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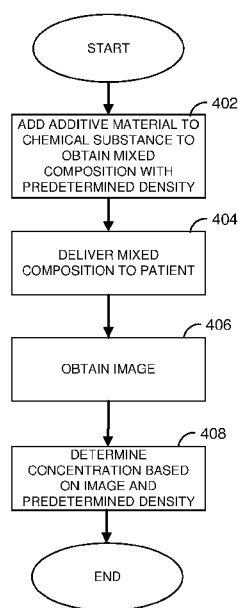


FIG. 4

(57) Abstract: A method of determining a concentration of a chemical substance in a body of a patient includes adding 402 an additive quantity of an additive material to a base quantity of a chemical substance to obtain a mixed composition having a predetermined density and delivering 404 the mixed composition to the body of the patient. The method also includes obtaining 406 an image of at least a portion of the body of the patient and determining 408 a concentration of the chemical substance in the at least a portion of the body of the patient based on the image and the predetermined density of the mixed composition.



**SYSTEM AND METHODS FOR QUANTIFICATION OF SUBSTANCE
CONCENTRATION IN BODY STRUCTURES USING
SPECTRAL COMPUTED TOMOGRAPHY**

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 63/342,503, filed May 16, 2022, which is hereby incorporated by reference for all purposes as if fully set forth herein.

FIELD

[0002] The present disclosure relates to methods for the quantification of substance concentration in body structures using spectral computed tomography (CT).

BACKGROUND

[0003] This section provides background information related to the present disclosure which is not necessarily prior art.

[0004] Chemical substances such as therapeutic substances/medicines are delivered to the body of a patient for various treatments and diagnostic purposes. Such chemical substances can be delivered into certain targeted areas of the body of patient such as target regions, organs or pathologies. It is desirable to deliver the chemical substance to the target location in sufficient and/or known concentrations to deliver a particular therapeutic or diagnostic result. Incorrect or insufficient concentrations may lead to ineffective treatments or results. The delivery of excessive or elevated

concentrations can lead to harmful effects to healthy tissues in the body of the patient or to inconclusive diagnostic results.

[0005] Existing and traditional method of determining concentrations of chemical substances suffer from many drawbacks. Existing and traditional methods may produce inaccurate or qualitative concentration determinations. In addition, existing and traditional methods may not be used in connection with some therapeutic or diagnostic procedures. There exists a need, therefore, for improved methods for determining the concentration of chemical substances in the bodies of patients.

SUMMARY

[0006] This section provides a general summary of the disclosure, and is not a comprehensive disclosure of its full scope or all of its features.

[0007] In some embodiments of the present disclosure, a system and methods are provided that allow the quantification of the concentration of chemical substance in the body of a patient. The chemical substance can include various substances such as therapeutic substances, chemotherapy substances, medicines, diagnostic substances and the like. The chemical substance can be delivered in various forms such as liquids, microspheres, embolic microspheres, radioembolic microspheres, nanoparticles or the like. The method of the present disclosure allows a quantitative determination of the concentration of the chemical substance using a labelling or marking material and the use of spectral or dual energy computed tomography (CT) imaging.

[0008] In some embodiments of the present disclosure, a method of determining a concentration of a chemical substance in a body of a patient includes introducing a marking additive to a chemical substance for introduction into a body of a patient and

obtaining an image of at least a portion of the body of the patient using a spectral computed tomography (CT) imaging device. The method can also include determining a concentration of the chemical substance in the body based on the image.

[0009] In some embodiments of the present disclosure, a method of determining a concentration of therapeutic particles in a body of a patient includes adding a marking quantity of marking particles to a therapeutic quantity of therapeutic particles to obtain a mixed quantity of particles. The marking particles are detectable by a spectral computed tomography (CT) imaging device. The method can also include delivering the mixed quantity of particles to the body of the patient, obtaining an image of at least a portion of the body of the patient using the CT imaging device, and determining a concentration of the therapeutic particles in the body based on the image.

[0010] In some embodiments of the present disclosure, a method of determining a concentration of a chemical substance in a body of a patient includes adding an additive quantity of an additive material to a base quantity of a chemical substance to obtain a mixed composition having a predetermined density. The method can also include delivering the mixed composition to the body of the patient, obtaining an image of at least a portion of the body of the patient, and determining a concentration of the chemical substance in the at least a portion of the body of the patient based on the image and the predetermined density of the mixed composition.

[0011] In some embodiments of the present disclosure, a system includes a source including a chemical substance and a marking additive that is spectrally visible; an imaging device; and a computing device configured to analyze an image captured by the imaging device of a tissue after the chemical substance and the marking additive

have been delivered to the tissue and determine a concentration of the chemical substance in the tissue.

[0012] In an aspect, the chemical substance is non-therapeutic.

[0013] In an aspect, the marking additive is one of iodine and gadolinium. In an aspect, the marking additive is incorporated into the chemical substance.

[0014] In an aspect, the chemical substance and the marking additive flow and deposit homogeneously in vasculature of the tissue.

