosure and/or as a representative basis for teaching one skilled in the art to variously employ the present disclosure.

**[0071]** Patents, publications, and applications mentioned in the specification are indicative of the levels of those skilled in the art to which the disclosure pertains. These patents, publications, and applications are incorporated herein by reference to the same extent as if each individual

patent, publication, or application was specifically and individually incorporated herein by reference.

**[0072]** The foregoing description is illustrative of particular embodiments of the disclosure, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the disclosure.

## CLAIMS

1. A balloon catheter for delivering a therapeutic agent to a blood vessel, the balloon catheter comprising:

an elongate member having a lumen and a distal end;

an expandable balloon attached to the distal end of the elongate member and in fluid communication with the lumen;

a coating layer overlying an exterior surface of the expandable balloon, the coating layer comprising a therapeutic agent or a polymer microparticle containing the therapeutic agent and an excipient; and

a protective layer overlying the coating layer, the protective layer comprising a hydrophilic polymer.

2. The balloon catheter of claim 1, wherein the hydrophilic polymer is selected from polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), polyacrylic acid (PAA), N-(2-hydroxypropyl) methacrylamide (HPMA), divinyl ether-maleic anhydride (DIVEMA), polyoxazoline, polyphosphate, polyphosphazene, xanthan gum, pectin, chitosan derivatives, dextran, carrageenan, guar gum, cellulose ethers, sodium CMC, HPC, HPMC, hyaluronic acid (HA), albumin, starch, or a combination thereof.

3. The balloon catheter of claim 1, wherein the hydrophilic polymer is PVA.

4. The balloon catheter of claim 1, wherein the hydrophilic polymer is HA.

5. The balloon catheter of claim 4, wherein the hydrophilic polymer has a molecular weight (MW) of from about 20 kDa to about 500 kDa.

6. The balloon catheter of claim 2, 3, or 4, wherein the hydrophilic polymer has a molecular weight (MW) of from 20 kDa to about 200 kDa.

7. The balloon catheter of claim 2, 3, or 4, wherein the protective layer has a thickness of of from about 2 μm to about 100 μm.

8. The balloon catheter of claim 2, 3, or 4, wherein the protective layer further includes an additive.

9. The balloon catheter of claim 8, wherein the additive is a second excipient.

10. The balloon catheter of claim 8, wherein the additive is kaolin.

11. The balloon catheter of claim 2, 3, or 4, wherein the excipient comprises a biodegradable polymer chosen from a fatty acid, a fatty acid ester, polylactic acid (PLLA,PDLA,PDLLA), polycaprolactone (PCL), sodium docusate, PLGA, PLGA-b-mPEG, polyglutamic acid, polyacrilic acid, hyaluronic acid, alginate, PVA, PVP, Pluronic (PEO-PPO-PEO),cellulose, CMC, HPC, starch, chitosan, human serum albumin (HSA), phospholipids, fatty acid, fatty acid esters, triglycerides, beeswax, cyclodextrin, Tween 20, Tween 80, TPGS, SLS, butylated hydroxytoluene, vitamin E, vitamin E succinate, tannic acid, polyethylene glycol, N-isopropylacrylamide, and sorbitol esters.

12. The balloon catheter of claim 2, 3, or 4, wherein the coating layer further comprises a hydrophobic material containing the therapeutic agent embedded therein.

13. The balloon catheter of claim 12, wherein the hydrophobic material comprises a hydrophobic material with a glass transition temperature of 37 °C or lower.

14. The balloon catheter of claim 12, wherein the hydrophobic material is semi-synthetic glycerides, methyl stearate, hydrogenated coconut oil, coconut oil, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, hard fats, petroleum jelly/petrolatum, a PEG-fatty acid ester, or a combination thereof.

