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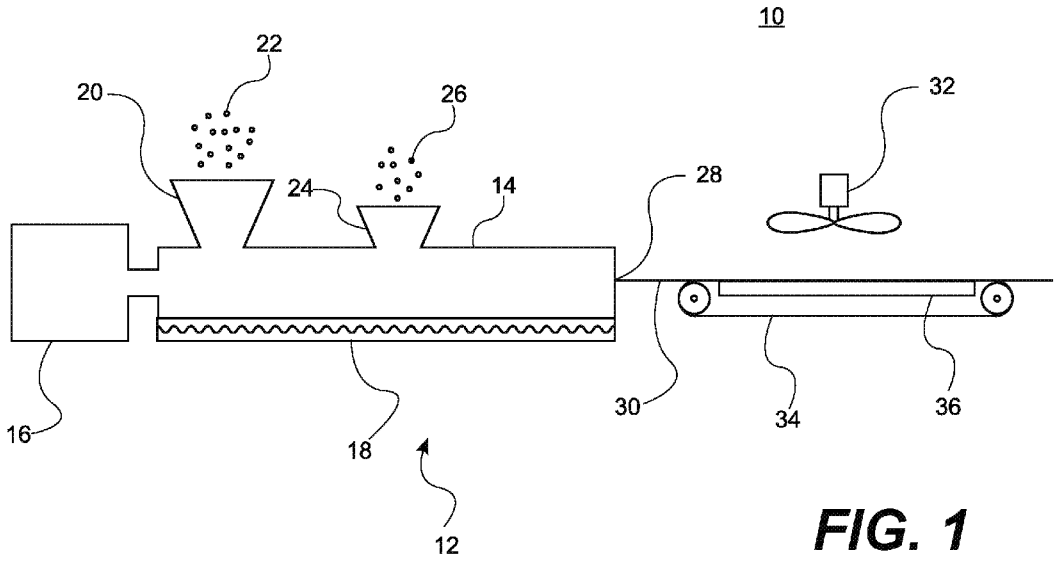

FIG. 1

(57) Abstract: The present disclosure relates to articles of manufacture having an active pharmaceutical ingredient (API) integrated in a thermoplastic polymer, as well as methods of using and making such articles. For example, using the articles in medical devices and treating patients.

[Continued on next page]

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COMPOUNDED ACTIVE PHARMACEUTICAL AGENTS IN THERMOPLASTIC POLYMER COMPOSITIONS AND METHODS OF MANUFACTURE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Ser. No. 63/511,102, filed June 29, 2023, the entire contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention generally relates to compounded compositions for medical devices having antimicrobial, antithrombogenic, and/or anti-inflammatory properties.

BACKGROUND OF THE INVENTION

[0003] Medical devices are commonly used to facilitate care and treatment of patients undergoing surgical procedures. Examples of such devices include catheters, grafts, stents, sutures, and the like. Unfortunately, organisms such as bacteria and fungi may infiltrate and/or form biofilms on these medical devices which may be difficult to treat. Such contamination may lead to infections and cause discomfort or illness. In addition to infections, indwelling catheters can result in the problem of pathological blood clot formation, and/or catheter-induced vein thrombosis. About half of hemodialysis catheters fail within a year, and up to two thirds of the failures are due to thrombosis.

[0004] The use of medical devices having antimicrobial and antithrombogenic properties may reduce the incidence of infection and thrombosis in the patient. Typically, the antimicrobial and/or antithrombogenic agent is applied as a coating on the conventional medical device or the antimicrobial agent is infused into the conventional medical device by soaking the device in a solution of the antimicrobial and antithrombogenic agent. In these and other

conventional methods of incorporating the antimicrobial and antithrombogenic agent to the medical device, this extra step of coating or soaking takes time and increases costs.

[0005] In addition to the added step and increased production time, soaking and coating may not achieve relatively high concentrations of antibiotic in the base material of the medical device. For relatively short procedures having a duration of a few hours, this relatively low antibiotic concentration may be sufficient. However, for longer procedures lasting several days, the antibiotic present in conventional devices may be insufficient. As such, these conventional devices must be replaced frequently as the antibiotic falls below effective levels.

[0006] Accordingly, it is desirable to provide an antimicrobial and antithrombogenic medical device and/or method of incorporating an antimicrobial and antithrombogenic agent to a medical device that is capable of overcoming the disadvantages described herein at least to some extent.

SUMMARY OF THE INVENTION

[0007] Embodiments of the disclosure include an active pharmaceutical ingredient (API) compounded into a polymer. The API compounded into the polymer can be used in a medical device. Methods of compounding the polymer and API are provided, as well as, methods of use.

[0008] Some embodiments are directed to an article of manufacture, having an API integrated in a thermoplastic polymer, wherein: the thermoplastic polymer has a water absorption capacity of about >1 to 90 % w/w of the article, preferably about 10 to 70 % w/w of the article, or most preferably about 15 to 30% w/w of the article, and/or the article further comprises a hydrophilic polymer blended with the thermoplastic polymer.

[0009] Some embodiments are directed to an implantable medical device having an API integrated in a thermoplastic polymer.

[0010] Embodiments of the disclosure include methods of removing or adding fluids to a patient, by implanting the medical device of having an API integrated in a thermoplastic polymer into a cavity or vein or artery of patient, wherein the medical device is a catheter; and removing or adding at least one fluid to the patient through the medical device.

[0011] There has thus been outlined, rather broadly, certain embodiments of the invention in order that the detailed description thereof herein may be better understood, and in order that the present contribution to the art may be better appreciated. There are, of course, additional embodiments of the invention that will be described below and which will form the subject matter of the claims appended hereto.

[0012] In this respect, before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and to the arrangements of the components set forth in the following description or illustrated in the drawings. The invention is capable of embodiments in addition to those described and of being practiced and carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein, as well as the abstract, are for the purpose of description and should not be regarded as limiting.

[0013] As such, those skilled in the art will appreciate that the conception upon which this disclosure is based may readily be utilized as a basis for the designing of other structures, methods and systems for carrying out the several purposes of the present invention. It is important, therefore, that the claims be regarded as including such equivalent constructions insofar as they do not depart from the spirit and scope of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 is a diagram of a system for compounding a thermo-polymer with an API.

[0015] FIG. 2 is a chart of API content per resin configuration.

[0016] FIG. 3 is a chart of API elution over time.

[0017] FIG. 4 is a chart of API content per resin configuration.

[0018] FIG. 5 is a chart of API content over time.

[0019] FIG. 6 is a chart of API content over time.

[0020] FIG. 7 is a chart of API content over time.

[0021] FIG. 8 is a high performance liquid chromatograph showing an analysis at a wavelength of 280 nm of a chlorhexidine diacetate (CHA) heated to a temperature of 210°C for 10 minutes.

[0022] FIG. 9 is a high performance liquid chromatograph showing an analysis at a wavelength of 280 nm of unheated CHA.

[0023] FIG. 10 is a high performance liquid chromatograph showing an analysis at a wavelength of 280 nm of a chlorhexidine dihydrochloride (CHD) heated to a temperature of 210°C for 10 minutes.

[0024] FIG. 11 is a high performance liquid chromatograph showing an analysis at a wavelength of 280 nm of unheated CHD.

[0025] FIG. 12 is a simplified view of an extruder and air-cooling device according to an embodiment of the invention.

[0026] FIG. 13 is a plot of actual API percentages is different polymer formulations after compounding and water cooling.

[0027] FIG. 14 is a plot of API percentages after compounding and air-cooling.

[0028] FIG. 15 is a plot of API percentages after compounding and air-cooling.

[0029] FIG. 16A is a chart of API content over time.

[0030] FIG. 16B is a chart of API content over time.

[0031] FIG. 17 is a chart of API content over time.

[0032] FIG. 18 is a chart of API content over time.

[0033] FIG. 19 is a chart showing antimicrobial performance.

DETAILED DESCRIPTION

[0034] Embodiments of the disclosure include a polymer compounded with an API for a medical device, and a method of compounding the polymer and API is provided, as well as, methods of use.

[0035] Embodiments of the disclosure provide a system and device for compounding an API into a polymer. Examples of APIs include active antimicrobial agents, antithrombogenic agents, anti-inflammatory agents, and the like. Particular examples of suitable antimicrobial agents include biguanides such as chlorhexidine and Alexidine. Examples of suitable polymers include thermoplastic polymers having a melt temperature of 160°C-280°C.

[0036] When compounding an API in an extruder, such as a twin or multi screw extruder, the thermoplastic polymer is heated to the melt temperature of the polymer. Once melted, the polymer remains in the melted state until the temperature falls to the solidification temperature. Depending on the polymer, there may be several degrees Celsius separating these states. As described herein, the API is incorporated downstream from the polymer inlet. It is an advantage that this action incorporates the API to the melted polymer at a portion of the screw extruder that is not actively heating the polymer to the melt temperature and may be cooler than the upstream portion of the extruder. In addition, by subjecting the API to the elevated temperature of the melted polymer for a shorter duration, the API may experience less thermal degradation.

[0037] The compounded polymer and API is quickly cooled after thorough mixing and extrusion. However, it has surprisingly been found that some methods of cooling in water can cause a significant loss of API from the compounded polymer. For the purpose of this disclosure, a significant loss of API is a loss of API that is 15% or greater. In some embodiments, the loss can be greater than 10% or greater than 5%. In addition to the added cost of the lost API, increasing the initial amount of API added to the polymer may have adverse effects such as clouding, crystallization of the API, and the like. For example, if water is used for cooling,

the exposure time has to be minimized to prevent significant loss of API. Alternatively, it has been advantageously found that the use of a sufficient amount of air-cooling has the same cooling performance while retaining the API in the compounded polymer.

[0038] FIG. 1 is a diagram of a system 10 for compounding a thermo-polymer with API. As shown in FIG. 1, the system 10 includes an extruder 12 with a body 14, a motor 16 to turn internal screws (not shown), and a heater 18. The body 14 includes a first port 20 for incorporating a polymer 22. The body 14 includes a second port 24 for incorporating an API 26. As shown, the API 26 is incorporated downstream from the first port 20 and the heater 18. In some examples, the second port 24 is disposed at least halfway along a length of the body 14.

[0039] The compounding mixture of the polymer 22 and API 26 is urged toward an outlet 28 as it is mixed. Once mixed and extruded through the outlet 28, a compounded mixture 30 is cooled via an air-cooling device 32. In some examples, the air-cooling device 32 includes one or more air rings. In other examples, the air-cooling device 32 includes one or more fans. Optionally, the system 10 may include a conveyer belt 34 to convey the compounded mixture 30 from the outlet 28. A chilled platen 36 may be configured to cool the conveyer belt 34 and, thereby, facilitate cooling of the compounded mixture 30. In various examples, the conveyer belt 34 may include a thermally conductive material such as, for example, stainless steel. The chilled platen 36 may include tubing for a flow of chilled water or refrigerant or the chilled platen 36 may include a piezoelectric chiller to provide cooling.

[0040] In some examples, the compounded mixture 30 is extruded into a medical device, such as medical tubing, a stent, a catheter or the like. In other examples, the compounded mixture 30 is processed into pellets for further processing into a medical device.

[0041] More particularly, the present invention relates to medical device composed of materials that allow the device to impart long term antimicrobial, antithrombogenic and anti-inflammatory effects due to the API releasing from the device for the period the device resides in body for a clinical indication; the said medical device is composed by using a method which

integrates the antimicrobial biguanide agents (chlorhexidine, alexidine, octinedine) and a hydrophilic material such as polyether polyurethane with PEG or a polyether block amide material in to the bulk device polymeric matrix enhancing the release of the antimicrobial agent from the device.

[0042] The polymers are aromatic polyurethanes (Tecothane, Isoplast), and aliphatic polyurethanes (e.g. Tecoflex, Carbothane, Quadrathane), the antimicrobials are chlorhexidine, alexidine, octinedine, and the hydrophilic polymers (e.g. PEBAX - Polyether Block Amide material, Tecophillic - Polyether polyurethane with PEG as its poly-ol). A device consisting of a polymer matrix composed of one of the following combinations allowing controlled release of the API over a long period of time. Some examples of suitable compounded polyurethane API mixtures include: aliphatic polyurethane + antimicrobial and/or antithrombogenic agent + polyether block amide; aromatic polyurethane + antimicrobial agent and/or antithrombogenic + polyether block amide; aliphatic polycarbonate polyurethane + antimicrobial agent and/or antithrombogenic + polyether block amide; aromatic polycarbonate polyurethane + antimicrobial agent and/or antithrombogenic + polyether block amide; and aromatic polycarbonate silicone polyurethane + antimicrobial agent and/or antithrombogenic + polyether block amide

[0043] A suitable medical device for use with the compounded mixture of the present invention may be adapted for contact with a vessel or cavity in the body. Examples of suitable polymers may be aromatic or aliphatic polyurethanes with bulk distributed APIs with a melt temperature above 200°C, the amount of antimicrobial and/or antithrombogenic agent is 0.5-15.0 wt/wt% and a bulk distributed hydrophilic polymer which results in a moisture uptake by the device at 5-35 wt/wt%, which results in both anti-thrombogenic and anti-microbial effects from the device. The antimicrobial agents include biguanide class of antimicrobials with a melt temperature above 200°C, e.g. CHX-DH (Chlorhexidine dihydrochloride) and ALX-DH

(Alexidine dihydrochloride). The antimicrobial agents preferably include biguanide class of antimicrobials which remains stable and do not degrade at temperature below 200°C.

[0044] To control the elution rate of the compounded API, the bulk distributed hydrophilic polymer preferably has at least a moisture uptake of 15-50% resulting in 5-35% moisture uptake from the device. In this manner, the medical device facilitates a release of API at least 1 % of the total loading of the API. In preferred examples, the medical device is constructed using a compounding process that maintains temperature below 200°C.

[0045] As described herein, the compounding process includes chilling agent or process, that excludes water. As described herein, use of water to chill the compounded mixture results in a loss of about 50% of the API from the compounded mixture. In preferred processes, less than 50% of the API is lost from the compounded mixture. In more preferred embodiments, the loss is less than 45%, less than 40%, less than 30%, or less than 25%. In the most preferred embodiments, the API loss is less than about 20%. In specific embodiments, the API is present between 5 and 25% of its theoretical limit, or more preferably 10 to 15%. As such, gas-cooling is the preferred agent or process to cool the extrudate into the medical device or to a temperature that is conducive to cutting into pellets.

[0046] Certain aspects of the disclosure include:

[0047] Aspect 1. A method of integrating an active pharmaceutical ingredient (API) with a thermoplastic polymer, the method comprising:

feeding the thermoplastic polymer and API into a first feed port of a multi-screw extruder;

or feeding the thermoplastic polymer into a first feed port of a multi-screw extruder;

conveying the thermoplastic polymer along the heated multi-screw extruder;

heating the thermoplastic polymer to a melt temperature of 160°C-280°C prior to the thermoplastic polymer being conveyed past a second feed port;

the second feed port is feeding the API into the heated screw extruder to mix with the melted thermoplastic polymer to generate a compounded mixture containing 85-100% of the starting API content;

extruding the compounded mixture from an outlet of the heated screw extruder; and

passing the extruded compounded mixture through an air-cooling device to cool the extruded compounded mixture such that the compounded mixture contains 85-100% of the starting API content.

[0048] Aspect 2. The method according to Aspect 1, wherein the second feed port is disposed at least halfway along a length of the multi-screw extruder.

[0049] Aspect 3. The method according to any of the preceding Aspects, wherein the air-cooling device provides a flow of air at a flow rate of 2-20 meters per second.

[0050] Aspect 4. The method according to any of the preceding Aspects, further including:

conveying the compounded mixture from the outlet with a conveyer belt; and

cooling the compounded mixture by cooling at least one of the conveyer belt and air contacting the compounded mixture with a chilled platen.

[0051] Aspect 5. The method according to any of the preceding Aspects, wherein the cooled compounded mixture is pelletized resulting in pellets containing 85-100% of the starting API content.

[0052] Aspect 6. The method according to any of the preceding Aspects, wherein the API is an antimicrobial, antithrombogenic and/or anti-inflammatory drug which is thermally stable at a temperature range of 200°C-280°C.

[0053] Aspect 7. The method according to any of the preceding Aspects, wherein the API is a salt of a biguanide agent which is thermally stable at a temperature range of 200°C-280°C.

[0054] Aspect 8. The method according to any of the preceding Aspects, wherein the API is a salt of chlorhexidine which is thermally stable at a temperature range of 200°C-280°C.

[0055] Aspect 9. The method according to any of the preceding Aspects, wherein the API is a salt of alexidine which is thermally stable at a temperature range of 200°C-280°C.

[0056] Aspect 10. The method according to any of the preceding Aspects, wherein the thermoplastic polymer includes a thermoplastic polyurethane polymer.