[0015] In an aspect, a ratio of the chemical substance to the marking additive is known and the concentration of the chemical substance is determined by converting a concentration of marking additive to the concentration of the chemical substance based on the ratio.

[0016] In an aspect, a density of a mixture of the chemical substance and the marking additive is known and the concentration of the chemical substance is determined by based on the density.

[0017] In an aspect, the imaging device is a spectral computed tomography (CT) device.

[0018] In some embodiments of the present disclosure, a method of determining a concentration of a chemical substance in a body of a patient includes obtaining an image of a portion of the body of the patient using a spectral computed tomography (CT) imaging device after a marking additive and the chemical substance have been introduced into the portion of the body of the patient; and determining a concentration of the chemical substance in the portion of the body of the patient based on the image.

[0019] In an aspect, the marking additive is applied as a coating to the chemical substance.

[0020] In an aspect, the concentration of the chemical substance is determined by directly observing and measuring the concentration of the chemical substance.

[0021] In an aspect, the chemical substance and the marking additive are mixed to obtain a mixed composition having a predetermined density, and the concentration of the chemical substance is determined based on the image and the predetermined density of the mixed composition.

[0022] In an aspect, the chemical substance is one of a liquid, microspheres, embolic microspheres, radioembolic microspheres, and nanoparticles.

[0023] In an aspect, the chemical substance and the marking additive are introduced into the body of the patient by subcutaneous, intramuscular, or intravenous injection.

[0024] In some embodiments of the present disclosure, a method of determining a concentration of delivery particles in a body of a patient includes adding a first quantity of marking particles to a second quantity of delivery particles to obtain a mixed quantity of particles, the marking particles detectable by a spectral computed tomography (CT) imaging device; delivering the mixed quantity of particles to the body of the patient; obtaining an image of a portion of the body of the patient using the CT imaging device; and determining a concentration of the delivery particles in the body based on the image.

[0025] In some embodiments of the present disclosure, use of a mixed composition of an additive material and a chemical substance in a predetermined ratio

as a detectable composition within a patient body by an imaging device to determine a concentration of the chemical substance in a portion of the patient body based on an image from the imaging device and the predetermined ratio of the mixed composition.

[0026] In an aspect, the additive material includes a spectrally detectable material such as iodine or gadolinium.

[0027] Further areas of applicability will become apparent from the description provided herein. The description and specific examples in this summary are intended for purposes of illustration only and are not intended to limit the scope of the present disclosure.

DRAWINGS

[0028] The drawings described herein are for illustrative purposes only of selected embodiments and not all possible implementations, and are not intended to limit the scope of the present disclosure.

[0029] FIG. 1 is a diagram illustrating an example treatment system in accordance with some embodiments of the present disclosure.

[0030] FIG. 2 is a flow chart illustrating an example method of determining a concentration of a therapeutic substance in a body of a patient in accordance with some embodiments of the present disclosure.

[0031] FIG. 3 is a flow chart illustrating an example method of determining a concentration of therapeutic particles in a body of a patient in accordance with some embodiments of the present disclosure.

[0032] FIG. 4 is a flow chart illustrating an example method of determining a concentration of a chemical substance in a body of a patient in accordance with some embodiments of the present disclosure.

[0033] Corresponding reference numerals indicate corresponding parts throughout the several views of the drawings.

DETAILED DESCRIPTION

[0034] Example embodiments will now be described more fully with reference to the accompanying drawings.

[0035] Example embodiments are provided so that this disclosure will be thorough, and will fully convey the scope to those who are skilled in the art. Numerous specific details are set forth such as examples of specific components, devices, and methods, to provide a thorough understanding of embodiments of the present disclosure. It will be apparent to those skilled in the art that specific details need not be employed, that example embodiments may be embodied in many different forms and that neither should be construed to limit the scope of the disclosure. In some example embodiments, well-known processes, well-known device structures, and well-known technologies are not described in detail.

[0036] The terminology used herein is for the purpose of describing particular example embodiments only and is not intended to be limiting. As used herein, the singular forms "a," "an," and "the" may be intended to include the plural forms as well, unless the context clearly indicates otherwise. The terms "comprises," "comprising," "including," and "having," are inclusive and therefore specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude

the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. The method steps, processes, and operations described herein are not to be construed as necessarily requiring their performance in the particular order discussed or illustrated, unless specifically identified as an order of performance. It is also to be understood that additional or alternative steps may be employed.

[0037] When an element or layer is referred to as being "on," "engaged to," "connected to," or "coupled to" another element or layer, it may be directly on, engaged, connected or coupled to the other element or layer, or intervening elements or layers may be present. In contrast, when an element is referred to as being "directly on," "directly engaged to," "directly connected to," or "directly coupled to" another element or layer, there may be no intervening elements or layers present. Other words used to describe the relationship between elements should be interpreted in a like fashion (e.g., "between" versus "directly between," "adjacent" versus "directly adjacent," etc.). As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items.

