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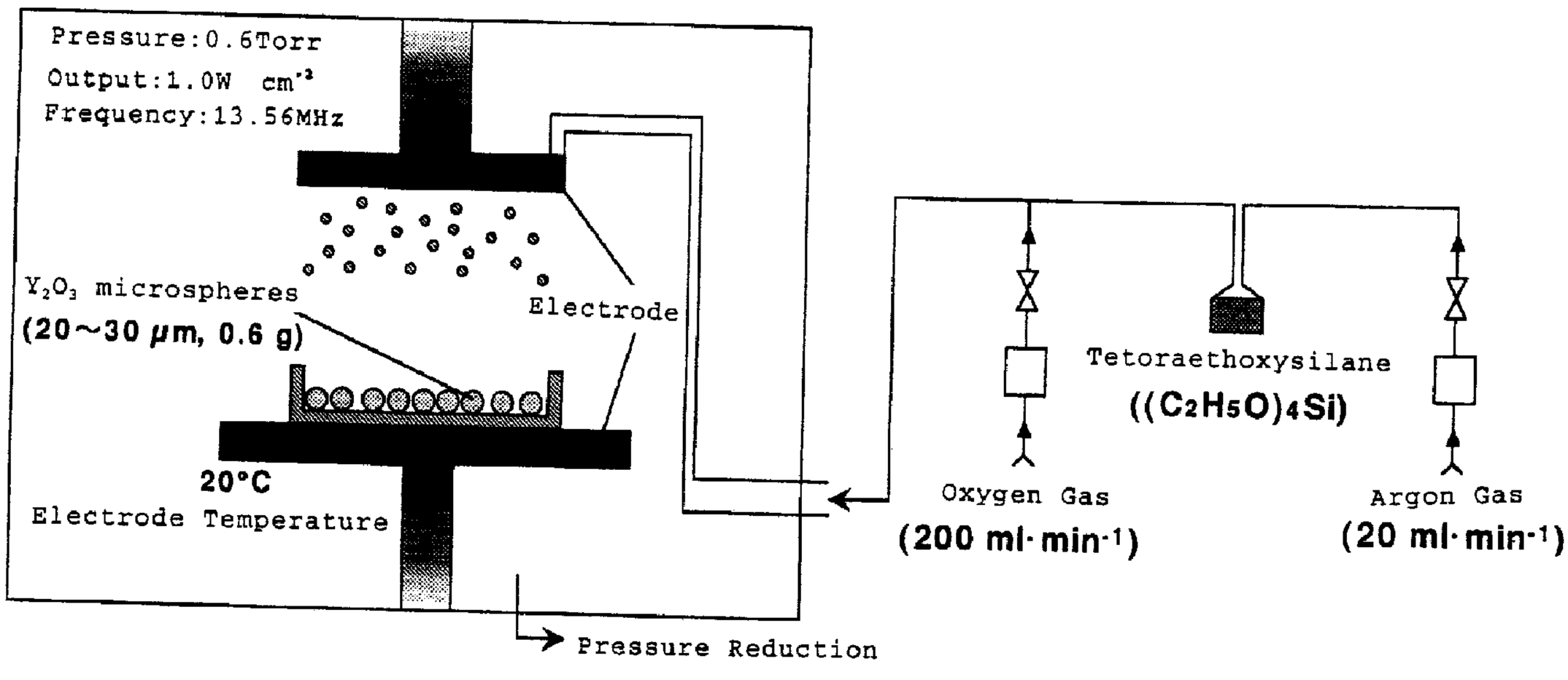
(71) Demandeurs/Applicants:
NETUREN CO, LTD., JP;
KANSAI TECHNOLOGY LICENSING ORGANIZATION CO., LTD., JP

(72) Inventeurs/Inventors:
SAWADA, YOSHIKI, JP;
SHIMIZU, YASUHIRO, JP;
YAMAZAKI, TAKAO, JP;
INOUE, YOSHIAKI, JP;
NAGATA, YASUSHI, JP;
...

