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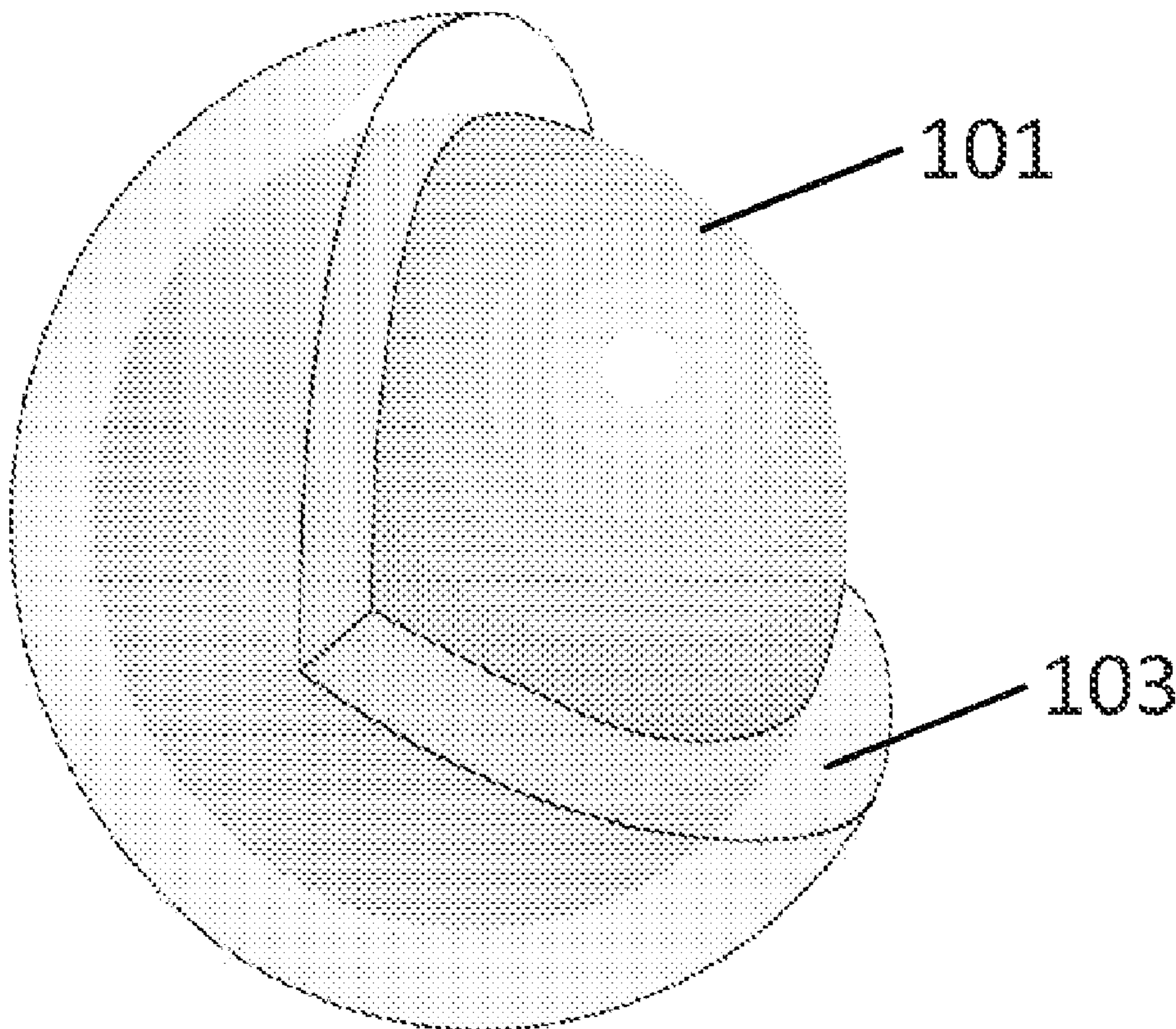
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(54) **Titre : PARTICULES EMBOLIQUES OPAQUES AUX RAYONS X**
(54) **Title: RADIOPAQUE EMBOLIC PARTICLES**



(57) **Abrégé/Abstract:**

A radiopaque particulate material one or more of SiO₂, TiO₂, La₂O₃, Na₂O and MgO and useful for embolization which optionally includes therapeutic components that are released in vivo.

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(54) Title: RADIOPAQUE EMBOLIC PARTICLES