[0038] 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 may be only used to distinguish one element, component, region, layer or section from another region, layer or section. Terms such as "first," "second," and other numerical terms when used herein do not imply a sequence or order unless clearly indicated by the context. Thus, a first element, component, region, layer or section

discussed below could be termed a second element, component, region, layer or section without departing from the teachings of the example embodiments.

[0039] Spatially relative terms, such as "inner," "outer," "beneath," "below," "lower," "above," "upper," and the like, may be used herein for ease of description to describe one element or feature's relationship to another element(s) or feature(s) as illustrated in the figures. Spatially relative terms may be intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if the device in the figures is turned over, elements described as "below" or "beneath" other elements or features would then be oriented "above" the other elements or features. Thus, the example term "below" can encompass both an orientation of above and below. The device may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein interpreted accordingly.

[0040] In various embodiments of the present disclosure, methods of determining a concentration of a chemical substance in the body of a patient are provided. The methods may utilize images obtained using a spectral or dual energy computed tomography (CT) imaging device. Such devices may include the use of two X-ray energy spectra for obtaining imaging information of a body or portion of a body of a patient. Marking or labeling materials may be added or combined with a therapeutic or chemical substance. The marking or labeling material can identify a location and concentration of the chemical substance in the body of a patient. The density of the material(s) delivered to the patient may be used to locate and determine a concentration of the material(s) via a spectral CT image.

[0041] The methods of the present disclosure are improvements over existing and traditional methods of determining or assessing the distribution of therapeutic or other materials in the body of a patient. In existing and traditional methods, a contrast agent may be introduced into the body of patient and then imaged to determine a vasculature or other information regarding blood flow of the patient. These methods do not directly determine a concentration or distribution of a therapeutic substance. Instead, an estimation or quantitative determination is made based on the contrast agent. Inaccuracies often result from such procedures. The existing methods are performed in a procedure prior to the actual clinical treatment. Furthermore, the contrast agent may not behave in the body of the patient in the same manner as the therapeutic substance.

[0042] In other existing methods, a radioactive tracer may be introduced and imaged using imaging devices that can detect such radioactive tracers such as single-photon emission computerized tomography (SPECT) devices or positron emission tomography (PET) devices. Such methods, however, may have similar disadvantages as those described above and do not provide a direct quantitative determination of concentrations of a therapeutic substance (e.g., a radioembolization microsphere).

[0043] The methods of the present disclosure, as described further below, are improvements over these existing or traditional methods by providing direct quantitative determinations of concentrations of chemical substances in the body of a patient undergoing a treatment or diagnostic procedure. The methods of the present disclosure may be employed in a variety of treatments and diagnostic procedures. In various examples, the methods of the present disclosure may be used to determine a

concentration of a therapeutic substance delivered via chemotherapy, an embolic microsphere treatment, a radioembolic microsphere treatment, and the like. In various other examples, the methods of the present disclosure may be used in the context of various diagnostic procedures that may be used to determine blood flow and/or blood volume, determine stroke risk and/or stroke treatments, determine tumor vasculature, determine liver deposits, determine kidney extraction, and the like.

[0044] Referring now to FIG. 1, an example treatment system 100 is shown. The treatment system 100 may include one or more devices that are used to perform a treatment or diagnostic process on a patient 110. The system 100 may include a source 102 that can be used to hold a volume or quantity of a chemical substance 104. The chemical substance can be a therapeutic substance such as a medicine, radioactive material, or the like. The chemical substance 104 can be in the form of a liquid, microparticle, microsphere, nanoparticle, or the like. The source 102 can be a suitable vial, syringe, container, bag or other particle. The chemical substance 104 can be delivered to the patient 110 to perform the treatment or procedure.

[0045] The system 100 may also include an imaging device 106 and a computing device 108. The imaging device 106 may be a dual energy or spectral computed tomography (CT) imaging device. Any suitable spectral CT imaging device can be used including source-based and detector-based spectral CT imaging devices. The computing device 108 can include a processor, memory and transceiver to allow the computing device to receive and send data, store data (such as executable instructions) and a processor to execute operations. The computing device 108 can be a

workstation, desktop computer, laptop, tablet, server, or other suitable computing device.

[0046] As will be further explained below, the methods of the present disclosure can be performed using a system such as the treatment system 100 of FIG. 1. In other examples, however, variations of the treatment system 100 can be used or other systems and apparatuses including systems and apparatuses with more than the elements shown in FIG. 1 or in systems and apparatuses including portions of the system 100.

[0047] Turning now to FIG. 2, an example method 200 of determining the concentration of a therapeutic substance is shown. The method 200 can be performed using treatment system 100, in some embodiments. In others, other systems and apparatuses can be used. The method 200 begins at step 202. At step 202, a marking additive can be introduced to a chemical substance such as a therapeutic substance. In some examples, the therapeutic substance may be a therapeutic microsphere configured to deliver a drug or other therapeutic chemical to a target region in the patient. The marking additive that is added to the therapeutic substance may be various suitable spectrally detectable materials such as Iodine or Gadolinium. The density of such materials, for example, may make the materials spectrally-visible.