(74) Agent: R. WILLIAM WRAY & ASSOCIATES

(54) Titre : MICROSPHERE RADIOACTIVE ET PROCEDE DE FABRICATION
(54) Title: RADIOACTIVE MICROSPHERE AND METHOD FOR PREPARATION THEREOF



(57) Abrégé/Abstract:
A microsphere which is capable of irradiating radioactive rays in a human body for a long period of time, is excellent in chemical durability, and has a diameter of 1 to 100 μm, characterized in that it comprises 99 wt % or more of a crystal of an oxide which contains 47 wt % or more of radioactive yttrium, such as Y_2O_3 or YPO_4, the balance being inevitable impurities.

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(72) **Inventeurs(suite)/Inventors(continued)**: HIRAOKA, MASAHIRO, JP; KAWASHITA, MASAKAZU, JP; KOKUBO, TADASHI, JP

ABATRACT

A microsphere which is excellent in chemical durability and capable of emitting a radiation for a long period of time in the body, and has a diameter of 1 to 100 μm, characterized in that it comprises not less than 99% by weight of an oxide crystal containing 47% by weight or more of radioactive yttrium, such as Y_2O_3 and YPO_4 and the balance of inevitable impurities.

(57)要約

化学的耐久性に優れ、体内で長期的に放射能を放射する直径１～１００μｍの微小球である。Y_2O_3やYPO_4などの放射性のイットリウムを４７重量％以上含む酸化物結晶９９重量％以上、残部不可避不純物からなることを特徴とする。

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SPECIFICATION

RADIOACTIVE MICROSPHERES EXCELLENT IN CHEMICAL DURABILITY AND METHOD FOR MANUFACTURING THE SAME

Technical Field

The present invention relates to radioactive microspheres excellent in chemical durability, in particular microspheres favorably applicable for treating affected regions of a cancer patient by directly irradiating the regions with a radiation after injecting the radioactive microspheres into the patient's body.

Background Art

The therapeutic methods for irradiating affected regions with a radiation for treating a cancer have an advantage that functional recoveries of organs can be expected over surgical methods by which the organs are excised. Among the methods described above, use of a therapeutic method for directly irradiating tumors with a radiation by injecting radioactive microspheres into the affected region through the blood vessel by means of a catheter is thought to be promising, since a sufficient dosage of radiation can be irradiated to the affected region without damaging normal tissues just under the surface of the body, as compared with a therapeutic method by which

the radiation is irradiated from the outside of the body.

However, the radioactive microspheres with a too large particle size may be detained before they arrive at the affected region, while those with a too small particle size will penetrate through capillary blood vessels to fail in retaining them at the affected region. When the microspheres are readily dissolved in the body, on the other hand, radioactive elements are transferred to other portions in the body and normal cells are also damaged. A too long half-life also damages the normal tissues by emitting radioactive rays after the therapy, and a too short half-life causes a rapid decay of radioactivity to make the therapy unavailable. From these situations, the microspheres are required to have a diameter of 1 to 100 μm, preferably 20 to 30 μm, to be excellent in chemical durability, and to have a proper half-life.

Materials to be used for the conventional microspheres include an yttria-alumina-silica glass or a glass containing a small amount of phosphorous, wherein the non-radioactive element yttrium or phosphorous in the glass is converted into a β-emitter yttrium or phosphorous by irradiating slow neutrons (Japanese Patent Application Publication No. 6-62439). The glass named as YAS-4 in the patent publication and having a composition ratio of Y_2O_3 : Al_2O_3 : SiO_2 = 40 : 20 : 20 in % by weight (Y_2O_3 : Al_2O_3 : SiO_2 = 19 : 17 : 64 in mol%) has a most excellent chemical

durability among the substances disclosed in the patent, and the microspheres having a proper particle size can be manufactured by a usual melting method.

Since β-emitter yttrium has a half-life as short as 64.1 hours, its radioactivity is remarkably decayed during transportation to a hospital after irradiating neutrons in a nuclear reactor. Accordingly, it is required for using the glass microspheres described in Japanese Patent Application Publication No. 6-62439 that the glass spheres contain as much yttria as possible.

However, the content of yttria is naturally restricted within a range capable of forming a glass, since the microspheres described in the patent publication is formed after manufacturing the glass. Since a large quantity of lactic acid is secreted at the tumors, pH in the vicinity of the microspheres is conjectured to be substantially low. The glass described in the patent publication above has a tendency that its chemical durability decreases as the content of yttria turns out to be high.