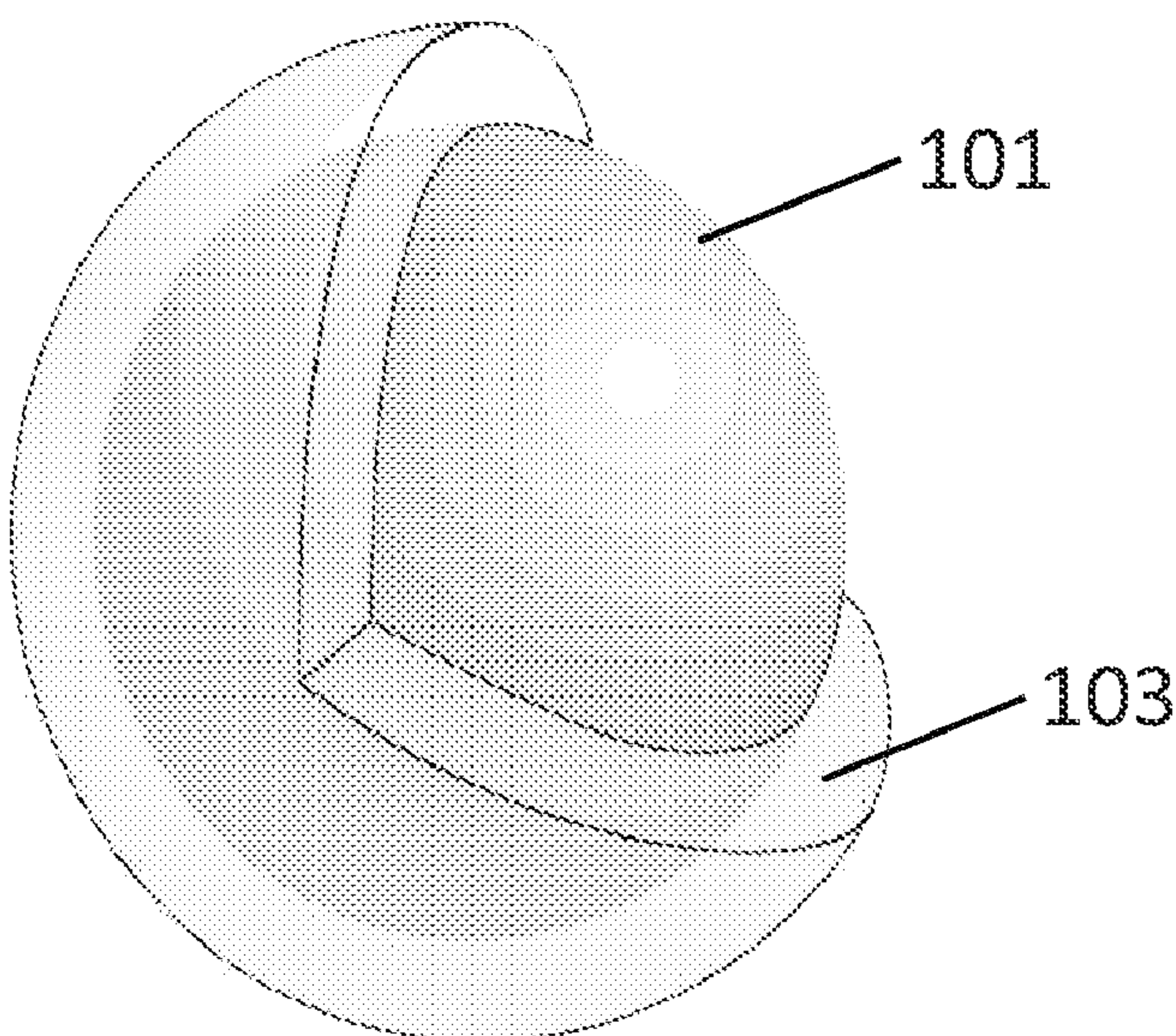


FIG. 1

(57) Abstract: A radiopaque particulate material one or more of SiO₂, TiO₂, La₂O₃, Na₂O and MgO and useful for embolization which optionally includes therapeutic components that are released *in vivo*.

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RADIOPAQUE EMBOLIC PARTICLES**Inventors: Daniel Boyd, Sharon Kehoe and Robert J. Abraham****[0001]****Field of the Invention**

[0002] The invention relates to particulate material that is radiopaque and suited for performing embolization.

BACKGROUND

[0003] Polymeric particles are frequently employed by interventional radiologists for the selective occlusion of blood vessels in the treatment of (but not limited to) hypervascular tumors such as leiomyoma uteri and vascular anomalies such as vascular malformations. However, current state of the art particles are beset with numerous drawbacks which limit market penetration for such products. The drawbacks include that the particles are not radiopaque. Thus, the clinician is not able to monitor placement of the particles radiographically. The result is that complications of embolization, such as reflux with non-target embolization and through embolization are not detectable. Current approaches to this problem include dispersing the particles in a medium that includes a contrast agent that is visible radiographically. This leads to its own complications however. Contrast-induced nephropathy occurs in about seven percent of patients exposed to contrast agents. Contrast-induced nephropathy is characterized by acute renal injury which can lead to renal failure. Exposure to contrast agents is the third most common cause of hospital acquired renal failure. Additionally, the degradation of the particles currently in use cannot be controlled. The ability to choose particles that are either non-degradable or that have differing degrees of degradability allows for more treatment options for the various lesions that are amenable to embolization. Use of particles that degrade with time may allow for revascularization of the occluded blood vessel after the treated lesion is gone resulting in recovery of blood flow to normal tissue. This would be

desired in instances such as the treatment of gastrointestinal hemorrhage. In other instances, use of a non-degradable particle prevents revascularization of the underlying vessel. This would be desired in vascular lesions such as vascular malformations.

[0004] Thus, what are needed are improved embolic particles that limit the addition of a contrast agent for radiographic imaging and whose degradation may be controlled.

SUMMARY

[0005] A particulate material comprising one or more of TiO_2 , La_2O_3 , Na_2O and MgO or SrO is provided. In one embodiment, the particulate material comprises: 0.4 – 0.7 mole fraction SiO_2 ; 0.04 – 0.7 mole fraction TiO_2 ; 0.04 – 0.5 mole fraction La_2O_3 ; 0.03 – 0.3 mole fraction MgO ; and 0.03 – 0.3 mole fraction Na_2O . In one embodiment, MgO is present at 0.05 to 0.2 mole fraction. The particulate material may optionally comprise SrO . When SrO is included, the MgO and the SrO together can be present at 0.05-0.3 mole fraction. Alternatively, the MgO and the SrO together are present at 0.05-0.2 mole fraction. The La_2O_3 can be present at 0.04 to 0.4 mole fraction or 0.04 to 0.3 mole fraction. The TiO_2 may be present at 0.04 to 0.3 mole fraction or 0.04 to 0.2 mole fraction. The SiO_2 may be present at 0.4-0.6 mole fraction or 0.4-0.5 mole fraction. The Na_2O is present at 0.03-0.2 mole fraction or 0.03-0.15 mole fraction.

[0006] In some aspects, the particulate material is radiopaque.

[0007] In some aspects, the particulate material is biocompatible.

[0008] The particulate material is optionally degradable *in vivo*. In one embodiment the particulate material degrades substantially in more than six months. Alternatively the particles are non-resorbable.

[0009] In some aspects, the particulate material releases therapeutic components under physiological conditions.

[0010] In some aspects, the particulate material has a Q-speciation of $Q^1 - Q^3$ or about Q^2 .

[0011] In some aspects, the particles of the particulate material have an average diameter of 45-1180 μm , 200-1000 μm , 100-300 μm , 300-500 μm , 500-710 μm or 710-1000 μm .

[0012] In some aspects, the particulate material comprises no more than 0.1 mole fraction aluminosilicates, phosphates or a combination thereof

[0013] The particulate material optionally includes a polymeric coating or is dispersed within a polymeric matrix. In one embodiment, the polymer comprises poly(lactic-co-glycolic acid). Additionally or alternatively, the polymer comprises a poloxamer. In one embodiment the poloxamer is Pluronic F127. The polymer optionally comprises therapeutic components which are released under physiological conditions.