[0057] Aspect 11. The method according to any of the preceding Aspects, wherein the thermoplastic polymer includes a hydrophilic polyurethane polymer with 5-40% water uptake.

[0058] Aspect 12. A medical device comprising:

a compounded thermoplastic polymer with a bulk distribution of an API in accordance with any of the preceding Aspects.

[0059] Aspect 13. The medical device according to any of the preceding Aspects, further comprising a second thermoplastic polymer without API, wherein the compounded thermoplastic polymer with bulk distributed API is co-extruded with the second polymer without the API.

[0060] Aspect 14. The medical device according to any of the preceding Aspects, wherein the compounded polymer with bulk distributed API is extruded on an inside portion of the medical device and the second polymer without API is extruded on an outside portion of the medical device.

[0061] Aspect 15. The medical device according to any of the preceding Aspects, wherein the compounded polymer with bulk distributed API is extruded along a first longitudinal portion of the thermoplastic medical device and the second thermoplastic polymer without API is extruded along a second longitudinal portion of the medical device, the second thermoplastic polymer without API being configured to be transparent to provide a viewing port for a user to see within the medical device.

[0062] Aspect 16. The medical device according to any of the preceding Aspects, wherein the compounded thermoplastic polymer with bulk distributed API is extruded along a first axial portion of the medical device and the second thermoplastic polymer without API is extruded along a second axial portion of the medical device, the second thermoplastic polymer without API being configured to be transparent to provide a viewing port for a user to see within the medical device.

[0063] Aspect 17. A medical device comprising:

a thermoplastic polymer integrated with an active pharmaceutical ingredient (API), wherein a method of integrating the API with the thermoplastic polymer comprises:

feeding the thermoplastic polymer and API into a first feed port of a twin-screw extruder;

or feeding the thermoplastic polymer into a first feed port of a twin-screw extruder, conveying the thermoplastic polymer along the heated multi-screw extruder, heating the thermoplastic polymer to a melt temperature of 160°C-280°C prior to the thermoplastic polymer being conveyed past a second feed port;

the second feed port is feeding the API into the heated multi-screw extruder to mix with the melted thermoplastic polymer to generate a compounded mixture containing 85-100% of the starting API content;

extruding the compounded mixture from an outlet of the heated screw extruder; and

passing the extruded compounded mixture through an air-cooling device to cool the extruded compounded mixture such that the compounded mixture contains 85-100% of the starting API content.

[0064] Aspect 18.The medical device according to any of the preceding Aspects, wherein the second feed port is disposed at least halfway along a length of the multi-screw extruder.

[0065] Aspect 19.The medical device according to any of the preceding Aspects, wherein the air-cooling device provides a flow of air at a flow rate of 2-20 meters per second.

[0066] Aspect 20.The medical device according to any of the preceding Aspects, further including:

a conveyer belt configured to convey the compounded mixture from the outlet; and

a chilled platen configured to facilitate cooling the compounded mixture by cooling at least one of the conveyer belt and air contacting the compounded mixture.

[0067] Aspect 21. The medical device according to any of the preceding Aspects, wherein the cooled compounded mixture is pelletized resulting in pellets containing 85-100% of the starting API content.

[0068] Aspect 22. The medical device according to any of the preceding Aspects, wherein the API is an antimicrobial, antithrombogenic and/or anti-inflammatory drug which is thermally stable at a temperature range of 200°C-280°C.

[0069] Aspect 23. The medical device according to any of the preceding Aspects, wherein the API is a salt of a biguanide agent which is thermally stable at a temperature range of 200°C-280°C.

[0070] Aspect 24. The medical device according to any of the preceding Aspects, wherein the API is a salt of chlorhexidine which is thermally stable at a temperature range of 200°C-280°C.

[0071] Aspect 25. The medical device according to claim 23, wherein the API is a salt of alexidine which is thermally stable at a temperature range of 200°C-280°C.

[0072] Aspect 26. The medical device according to any of the preceding Aspects, wherein the thermoplastic polymer includes a thermoplastic polyurethane polymer.

[0073] Aspect 27. The medical device according to any of the preceding Aspects, wherein the thermoplastic polymer includes a hydrophilic polyurethane polymer with 5-40% water uptake.

[0074] Aspect 28. The medical device according to any of the preceding Aspects, further comprising a second thermoplastic polymer.

[0075] Aspect 29. The medical device according to any of the preceding Aspects, further comprising a second thermoplastic polymer without API, wherein the compounded thermoplastic polymer with a bulk distributed API is co-extruded with the second polymer without API.

[0076] Aspect 30. The medical device according to any of the preceding Aspects, wherein the compounded thermoplastic polymer with bulk distributed API is extruded on an inside portion of the medical device and the second thermoplastic polymer without API is extruded on an outside portion of the medical device.

[0077] Aspect 31. The medical device according to any of the preceding Aspects, wherein the compounded thermoplastic polymer with bulk distributed API is extruded along a first longitudinal portion of the medical device and the second thermoplastic polymer without API is extruded along a second longitudinal portion of the medical device, the second thermoplastic polymer without API being configured to be transparent to provide a viewing port for a user to see within the medical device.

[0078] Aspect 32. The medical device according to any of the preceding Aspects, wherein the compounded polymer with bulk distributed API is extruded along a first axial portion of the medical device and the second polymer without API is extruded along a second axial portion of the medical device, the second polymer without API being configured to be transparent to provide a viewing port for a user to see within the medical device.

[0079] Aspect 33. The medical device according to any of the preceding Aspects, wherein the medical device is a catheter.

[0080] Aspect 34. The catheter according to Aspect 33, wherein the catheter is inserted in a body cavity to provide access for therapy, nutrition, drainage of fluids, blood gas monitoring, blood draw and other interventional medical procedures.

[0081] Specific embodiments of the disclosure relate articles of manufacture including, *e.g.*, polymer pellets which can be used to produce medical devices. The articles of manufacture include a thermoplastic polymer integrated with an active pharmaceutical ingredient (API). In certain embodiments, the thermoplastic polymer has a water absorption capacity of about 1 to 90 % w/w of the article, preferably about 10 to 70 % w/w of the article, or most preferably about 15 to 30% w/w of the article. For example, the water absorption capacity can be about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30%, or any range created by such numbers, for example 15 to 20%, 20 to 25%, or 25 to 30%.

[0082] The water absorption capacity of the thermoplastic polymer can be controlled by incorporating water absorptive groups into the thermoplastic polymer, for example, as covalently linked groups onto the thermoplastic polymer or as random monomers, oligomers, block portions, etc. incorporated into the polymer itself.

[0083] Thermoplastic polymer can be selected from PVC, aromatic polyether polyurethane, aliphatic polyether polyurethane, aromatic polycarbonate polyurethane, aliphatic polycarbonate polyurethane, rigid polyurethane, aromatic polycarbonate silicone polyurethane, aromatic polyether silicone polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, thermoplastic elastomer, polyether block amide, preferably aromatic polyether polyurethane, aliphatic polyether polyurethane, aromatic polycarbonate polyurethane, aliphatic polycarbonate polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, thermoplastic elastomer, polyether block amide, or most preferably aromatic polyether polyurethane, aliphatic polyether polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane.

[0084] In certain embodiments, the article has a hydrophilic polymer blended with the thermoplastic polymer. The hydrophilic polymer can increase water absorption of the article and facilitate elution of the API.

[0085] In general, hydrophilic polymers are known in the art and include polymers which dissolve in, or are swollen by, water. Hydrophilic polymer can be acrylics, epoxies, polyethylene, polystyrene, polyvinylchloride, polytetrafluorethylene, polydimethylsiloxane, polyesters, and polyurethanes. In particular, the hydrophilic polymer can be selected from aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, and polyether block amide hydrophilic polyurethane; or most preferably aliphatic polyether hydrophilic polyurethane and aromatic polyether hydrophilic polyurethane. The hydrophilic polymers can be added such that the article has a water absorption capacity of about 1 to 90 % w/w, preferably about 10 to 70 % w/w, or most preferably about 15 to 30% w/w. For example, the water absorption capacity of the article can be about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30%, or any range created by such numbers, for example 15-20%, 20-25%, 25-30%, etc.

[0086] As discussed above, the hydrophilic polymer preferably has at least a water uptake of 15-50%. For example, the hydrophilic polymer can have a water uptake of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, or any range created by such numbers, for example, 15-20%, 20-25%, 25-30%, 30-35%, 35-40% 40-45%, 45-50%, 20-40%, 25-50%, 30-45%, etc. In some embodiments, the hydrophilic polymer has a water uptake of at least 25%, at least 40%, at least 50%, at 60%, or at least 75%.

[0087] In some embodiments, the article of manufacture can be a thermoplastic polymer integrated with an API, wherein the API is present in an amount of about 100 to 5000 μg/cm of the article; preferably about 150 to 3500 μg/cm of the article; most preferably about 200 to 2000 μg/cm of the article.

[0088] Depending on the embodiment, the API is homogenously distributed throughout at least a portion of the bulk of the thermoplastic polymer; and/or the API distributed as a gradient with the API concentrated on an outer most and an inner most layers of the article. A gradient can be formed using, *e.g.*, a three-layered extrusion to make the article. In such embodiments, no API and hydrophilic components would be included in the middle layer. For example, the article would include a first layer having an API, and optionally a hydrophilic polymer, a second layer in contact and parallel to the first layer, the second layer not having the API, and a third layer in contact with the second layer and parallel to the first and the second layer, the third layer containing having an API, and optionally a hydrophilic polymer. Stated differently, the middle layer can be sandwiched between layers of polymer with the compounded API and hydrophilic polymer to provide antimicrobial properties at the surface yet maintaining mechanical strength which may be compromised due to excessive water absorption. In specific embodiments, the second, or middle layer, can comprise multiple layers.

[0089] In some embodiments, the API can be defined by its heat stability. As used herein, heat stability means that less than 25%, preferably less than 20%, less than 15%, less than 10%, or less than 5% of the API degrades after 10 minutes at 210°C. In the most preferred embodiments, non of the API degrades after 10 minutes at 210°C. Some APIs which can be used herein, can be defined by their melting. In preferred embodiments, the API has a higher melting point than the thermoplastic polymer or thermoplastic polymer blend. In specific embodiments, the API has melting point that is at least 10°C higher than the thermoplastic or thermoplastic polymer blend; more preferably at least 15°C higher; at least 20°C higher, or at least 25°C higher. In specific embodiments, the API has a melting point above 200°C.

[0090] In the articles of manufacture, the thermoplastic polymer can be about 5 to 95 % w/w of the article, preferably about 10 to 70 % w/w of the article. For example, the thermoplastic polymer can be present at 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52,

53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% w/w, or any range created by such numbers, for example, 10-15%, 15-20%, 20-25%, 25-30%, 30-35%, 35-40%, 40-45%, 45-50%, 50-55%, 55-60%, 60-65%, 65-70%, 10-30%, 30-60%, 60-70%, 40-65%, 35-65%, etc.

[0091] The API can be about 1 to 30 % w/w of the article, preferably about 1.5 to 20 % w/w of the article, or most preferably about 2 to 15% w/w of the article. For example, the API can be present at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% w/w, or any range created by such numbers, for example, 2-5%; 5-10 %; 10-15%; 5-12%, etc.

[0092] The hydrophilic polymer, if present, can be up to about 60 % w/w of the article, preferably about 5 to 40 % w/w of the article, or most preferably about 10 to 35% w/w of the article. For example, the hydrophilic polymer can be present at 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% w/w, or any range created by such numbers, for example, 10-15%, 15-20%, 20-25%, 25-30%, 30-35%, 10-20%, 15-25%, etc.

[0093] In certain embodiments, the article of manufacture can include: a second thermoplastic polymer; a second API; and/or a second hydrophilic polymer. The second thermoplastic polymer can be different from the thermoplastic polymer; the second API can be different from the API; and the second hydrophilic polymer can be different from the hydrophilic polymer. With respect to the second API, the second API can be compounded into the article of manufacture, however, the second API can also be coated or impregnated into the article of manufacture. In embodiments where the second API is coated or impregnated into the article of manufacture, coating or impregnation is preferably performed when the article of manufacture is a medical device, *e.g.*, a catheter.

[0094] In general, the articles of manufacture can include additional excipients. Excipients are inert ingredients that are used in product formulations, and are generally known in the art, if not defined by regulatory agencies. Excipients have limited (if any) pharmacological activity, unlike APIs. In general, excipients may perform a variety of functional roles in the pharmaceutical product,

e.g., lubrication, binder, pH adjusters, radio-opacifier, pigments, plasticizers, stabilizers, antioxidants, etc. Examples of radio-opacifier include barium sulfate, bismuth oxychloride, and tungsten. The articles of manufacture be about 10 to 40 % w/w of excipients, preferably about 15 to 35 % w/w of excipients; or most preferably about 20 to 30 % w/w of excipients. Excipients can be added into the bulk of the article of manufacture or incorporated into or on the article of manufacture after compounding. For example, the excipients can be present at 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% w/w, or any range created by such numbers, for example, 15-20%, 20-25%, 25-30%, 30-35%, 10-20%, 15-25%, etc.

[0095] APIs are biologically active components that produces an intended effects to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. As used herein, API refers to both a pharmaceutical ingredients, APIs, as traditionally understood, and explained above, as well as, an active moiety (AM). In certain embodiments, the API is not an AM. Alternatively, the API is an AM. Accordingly, APIs are generally recognized by a person of ordinary skill in the art and defined by regulatory agencies. Preferred APIs are antimicrobial, antithrombogenic, or antifouling agents. In certain embodiments the API is an inorganic, small molecule. Alternatively, the API is an organic, small molecule.

[0096] The API can be an antiseptic, an antibiotic, an anticoagulant, a metallic compound/metal ion, a fibrinolytic, a polyethylene glycol, a poly(glycerol), a poly(2-methyl-2-oxazoline), a zwitterionic polymeric sulfobetaine (polySB), or most preferably antimicrobial agent selected from chlorhexidine dihydrochloride, alexidine dihydrochloride, octenidine dihydrochloride, polyhexamethylene biguanide, silver sulfadiazine, zinc pyrithione; an anticoagulant selected from sodium citrate, sodium EDTA, or an antifouling agent selected from an polyethylene glycol and an poly(glycerol).

[0097] The articles as described herein can be incorporated into medical devices, in particular, implantable medical devices. Such medical devices include a vascular catheter, urinary

catheter, endotracheal tube, graft, stent, suture, dressing, gauge, balloon; preferably vascular catheter, urinary catheter, endotracheal tube; most preferably an arterial or venous catheter.

[0098] The implantable medical devices can provide at least one property selected from:

[0099] (1) Antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 70%; preferably antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 80%; most preferably antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 90%. In some embodiments, a maximum protection of 99.99%, 99.9999%, or 100% is provided.

[00100] (2) Antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 25%; preferably antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 50%; most preferably antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 75%. In some embodiments, a maximum protection of 95%, 99%, or 100% is provided.

[00101] (3) anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 25%; preferably anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 50%; most preferably anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 75%. In some embodiments, a maximum protection of 95%, 99%, or 100% is provided.

[00102] Preferably at least two of the at least one property, or most preferably at least three of the at least one property. For example, combinations of properties can be: (1) + (2); (1) + (3); (2) + (3); and (1) + (2) + (3).

[00103] In general, the article is capable or configured to remain efficacious in a patient for at least 2 hours to 90 days; for example about 1 day to 7 days; preferably about 3 to 14 days; or most preferably about 7 to 30 days; alternatively at least 30 days, at least 31 days, at least 35 days up to 90 days. As used herein, the term "efficacious" and the like, means providing clinical benefit to a patient.

[00104] Embodiments of the disclosure include methods of using the articles of manufacture disclosed herein. For example, to form or be incorporated into medical devices. The articles or medical devices, as applicable, can be used to treat patients or to facilitate the treatments of patients. For example, one embodiment of the disclosure includes a method of removing or adding fluids to a patient, implanting the medical device of the disclosure into a cavity or vein or artery of patient, wherein the medical device is a catheter, and removing or adding at least one fluid to the patient through the medical device. In specific embodiments, the medical device is implanted for at least 90 days; for example about 1 to 90 days; preferably about 3 to 60 days; or most preferably about 7 to 30 days; alternatively at least 30 days, at least 31 days, at least 35 days up to 90 days.

[00105] The articles of the disclosure can further include a lubricious overcoat. The lubricious overcoat can be used to further control release of the API. Examples of materials to be used in a lubricious overcoat include dichloromethane, heptane, and isopropyl alcohol as solvents, polyethylene oxide or dimethyl siloxane as a lubricious agent, and adhesive agents to adhere the lubricious coating to the article. The lubricious overcoat can be applied to the article by restricting internal surface exposure, exposing the external surface of the article to the coating composition via dipping for 1-2 seconds, and allowing the article to cure. The overcoating composition can contain about 0.25% to 7%, preferably 0.5% to 6%, and most preferably 1%

to 5% lubricious agent by weight. The amount of lubricious material on the coated article can be up to 5%, preferably up to 3%, and most preferably up to 1% by weight.