Phosphorous is also converted from a non-radioactive element to a β-emitter as in the case of yttrium by irradiating with slow neutrons. The β-emitter phosphorous has a considerably longer half-life of 14.3 days.

However, a glass containing a large quantity of phosphorous while being excellent in chemical durability

has not been developed yet. Phosphorous in the currently available glass containing a large quantity of phosphorous is rapidly dissolved out of the glass in the body.

Accordingly, the object of the present invention is to provide microspheres being excellent in chemical durability, emitting a radiation for a long period of time in the body, and having a diameter of 1 to 100 μm.

Disclosure of Invention

Radioactive microspheres for attaining the object of the present invention comprise not less than 99% by weight of an oxide crystal containing 47% by weight or more of radioactive yttrium, and the balance of inevitable impurities.

The conventional yttria-alumina-silica glass (with a composition ratio of Y_2O_3 : Al_2O_3 : SiO_2 = 40 : 20 : 40 in % by weight) contains yttrium in a proportion of 31.5 % by weight (40 $\times$ 88.91 $\times$ 2/225.82). On the contrary, the radioactive microspheres according to the present invention having the composition as described above contain yttrium in a proportion of 47% $\times$ 0.99 = 46.5 % by weight or more, which is by 1.47 times as much as the yttrium content in the conventional glass. Accordingly, the remaining content of radioactive yttrium amounts 1.47 times as high as the radioactive yttrium in the conventional glass even after the half-life.

Since the weight fraction of yttrium in yttria is 88.91 × 2/225.82 when the oxide crystal is represented by Y_2O_3, the yttrium content is 78 % by weight or more, which is 2.47 times as high as the yttrium content in the conventional glass. Accordingly, a radiation with a dosage by 2.47 times as large as that of the conventional glass can be irradiated on the affected region.

The oxide crystal may be YPO_4, or a mixture of Y_2O_3 and YPO_4. While the lower limit of the yttrium content in the entire microspheres decreases to 48 % by weight when the oxide crystal is represented by YPO_4, the Y content remains to be higher than the conventional glass. Furthermore, since phosphorous having a substantially longer half-life is involved in place, radioactivity is additionally increases.

The radioactive microspheres according to the present invention may be coated with a film comprising at least one of the compounds selected from silica (SiO_2), titania (TiO_2), alumina (Al_2O_3), iron (III) oxide (Fe_2O_3), silicon nitride (Si_2N_3, SiN, Si_3N_4), aluminum nitride (AlN), titanium nitride (TiN), iron nitride (Fe_2N, Fe_4N), silicon carbide (SiC) and titanium carbide (TiC). Since these coating films do not emit harmful α- or γ-ray after irradiating with neutrons while having an acid resistant property, the radioactive elements are not dissolved in the strongly acidic body fluid at the tumors to enable a long

irradiation of the tumor with the radiation. The preferable thickness of the coating film is 0.01 to 5 μm. When the thickness is less than 0.01 μm, erosion of acids is not effectively prevented while, when the thickness exceeds 5 μm, the proportion of yttrium in the entire microspheres becomes too small. Silica is the most preferable material for forming the coating film.

An appropriate method for manufacturing the microspheres according to the present invention is as follows.

At first, an oxide powder as a starting material containing yttrium, or yttrium and phosphorous, is melted by allowing the powder to pass through a thermal-plasma to obtain microspheres containing non-radioactive yttrium (or yttrium and phosphorous). The powder material can be melted, for example, by allowing it to pass through a thermal-plasma or laser beam. Yttria may be efficiently formed into spheres by the high temperature of the thermal-plasma, and phosphorous components in yttrium phosphate is not decomposed since the thermal-plasma is a heat source that does not use reactive gases such as oxygen and steam. However, the heating means are not restricted to the thermal-plasma and laser beam. Then, yttrium (or yttrium and phosphorous) is (are) turned into a radioactive element (elements) by irradiating with an effective dosage of neutrons. In order to enhance chemical durability, it

is recommended to heat the microspheres in an oxidizing atmosphere before irradiating with the neutrons.