[0014] In one aspect, the particulate material of any of the previous claims is used for vascular occlusion. The vascular occlusion may be for treatment of vascular malformations, organ ablation, chemoembolization, treatment of hemorrhage or uterine fibroid embolization.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 illustrates a particle according to one embodiment.

[0016] FIG. 2 are DSC traces for eight particles.

[0017] FIG. 3 are XRD patterns for synthesized exemplary particles.

[0018] FIG. 4 are contour plots for synthesized exemplary particles.

[0019] FIG. 5 morphological data (SEM) for ORP5 and control sample from Contour™.

[0020] FIG. 6 illustrates chemical (EDX) data for ORP5.

[0021] FIG. 7 illustrates ^{29}Si MAS-NMR spectra for experimental embolic materials.

[0022] FIG. 8 illustrates ^{29}Si MAS-NMR spectra for experimental embolic material ORP6.

[0023] FIG. 9 illustrate contour plots based on the ^{29}Si MAS-NMR spectra of FIG. 7.

[0024] FIG. 10 illustrate additional contour plots based on the ^{29}Si MAS-NMR spectra of FIG. 7.

[0025] FIG. 11 presents ion release profiles for Si (FIG. 11A) and Na (FIG. 11B) release of the eight embolic particulates.

[0026] FIG. 12 presents ion release profiles for Ca (FIG. 12A) and Sr (FIG. 12B) release of the eight embolic particulates.

[0027] FIG. 13 presents ion release profiles for Ti (FIG. 13A) and La (FIG. 13B) release of the eight embolic particulates.

[0028] FIG. 14 presents an ion release profile for Mg (FIG. 14A) and mean ($\pm$ SD) release levels for Zn (FIG. 14B) of the eight embolic particulates.

[0029] FIG. 15 presents the effect of embolic material composition on release levels for Si (FIG. 15A) and Na (FIG. 15B) after 120h incubation periods.

[0030] FIG. 16 presents the effect of embolic material composition on release levels for Ca (FIG. 16A) and Sr (FIG. 16B) after 120h incubation periods.

[0031] FIG. 17 presents the effect of embolic material composition on release levels for Ti (FIG. 17A); La (FIG. 17B) and Mg (FIG. 17C) after 120h incubation periods.

[0032] FIG. 18 presents cell viability and cell toxicity data.

[0033] FIG. 19 presents contour plots' showing the compositional-interaction effects on the experimental embolic materials cell viability (%) at four various additions of Ti.

[0034] FIG. 20 presents a comparison of radiopacity for ORP vs. PVA in various dilutions of saline/contrast agent.

[0035] FIG. 21 presents histological data, derived from one animal in each group, with respect to the performance of ORP5 and Contour.

[0036] FIG. 22 illustrates the intracutaneous irritation test design of NZW Rabbits.

[0037] FIG. 23 are images of the intradermal injection sites for the three NZW rabbits after 24, 48 and 72h observations.

[0038] FIG. 24 illustrates changes in Fg conformation monitored by far-ultraviolet circular dichroism (CD) spectroscopy as a function of the ionic dissolution products with respect to time.

[0039] FIG. 25 illustrates results for platelet LDH assay (ORP5 vs. PVA) with (FIG. 25A) and without (FIG. 25B) outlier.

DETAILED DESCRIPTION

[0040] The particles of the particulate material comprise a core and an optional compressible shell/matrix. The core comprises one or more of SiO₂, La₂O₃, Na₂O, MgO and SrO. The optional compressible shell/matrix comprises a biocompatible

polymer. Additional provided particulate materials have a core comprising one or more of SiO_2 , La_2O_3 , TiO_2 , ZnO , MgO , Na_2O , SrO , and CaO . In some embodiments, the particulate material is substantially free of phosphates and aluminosilicates. In some embodiments, the particulate material comprises no more than 0.1 mole fraction aluminosilicates, phosphates or a combination thereof. Surprisingly, the particulate materials are biocompatible and yet do not require phosphates or aluminosilicates.

Core

[0041] In one embodiment, the particulate material has the properties of a glass ceramic. In such an embodiment, the components make up a network, which can be amorphous or crystalline. Components include SiO_2 , La_2O_3 , TiO_2 , ZnO , MgO , Na_2O , SrO , and CaO . Modifying the amounts of the various core components (as well as the ratios of components to each other) allows for tuning the characteristics of the material to its intended use.

Network Components

[0042] La_2O_3 is present at a mole fraction of 0.04 to 0.5. In another embodiment, La_2O_3 is present at 0.04 to 0.4 mole fraction. In another embodiment, La_2O_3 is present at 0.04 to 0.3 mole fraction. La_2O_3 provides radiopacity to the particulate material. Lanthanum has been used for decades in dental applications as a radiopacifying agent in glass ceramics and dental composites. The La_2O_3 provides superior radiopacity over current state of the art embolic agents. The release of La^{3+} as the material degrades has the additional potential benefit of providing therapeutic benefit. The La^{3+} , for example, facilitates anoikis of certain cancers and is thus beneficial when the intended use of the particulate material is to initiate anoikis of those cancers. For those uses the amount of lanthanum is tuned for that purpose.

[0043] Another component of the particulate material is titanium. TiO_2 is present in 0.04 to 0.7 mole fraction. In some embodiments, TiO_2 is present at 0.04 to 0.3 mole fraction. In some embodiments, TiO_2 is present at 0.04-0.2 mole fraction. Titanium is thrombogenic and its inclusion in the particulate material increases thrombogenicity around the particles *in vivo*. The thrombogenicity of the particulate material may be tuned by the amount of TiO_2 present. Depending on the intended application, a greater or lesser amount of thrombogenicity is required.

[0044] A third component of the particulate materials is silicon. SiO_2 is present in the particulate material at 0.4-0.7 mole fraction. In one embodiment, the SiO_2 is present at 0.4-0.6 mole fraction. In yet another embodiment, the SiO_2 is present at 0.4-0.5 mole fraction.