[0048] The marking additive can be directly applied to the therapeutic substance. The marking additive can be inherently incorporated into the therapeutic substance by forming microspheres with the marking additive, in some examples. In other examples, the marking additive can be applied as a layer or coating to therapeutic particles, such

as to microspheres. In other examples, other processes can be used to incorporate the marking additive into the therapeutic substance.

[0049] At step 204, an image of the patient is obtained. The image at step 204 is obtained using a spectral CT imaging device, such as imaging device 106 previously described. The image is typically obtained for region of interest such as to an organ, body tissue, vasculature or other portion of the body of the patient. While not shown in FIG. 2, the therapeutic or other chemical substance was previously delivered to the region of interest of the patient. A suitable catheter, syringe, and/or other delivery equipment can inject the therapeutic substance into the patient prior to the imaging at step 204. In this manner, the image obtained at step 204 can indicate a location, distribution and/or concentration of the therapeutic material since such therapeutic material has been marked with marking additive and is spectrally visible.

[0050] At step 206, the concentration of the therapeutic substance can be determined using the image obtained at step 204. Rather than using modeling, prediction, or surrogate measurement, the concentration can be determined by observing and measuring the concentration of the therapeutic material directly. Such determination overcomes and/or improves the shortcomings of existing processes. The determination of concentration of the therapeutic substance is more accurate and can be performed in real-time rather than using pre-treatment or post-treatment procedures.

[0051] Another example method 300 is shown in FIG. 3. The method 300 provides for determining a concentration of therapeutic particles in the body of a patient. The method 300 may begin at step 302. At step 302, marking particles can be added to a quantity of therapeutic particles. The marking particles may be spectrally-visible such

that the marking particles can be detected using a spectral CT imaging device. The marking particles may be various suitable particles. In some examples, the marking particles are chosen based on the type and characteristics of the therapeutic particles being used in a particular treatment for a patient.

[0052] In one example, the marking particle can be a particle that biocompatible with the therapeutic particle and includes a spectrally-visible metal such as Iron. The Iron can be incorporated into a microparticle that has similar characteristics to the therapeutic particle. If the therapeutic particle is an embolic microsphere, the marking particle can be prepared or selected to have a similar density, size, shape and other characteristics of the therapeutic particle. The marking particle can be selected so as to have similar flow characteristics of the therapeutic particle so that when the mixture of marking particles and therapeutic particles is delivered to the patient, the mixture flows and deposits homogeneously in the vasculature of the patient. In some examples, the marking particles can be produced to have desired characteristics for use with a particular treatment and complimentary therapeutic particle. In other examples, various marking particles can be produced with various predetermined characteristics and a marking particle can be selected from the various marking particle options.

[0053] The marking particles and the therapeutic particles can be mixed in predetermined quantities. In one example, a predetermined marking quantity of the marking particles and a predetermined therapeutic quantity of therapeutic particles can be combined at step 302. With known or predetermined quantities of each type of particle, the mixture defines a known ratio of marking particles to therapeutic particles.

The quantities can be measured and combined using weighing, volumetric or other measuring techniques.

[0054] At step 304, the mixed particles (i.e., the mixture of marking particles and therapeutic particles) can be delivered to the body of the patient. While not shown in FIG. 3, the mixed particles can be stirred, agitated, shaken or otherwise mixed to increase the homogeneity of the mixture. It is important to have a homogenous mixture to improve the accuracy of the concentration determination that will be performed later in the method. The mixture can be delivered using a syringe, catheter and/or other delivery tools. The mixture can be delivered to predetermined target tissue, tumor, vasculature, or other body tissue.

[0055] At step 306, the patient is imaged using a spectral CT imaging device, such as the imaging device 106 previously described. Since the marking particles are spectrally-visible, the marking particles are visible and/or detectable in the image.

[0056] At step 308, the concentration of the therapeutic particles is determined. The concentration can be determined by observing and/or detecting the concentration of marking particles and then converting the concentration of marking particles to the concentration of therapeutic particles. The ratio and/or relationship between the marking particles and the therapeutic particles can be known based on the relative quantities of particles combined at step 302. In other examples, modeling of the vasculature and/or experimental testing can be used to determine a relationship between the concentrations of the marking particles and/or the therapeutic particles.

[0057] Another example method 400 of the present disclosure is shown in FIG. 4. The method 400 provides an example method for determining a concentration of a

chemical substance in the body of a patient. The method 400 may be performed, for example, using the treatment system 100. In other examples, other systems and/or apparatuses can be used.

[0058] The method 400 may begin at step 402. At step 402, an additive material may be combined with a chemical substance to obtain a composition with a predetermined density. The chemical substance may be various therapeutic substances or diagnostic substances. The chemical substance may be, for example, a drug, chemotherapy agent, an embolic microsphere containing a therapeutic drug, a diagnostic agent or the like. The additive material may be a second type of particle, microsphere, nanoparticle, fatty material, microbubble or the like.