[00106] Unless stated otherwise, all values in this disclosure are w/w.

[00107] A reference to acronyms and tradenames is provided in Table A, below.

Term	Description
API	active pharmaceutical ingredient
CHA	chlorhexidine diacetate
CHD	chlorhexidine dihydrochloride
Tecothane®	Tecothane® is aromatic polyether-based thermoplastic polyurethanes (TPUs).
ALX	Alexidine
ALX-D	Alexidine dihydrochloride
PEBAX®	PEBAX® are elastomers are block copolymers made up of rigid polyamide blocks and soft polyether blocks. PEBAX® is a plasticizer-free block copolymer thermoplastic elastomer. The ratio of each block determines the flexibility of the polymer.
Tecoflex®	Tecoflex® are aliphatic polyether-based thermoplastic polyurethanes
Pellethane®	thermoplastic polyurethanes
THF	tetrahydrofuran

Examples

[00108] Example 1: Tecothane® + ALX + PEBAX® (0%, 20% and 40%) - formulation composition, content, elution, antimicrobial efficacy.

[00109] Tecothane® polyurethane material was compounded with 5% alexidine followed by extruding to form 7french 3-lumen catheters, and tested for content, elution, and efficacy. The alexidine content results were 887 μg/cm. When these catheters were tested for antimicrobial efficacy, the performance was poor because the elution rate was low. To enhance alexidine elution, hydrophilic material, PEBAX®, was added at 20% and 40% ratio during the

compounding process. FIG. 2 shows the content of each of the blends. FIG. 3 shows the results of the elution testing. Adding the 20% and 40% PEBAX® had an effect that enhanced the elution rate of the alexidine. Table 1 shows the results of the Efficacy testing against *C. albicans, E. faecalis, and K. pneumoniae*, 20% and 40% had greater than 4 log reduction on day 14 challenge.

Table 1 - Antimicrobial Efficacy of the external surface of extrusions composed of Tecothane® + ALX + PEBAX (20% and 40%)

	LR 2019-014: External Efficacy Experiment 150				
	Day 14	5% Alexidine + 20% PEBAX®		5%Alexidine + 40% PEBAX®	
		CFU/Segment	Log_{10} Reduction Control	CFU/Segment	Log10 Reduction Control
Candida albicans ATCC 10231	Replicate 1	0.00E+00	5.4	0.00E+00	5.4
	Replicate 2	0.00E+00		0.00E+00	
	Replicate 3	0.00E+00		0.00E+00	
Enterococcus faecalis ATCC 51299	Replicate 1	0.00E+00	5.8	6.13E+01	4.4
	Replicate 2	0.00E+00		0.00E+00	
	Replicate 3	0.00E+00		1.83E+02	
Klebsiella pneumoniae ATCC 10031	Replicate 1	0.00E+00	4.3	1.33E+00	4.3
	Replicate 2	0.00E+00		0.00E+00	
	Replicate 3	0.00E+00		0.00E+00	

[00110] Example 2: Tecoflex® + ALX + PEBAX (0%, 20%) - formulation composition, content, elution, antimicrobial efficacy

[00111] Tecoflex® polyurethane material was compounded with 2.5% alexidine and 20% PEBAX® followed by extruding to form 7french 3-lumen catheters, and testing for content, elution, and efficacy. Content results are in FIG. 4, elution results are in FIG. 5, and the efficacy results are in Table 2. The results in Table 2 show the catheters resulted in at least 4-Log_{10} reduction in all of the 8 tested organisms.

Table 2 - Antimicrobial Efficacy of the external surface of extrusions composed of Tecoflex® + 5% ALX + 20% PEBAX

Organism	Day 14 Log_{10} Reduction Compared to Control
Candida albicans	5.6
Enterococcus faecalis	4.3
Klebsiella pneumoniae	5.3
Escherichia coli	6.4
Staphylococcus aureus	5.1
Staphylococcus epidermidis	4.4
Enterococcus cloacae	4.0
Candida tropicalis	5.6

[00112] Example 3: Pellethane® + ALX (2,3%) + PEBAX (0, 20%) -- formulation composition, content, elution, antimicrobial efficacy

[00113] Pellethane® polyurethane material was compounded with 2% or 3% alexidine, and 20% PEBAX® followed by extruding to form single lumen catheter extension line extrusions, and testing for content, elution, and efficacy. The content is shown in FIG. 6, the elution is shown in FIG. 7, and the results of the efficacy are shown in Table 3. The results in Table 3 show the efficacy results to have had at least a 4 log kill on 3 out of 3 organisms.

Table 3 - Antimicrobial Efficacy of the external surface of extrusions composed of Pellethane® + 2% or 3% ALX + 20% PBAX

Organism	Log_{10} Reduction Compared to Control	
	3% Alexidine + 20% PEBAX®	2% Alexidine + 20% PEBAX®
Candida albicans	4.5	4.5
Enterococcus faecalis	4.2	4.4
Klebsiella pneumoniae	6.4	6.4

[00114] Example 4: Thermal stability assessment of CHA (Chlorhexidine diacetate), CHD (chlorhexidine dihydrochloride), and ALX-D (Alexidine dihydrochloride)

[00115] The antimicrobial agents were placed into an oven set at 210°C for 10 mins (to mimic condition in which the antimicrobial agent would be exposed to heat during the compounding and extrusion processes). Another set of the same antimicrobial agents was not exposed to any heat. The unheated and heated samples were then examined through HPLC method for presence of degradants (extra peaks). Results of CHA and CHD are in FIGS. 8, 9, 10, and 11. CHA results in FIG. 8 is for the heated sample and there were several extra peaks from degradants detected along the baseline when compared to FIG. 9 which was the un-heated sample. FIG. 10 and 11 which was the heated and unheated samples of CHD respectively, there was absence of any extra peaks on either sample showing thermal stability of CHD and hence the suitability for including it in the device through compounding process. Similar to CHD, ALX-D was also found stable at 210°C for 10 mins and was found suitable for including in the device through compounding process.

[00116] Example 5: Cooling during compounding process.

[00117] Compounding an API into a polyurethane polymer occurred at an outside vendor. The vendor uses normal compounding procedures and used an underwater pelletization set up. This resulted in the loss of about 50% of the drug that was placed into the polymer matrix.

[00118] Example 6: Air-cooling device.

[00119] In this example, leaching of the API from the compounded polymer was reduced by eliminating the water tank and cooling the extrudate with a plurality air rings. In a first experiment, two air rings were used to cool the extrudate and the extrudate was not cool enough to cut in the pelletizer. In subsequent experiments, more air rings were added to a base and fixtures so placement of the air rings could be adjusted to a suitable distance between them. The starting % alexidine in the experiment was 3%. FIG. 12 shows the set-up of the air rings.

[00120] As shown in FIG. 12, the compounded mixture 30 is extruded from the extruder 12. In this example, the air-cooling device 32 is a series of air rings 40 disposed on an adjustable fixture 42 and provided a supply of pressurized air via an air supply 44. Once cooled,

the compounded mixture 30 is fed into a pelletizer 46. The pelletizer 46 is configured to cut and form the compounded mixture into pellets 50. The results, after implementing air-rings, reduced the Alexidine loss to 20% compared to the 50% loss observed with the water-cooling method.

[00121] Example 7: Position of API feeding in the extruder.

[00122] In previous attempts at compounding the Alexidine into the polyurethane, the base polyurethane resin, hydrophilic resin, and the Alexidine was fed into the same feed throat. This approach was leading to some of the powder getting caked onto the screw and not flowing with the resin through the compounder. To eliminate this issue, Alexidine was incorporated into the melt stream of the polymer downstream of the polymer feeding throat. This indeed helped reduce the measured loss of API through the extrusion process. FIG. 14 illustrates a chart showing the measured API % is between 10 and 15 % of the theoretical % in the compounding process.

[00123] Example 8: Use of an ionizer to reduce API buildup on metal surfaces of extruder.

[00124] Although some improvements were observed on the compounding process in reducing alexidine loss, there were still issues with alexidine attaching to the metal pieces of the feeder and feed throat, as well as seeing the Alexidine was not well distributed into the bulk of the polymer. To address this issue, an ionizer was attached to the extruder to help eliminate the static and to prevent alexidine from attaching to the metal parts. A minor increase in content was observed when the ionizer was employed. This may have been because the fan may be aerosolizing the Alexidine into the air.

[00125] Example 9: Comparison of impregnated/coated to compounded catheters

[00126] Using the above-described methods, catheters were prepared and analysis of extrusions with compounded chlorhexidine dihydrochloride (CHD) were compared with coated samples (internal or external). The coated catheter body material was Tecothane® 60D

with 20% $BaSO_4$. For external coating 80% tetrahydrofuran (THF), 20% Methanol, 8% Tecothane 95A, 6% CHA, at 181.2 cP was used. For internal coating: 45% THF, 55% Methanol, 2% CHA, 2.5% CHX was used. The compounded catheter included Tecothane 60D with 20% $BaSO_4$ and 10% CHD.

[00127] To analyze the catheters one cross section was cut from extrusions followed by SEM/EDS in four quadrants of the cross section with low vacuum mode without sputter coating. The internal impregnated (coated) samples did not have a measurable chlorine signature when analyzing the inner wall of the internally impregnated samples. The external impregnated (coated) sample had a chlorine signature on the outside wall of the extrusion, there was no chlorine signature in the bulk on either internal or external impregnated (coated) extrusions.

[00128] The compounded sample had chlorine signatures on the outside, inside and bulk of the extrusion.

[00129] Example 10: Evaluation of hydrophilic polymer to promote elution of API

[00130] Using the above-described methods, tecothane® pellets were compounded with 8% CHD. Tecothane® pellets were also compounded with a hydrophilic material (PEBAX® MV1074) in ratios of 5%, 10% and 15% w/w and 8% w/w CHD. All compositions were made into 12 fr 3-Lumen extrusions and submitted for elution studies. 1 cm sections of each extrusion were placed in 1 L of deionized water at 37°C. Five samples of each were removed and tested for the amount of chlorhexidine dihydrochloride that remained in the extrusion at day 1, 2, 3, and 7. It was found that tecothane without hydrophilic material releases less API than with hydrophilic material added. As the composition has an increasing amount of hydrophilic resin the release of API increases. The results are shown in FIG. 16A and 16B. Each data point is an average of n=5 samples. FIG. 16A excludes the results of the 15% hydrophilic material for improved scale.

[00131] Example 11: Evaluation of hydrophilic polymer to promote elution of API

[00132] Using the above-described methods, further samples were prepared and tested of API release. The preparation and testing were consistent with Example 10. The results are provided in FIG. 17.

[00133] Example 12: Evaluation of catheters compounded with API and with a lubricious overcoat to promote easy insertion of catheter

[00134] Catheters varying the amounts of CHD and two types of lubricious overcoat were prepared, to the specifications of Table 4.

Table 4

	%CHD	**overcoat**
Catheter 1	10	Treatment A
Catheter 2	13.3	Treatment A
Catheter 3	13.3	Treatment B

[00135] Treatment A: The catheters were occluded internally, and then externally exposed to a lubricious overcoat composition using a solvent of dichloromethane with 1% polyethylene oxide of molecular weight 100,000 g/mol and 1.1% adhesive bonding agent. The catheters were dipped for 1-2 seconds and allowed to cure at ambient conditions for 15 minutes.

[00136] Treatment B: The catheters were occluded internally, and then externally exposed to a lubricious overcoat composition using a solvent of 70% isopropyl alcohol and heptane with 5% dimethyl siloxane silicone dispersion. The catheters were dipped for 1-2 seconds and immediately steam cured for 10 seconds, then additionally allowed to cure for 24 hours at ambient conditions.

[00137] The catheters were prepared by overcoating the catheter and trimming it into testable lengths of 1.5cm, additionally cutting the circular cross section in half into two semicircular cross sections to ensure internal surface exposure, resulting in one replicate of four

1.5cm semicircular lengths of test article. The elution of the catheters was then studied over 30-days. The study was performed by submerging the lengths of test article in 800µl of test solution. The test solution is a 1:1 ratio of 0.9% saline and filtered pooled plasma. Test solution was exchanged daily to ensure solubility limits were not reached, and solution extracts were taken on days 1, 6, 13, 20, and 29 to determine release rate at each timepoint. The results are provided in FIG. 18 (Catheter 1 = circle; Catheter 2 = square; Catheter 3 = diamond). Catheter 1 provided the lowest avg µg/mL; Catheter 3 provided the highest avg µg/mL.

[00138] Example 13: Antimicrobial efficacy performance over 30-days from catheters compounded with API

[00139] Catheter were prepared as described in Example 12. The antimicrobial performance of the catheters was studied over 30-days against *C. albicans*, *E. faecalis*, *K. pneumoniae*, and *S. aureus*. The study was performed as described in Example 12, however, this study was performed in a sterile environment using aseptic technique. Additionally, following 29 days of simulated elution, catheters were challenged by exposure to the microorganisms listed above. Microbial colonies were recovered and counted on day 30, concluding testing. The results are provided in FIG. 19 (Catheter 1 = left most bar; Catheter 2 = middle bar; Catheter 3 = right most bar).

[00140] The many features and advantages of the invention are apparent from the detailed specification, and thus, it is intended by the appended claims to cover all such features and advantages of the invention which fall within the true spirit and scope of the invention. Further, since numerous modifications and variations will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation illustrated and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of the invention.

What is claimed is:

1. An article of manufacture, comprising:

an active pharmaceutical ingredient (API) integrated in a thermoplastic polymer, wherein:

(A) the thermoplastic polymer has a water absorption capacity of about >1 to 90 % w/w of the article, preferably about 10 to 70 % w/w of the article, or most preferably about 15 to 30% w/w of the article, and/or

(B) the article further comprises a hydrophilic polymer blended with the thermoplastic polymer.

2. The article of claim 1, wherein the API is present in an amount of about 100 to 5000 μg/cm of the article; preferably about 150 to 3500 μg/cm of the article; most preferably about 200 to 2000 μg/cm of the article.

3. The article of claim 1, wherein:

(A1) the API is homogenously distributed throughout at least a portion of the bulk of the thermoplastic polymer; or

(B1) the API distributed as a gradient with the API concentrated on an outer most and an inner most layers of the article.

4. The article of claim 1, wherein:

(A2) the hydrophilic polymer is homogenously distributed throughout at least a portion of the bulk of the thermoplastic polymer; and/or

(B2) the hydrophilic polymer distributed as a gradient with the hydrophilic polymer concentrated on an outer most and an inner most layers of the article.

5. The article of claim 1, wherein the thermoplastic polymer is about 5 to 95 % w/w of the article, preferably about 10 to 70 % w/w of the article.

6. The article of claim 1, wherein the API is about 1 to 30 % w/w of the article, preferably about 1.5 to 20 % w/w of the article, or most preferably about 2 to 15% w/w of the

article.

7. The article of claim 1, wherein the hydrophilic polymer is about 1 to 60 % w/w of the article, preferably about 5 to 40 % w/w of the article, or most preferably about 10 to 35% w/w of the article.

8. The article of claim 1, wherein the thermoplastic polymer is selected from PVC, aromatic polyether polyurethane, aliphatic polyether polyurethane, aromatic polycarbonate polyurethane, aliphatic polycarbonate polyurethane, rigid polyurethane, aromatic polycarbonate silicone polyurethane, aromatic polyether silicone polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, thermoplastic elastomer, polyether block amide, preferably aromatic polyether polyurethane, aliphatic polyether polyurethane, aromatic polycarbonate polyurethane, aliphatic polycarbonate polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, thermoplastic elastomer, polyether block amide polyurethane, or most preferably aromatic polyether polyurethane, aliphatic polyether polyurethane, aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane.

9. The article of claim 1, wherein the contains an antimicrobial, an antithrombogenic, or an antifouling agent.

10. The article of claim 1, wherein the hydrophilic polymer is selected from aliphatic polyether hydrophilic polyurethane, aromatic polyether hydrophilic polyurethane, and polyether block amide hydrophilic; or most preferably aliphatic polyether hydrophilic polyurethane and aromatic polyether hydrophilic polyurethane.

11. The article of claim 1, further comprising a second thermoplastic polymer.

12. The article of claim 1, further comprising a second API.

13. The article of claim 1, further comprising a second hydrophilic polymer.

14. The article of claim 1, further comprising about 10 to 40 % w/w of excipients, preferably about 15 to 35 % w/w of excipients; or most preferably about 20 to 30 % w/w of excipients.