[0045] Magnesium is present in the particulate material in the form of MgO at a mole fraction of 0.03 to 0.3. In one embodiment, the MgO is present at 0.03 to 0.2 mole fraction. In alternative embodiments, MgO is present at 0.05 to 0.3 or 0.05 to 0.2 mole fraction. Magnesium is a thrombogenic material and its inclusion in the particulate material increases thrombogenicity around the particles *in vivo*. Further, magnesium, a metallic element, enhances the imaging qualities of the particulate material and also provides additional control over the structure of the particulate material. In some embodiments, a second alkaline earth metal oxide is also used, SrO . The ratio of MgO to SrO allows tuning the biocompatibility of the particulate material as needed for different applications. For example, increased MgO results in a less stable glass network which would result in faster degradation which is desirable for some applications. Increasing SrO increases radiopacity and so the ratio of MgO to SrO also allows for tuning of this functional aspect of the particulate material.

[0046] Sodium imparts degradability to the particulate material. The more sodium present in the particulate material, the more quickly the particulate material degrades *in vivo*. Na_2O is present in the particulate material at 0.03-0.3 mole fraction. In some embodiments, Na_2O is present in the particulate material at 0.03-0.2 mole fraction. In yet other embodiments, Na_2O is present in the particulate material at 0.03-0.15 mole fraction. In one embodiment, the particles take more than six months to degrade. Particles with this rate of degradation are useful when early recanalization of vessels is undesirable. Examples of such situations include organ ablation (i.e. embolization of native kidneys that are causing hypertension in a dialysis patient or a patient with a kidney transplant) or malignant tumor embolization (i.e. hormonally active metastatic disease to the liver such as a carcinoid tumor, renal cell carcinoma, etc).

Additional Components

[0047] Additional components having therapeutic properties can be added to the particulate material. In one embodiment such therapeutic components release as a

function of *in vivo* surface modifications to the particle. These components are then released from the particle in the body. The make-up of the network-modifying components is used to control the release of the therapeutic components. Examples of such components include therapeutic ions and chemotherapeutic agents. Therapeutic ions include, for example, Ca^{2+} , which aids in coagulation. In one embodiment, calcium is provided in the particle in the form of CaO .

Nature of Core/Particle

[0048] In one embodiment, the particulate material is a ceramic. Ceramics are inorganic, non-metallic materials prepared by heating and subsequent cooling. Ceramics are usually formed between metallic and nonmetallic elements, such as, for example, aluminum and oxygen, calcium and oxygen and silicon and nitrogen. Ceramics can have crystalline, partly crystalline or amorphous structures and include ceramic glasses, also referred to as glasses. Other ceramics include enamels, glass-ceramics (glasses containing ceramic crystals), and inorganic cement-type materials (cement, plaster and lime). In one embodiment, the particulate material is a glass. Glass is any solid with a non-crystalline, or amorphous, structure and exhibits a glass transition upon heating.

[0049] Q-speciation is known in the art as a system for characterizing glass materials. It is a measure of how many of the oxygens surrounding silicon are bridging oxygens. The superscript, n , in Q^n is higher the more bridging oxygens there are in the tetrahedral units of the network. The superscript n can be from 0 to 4. In one embodiment, the particulate material of the invention has a Q-speciation between Q^1 and Q^3 with a corresponding network connectivity of between 1 and 3. In one embodiment, the particulate material has a Q-speciation of Q^2 .

Compressible Shell/Matrix

[0050] FIG. 1 illustrates a particle according to one embodiment. The particle includes the core 101 described above and also a compressible shell/matrix 103 of a biocompatible polymer. Such an embodiment is illustrated in FIG. 1. As mentioned previously, the core can also be suspended in a polymer matrix. Possible polymers include poly(lactic-co-glycolic acids) ("PLGA") and poloxamers. In one embodiment, the shell/matrix includes Pluronic F127 available from BASF. This shell/matrix allows for drug elution for therapeutic benefit. Examples include

chemoembolization of malignant tumors. Specific examples include hepatocellular carcinoma of the liver. Additional drugs that can be eluted include, for example, thrombogenic agents that enhance the degree of vascular occlusion. The compressibility of the shell/matrix is useful in clinical deployment of the particulate material.

Size of Particulate Material

[0051] The individual particles of the particulate materials are between 45 and 1180 μm in average diameter. Alternatively the particles are between 200 and 1000 μm in average diameter. Various uses for the particles require different sizes of particles. Thus, in one embodiment, the particles have an average diameter of 100 – 300 μm which are useful for deep tumor necrosis as may be needed in malignant tumor embolization. In another embodiment, the particles have an average diameter of 300-500 μm and are used for treating gastrointestinal or traumatic bleeding. The 300-500 μm particles can also be used as the initial size of particle for uterine fibroid embolization and most other organ or tumor embolizations. In another alternative embodiment, the particles have an average diameter of 500-710 μm . The 500-710 μm particles are also used in embolization of uterine fibroids. Which size range, 300-500 μm or 500-710 μm , to use for embolization of uterine fibroids depends on other characteristics of the particle. In yet another alternative, the particles have an average diameter of 710-1000 μm and are useful for proximal embolization to reduce the “head pressure” to a site of hemorrhage such as in gastrointestinal hemorrhage or traumatic hemorrhage.

Additional Uses of Particulate Material

[0052] The particulate material of the invention may be used for vascular occlusion. In one embodiment, vascular occlusion is used in the treatment of uterine fibroids, vascular malformations and other vascular anomalies or lesions, organ ablation including portal vein embolization, chemoembolization and hemorrhage from any cause.

Examples

Synthesis of Glass Particulate Materials

[0053] Generally, appropriate amounts of analytical grade reagents are weighed out as appropriate and thoroughly mixed by shaking (30mins) in a plastic container.

Each batch of powder is fired at the appropriate temperature (initially 1520°C for 1 hour) in a platinum crucible. The glass melt is then shock quenched into water. The resulting glass frit is dried in an oven (120°C, 1 day), ground and sieved to retrieve glass powder for subsequent analysis. Tables 1 and 2 show example compositions for particulate materials. Table 2 as appended at the end of the specification.

Table 1. 13 glass compositions (mol. fraction) formulated using design of experiments. The Network Modifying (NM) components (Ca; Mg; Sr and Na) are kept constant at 0.035 mol. fraction.