[0059] The density of the chemical substance and the density of the additive material may be known or predetermined prior to the performance of the method 400. In other examples, the additive material may be produced to have a density of a predetermined value. When the additive material is added to the chemical substance, the mixed composition may have a combined density that is known or predetermined. The additive material can be produced and/or configured to make the combined mixture of the chemical substance and the additive material spectrally-visible via a spectral CT imaging device.

[0060] The combined mixture of the additive material and the chemical substance can be delivered to the patient at step 404. The mixed composition can be delivered using various delivery tools such as a catheter, syringe, pump, needle or the like. The mixed composition can be delivered to a target tissue such as a tumor, organ, region of the body, or other region of interest.

[0061] At step 406, an image can be obtained of the region of interest. The image can be obtained by the imaging device 106. The imaging device can be a spectral CT imaging device. Through the use of the spectral CT imaging device and the known density of the mixture composition, the mixed composition can be detected and/or is spectrally-visible in the image.

[0062] At step 408, the concentration of the chemical substance can be determined based on the image obtained at step 406 and the predetermined density of the mixed composition. Because the spectral properties of the mixed composition is known, the concentration of the chemical substance can be determined by observing and/or analyzing the image of the region of interest.

[0063] The methods 200, 300, 400 are improvements over existing and traditional methods by providing methods for determining the concentration of chemical substances in the body of a patient with improved accuracy and speed. Since the substances that are delivered to the patient are spectrally visible, the location and distribution of the chemical substances can be directly visible during treatment without the need to wait for post-treatment imaging systems. In addition, the medical professionals performing the treatment can obtain real-time information during treatment to make adjustments, changes or modifications during treatment. These improvements increase the likelihood of an effective treatment.

[0064] As discussed above, the use of spectral CT imaging equipment can allow the capture of information characterizing the concentration of a chemical substance in the tissue of a patient. When the densities of the chemical substance and an additive material are known, the concentration of the chemical substance can be determined.

Furthermore, spectral CT imaging can be used to monitor and/or determine a perfusion measurement and a concentration achieved during a treatment. After the two-part composition (including a therapeutic substance and a marking substance, e.g., iodine or gadolinium) is delivered to the target tissue, spectral CT imaging can be used to determine a concentration that is delivered to the target tissue and then the concentration of the therapeutic that remains in the tissue. The changes in density in the tissue can be used and imaged using the spectral CT imaging device to determine the achieved concentration and the concentration of therapeutic that remains in the tissue.

[0065] The use of the density of the chemical substance and/or the additive material can be used to determine a location and concentration of material in a target tissue of the patient. The methods of the present disclosure can be used to determine a concentration of a therapeutic after the therapeutic is delivered to the patient. In addition, the methods of the present disclosure can also be used to continuously monitor the administration of therapeutic over time. By using region-of-interest (ROI) imaging, a focused aperture can be used to focus imaging energy on a targeted region of interest. The imaging can provide continuous (or semi-continuous) information regarding the concentration of a therapeutic substance in a body tissue. This information can be used to control a dosing of the therapeutic to prevent under or over dosing of the therapeutic. Such a method of treatment can be useful, for example, in the context of chemotherapy.

[0066] In addition to providing valuable information for the delivery and administration of therapeutics, this use of a spectral CT scan can also be applied in

diagnostic procedures. For example, the methods of the present disclosure can be used to determine a vasculature of various organs such as the brain, lung, liver, kidney and others.

[0067] One or more steps of the methods 200, 300, 400 may be performed by a computing device such as computing device 108 (FIG. 1). The computing device 108 may include a concentration determination engine that can determine a concentration of the therapeutic or other chemical substance automatically based on the image obtained from the imaging device 106. Such information can be displayed to a medical professional or other user via a suitable user interface or other reporting tool.

[0068] The foregoing description of the embodiments has been provided for purposes of illustration and description. It is not intended to be exhaustive or to limit the disclosure. Individual elements or features of a particular embodiment are generally not limited to that particular embodiment, but, where applicable, are interchangeable and can be used in a selected embodiment, even if not specifically shown or described. The same may also be varied in many ways. Such variations are not to be regarded as a departure from the disclosure, and all such modifications are intended to be included within the scope of the disclosure.

CLAIMS

What is claimed is:

1. A system comprising:
a source including a chemical substance and a marking additive that is spectrally visible;
an imaging device; and
a computing device configured to analyze an image captured by the imaging device of a tissue after the chemical substance and the marking additive have been delivered to the tissue and determine a concentration of the chemical substance in the tissue.
2. The system of claim 1, wherein the chemical substance is non-therapeutic.
3. The system of claim 1 or 2, wherein the marking additive is one of iodine and gadolinium.
4. The system of claim 1, 2, or 3, wherein the marking additive is incorporated into the chemical substance.
5. The system of claim 1 or 2, wherein the chemical substance and the marking additive flow and deposit homogeneously in vasculature of the tissue.
6. The system of claim 5, wherein a ratio of the chemical substance to the marking additive is known and the concentration of the chemical substance is determined by converting a concentration of marking additive to the concentration of the chemical substance based on the ratio.
7. The system of claim 5, wherein a density of a mixture of the chemical substance and the marking additive is known and the concentration of the chemical substance is determined based on the density.