15. The balloon catheter of claim 14, wherein the hydrophobic material is hydrogenated coconut oil, coconut oil, mineral oil, cetyl alcohol, petroleum jelly, decanol, tridecanol, dodecanol, long chain saturated fatty acids, long chain unsaturated fatty acid, fatty acid esters, fatty acid ethers, witepsol, solid lipids, methyl stearate, triglycerides, glyceryl monostearate, glyceryl

palmitostearate, stearic acid, palmitic acid, decanoic acid, behenic acid, beeswax, carnauba wax, paraffin, a fatty acid triglycerides, a fatty acid alcohol, or a combination thereof.

16. The balloon catheter of claim 2, 3, or 4, wherein the polymer microparticle comprises poly(lactic-co-glycolic) acid (PLGA) and the therapeutic agent loaded therein.

17. The balloon catheter of claim 16, wherein the therapeutic agent is loaded in the polymer microparticle at 30-50 % weight of the polymer microparticle.

18. The balloon catheter of claim 17, wherein the polymer microparticles are of a first size grouping and a second size grouping, wherein the first size grouping has an average size of 10 μm and further wherein the second size grouping has an average size different from the first size grouping.

19. The balloon catheter of claim 18, wherein the second size grouping has an average size of 30 μm, 35 μm, or 40 μm.

20. The balloon catheter of claim 2, 3, or 4, wherein the therapeutic agent is crystalline particles.

21. The balloon catheter of claim 20, wherein the average size of the crystalline particles is of 0.1 μm to 100 μm.

22. The balloon catheter of claim 2, 3, or 4, wherein the coating layer further comprises a hydrophilic material chosen from poly(ethylene glycol), polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polyacrylamides, N-(2-Hydroxypropyl) methacrylamide (HPMA), divinyl ether-maleic anhydride (DIVEMA), polyoxazoline, xanthan gum, pectins, chitosan derivatives, dextran, casein sodium, cellulose ethers, sodium carboxy methyl cellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hyaluronic acid (HA), albumin, or a combination thereof.

23. A method for treating a blood vessel in a subject comprising introducing the balloon catheter of claim 1 into the blood vessel of the subject; maneuvering the balloon catheter to a atherosclerotic plaque in the blood vessel; and, expanding the expandable balloon, wherein the protective coating dissolves prior to expanding the expandable balloon.