Embohc Designa- tion	NC	Design points ^a	SiO ₂	CaO	ZnO	MgO	La ₂ O ₃	SrO	Ti ₂ O	Na ₂ O
ORP1	2	V	0.553	0.035	0.137	0.035	0.137	0.035	0.033	0.035
ORP2	2	V	0.570	0.035	0.240	0.035	0.000	0.035	0.050	0.035
ORP3	2	V	0.537	0.035	0.213	0.035	0.068	0.035	0.042	0.035
ORP4	2	V	0.570	0.035	0.000	0.035	0.240	0.035	0.050	0.035
ORP5	2	V	0.562	0.035	0.188	0.035	0.068	0.035	0.042	0.035
ORP6	2	V	0.562	0.035	0.068	0.035	0.188	0.035	0.042	0.035
ORP7	2	A-CB	0.562	0.035	0.213	0.035	0.068	0.035	0.017	0.035
ORP8	2	A-CB	0.570	0.035	0.000	0.035	0.290	0.035	0.000	0.035
ORP9	2	A-CB	0.520	0.035	0.290	0.035	0.000	0.035	0.050	0.035
ORP10	2	A-CB	0.520	0.035	0.000	0.035	0.290	0.035	0.050	0.035
ORP11	2	A-CB	0.570	0.035	0.290	0.035	0.000	0.035	0.000	0.035
ORP12	2	A-CB	0.562	0.035	0.068	0.035	0.213	0.035	0.017	0.035
ORP13	2	C	0.537	0.035	0.068	0.035	0.213	0.035	0.042	0.035

[0054] The optional compressible shell/matrix are added by a modified emulsification method. PLGA of various molecular weights are supplemented with glass particles at various wt%. PLGA are dissolved in methylene chloride, and then the glass will be added, at the preferred level, into the solution. The mixture is then added, drop-wise, into a stirred PVA solution. Micro-spheres are isolated by filtration,

washed with deionized water air dried then vacuum dried. Table 3 provides the make-up of example particulate materials with a polymer coating.

Table 3. 9 composite variations (wt. %) formulated using design of experiments. The glass is expressed as a wt. % of the PLGA base.

Std.	Run.	PLGA	Glass
ORP2	1	25.00	5.00
ORP8	2	25.00	60.00
ORP1	3	15.00	5.00
ORP9	4	25.00	60.00
ORP7	5	10.00	60.00
ORP6	6	10.00	60.00
ORP4	7	10.00	32.50
ORP3	8	25.0	5.00
ORP5	9	15.0	41.67

Example 1 – Particle Compositions

[0055] Particle compositions (mol. fraction) $(0.52-0.57)\text{SiO}_2-0.035\text{CaO}-(0.00-0.29)\text{-ZnO}-0.035\text{MgO}-(0.00-0.188)\text{La}_2\text{O}_3-0.035\text{SrO}-(0.00-0.05)\text{TiO}_2-0.035\text{Na}_2\text{O}$ were synthesized for this work. Analytical grade reagents: silicon dioxide, calcium carbonate, zinc oxide, magnesium oxide, lanthanum (III) oxide, strontium carbonate, titanium dioxide and sodium carbonate (Sigma Aldrich, Canada) were weighed and homogeneously mixed in a plastic container (Nalgene™, Sigma Aldrich, Canada) for 1 hour. Each batch of powder was placed in platinum crucibles (50mL), then fired (1480°C , 1 hour) using a Bench-Top High Temperature Muffle Furnace (EQ-KSL, MTI Corporation, USA) and shock quenched into water. The resulting frit was dried in an oven (120°C , 1 day), pulverized in an agate planetary mill (Pulverisette 7; Laval Labs Inc., Canada) and sieved through various aperture to produce powder particulates in the following size ranges: $<45\mu\text{m}$; $45-212\mu\text{m}$; $212-300\mu\text{m}$; $355-$

500 μ m; >500 μ m. All batches of particles produced in this work were subsequently stored in dry dessicators for further evaluation.

Characterization of Particulate Materials

Differential Scanning Calorimetry (DSC)

[0056] Generally, DSC is used to determine the onset of the glass transition temperature (T_g) for each glass using a differential scanning calorimeter (DSC). Temperature intervals of 258.15°C (up to 725°C) are employed in an air atmosphere with alumina (or other appropriate reference) in a matched platinum crucible. The tolerance of the DSC used is on the order of 2%.

Example 2

[0057] DSC analysis of the particles made in Example 1 was performed to obtain the values of the glass transition temperature (T_g). Samples (~80 mg) were heated in a platinum crucible in a nitrogen environment alongside an empty reference crucible. A standard reference material is already pre-selected for a given temperature range. T_g was measured in a differential scanning calorimeter (DSC; TA Instruments-DQ200) between 25 °C and 725 °C at temperature intervals of 258.15 °C. DSC traces for the eight particles (ORP1-3, ORP5-7, ORP9 and ORP11) are shown in FIG. 2. Table 4 is an abstracted ANOVA table for the T_g reduced linear mixture polynomial model. A tabulated comparison between observed and calculated T_g behaviors for each material composition, is provided for in Table 5, as based on the regression model developed in terms of L-Pseudo component coding. The final mathematical model in terms of L-Pseudo components is shown as follows in Equation 1:

$$T_g (^{\circ}\text{C}) = +634.82\text{ZnO} + 833.28\text{La}_2\text{O}_3 + 677.19\text{SiO}_2 + 699.01\text{TiO}_2 \quad \text{Eqn. 1}$$

Table 4

Response (sig./non sig.)	SD	Mean	F Value	Prob.>F Model	R ²	Adj-R ²	Pred-R ²	CV %	Adq.Pre c.
$T_g (^{\circ}\text{C})$ significant	5.05	662.27	31.54	0.0309	0.9793	0.9482	0.7089	0.76	10.728

Table 5. Residuals of the T_g study.

Embolic Composition	ORP2	ORP3	ORP5	ORP7	ORP9	ORP11
Calculated T _g (°C)	646.08	680.971	684.087	681.573	639.845	641.05
Experimental T _g (°C)	643.65	680.20	688.94	677.49	640.23	643.09
Residual (Difference)	2.43	-0.78	4.85	-4.08	0.39	2.04

X-ray Diffraction (XRD)

[0058] Generally, XRD is employed to validate the amorphous nature of the glasses. Powdered samples of each glass are pressed to form discs (Ø32mm×3mm). Diffraction patterns are collected using an X-ray Diffraction Unit with monochromated CuK α ($\lambda=1.54060\text{\AA}$) radiation at 40KV and 35 mA. The scanning angle range (2θ) is performed from 10° to 70° with a step size 0.033423° and step time of 59.69s.