15. The article of claim 14, wherein the excipients include a plasticizer, a stabilizer, an antioxidants, or a radio-opacifier, preferably at least an radio-opacifier which is preferably selected from barium sulfate, bismuth oxychloride, or tungsten.

16. An implantable medical device, comprising: the article of any one of claims 1-15.

17. The implantable medical device of claim 16, further comprising a lubricious overcoat on the article.

18. The implantable medical device of claim 17, wherein the lubricious overcoat comprises a lubricious agent, which is preferably a polyethylene oxide polymer or dimethyl siloxane, and an adhesive agent configured to adhere the lubricous coating to the article.

19. The implantable medical device of claim 16, wherein the article can safely remain implanted in a patient for at least 2 hours to 90 days; for example about 1 day to 7 days; preferably about 3 to 14 days; or most preferably about 7 to 30 days; alternatively at least 30 days, at least 31 days, at least 35 days up to 90 days.

20. The implantable medical device of claim 16, wherein the article has at least one property selected from:

(1) antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 70%; preferably antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 80%; most preferably antimicrobial property leading to reduction in colonization by broad spectrum microorganisms including gram positive bacteria, gram negative bacteria or fungi by at least 90%,

(2) antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 25%; preferably antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 50%; most preferably antithrombogenic property leading to reduction in platelet adhesion, fibrin sheath formation, fibroblastic sleeve formation, intraluminal thrombus, extraluminal thrombus, intimal hyperplasia, or vascular thrombosis by at least 75%;

(3) anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 25%; preferably anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 50%; most preferably anti-inflammatory property leading to reduction in insertion site redness, swelling, pain, phlebitis, or thrombophlebitis by at least 75%,

preferably at least two of the at least one property, or most preferably at least three of the at least one property.

21. The implantable medical device of claim 16, wherein the API is released over a period of 1 day to 180 days, preferably 3 days to 120 days, most preferably 7 days to 90 days.

22. The implantable medical device of claim 16, wherein the medical device is a vascular catheter, urinary catheter, endotracheal tube, graft, stent, suture, dressing, gauge, balloon; preferably vascular catheter, urinary catheter, endotracheal tube; most preferably an arterial or venous catheter.

23. A method of removing or adding fluids to a patient, comprising:

implanting the medical device of claim 22 into a cavity or vein or artery of patient, wherein the medical device is a catheter; and

removing or adding at least one fluid to the patient through the medical device.

24. The method of claim 23, wherein the medical device is implanted for at least 90 days; for example about 1 to 90 days; preferably about 3 to 60 days; or most preferably about 7 to 30 days; alternatively at least 30 days, at least 31 days, at least 35 days up to 90 days.

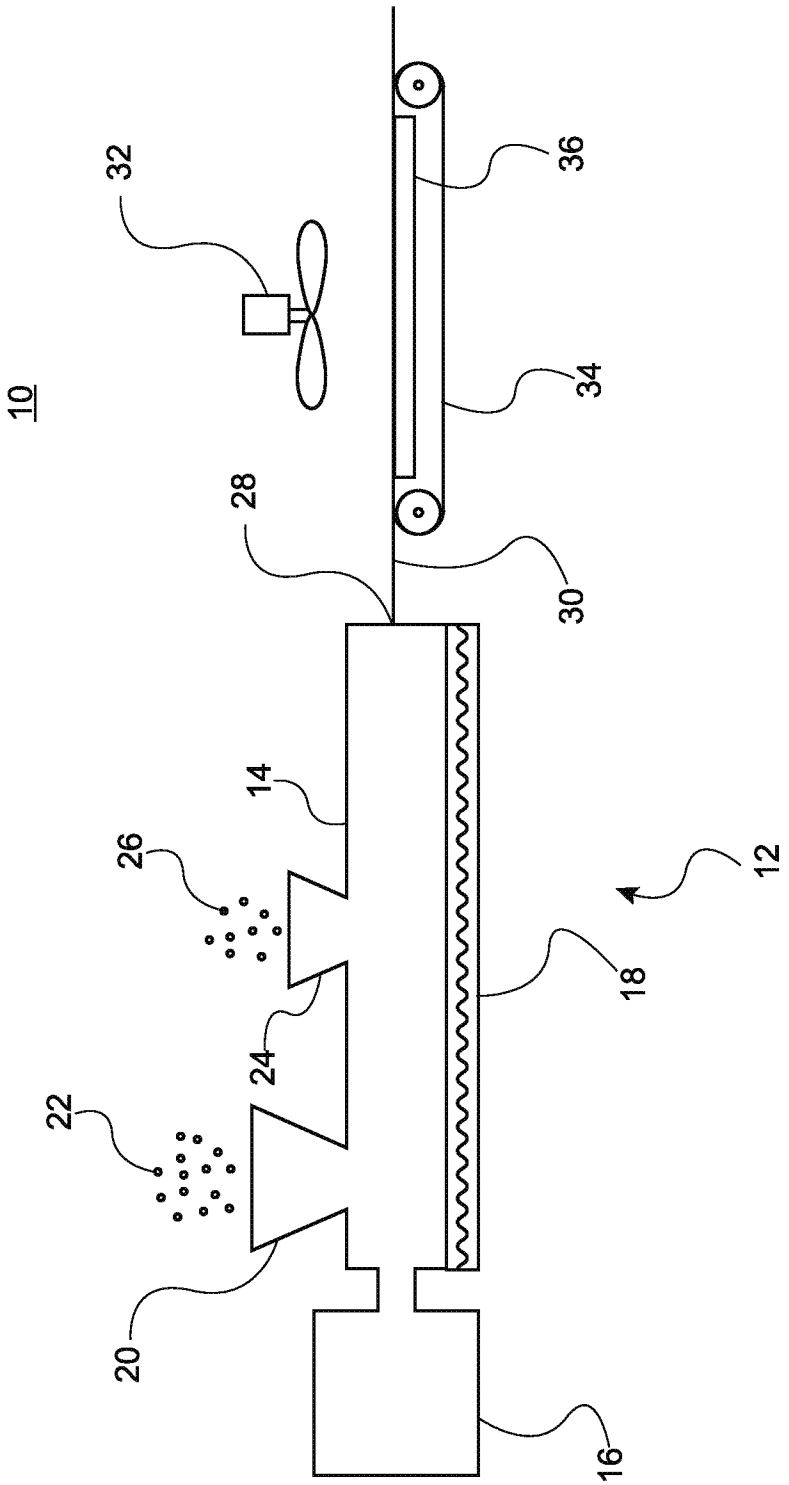

FIG. 1

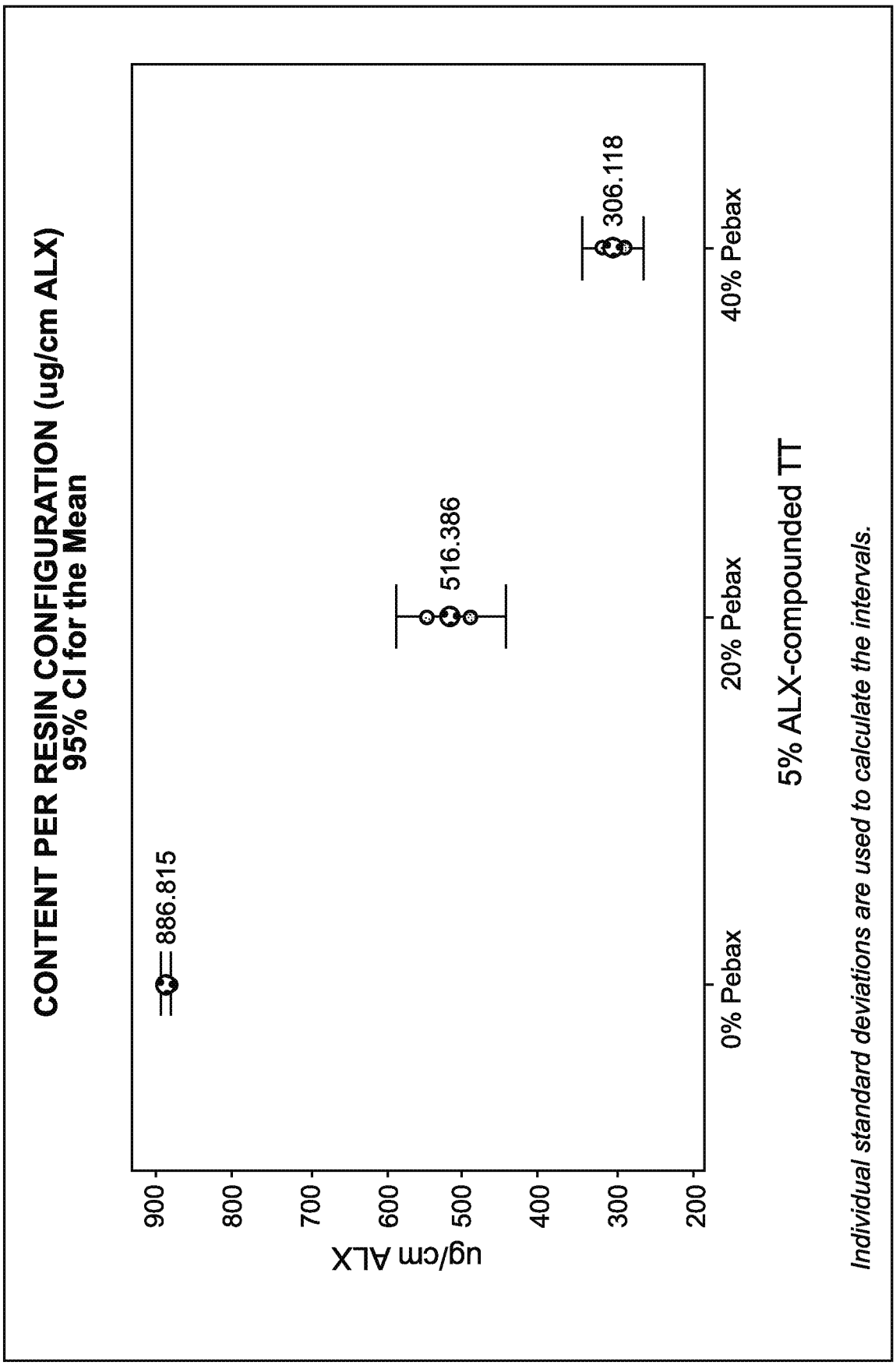
CONTENT PER RESIN CONFIGURATION (ug/cm ALX)
95% CI for the Mean
ug/cm ALX
900
800
700
600
500
400
300
200
886.815
516.386
306.118
0% Pebax
20% Pebax
40% Pebax
5% ALX-compounded TT
Individual standard deviations are used to calculate the intervals.

FIG. 2

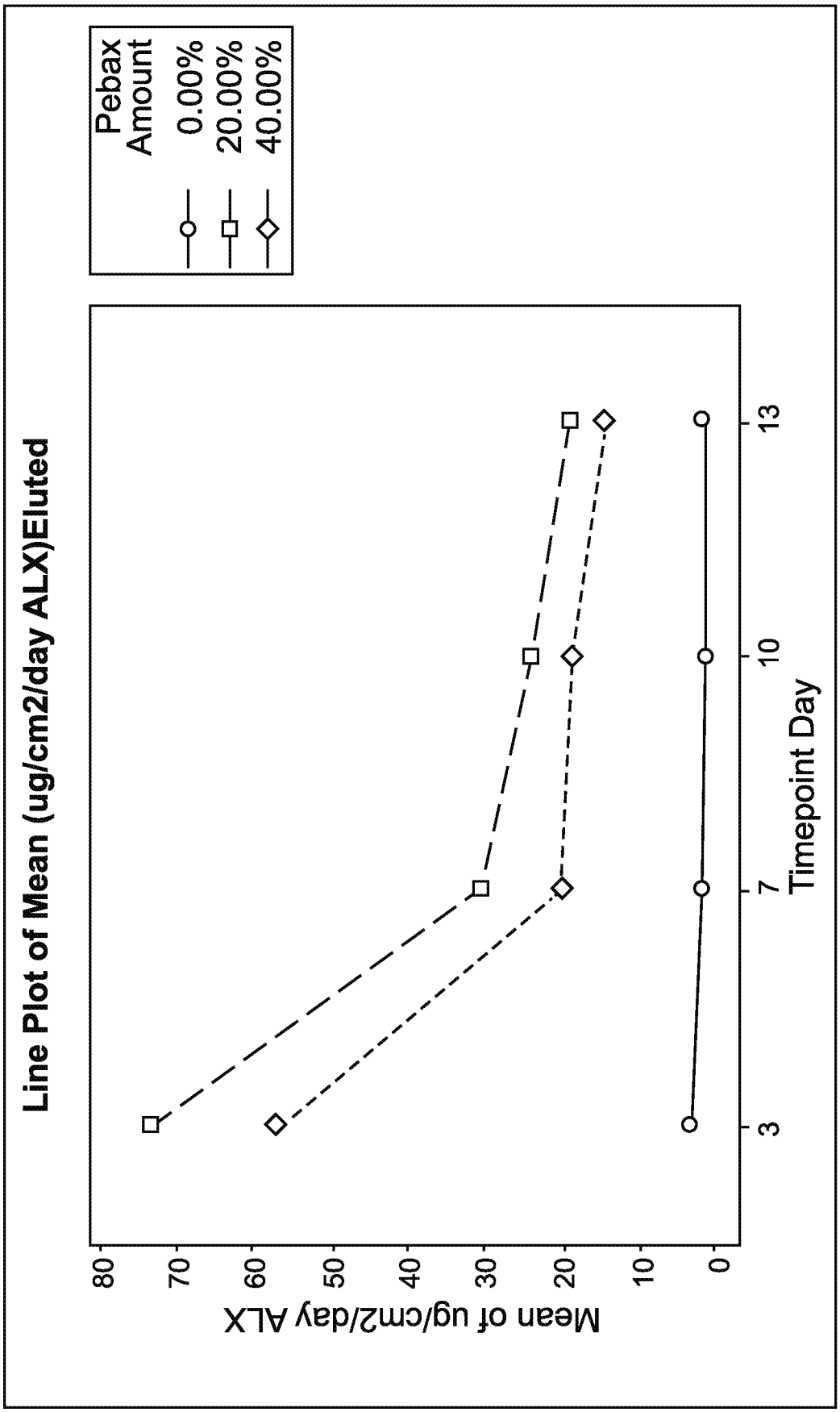
Line Plot of Mean (ug/cm2/day ALX)Eluted
Pebax Amount
0.00%
20.00%
40.00%
Mean of ug/cm2/day ALX
0
10
20
30
40
50
60
70
80
3
7
10
13
Timepoint Day

FIG. 3

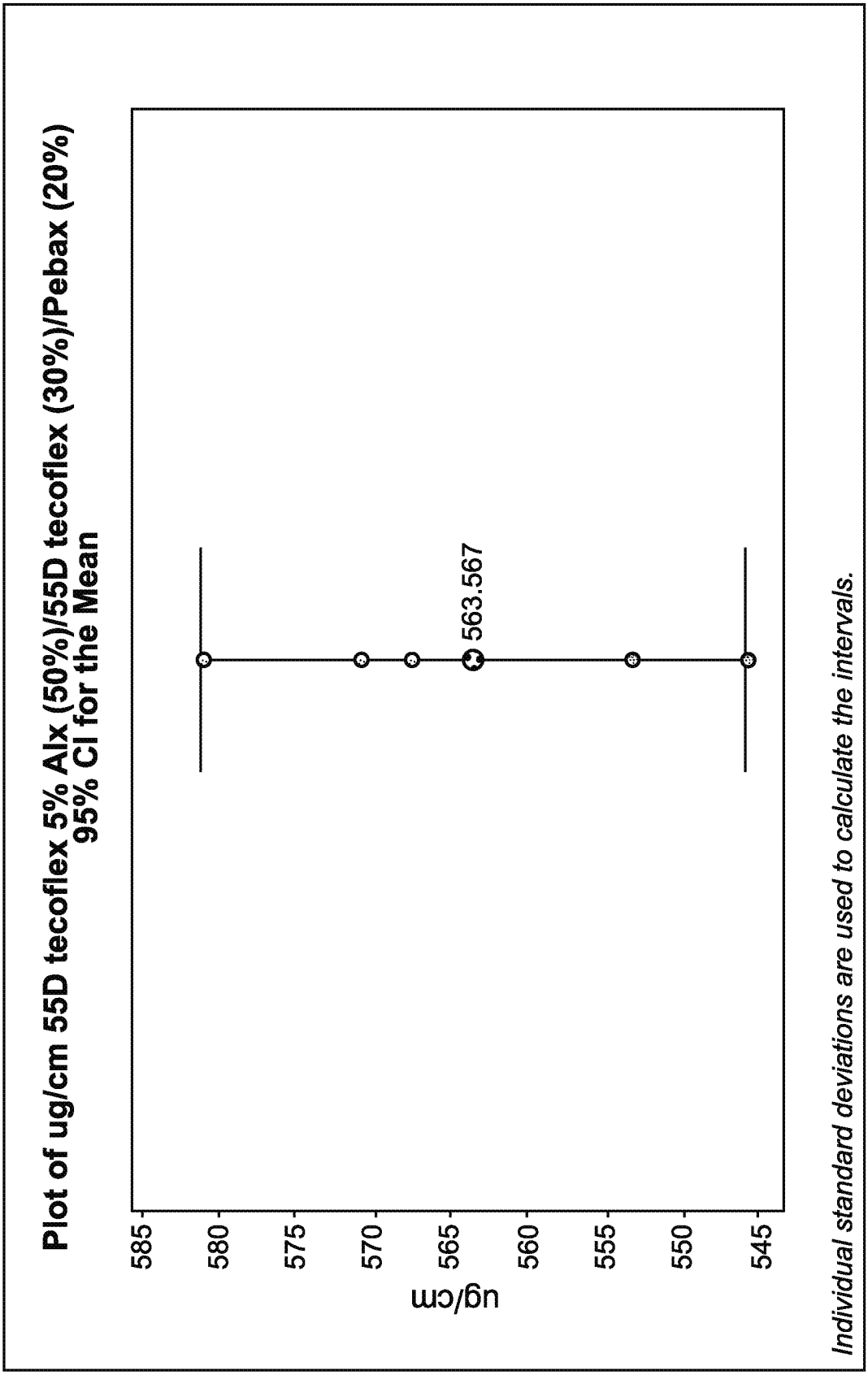
Plot of ug/cm 55D tecoflex 5% Alx (50%)/55D tecoflex (30%)/Pebax (20%)
95% CI for the Mean
563.567
585
580
575
570
565
560
555
550
545
ug/cm
Individual standard deviations are used to calculate the intervals.