For forming the oxide coating film on the surface, the microspheres and a starting material of the coating film are placed in a plasma polymerization apparatus to form the coating film on the surface of the microspheres by plasma polymerization, followed by irradiating an effective dosage of neutrons to yttrium (or yttrium and phosphorous). Si, Ti, Al, Fe, O, N and C constituting the coating film are preferable as the coating film materials since they do not emit harmful radiation (α-ray and γ-ray) by being irradiated with neutrons. While plasma polymerization is one example of the methods for forming the coating film, other methods such as a sputtering method, a vacuum deposition method, a deposition method from solution, a chemical vapor deposition method, a molecular beam epitaxy method, ion-beam vapor deposition method and a sol-gel method may be used.

Brief Description of the Drawings

Fig. 1 describes a condition for forming the coating film on the substrate by plasma polymerization.

Fig. 2 shows a SEM photograph for observing the spherical shapes of the microspheres before and after forming the coating film.

Best Mode for Carrying Out the Invention

EXAMPLE 1

A fine powder containing 99.9 % by weight of yttria was melted with a high frequency induction thermal-plasma under the following condition to form into spheres.

Powder feed carrier gas: Ar 5L/min

Plasma gas composition: Ar 90 L/min + O_2 5L/min

High frequency generator: anode input 40 kW,

output frequency 4 MHz

A group of the microspheres were dispersed in ultra pure water with a specific conductance of 18 $M\Omega \cdot cm$, and classified with a nylon sieve to obtain microspheres containing not less than 99 % by weight of Y_2O_3 and having a diameter of 20 to 30 μm. The microspheres obtained were subjected to the following chemical durability test.

The microspheres (0.2g) were placed in a polypropylene bottle together with 20 ml of distilled water and, while maintaining the water temperature at 95°C in an oil bath, the bottle was shaken for 7 days with a stroke length of 3 cm at a speed of 120 strokes/min. After filtering the solution, the yttrium content in the filtrate was assayed by a high frequency inductively coupled plasma atomic emission spectrometry (ICP). The result showed that the proportion of dissolved yttrium is 1 ppm or less.

COMPARATIVE EXAMPLE 1

The chemical durability test was carried out under

the same condition as in Example 1, except that a glass with a composition ratio of Y_2O_3 : Al_2O_3 : SiO_2 = 40 : 20 : 20 was used for the radioactive microspheres, in place of the microspheres in Example 1. The result showed that the proportion of dissolved yttrium is 6 ppm.

A comparison of the result in Example 1 with the result in Comparative Example 1 shows that the microspheres comprising yttria according to the present invention are superior to the glass microspheres in chemical durability.

EXAMPLE 2

Microspheres containing 99 % by weight or more of YPO_4 and having a diameter of 20 to 30 μm were manufactured by the same method as in Example 1 for manufacturing the yttria microspheres. These microspheres were heated at 900°C in the atmosphere for four hours.

The microspheres after heating were subjected to the same chemical durability test as in Example 1. The result showed that the proportion of dissolved yttrium and dissolved phosphorous were 1.2 ppm and 1.7 ppm, respectively. When the same chemical durability test was applied to the microspheres before heating in the atmosphere, the proportion of dissolved yttrium and dissolved phosphorous were 0.73 ppm and 85 ppm, respectively.

Accordingly, it was made clear that chemical durability is remarkably improved by heat treating the microspheres comprising the oxide crystal according to the

present invention, even when the microspheres contain phosphorous that is liable to be readily dissolved out.

EXAMPLE 3

Microspheres (0.6g) obtained by the same manufacturing method as in Example 1 and containing 99 % by weight or more of Y_2O_3 with a diameter of 20 to 30 μm were placed in a polystyrene container with a size of 20 × 20 × 5 mm^3. The container was placed in a plasma polymerization apparatus (Moldel BP-2, made by Samco International Research Laboratories, Co.) as shown in Fig. 1 to coat the surface of the microspheres with a SiO_2 film. Tetraethoxy silane (made by Shinetsu Chemical Industry Co.) was used as the starting material of SiO_2, oxygen was used as the reactive gas, and argon was used as a carrier gas. The conditions in this example were: inner pressure of the reaction chamber - 0.6 Torr; output - 1.0 $w \cdot cm^{-2}$; oxygen gas flow rate - 200 ml/min^{-1}, argon gas flow rate - 20 ml/min^{-1}; and electrode temperature - 20°C. For uniformly coating the entire surface of the microspheres, the film deposition time was adjusted to 15 minutes per one film deposition run, the polystyrene container was shaken after the first film deposition run, and the film deposition process was repeated again. The film deposition was repeated 4 times in total.