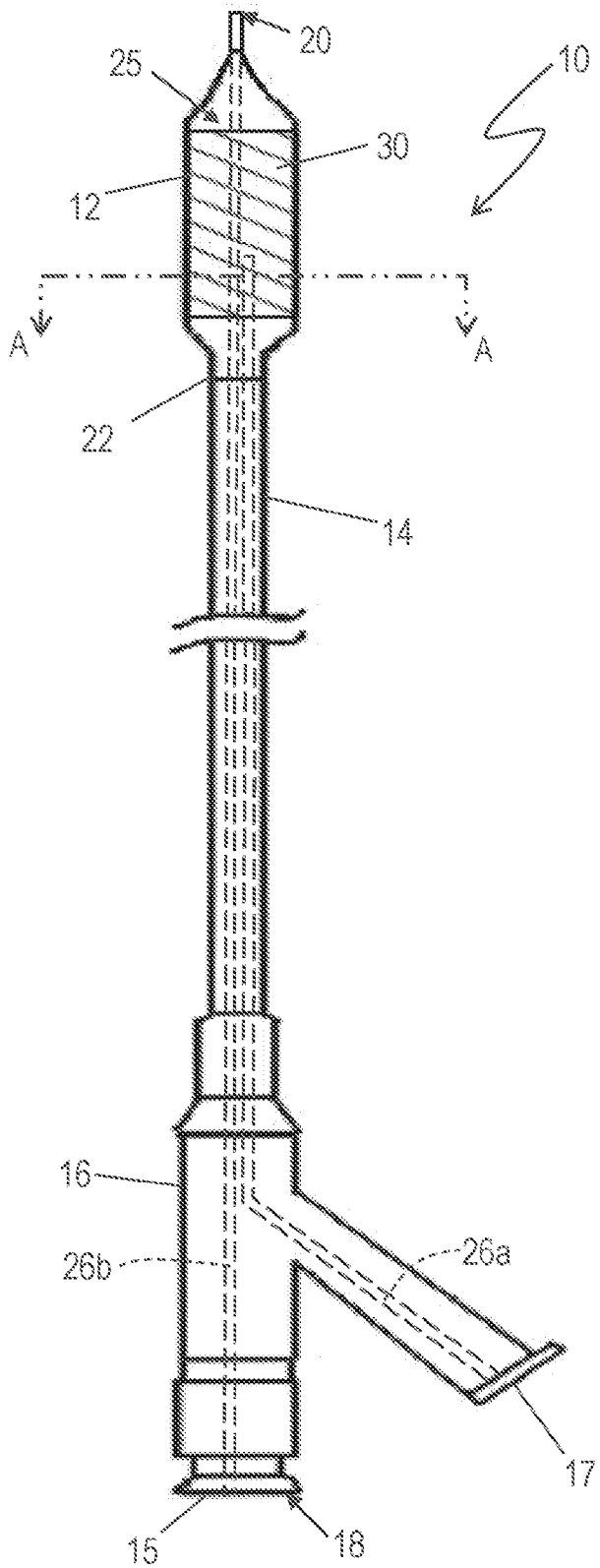


FIG. 1

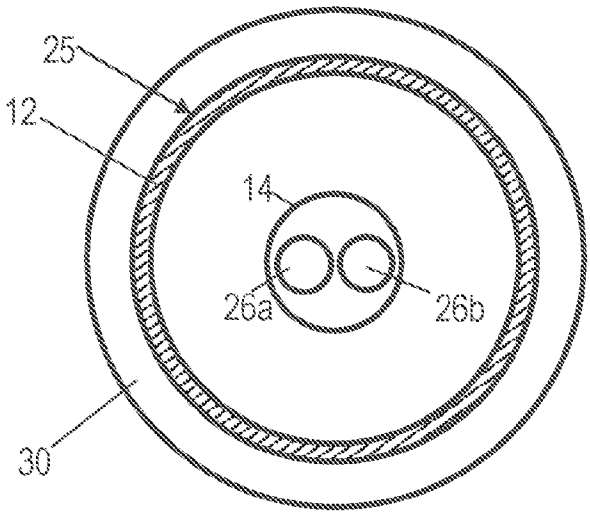


FIG. 2A

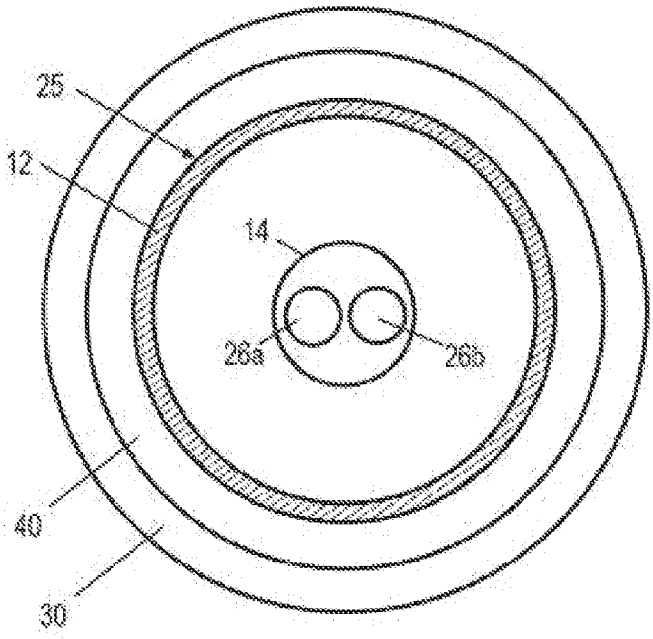


FIG. 2B

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/025699

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L29/08 A61L29/16
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 12 December 2023 | 20/12/2023 |

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

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International application No
PCT/US2023/025699

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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