FIG. 4

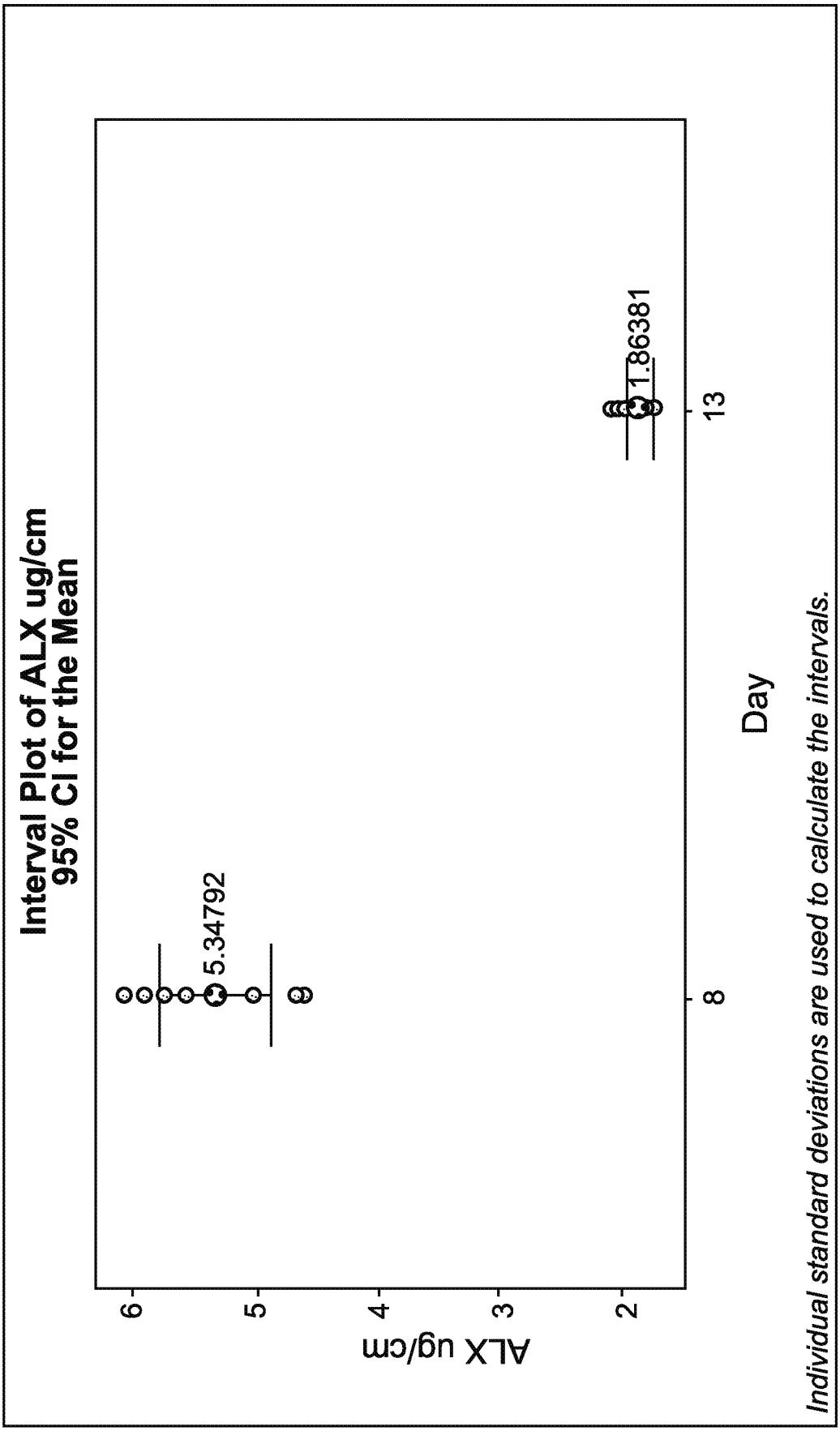
Interval Plot of ALX ug/cm
95% CI for the Mean
5.34792
1.86381
ALX ug/cm
6
5
4
3
2
8
13
Day
Individual standard deviations are used to calculate the intervals.

FIG. 5

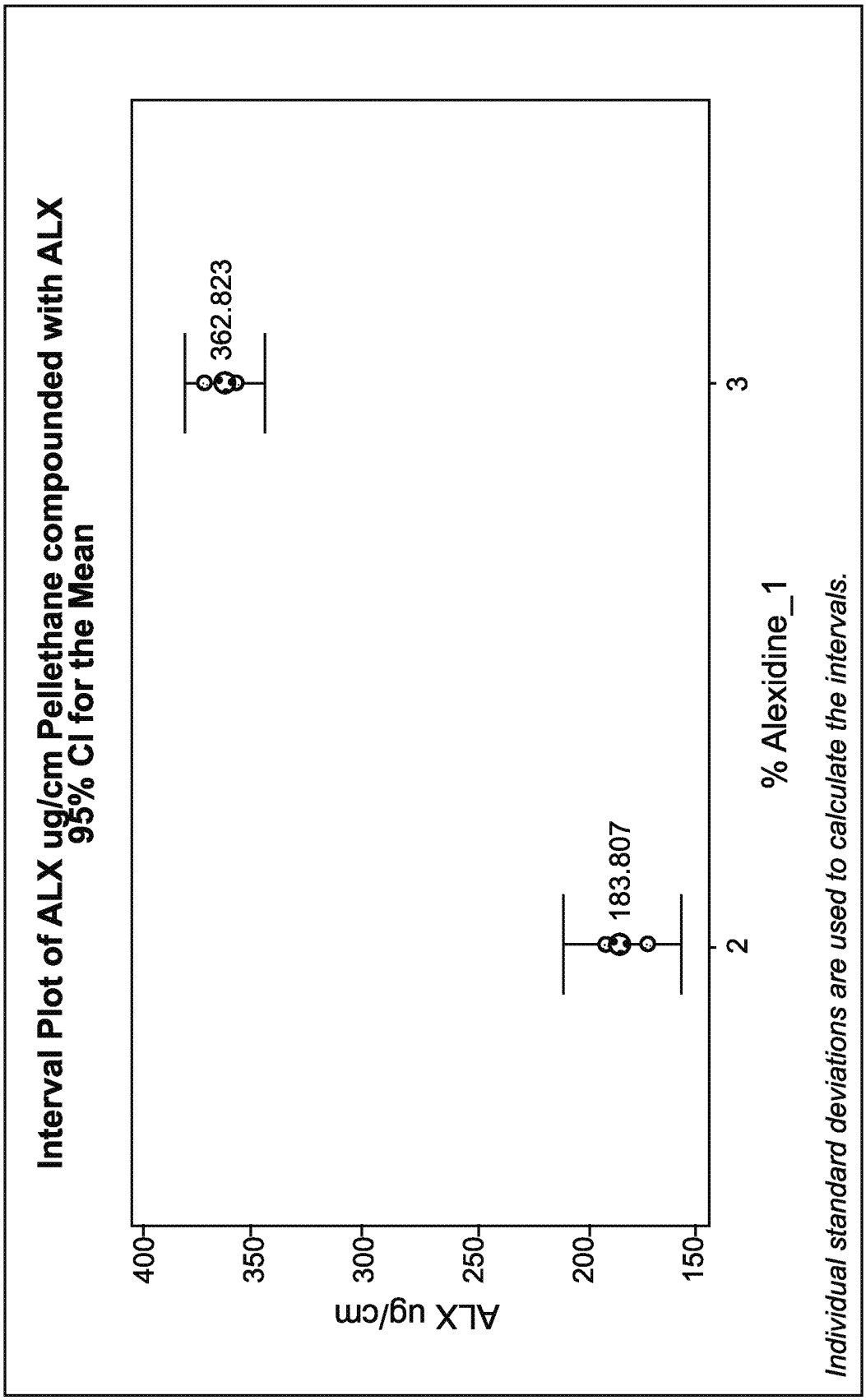
Interval Plot of ALX ug/cm Pellethane compounded with ALX
95% CI for the Mean
ALX ug/cm
400
350
300
250
200
150
362.823
183.807
2
3
% Alexidine_1
Individual standard deviations are used to calculate the intervals.

FIG. 6

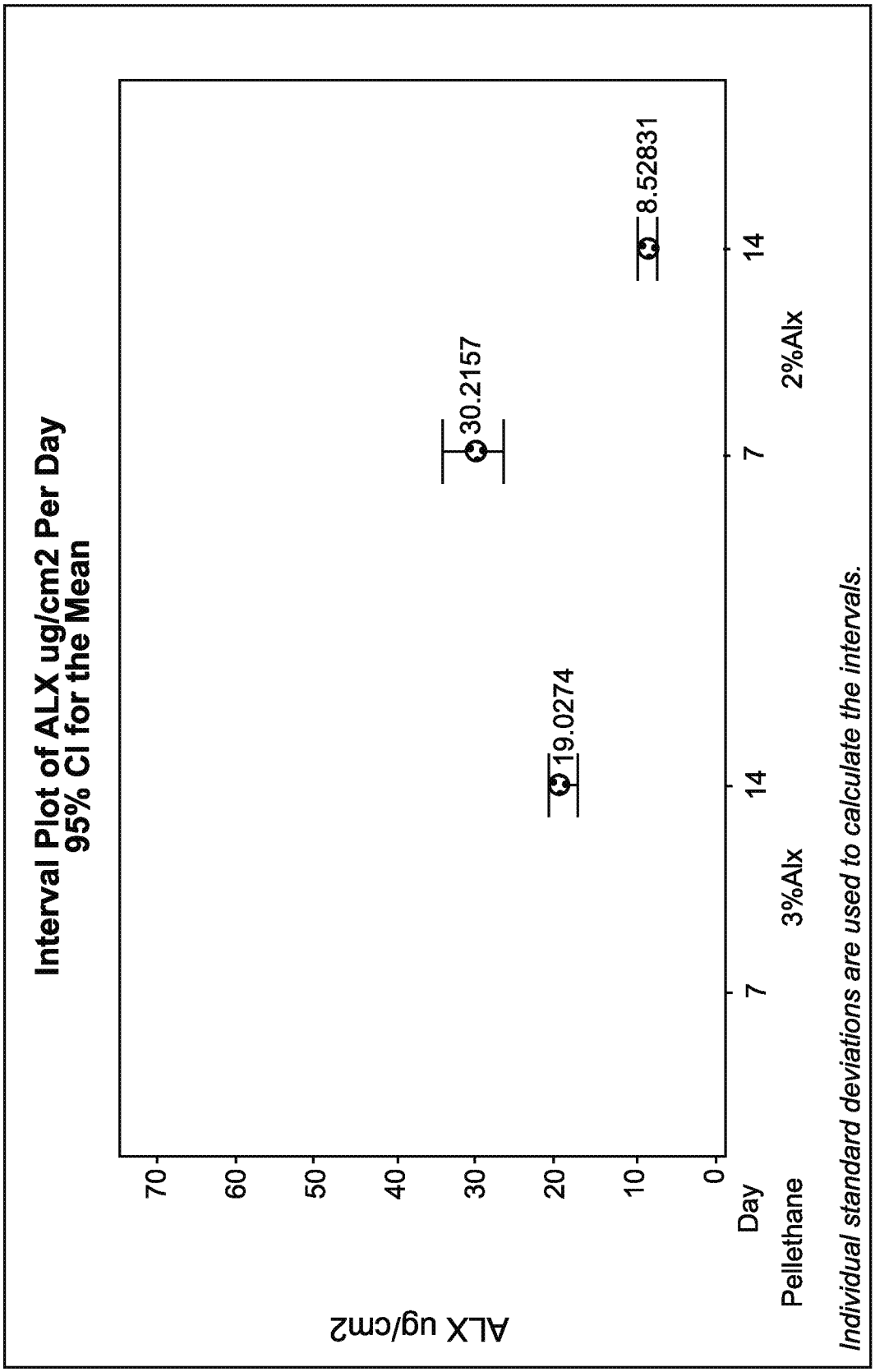
Interval Plot of ALX ug/cm2 Per Day
95% CI for the Mean
ALX ug/cm2
70
60
50
40
30
20
10
0
30.2157
19.0274
8.52831
Day
7
14
7
14
Pellethane
3%Alx
2%Alx
Individual standard deviations are used to calculate the intervals.