8. The system of any of claims 1 to 7, wherein the imaging device is a spectral computed tomography (CT) device.

9. A method of determining a concentration of a chemical substance in a body of a patient, the method comprising:

obtaining an image of a portion of the body of the patient using a spectral computed tomography (CT) imaging device after a marking additive and the chemical substance have been introduced into the portion of the body of the patient; and

determining a concentration of the chemical substance in the portion of the body of the patient based on the image.

10. The method of claim 9, wherein the chemical substance is a non-therapeutic substance.

11. The method of claim 9 or 10, wherein the marking additive is applied as a coating to the chemical substance.

12. The method of any of claims 9-11, wherein the concentration of the chemical substance is determined by directly observing and measuring the concentration of the chemical substance.

13. The method of claim 9, wherein
the chemical substance and the marking additive are mixed to obtain a mixed composition having a predetermined density, and
the concentration of the chemical substance is determined based on the image and the predetermined density of the mixed composition.

14. The method of any of claims 9-13, wherein the chemical substance is one of a liquid, microspheres, embolic microspheres, radioembolic microspheres, and nanoparticles.

15. The method of any of claims 9-14, wherein the chemical substance and the marking additive are introduced into the body of the patient by subcutaneous, intramuscular, or intravenous injection.

16. A method of determining a concentration of delivery particles in a body of a patient, the method comprising:

adding a first quantity of marking particles to a second quantity of delivery particles to obtain a mixed quantity of particles, the marking particles detectable by a spectral computed tomography (CT) imaging device;

delivering the mixed quantity of particles to the body of the patient;

obtaining an image of a portion of the body of the patient using the CT imaging device; and

determining a concentration of the delivery particles in the body based on the image.

17. The method of claim 16, wherein the delivery particles are a non-therapeutic substance.

18. The method of claim 16 or 17, wherein the marking particles and the delivery particles flow and deposit homogeneously in vasculature of the body of the patient.

19. Use of a mixed composition of an additive material and a chemical substance in a predetermined ratio as a detectable composition within a patient body by an imaging device to determine a concentration of the chemical substance in a portion of the patient body based on an image from the imaging device and the predetermined ratio of the mixed composition.

20. The use as defined in claim 19, wherein the additive material includes a spectrally detectable material such as iodine or gadolinium.

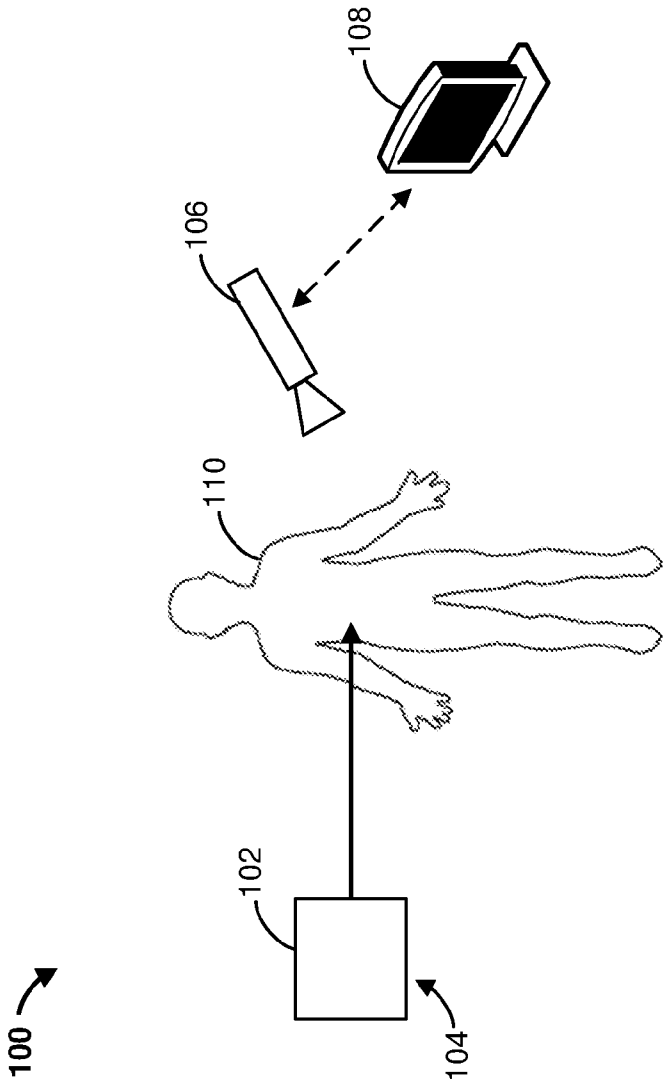
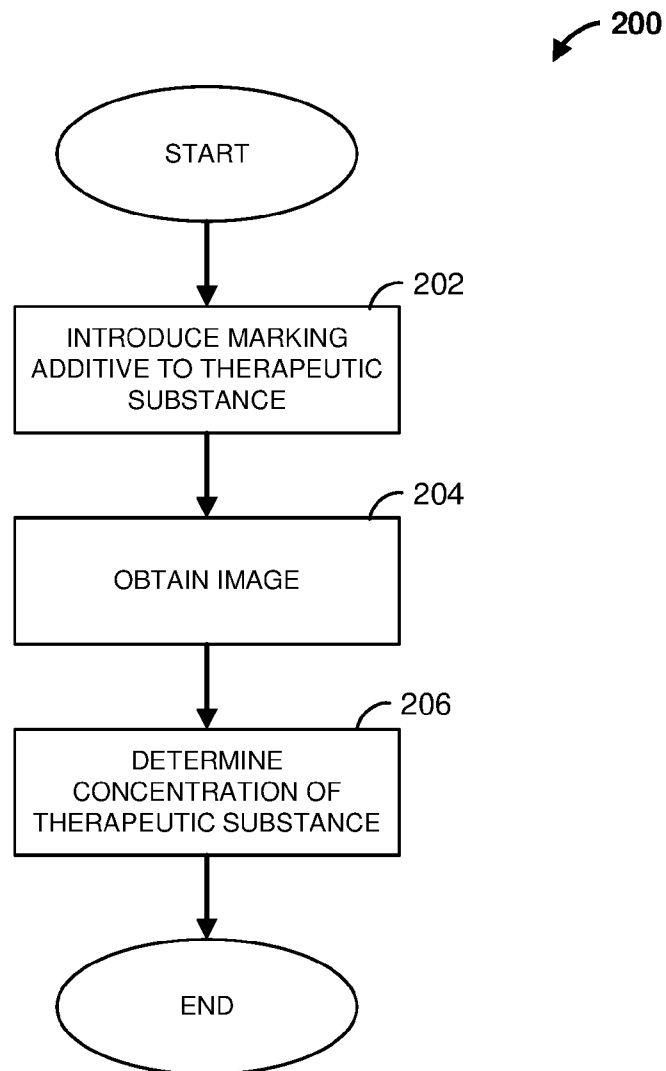