Example 3

[0059] X-ray diffraction (XRD) measurements for the particles were performed using an INEL CPS-120 diffractometer with a curved position sensitive detector coupled to an X-ray generator (40kV; 35mA) and equipped with a Cu target X-ray tube. Samples were prepared by pressing the selected particle particles (45-212 μm) into hollow square steel wafers. A monochromator in the incident beam path limits the wavelengths striking the sample to Cu K α_1, α_2 . The X-ray beam is incident upon the sample at approximately 6° and the curved position sensitive detector collects all scattered X-rays in the scan angle range $10^\circ < 2\theta < 110^\circ$. Collection time for the XRD spectra is 1800 seconds. The powder samples were placed on the INEL's x-y translating stage that allows measurement and move operations to be sequentially programmed.

[0060] FIG. 3 illustrates XRD patterns for each material synthesized (A) glasses ORP 2,3,5,7,9,11 and (B) ORP 1 and 6. The x axis denotes the scattering angle as

measured in degree 2-theta and the y-axis in arbitrary units. Table 6 provides the legend for phase identification.

Table 6.

Peak Identifier	JCPDS Card No.	Phase Identifier	Chemical Formula	Present in Composition:
B	00-050-0522	Strontium-Lanthanum-Titanium oxide	$\text{Sr}_3\text{La}_2\text{Ti}_2\text{O}_{10}$	ORP1,6
C	00-042-0423	Perovskite, Calcium Titanium Oxide	CaTiO_3	ORP6
D	00-049-1433	Titanium oxide	TiO_2	ORP6
E	00-039-0190	Zinc-Titanium oxide	ZnTiO_3	ORP1

[0061] Surprisingly T_g for these complex multi-component systems is increased by increasing any of the four compositional variants, with its level of statistical significance for the compositional variants following the order:

$\text{La}_2\text{O}_3 > \text{TiO}_2 > \text{SiO}_2 > \text{ZnO}$. One might have expected that only increasing SiO_2 content would lead to increases in T_g . Interestingly, with a decrease in T_g attributed to the formation of a weaker glass network, the strongest to weakest networks formed for the series of glasses herein therefore, follows the order:

ORP5>ORP3>ORP7>ORP2>ORP11>ORP9.

Network Connectivity

Example 4

[0062] The network connectivity (NC) of each composition was calculated using Equation 2 and the molar compositions of the glass.^{1,2} The results are shown in Table 1.

$$NC = \frac{\text{No. BOs} - \text{No. NBOs}}{\text{Total No. Bridging species}}$$

Eq.2

Wherein NC= Network Connectivity; BO = Bridging Oxygens and NBO = Non-Bridging Oxygens

Generation and Application of Mathematical Models using a Design of Experiments (DoE) Approach

[0063] To estimate the coefficients of a second order canonical Scheffé polynomial^{3,4}, a quadratic user-defined design with thirteen experiments representing different compositional variants (design points) within a defined domain (design space) was constructed using Design-Expert 8.0.4 software (Stat-Ease, Inc.). These design points were determined based on the constrained ranges for each composition: with six experiments set at the extreme vertices; a further six investigating axial check-blends and one overall centroid within the defined design space. These points are in clear agreement with Scheffé's proposal that the interesting points of a domain are at its tops, at the middle of the sides, at the middle of the faces and its centre of gravity (See Table 1). With the mixture design method, an equation is obtained. This formula connects Y, with the four compositional factors (ZnO, La₂O₃, SiO₂ and TiO₂, noted respectively as X₁, X₂, X₃ and X₄).

[0064] The ordinary second-order Scheffé (linear) polynomial equation fitted for Magic Angle Spinning - Nuclear Magnetic Resonance (MAS-NMR) spectroscopy and DSC responses (chemical shift and line width) is:

$$Y_A = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + e \quad \text{Eq. 3}$$

where X₁ to X₄ represent the compositional factors, $\beta_1 - 4$ coefficients represent the effect of the individual compositional factors X_{1 - 4}. e is called residual, this value is the difference between calculated and experimental values for each selected glass. It is equal to 0 if the number of retained glasses is the same as the number of coefficients in the formula. In the case of a number of chosen glasses higher than the number of coefficients, residual has a different value for each experiment.

[0065] The canonical Scheffé second-order polynomial equation fitted for density and cell viability responses is:

$$Y = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{14} X_1 X_4 + \beta_{23} X_2 X_3 + \beta_{24} X_2 X_4 + \beta_{123} X_1 X_2 X_3 + \beta_{124} X_1 X_2 X_4 + \beta_{134} X_1 X_3 X_4 + \beta_{234} X_2 X_3 X_4 + e$$

Eq. 4

where X₁ to X₄ represent the compositional factors, $\beta_1 - 4$ coefficients represent the

effect of the individual compositional factors X_{1-4} ; β_{12-24} , are the coefficients of regression which represent the effects of two-way interactions between the compositional factors; $\beta_{123-234}$, are the coefficients of regression which represent the effects of three-way interactions between the compositional factors and e is the residual.

[0066] From the estimated coefficients of a quadratic model presented in pseudo and actual values, the effect of each component can be derived. All mixture experiment models were developed relating the response variables to proportions of pseudo-components. Pseudo-component proportions (z_i) are calculated as:

$$z_i = (x_i - L_i) / (1 - \sum L) \quad \text{Eq. 5}$$

where x_i stands for the original component proportions, L_i stands for the lower bound constraint (limit) for the i^{th} component, L stands for the sum of all lower bound constraints (limits) for all components in the design, and 1 represents the mixture total.

[0067] The pseudo-components are combinations of the original (actual) components, which rescale the constrained composition region so that the minimum allowable proportion of each pseudo-component is zero. This transformation provides for estimating model coefficients more precisely compared to using the actual component system, and as such the coefficients derived based on the pseudo-component scaling is referred to in the context of the discussion to follow. Model validity, in terms of experimental versus calculated data points and graphical representation (contour plots) however, is presented in terms of actual component coding.

[0068] If several response characteristics $y_1, y_2, \dots, y_n$ have been modeled in the proportions of the same set of q components, where in the composition space the best overall set of properties are obtained by implementing the desirability function approach. Using the models, which are based on the response characteristics, compositions for particulate materials having desired properties for a particular purpose can be determined.