The microspheres coated with the SiO_2 film were observed under a scanning electron microscope (SEM, Model S-2500CX, made by Hitachi, Ltd.) to compare the coated

microspheres with those before coating. The result in Fig. 2 showed that the shape was not changed even after coating, indicating that the coating film can be formed on the surface without changing the shape of the microspheres.

The microspheres with the coating film was subjected to the chemical durability test under the same condition as in Example 1, showing that the proportion of dissolved yttrium was 1 ppm or less.

EXAMPLE 4

The chemical durability test was applied to the microspheres with the coating film in Example 3 by the same condition as in Example 3, except that a buffer solution with pH 4 (0.05 M potassium hydrogen phthalate ($C_6H_4(COOK)(COOH)$) was used in place of distilled water. The assay result showed that the proportion of dissolved yttrium was 3 ppm.

REFERENCE EXAMPLE

The chemical durability test was applied to the microspheres used in Example 1 under the same condition as in Example 4 without forming the coating film. The result showed that the proportion of dissolved yttrium reaches 120 ppm.

COMPARATIVE EXAMPLE 2

The chemical durability test was applied to the glass microspheres used in Comparative Example 1 under the same condition as used in Example 4. The assay result showed

that the proportion of dissolved yttrium was 1.59×10^3 ppm.

Comparisons of the results in Examples 3 and 4 with the results in Reference Example and Comparative Example 2 showed that acid resistance remarkably increases by forming the coating film on the surface of the microspheres.

Industrial Applicability

The radioactive microspheres of the present invention as hitherto described contains a high concentration of radioactive elements that are hardly dissolved. Accordingly, the microspheres are useful as a medical material for treating tumors by direct irradiation of radiation by embedding the microspheres in the vicinity of the tumors.

CLAIMS

1. A radioactive microsphere comprising not less than 99% by weight of an oxide crystal containing 47% by weight or more of radioactive yttrium, and the balance of inevitable impurities.

2. The radioactive microsphere according to claim 1, wherein the oxide crystal consists essentially of Y_2O_3.

3. The radioactive microsphere according to claim 1, wherein the oxide crystal consists essentially of YPO_4, or a mixture of Y_2O_3 and YPO_4.

4. The radioactive microsphere according to claim 1, wherein the microsphere has a diameter of 1 to 100 μm.

5. The radioactive microsphere according to claim 1, wherein the microsphere has a diameter of 20 to 30 μm.

6. The radioactive microsphere according to any one of claims 1 to 5, wherein the microsphere is coated with a film comprising at least one of the compounds selected from silica (SiO_2), titania (TiO_2), alumina (Al_2O_3), iron (III) oxide (Fe_2O_3), silicon nitride (Si_2N_3, SiN, Si_3N_4), aluminum nitride (AlN), titanium nitride (TiN), iron nitride (Fe_2N,

Fe_4N), silicon carbide (SiC) and titanium carbide (TiC).

7. The radioactive microsphere according to claim 6, wherein the film has a thickness of 0.01 to 5 μm.

8. A method of producing a radioactive microsphere, the method comprising preparing a microsphere comprising not less than 99% by weight of an oxide crystal containing 47% by weight or more of non-radioactive yttrium, and the balance of inevitable impurities through melting of a starting material, followed by irradiating with an effective dosage of slow neutrons to turn non-radioactive yttrium into a radioactive element.

9. A method of producing a radioactive microsphere, the method comprising preparing a microsphere comprising not less than 99% by weight of an oxide crystal containing 47% by weight or more of non-radioactive yttrium and an amount of phosphrous, and the balance of inevitable impurities through melting of a starting material, followed by heating the microsphere in an oxidizing atmosphere and then irradiating with an effective dosage of slow neutrons to turn non-radioactive yttrium into a radioactive element.