FIG. 7

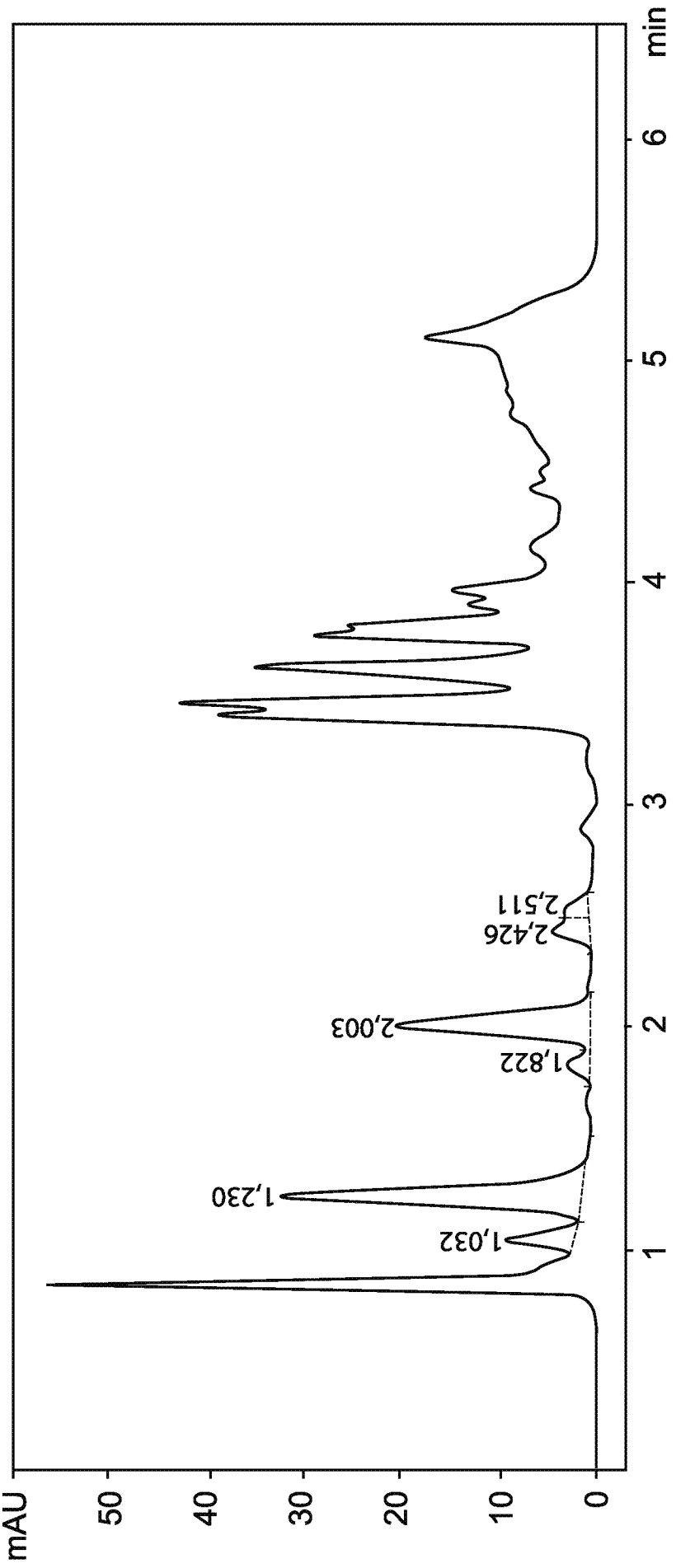

FIG. 8

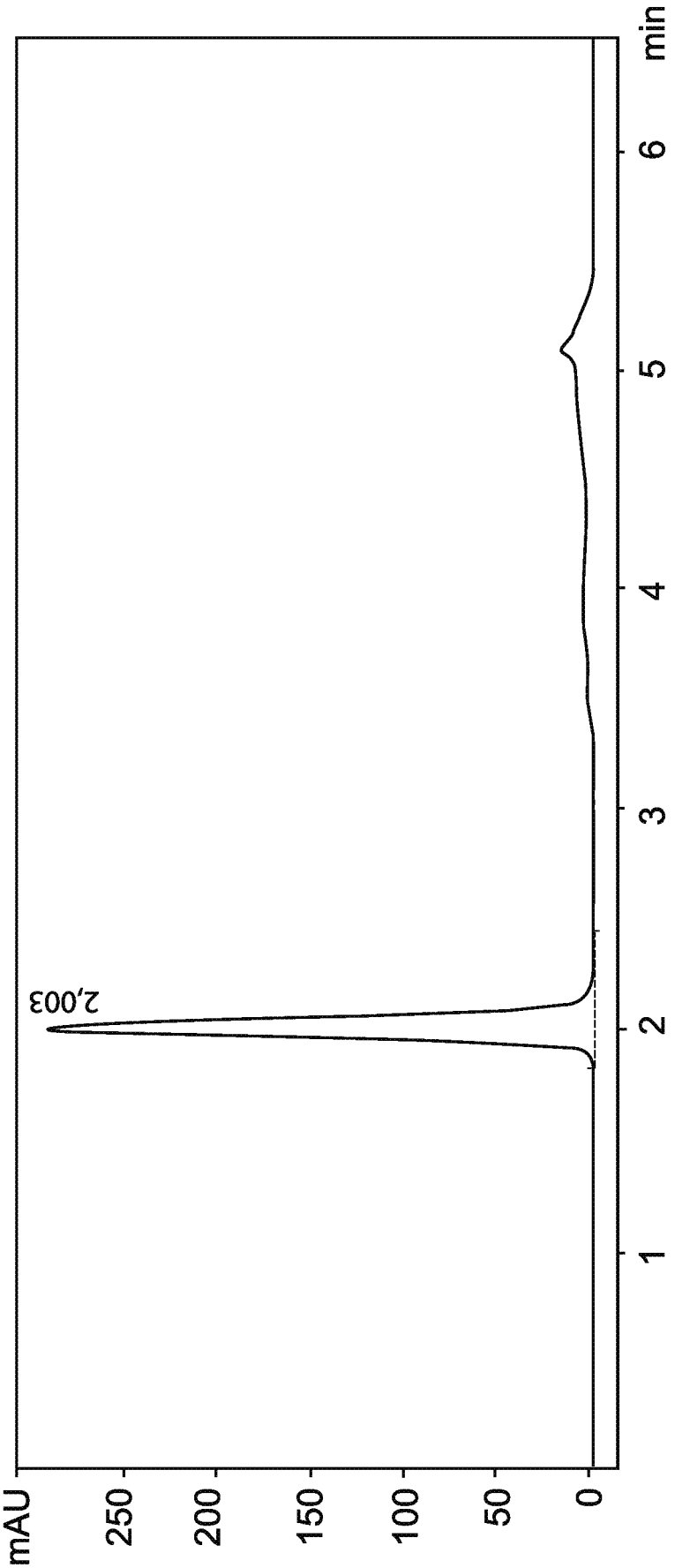

FIG. 9

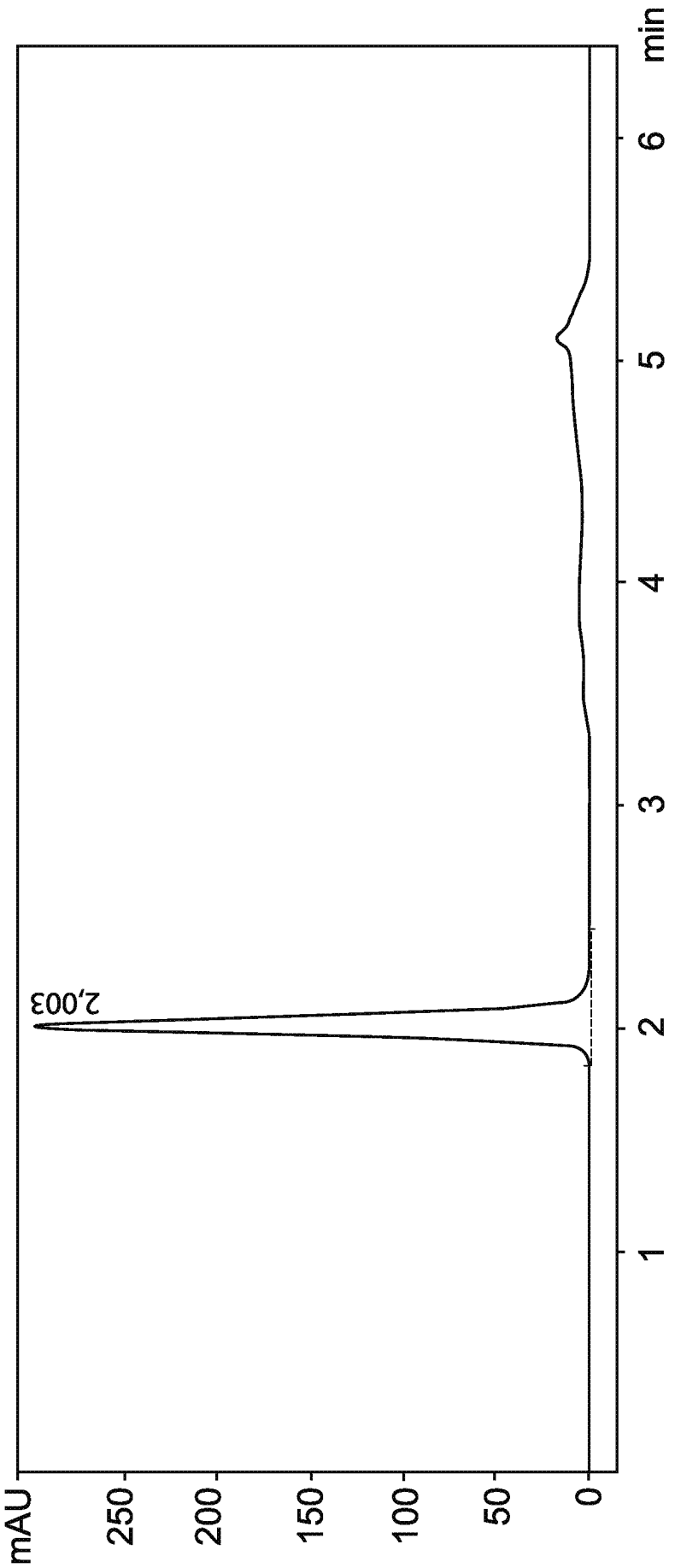

FIG. 10

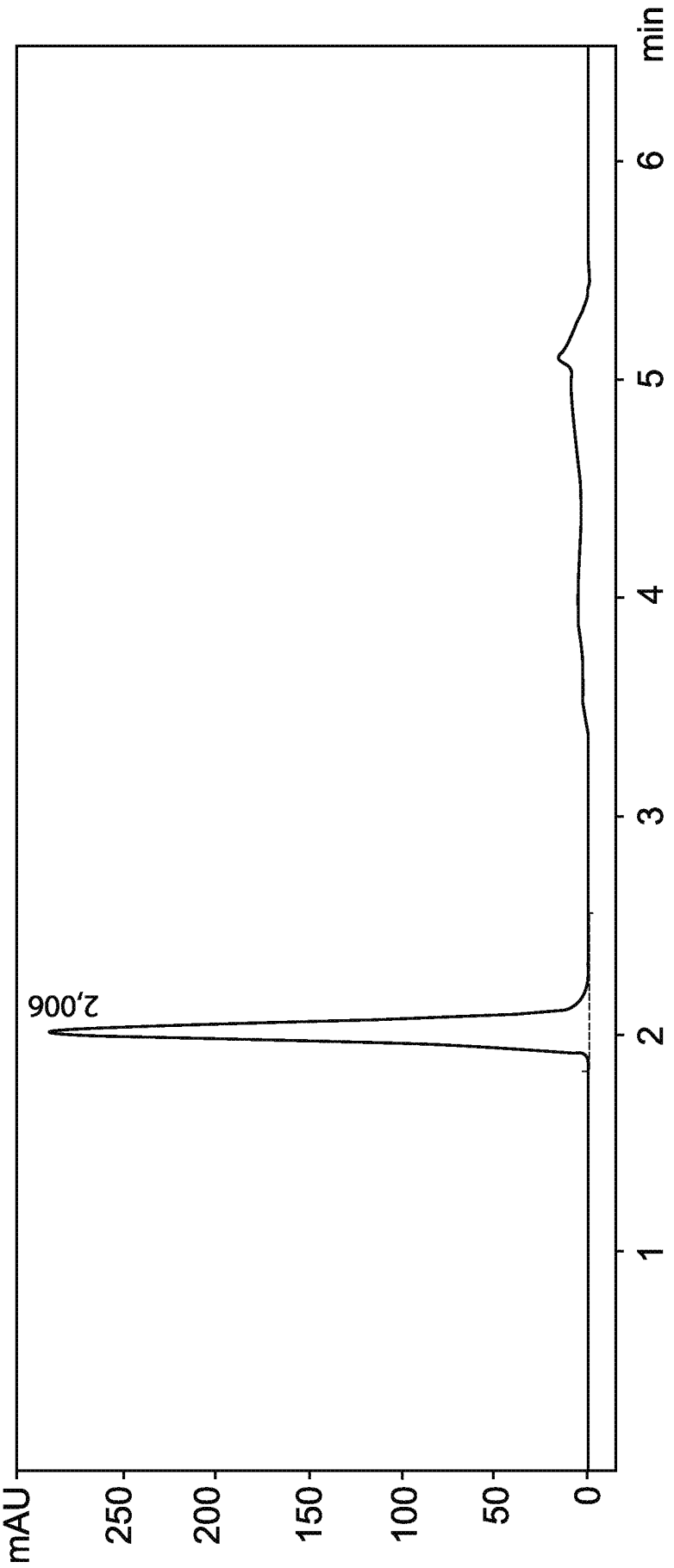

FIG. 11

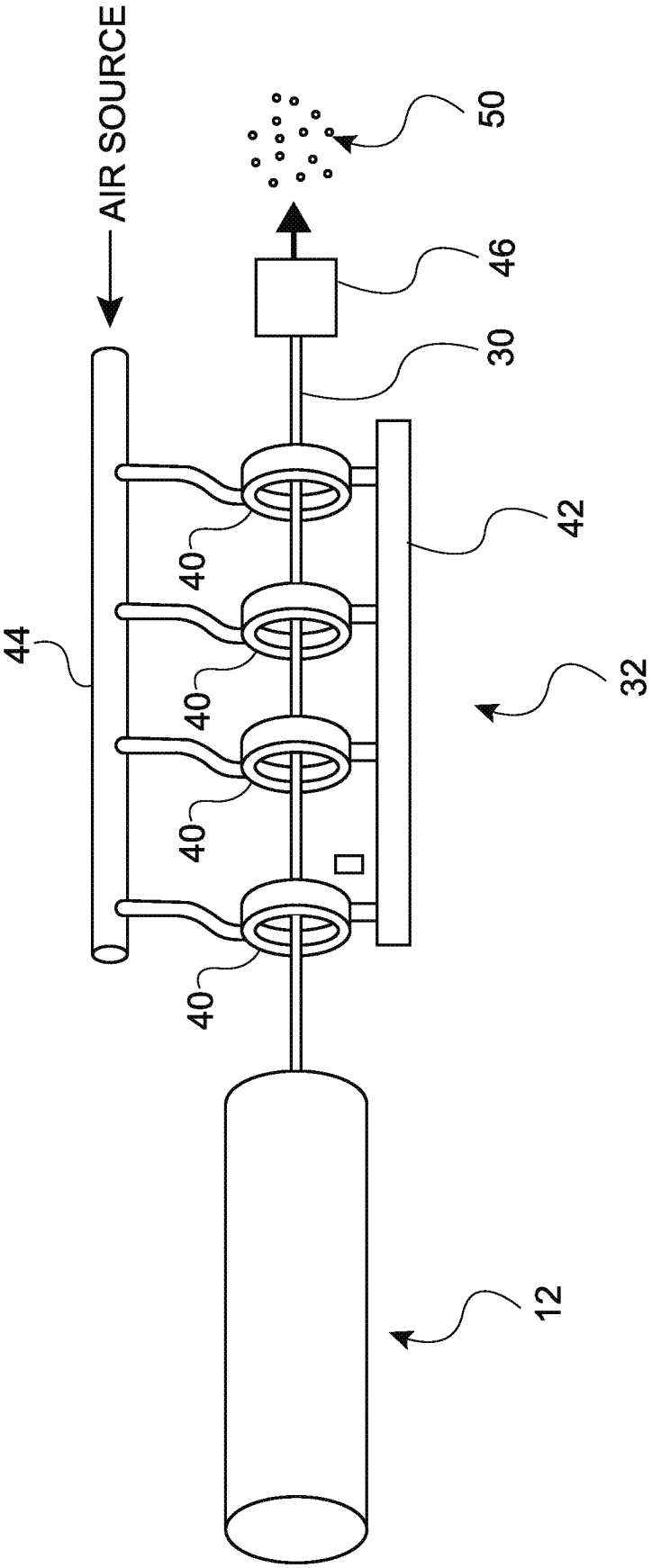

FIG. 12

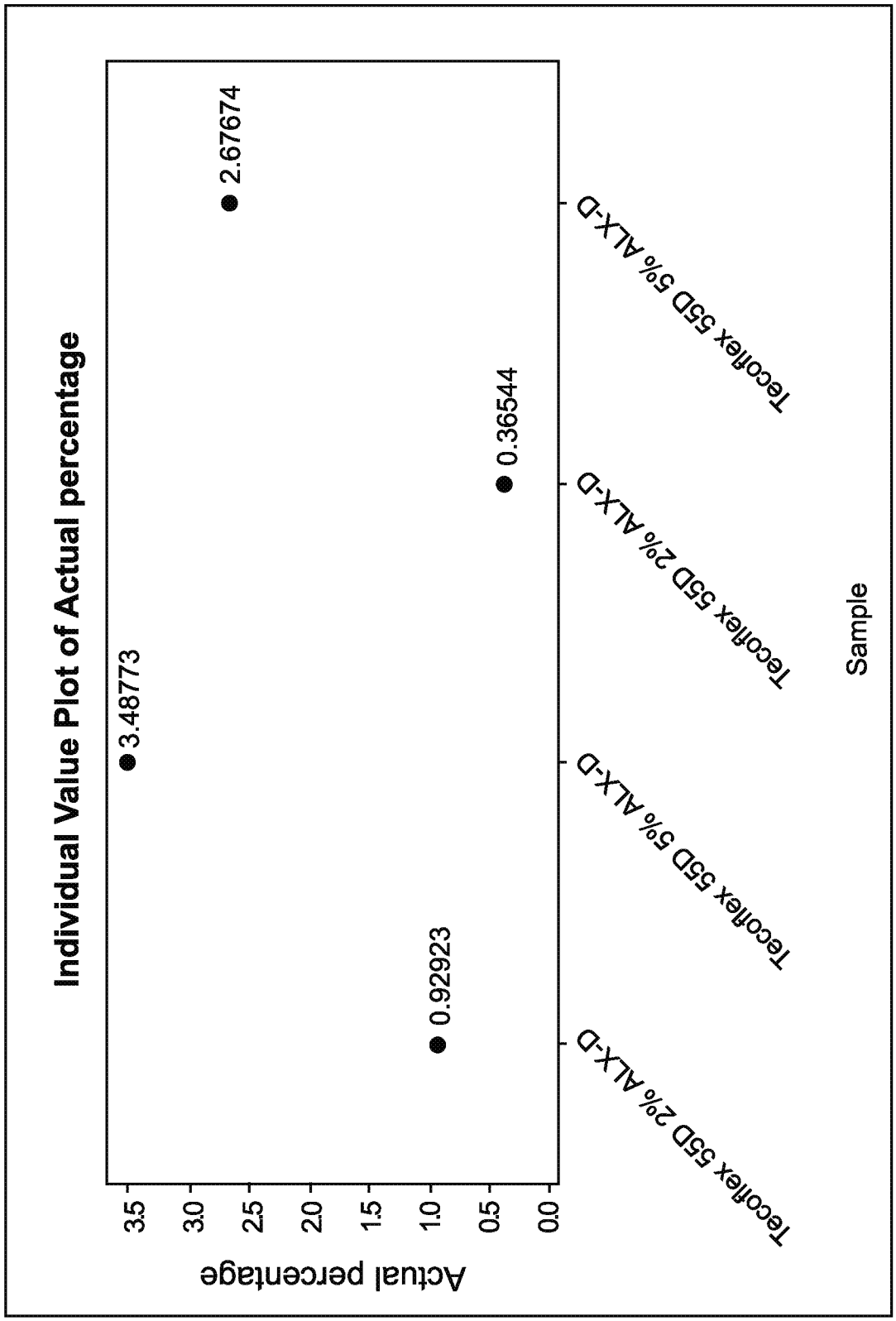
Individual Value Plot of Actual percentage
3.48773
2.67674
0.36544
0.92923
Actual percentage
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Tecoflex 55D 5% ALX-D
Tecoflex 55D 2% ALX-D
Tecoflex 55D 5% ALX-D
Tecoflex 55D 2% ALX-D
Sample