True Densities

Example 5

[0069] The true densities were measured using a helium pycnometer (AccuPyc 1340, Micromeritics) for all the particles synthesized herein and, also for the commercial control material: Contour™ (PVA particulates). Results are representative of an average of five recorded measurements. FIGS. 4A and 4B are resulting contour plots showing the compositional-interaction effects on the experimental particles density (g/cc) at four various additions of Ti (0.017, 0.033, 0.042 and 0.05 mol.) in actual component coding. (A) is Ti: 0.017 mol. fraction; (B) is Ti: 0.033 mol. fraction; (C) is Ti: 0.042 mol. fraction; and (D) is Ti: 0.050 mol. fraction.

[0070] Table 7 illustrates final regression equations in terms of L_Pseudo (1); Actual components (2) and R^2 values; and summarized ANOVA for density. The ANOVA data demonstrates that the model adequately predicts the characteristics of the particulate material.

Table 7

Response		Regression Models	Summarized ANOVA					
			R^2	$R^2_{adj.}$	$R^2_{pred.}$	Prob > F	CV (%)	Adeq. Prec.
Density (g/cc)	1	+3.39ZnO + 5.12La ₂ O ₃ + 2.43SiO ₂ + 2.92TiO ₂ + 1.07ZnO * La ₂ O ₃	0.9989	0.9975	0.9859	<0.0001	0.55	69.809
	2	+5.65559ZnO + 10.72595La ₂ O ₃ + 2.82345SiO ₂ + 4.26905TiO ₂ + 9.211775ZnO * La ₂ O ₃						

[0071] Table 8 is a summary of the significant (positive and negative) main, interaction and quadratic compositional factors (ranked highest to lowest) and its effect on increasing density; where $\uparrow$ denotes an increase and $\downarrow$ a decrease. Based on actual component coding.

Table 8

Ranking of Compositional Factors	Density Response
1	$\uparrow\text{La}_2\text{O}_3$
2	$\uparrow\text{ZnO}$
3	$\uparrow\text{TiO}_2$
4	$\uparrow\text{SiO}_2$
5	$\uparrow\text{ZnO}*\text{La}_2\text{O}_3$

[0072] As illustrated, density may be increased by increasing any of the four compositional variants in the order $\text{La}_2\text{O}_3 > \text{ZnO} > \text{TiO}_2 > \text{SiO}_2$. Interestingly, increasing the interaction of ZnO and La_2O_3 (fifth most influencing factor) may result in an increase in material density, a feature which would not have been predicted but which the disclosed models do predict for the disclosed compositions. The lowest levels of density achieved (3.2 g/cc (ORP2) and 3.3 (ORP11)) in the design matrix tested, demonstrate how a slight variation in compositional variants from ORP2 to ORP11 (increased ZnO (0.05 mol. fraction) and reduced TiO_2 (0.5 mol. fraction) content) may adversely affect the final cell viability obtainable; by reducing it from 84 to 61%, respectively. Interestingly, density in the range of 3.5 g/cc (± 0.3) (for ORP2, 3 and 5) was also representative of the top three compositional variations in terms of cell viabilities (86% (± 5)) attainable.

Specific Surface Area Determination

[0073] N_2 adsorption/desorption will be determined using the Brunauer-Emmett-Teller (BET) method to determine the specific surface area (SSA) and porosimetry of the prepared glass powders. Glass samples ($\sim 0.15\text{g} \pm 0.05\text{g}$) will be placed under a nitrogen atmosphere at 77.35 K with an equilibration interval of 10s.

Example 6

[0074] The theoretical external specific surface areas for the particle particulates and ContourTM were calculated according to the following equation⁵, under the assumption of spherical particulate morphology

$$A = \frac{6}{\rho d}$$

Eq. 6.

[0075] Table 9 provides specific surface area measurements (45 micron (Lower Level, LL) and 212 micron (Upper Level, UL)).

Table 9.

Sample ID	Density	SD	PD (LL)	PD (UL)	SSA (LL)	SSA (UL)		
	(g/cc)	(g/cc)	cm	cm	cm ² /g	cm ² /g		
ORP1	4.09	0.002	0.045	0.212	32.600	6.920		
ORP2	3.17	0.001	0.045	0.212	42.048	8.925		
ORP3	3.77	0.001	0.045	0.212	35.395	7.513		
ORP5	3.70	0.002	0.045	0.212	36.075	7.657		
ORP6	4.29	0.001	0.045	0.212	31.087	6.599		
ORP7	3.73	0.002	0.045	0.212	35.737	7.586		
ORP9	3.32	0.001	0.045	0.212	40.136	8.520		
ORP11	3.25	0.003	0.045	0.212	41.038	8.711		
Contour	1.77	0.003	0.045	0.212	75.406	16.006		
Sample ID	Density	Density SD	PD (LL)	PD (UL)	SSA (LL)	SSA (UL)	1m ²	1cm ²
	g/m ³	g/m ³	m	m	m ² /g	m ² /g	g	g
ORP1	4090000	2000	0.000045	0.000212	0.033	0.007	144.51	0.14
ORP2	3171000	1000	0.000045	0.000212	0.042	0.009	112.04	0.11
ORP3	3767000	1000	0.000045	0.000212	0.035	0.008	133.10	0.13

ORP5	3696000	2000	0.000045	0.000212	0.036	0.008	130.59	0.13
ORP6	4289000	1000	0.000045	0.000212	0.031	0.007	151.54	0.15
ORP7	3731000	2000	0.000045	0.000212	0.036	0.008	131.83	0.13
ORP9	3322000	1000	0.000045	0.000212	0.040	0.009	117.38	0.12
ORP11	3249000	3000	0.000045	0.000212	0.041	0.009	114.80	0.11
Contour™	1768200	3000	0.000045	0.000212	0.075	0.016	62.48	0.06

Scanning Electron Microscopy

Example 7

[0076] For scanning electron microscopy (SEM) observations, powder samples (particle size range: 355-500 μ m) were mounted onto 10mm diameter x 3mm high Al stubs and coated with ~27nm platinum using a gold-sputter coater (SC7640, Fisons Instruments). The samples were subsequently transferred to the chamber of a Hitachi S-4700 FEG-SEM equipped with an Oxford Inca energy dispersive x-ray spectroscopy (EDS) system for morphological and chemical analysis. An accelerating voltage of 5.0kV and a working distance of 11-12mm were used with the lower secondary electron (SE) detector.