10. The method according to claim 8 or 9, further comprising coating the microsphere with a film after preparing the

microsphere or heating in the oxidizing atmosphere and before irradiating with an effective dosage of slow neutrons, the film comprising at least one of the compounds selected from silica (SiO_2), titania (TiO_2), alumina (Al_2O_3), iron (III) oxide (Fe_2O_3), silicon nitride (Si_2N_3, SiN, Si_3N_4), aluminum nitride (AlN), titanium nitride (TiN), iron nitride (Fe_2N, Fe_4N), silicon carbide (SiC) and titanium carbide (TiC).

FIG. 1

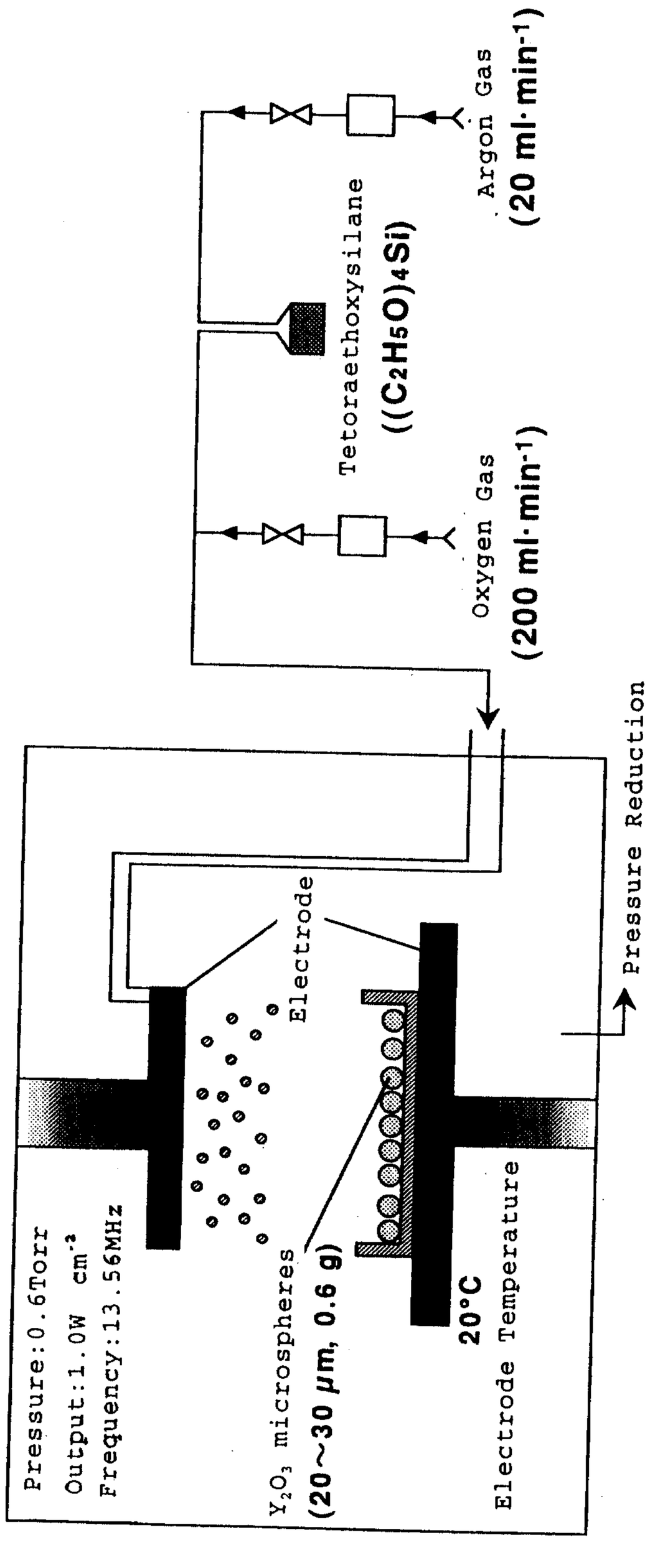
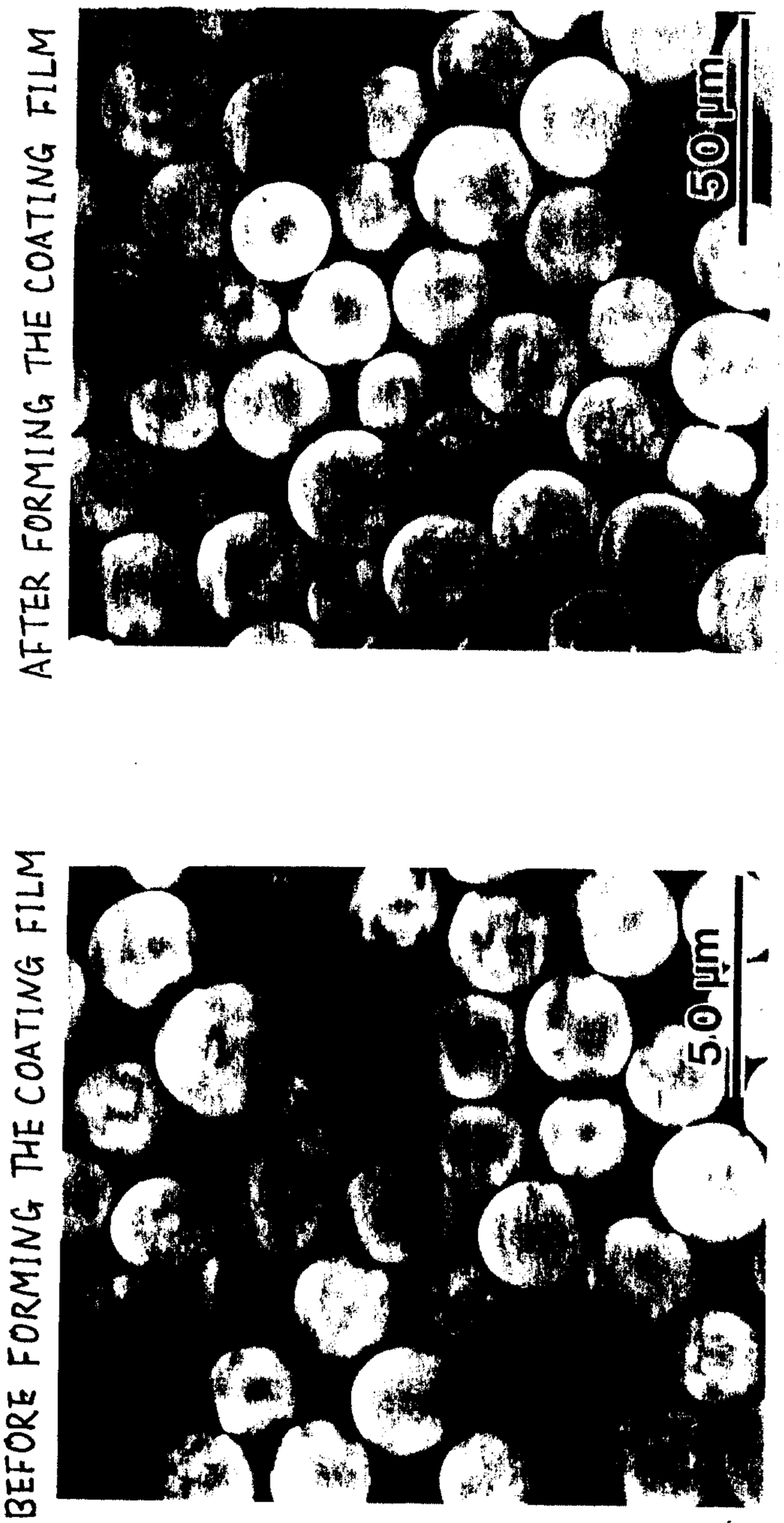

Argon Gas
(20 ml·min-1)
Tetoraethoxysilane
((C2H5O)4Si)
Oxygen Gas
(200 ml·min-1)
Pressure Reduction
Electrode
Pressure:0.6Torr
Output:1.0W cm-2
Frequency:13.56MHz
Y2O3 microspheres
(20~30 μm, 0.6 g)
20°C
Electrode Temperature