FIG. 13

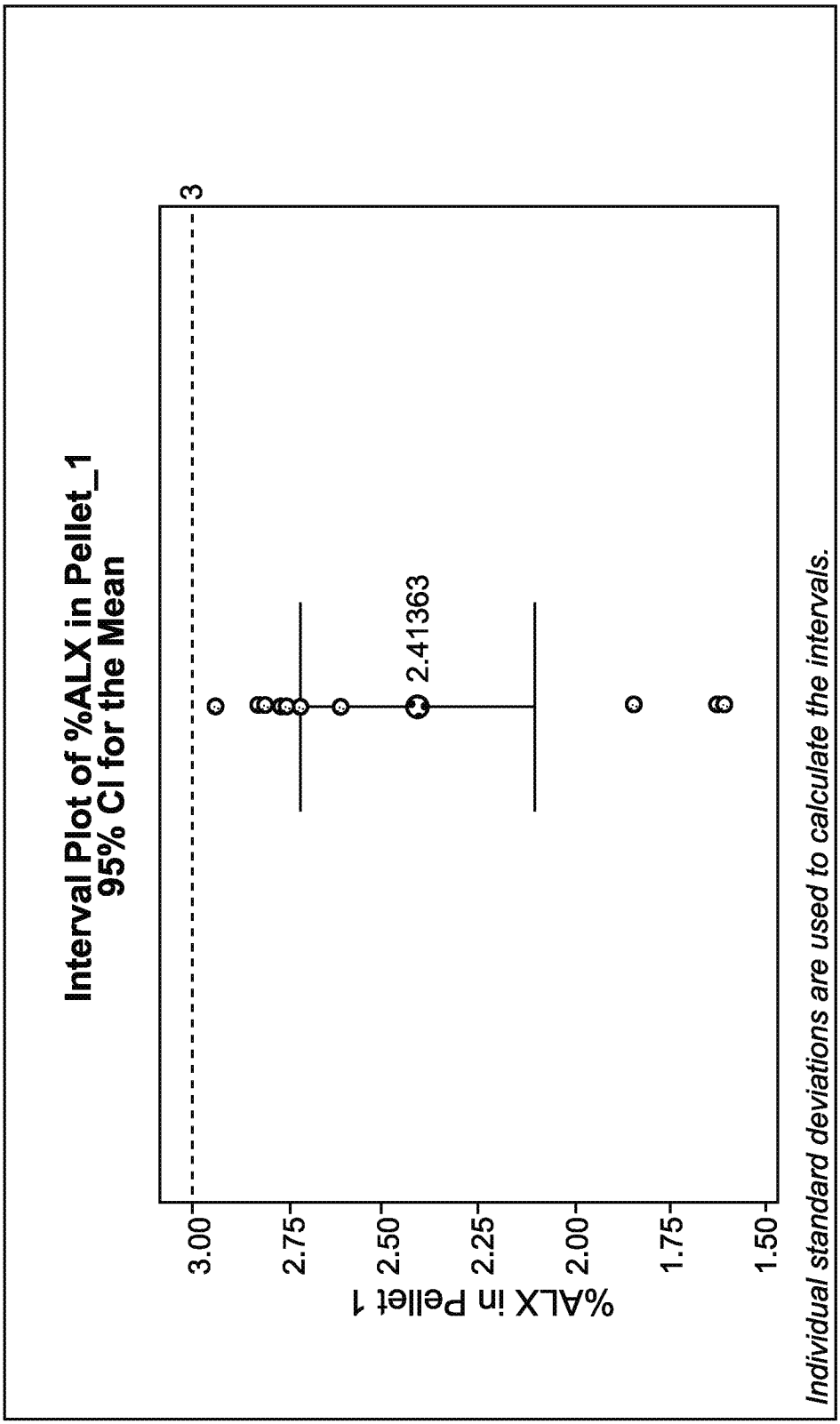
Interval Plot of %ALX in Pellet_1
95% CI for the Mean
%ALX in Pellet 1
3.00
2.75
2.50
2.25
2.00
1.75
1.50
3
2.41363
Individual standard deviations are used to calculate the intervals.

FIG. 14

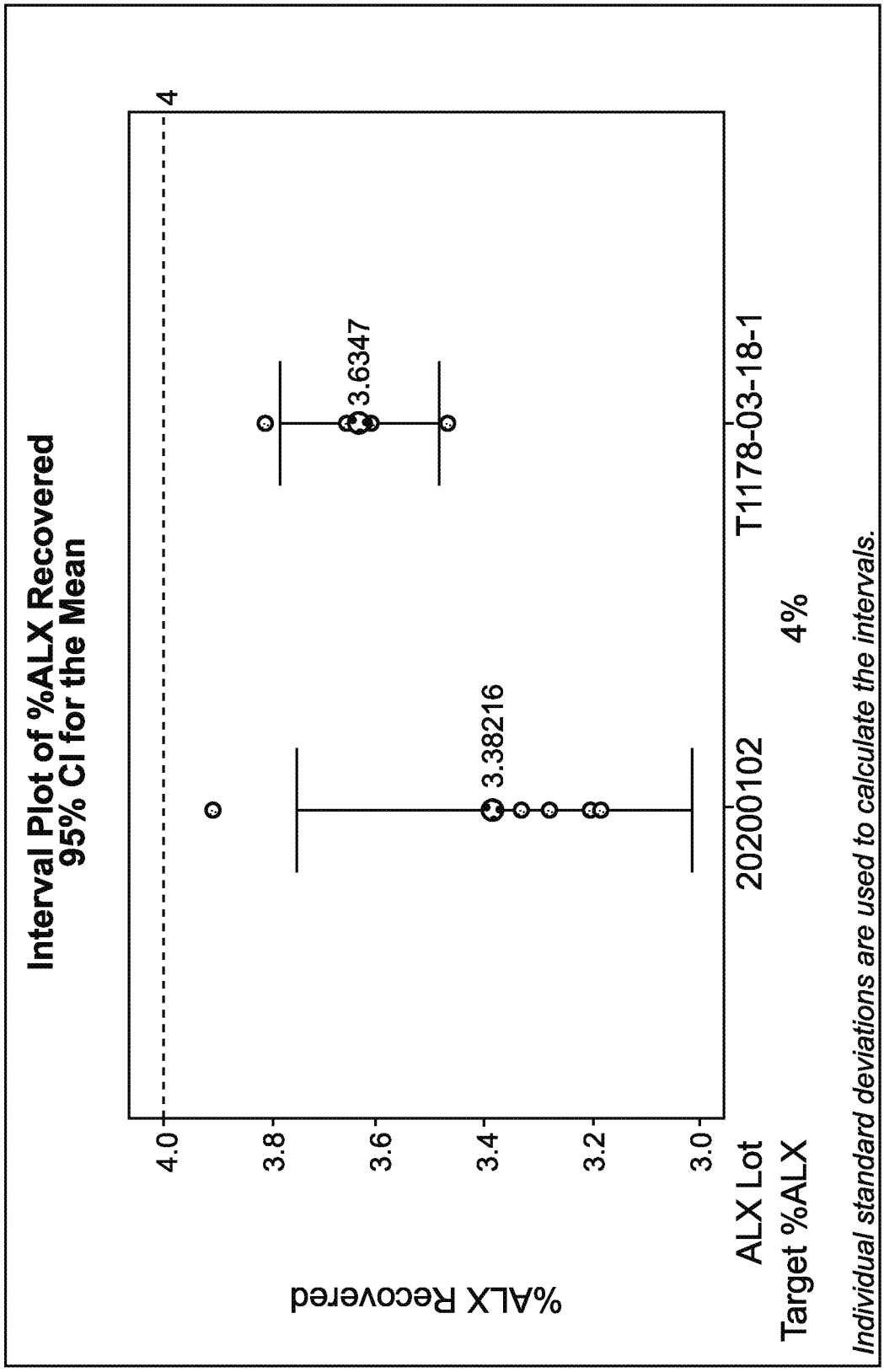
Interval Plot of %ALX Recovered
95% CI for the Mean
4
4.0
3.8
3.6
3.4
3.2
3.0
3.6347
3.38216
%ALX Recovered
ALX Lot
20200102
T1178-03-18-1
Target %ALX
4%
Individual standard deviations are used to calculate the intervals.

FIG. 15

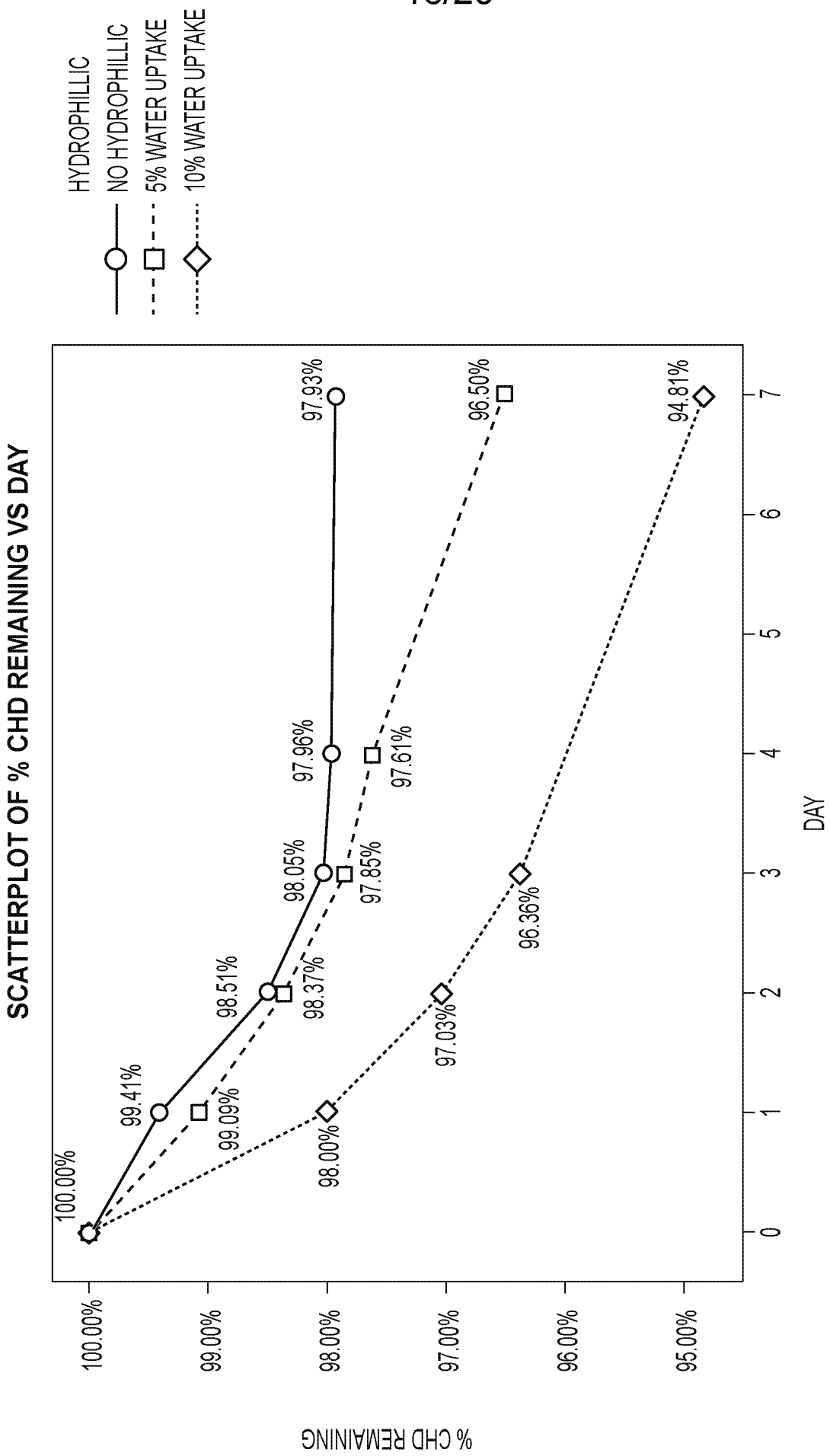
SCATTERPLOT OF % CHD REMAINING VS DAY
HYDROPHILLIC
NO HYDROPHILLIC
5% WATER UPTAKE
10% WATER UPTAKE
% CHD REMAINING
DAY
100.00%
99.00%
98.00%
97.00%
96.00%
95.00%
0
1
2
3
4
5
6
7
100.00%
99.41%
98.51%
98.05%
97.96%
97.93%
100.00%
99.09%
98.37%
97.85%
97.61%
96.50%
100.00%
98.00%
97.03%
96.36%
94.81%

FIG. 16A

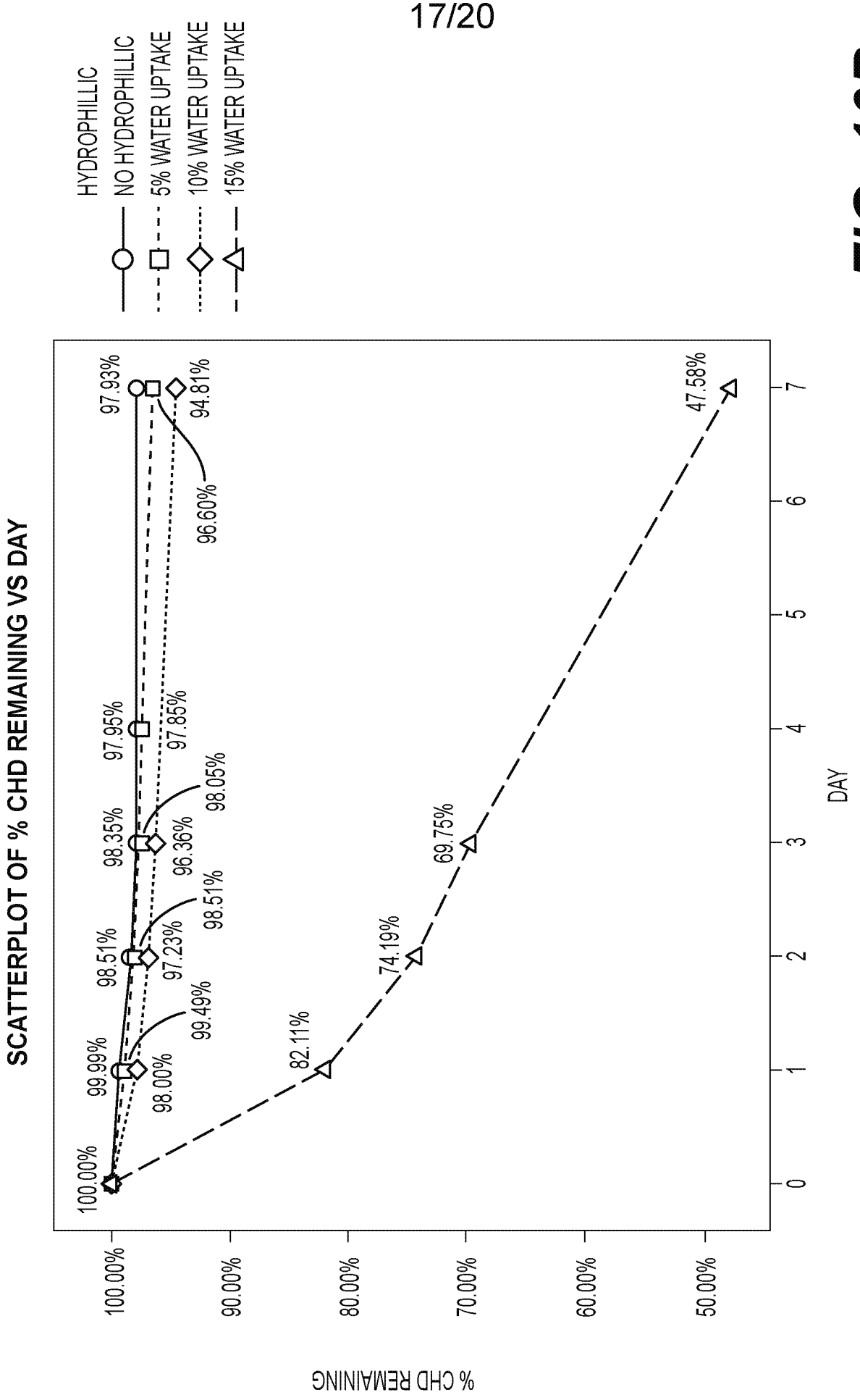
SCATTERPLOT OF % CHD REMAINING VS DAY
HYDROPHILLIC
NO HYDROPHILLIC
5% WATER UPTAKE
10% WATER UPTAKE
15% WATER UPTAKE
% CHD REMAINING
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
DAY
0
1
2
3
4
5
6
7
100.00%
99.99%
98.51%
97.95%
97.93%
99.49%
98.00%
98.35%
97.23%
96.36%
94.81%
98.51%
98.05%
97.85%
96.60%
82.11%
74.19%
69.75%
47.58%