FIG. 1

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**FIG. 2**

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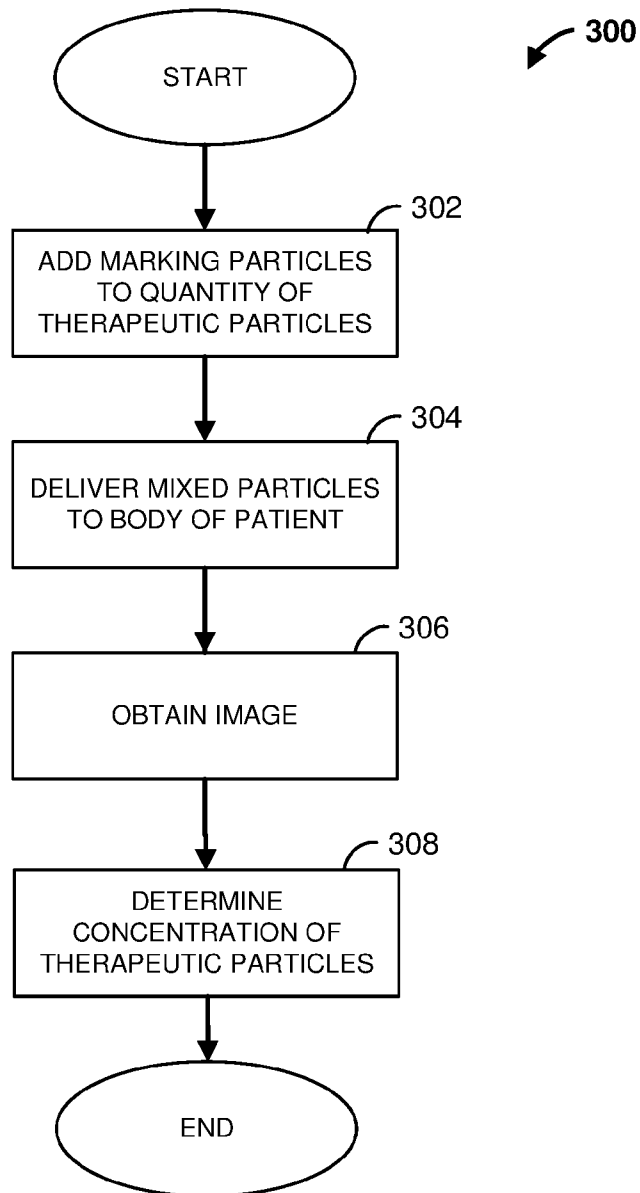