FIG. 2


AFTER FORMING THE COATING FILM
50 μm
BEFORE FORMING THE COATING FILM
50 μm

UNSCANNABLE ITEM

RECEIVED WITH THIS APPLICATION

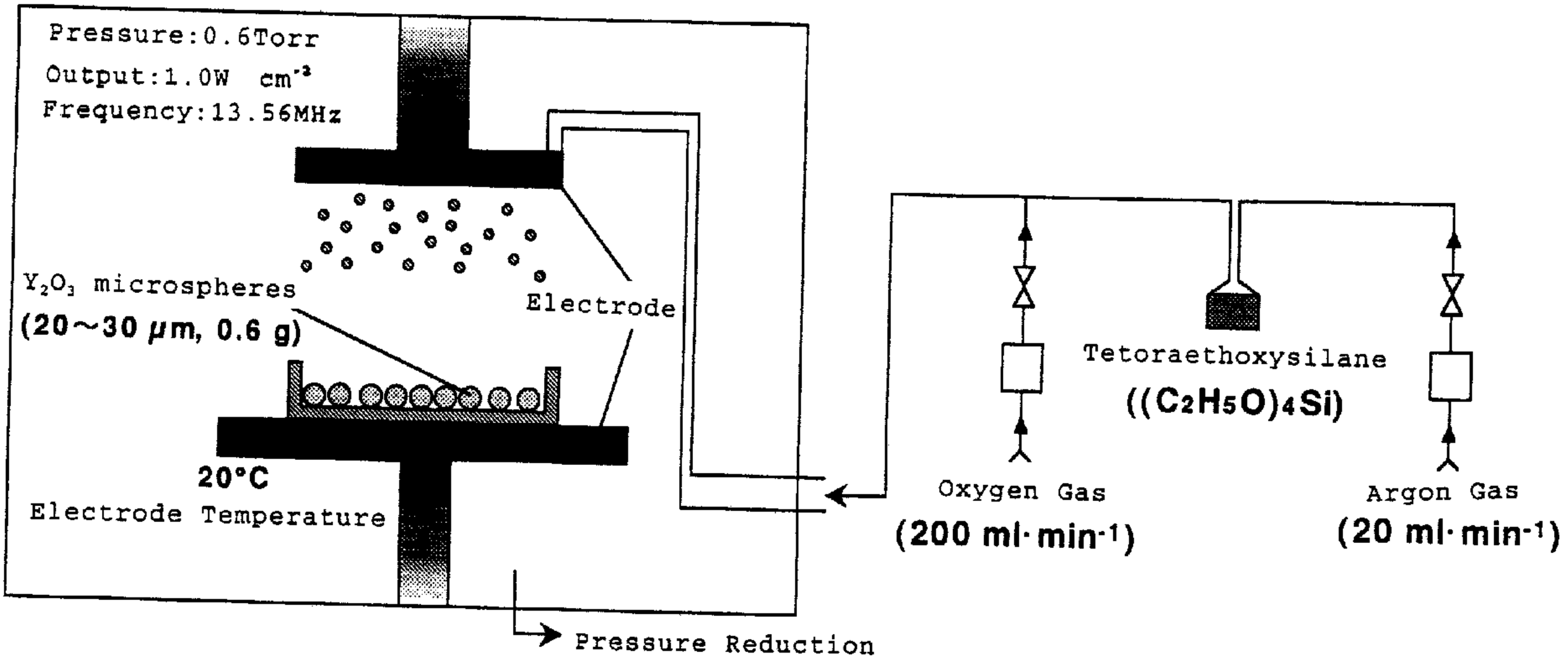
(ITEM ON THE 10TH FLOOR ZONE 5 IN THE FILE PREPARATION SECTION)

JP 000 1443

DOCUMENT REÇU AVEC CETTE DEMANDE

NE POUVANT ÊTRE BALAYÉ

(DOCUMENT AU 10 IÈME ÉTAGE AIRE 5 DANS LA SECTION DE LA PRÉPARATION DES DOSSIERS)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Output:1.0W cm⁻²
Frequency:13.56MHz
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(20~30 μm, 0.6 g)
Electrode
20°C
Electrode Temperature
Pressure Reduction
Tetoraethoxysilane
((C2H5O)4Si)
Oxygen Gas
(200 ml·min⁻¹)
Argon Gas
(20 ml·min⁻¹)