FIG. 16B

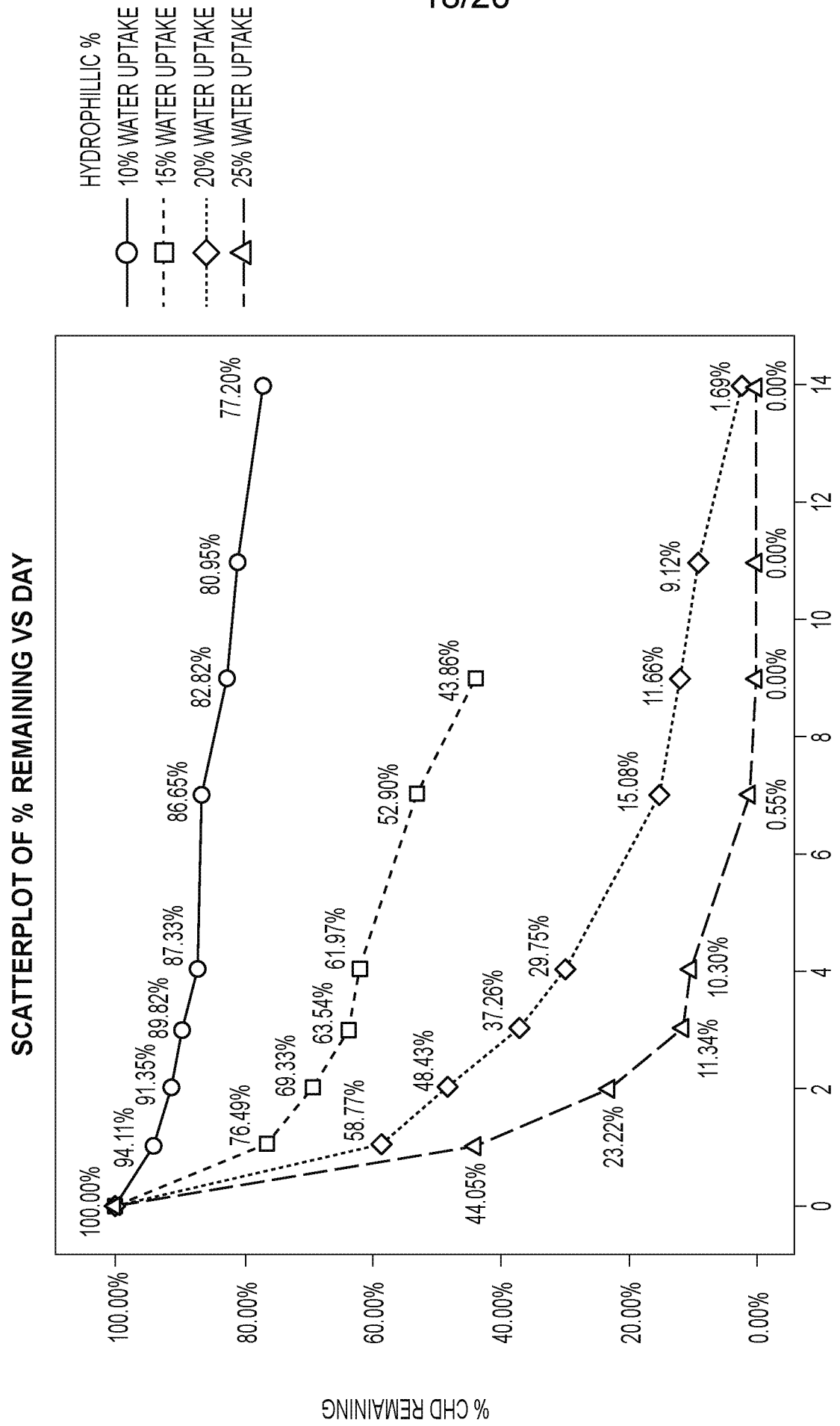
SCATTERPLOT OF % REMAINING VS DAY
HYDROPHILLIC %
10% WATER UPTAKE
15% WATER UPTAKE
20% WATER UPTAKE
25% WATER UPTAKE
% CHD REMAINING
DAY
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
0
2
4
6
8
10
12
14
100.00%
94.11%
91.35%
89.82%
87.33%
86.65%
82.82%
80.95%
77.20%
76.49%
69.33%
63.54%
61.97%
52.90%
43.86%
58.77%
48.43%
37.26%
29.75%
15.08%
11.66%
9.12%
1.69%
44.05%
23.22%
11.34%
10.30%
0.55%
0.00%
0.00%
0.00%

FIG. 17

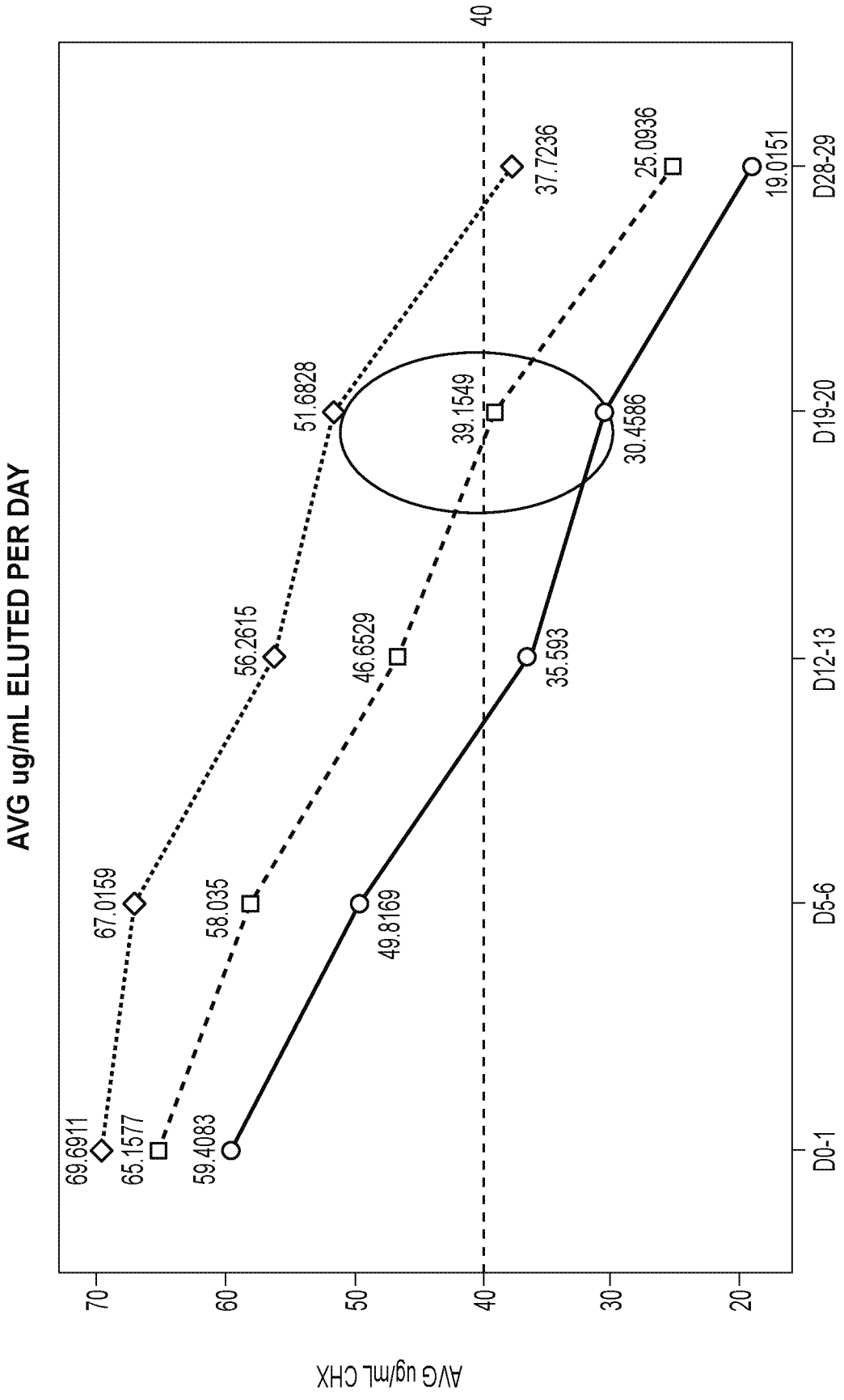
AVG ug/mL ELUTED PER DAY
AVG ug/mL CHX
TIMEPOINT
D0-1
D5-6
D12-13
D19-20
D28-29
70
60
50
40
30
20
69.6911
65.1577
59.4083
67.0159
58.035
49.8169
56.2615
46.6529
35.593
51.6828
39.1549
30.4586
37.7236
25.0936
19.0151

FIG. 18

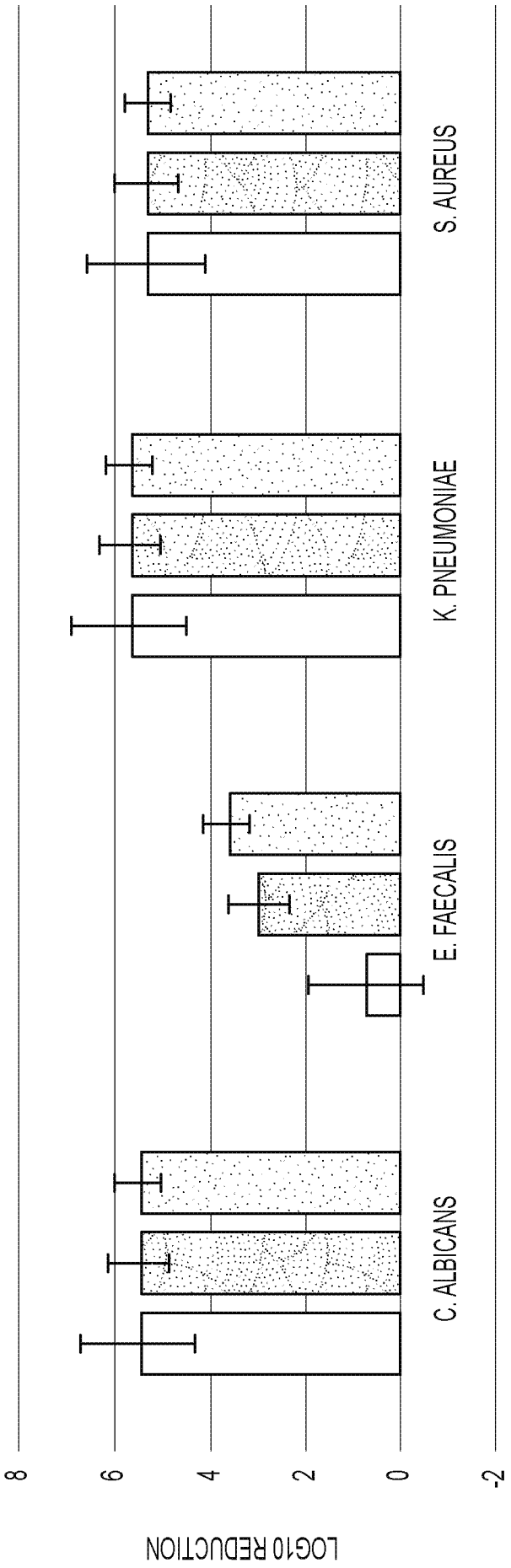
8
6
4
2
0
-2
LOG10 REDUCTION
C. ALBICANS
E. FAECALIS
K. PNEUMONIAE
S. AUREUS
ORGANISM

FIG. 19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036008

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61L 29/08*** (2024.01); ***A61L 29/12*** (2024.01); ***A61L 31/04*** (2024.01); ***A61K 31/155*** (2024.01); ***A61L 29/04*** (2024.01); ***C08L 75/04*** (2024.01); *A61M 25/00* (2024.01)

CPC: ***A61L 29/085; A61L 29/049; A61L 29/126; A61K 31/155; C08L 75/04; A61L 31/041;*** *C08L 2203/02; A61L 2300/206; A61L 2300/404; A61L 2300/42; A61L 2420/06; A61M 2025/0056; A61M 25/0045*

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 2008/0172011 A1 (HEROUX et al.) 17 July 2008 (17.07.2008)	
X	entire document	1-10, 12, 16-24
Y	entire document	13
	US 5,073,379 A (KLIMESCH et al.) 17 December 1991 (17.12.1991)	
X	entire document	1, 11
Y	entire document	14, 15
	US 2013/0253636 A1 (ANGIOTECH BIOCOATINGS CORP. et al.) 26 September 2013 (26.09.2013)	
Y	entire document	13
	US 2015/0110843 A1 (HYDROAIR GLOBAL LLC) 23 April 2015 (23.04.2015)	
Y	entire document	14, 15

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2024 (23.08.2024)	**05 November 2024 (05.11.2024)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450 UNITED STATES OF AMERICA**	**TAINA MATOS**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036008

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US 2023/0211052 A1 (TELEFLEX MEDICAL INCORPORATED) 06 July 2023 (06.07.2023) entire document	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036008

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-15 are drawn to articles of manufacture.

Group II: claims 16-24 are drawn to implantable medical devices, and methods of removing or adding fluids to a patient thereof.

The inventions listed in Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, articles of manufacture, are not present in Group II; and the special technical features of Group II, implantable medical devices, and methods of removing or adding fluids to a patient, are not present in Group I.

Additionally, even if Groups I and II were considered to share the technical features of an article of manufacture, comprising: an active pharmaceutical ingredient (API) integrated in a thermoplastic polymer, wherein: (A) the thermoplastic polymer has a water absorption capacity of about >1 to 90 % w/w of the article, and/or (B) the article further comprises a hydrophilic polymer blended with the thermoplastic polymer, these shared technical features do not represent a contribution over the prior art as disclosed by US 5,073,379 A to Klimesch et al. (hereinafter, "Klimesch").

Klimesch teaches an article of manufacture (abstract, A mixture… is tableted; column 1, line 6, preparation of solid pharmaceutical forms), comprising: an active pharmaceutical ingredient (API) integrated in a thermoplastic polymer (column 3, lines 24-25 and 39-40, extrudable… NVP polymers which, when mixed with the active compound; column 8, line 13, theophylline), wherein: (A) the thermoplastic polymer has a water absorption capacity of about >1 to 90 % w/w of the article (column 3, lines 67-68; column 4, lines 1 and 6-7, the NVP polymer can be rendered hydrophilic via the type and amount of comonomer… they absorb more than 10% by weight of water on storage at 90% relative humidity), and/or (B) the article further comprises a hydrophilic polymer blended with the thermoplastic polymer (column 3, lines 1-6, with one or more auxiliaries; column 4, lines 30-36, Conventional pharmaceutical auxiliaries… for example… methylcellulose, sodium carboxymethylcellulose… cereal starch or corn starch or potato starch; column 8, line 14, starch).

The inventions listed in Groups I and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036008

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

1. ☑ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☑ No protest accompanied the payment of additional search fees.