FIG. 3

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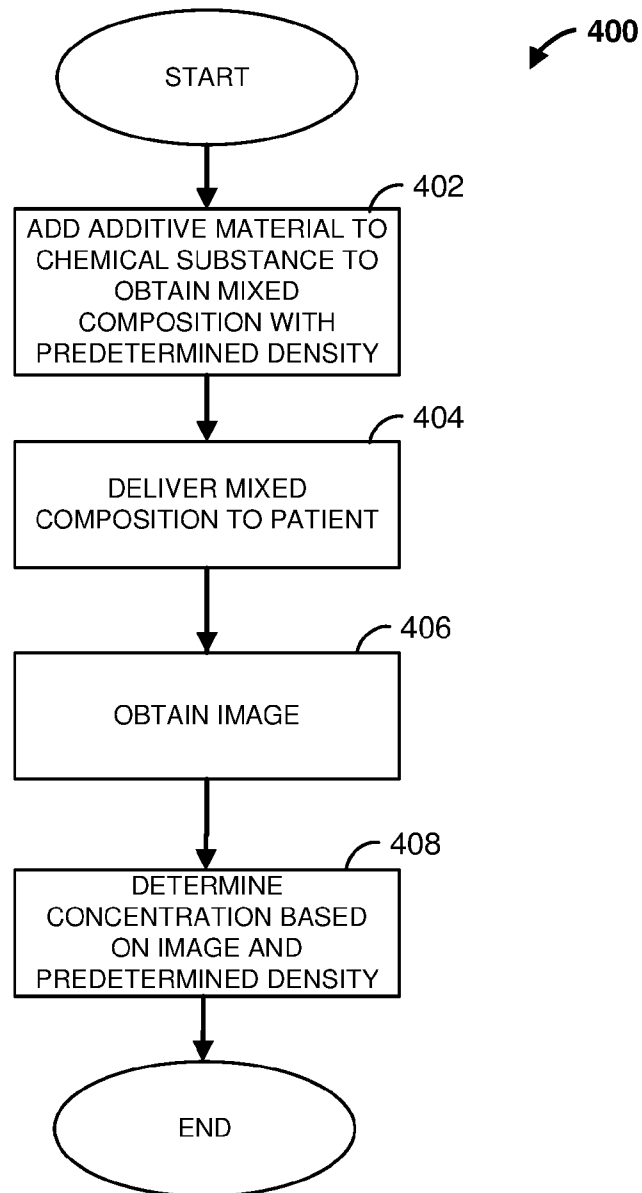


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/022249

A. CLASSIFICATION OF SUBJECT MATTER INV. A61B6/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61B		
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		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/301082 A1 (ALLMENDINGER THOMAS [DE] ET AL) 19 October 2017 (2017-10-19)	1-5, 7, 8
Y	abstract figures 1-7 paragraph [0003] - paragraph [0237] -----	6
X	US 2013/116554 A1 (KAISER CLEMENS [GB] ET AL) 9 May 2013 (2013-05-09) abstract figures 1-12 paragraph [0001] - paragraph [0107] -----	1
Y	US 2018/110492 A1 (YEH BENJAMIN M [US] ET AL) 26 April 2018 (2018-04-26) abstract figures 1-20 paragraph [0003] - paragraph [0176] -----	6
☐ 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 "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
24 August 2023		31/08/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Moehrs, Sascha

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/022249

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **9-20**
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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:

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 an 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 9-20

Method claim 9 discloses the determination of a concentration of a chemical substance in a body of a patient. From the description as well as from dependent claim 15, it is apparent that the chemical substance has to be administered to the patient, e.g. via intravenous injection. Such an administration is not considered to be optional step in the present context, thus, independent claim 9 also encompasses the injection. Independent method claim 9 is therefore considered as a method for treatment of the human or animal body by surgery for which no search and no preliminary examination is carried out (Rules 39.1(iv) and 67.1(iv) PCT). The above argumentation applies mutatis mutandis to the method and use claims 10 - 20, as all of them require the administration of the substance.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2023/022249

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2017301082 A1	19-10-2017	CN 106815813 A DE 102016221684 A1 US 2017301082 A1	09-06-2017 01-06-2017 19-10-2017
US 2013116554 A1	09-05-2013	AU 2011278377 A1 BR 112012033776 A2 CA 2801828 A1 CL 2013000100 A1 CN 102985114 A CN 105194692 A EP 2593143 A1 IL 223469 A JP 2013531685 A JP 2016193921 A KR 20130116237 A NZ 605674 A RU 2012155122 A SG 186905 A1 TN 2012000621 A1 US 2013116554 A1 WO 2012007456 A1	21-02-2013 01-11-2016 19-01-2012 19-07-2013 20-03-2013 30-12-2015 22-05-2013 29-10-2015 08-08-2013 17-11-2016 23-10-2013 28-11-2014 20-08-2014 28-02-2013 01-04-2014 09-05-2013 19-01-2012
US 2018110492 A1	26-04-2018	CA 2978203 A1 CN 107847445 A CN 113499451 A EP 3285743 A1 EP 3960159 A1 ES 2890328 T3 JP 6947636 B2 JP 2018513837 A JP 2022003054 A PL 3285743 T3 US 2018110492 A1 US 2022096030 A1 WO 2016172256 A1	27-10-2016 27-03-2018 15-10-2021 28-02-2018 02-03-2022 18-01-2022 13-10-2021 31-05-2018 11-01-2022 06-12-2021 26-04-2018 31-03-2022 27-10-2016