[0077] FIG. 5 presents morphological data (SEM) derived from one experimental composition (ORP5); whose morphology is representative of the full set of multi-component systems examined and compared to the commercially available predicate device, Contour. FIG. 5A is a control sample of Contour™ with particle size range of 355-510 μ m. FIG. 5B is an experimental sample of ORP5 having particle size range of 355-510 μ m.

[0078] Chemical (EDX) data for ORP5 is presented in FIG. 6 demonstrates that the synthesized composition is as reported in Table 1.

Magic Angle Spinning - Nuclear Magnetic Resonance (MAS-NMR) Spectroscopy for Determination of Non-Bridging Oxygens

[0079] Generally, the ^{29}Si MAS-NMR spectra of the glasses are recorded at a spinning frequency of 5 kHz using a high power pulse (P1) acquisition of 1.5 μ s for silicon. The ^{29}Si MAS-NMR samples are spun with a recycle/delay time set to ~2 s.

^{29}Si NMR chemical shifts are reported in ppm and recorded at an ambient probe temperature with ^{29}Si referenced externally relative to 2,2-dimethyl-2 silapentane-5-sulfonate sodium salt (DSS) or other appropriate reference. For solid state NMR, shifts recorded using MAS are independent of the isotropic bulk magnetic susceptibility of the sample. The estimated error of chemical shift for data is ca. 0.1ppm for an ideal material; small variations above this value may be observed.

Example 8

[0080] ^{29}Si magic angle spinning (MAS) NMR studies were carried out on a Bruker Avance NMR spectrometer with a 9.4T magnet (79.51MHz ^{29}Si Larmor frequency) using a probe head for 7mm rotor diameters. The specimens (<45 μm) were spun at 5.00kHz. 200 scans were accumulated with single pulse excitation using a pulse length of eighty degrees at 28kHz rf field strength. The recycle delays were chosen to be three times the spin lattice relaxation times as determined by inversion recovery sequences. Spin lattice relaxation times range between 15 and 26 seconds. The chemical shift scale was referenced externally against Kaolin as secondary chemical shift standard at -91.34ppm. Error bars on the peak maxima and peak widths are $\pm 1\text{ppm}$.

[0081] FIG. 7 illustrates ^{29}Si MAS-NMR spectra for each experimental embolic material (peak maxima and peak width for each is recorded in Table 10, respectively) sorted by decreasing line width (a: ORP11, b: ORP2, c: ORP9, d: ORP7, e: ORP6, f: ORP5, g: ORP3, h: ORP1). To ensure that no crystal signals were missed due to too fast pulsing (50s) an additional ^{29}Si MAS NMR spectrum for ORP6 was acquired at longer repetition times (90s). FIG. 8 illustrates those results - ^{29}Si MAS-NMR spectra for experimental embolic material ORP6 at (a) 90s and (b) 50s repetitions times and (c) their scaled difference; verifying that silica is not part of the crystals detected by XRD. In both spectra, no crystalline components were evident. The XRD diffractograms for ORP1 and ORP6 indicate the presence of some crystalline species which were identified in Table 6.

[0082] FIG. 9 illustrates contour plots' showing the compositional-interaction effects on the experimental embolic materials ^{29}Si MAS-NMR chemical shift (in ppm) at four various additions of Ti ((FIG. 9A)0.017, (FIG. 9B) 0.033, (FIG. 9C) 0.042 and (FIG. 9D) 0.05 mol.) in actual component coding.

[0083] FIG. 10 illustrates contour plots' showing the compositional-interaction effects on the experimental embolic materials ^{29}Si MAS-NMR spectra line width (ppm) at four various additions of Ti ((FIG. 10A) 0.017, (FIG. 10B) 0.033, (FIG. 10C) 0.042 and (FIG. 10D) 0.05 mol.) in actual component coding.

[0084] Table 10 illustrates the total number of positive charges and associated NMR max. position and line width from the nominal compositions outlined in Table 1 (where SiO_2 , TiO_2 , ZnO and La_2O_3 are varied with equimolar concentrations of CaO , Na_2O MgO and SrO).

Table 10.

ORP Sample	SiO_2	TiO_2	ZnO	La_2O_3	#charges /Si	Maximum position	width	Morphology
mol fraction						± 1 ppm	± 1 ppm	
11	0.570	0.000	0.290	0.000	1.51	-86.2	26.9	glassy
2	0.570	0.050	0.240	0.000	1.68	-89.8	26.9	
9	0.520	0.050	0.290	0.000	2.04	-85.5	24.7	
7	0.562	0.017	0.213	0.068	2.10	-83.6	19.7	glassy + crystalline
5	0.562	0.042	0.188	0.068	2.19	-84.3	19.9	
3	0.537	0.042	0.213	0.068	2.39	-82.2	18.8	
1	0.553	0.033	0.137	0.137	2.73	-82.4	15.7	frit synthesis impossible
6	0.562	0.042	0.068	0.188	3.05	-84.1	19.0	
12	0.562	0.017	0.068	0.213	3.14			
4	0.570	0.050	0.000	0.240	3.37			
13	0.537	0.042	0.068	0.213	3.47			
8	0.570	0.000	0.000	0.290	3.54			
10	0.520	0.050	0.000	0.290	4.27			

[0085] Table 11 illustrates regression equations in terms of L_{Pseudo} (1); Actual components (2) and R^2 values; and summarized ANOVA for each response. The ANOVA data demonstrates that the model adequately predicts the characteristics of the particulate material for responses A and B.

Table 11.

Response			Regression Models	Summarized ANOVA					
				R^2	$R^2_{adj.}$	$R^2_{pred.}$	$Prob > F$	CV (%)	AP
A	Chemical Shift	1	-82.25ZnO - 63.59La ₂ O ₃ - 111.10SiO ₂ - 103.60TiO ₂	0.9836	0.9589	0.7689	0.0246	0.62	16.512
	(ppm)	2	-44.32971ZnO + 10.55810La ₂ O ₃ - 129.18571SiO ₂ - 107.11371TiO ₂						
B	Line Width	1	+24.65ZnO - 8.69La ₂ O ₃ + 39.61SiO ₂ + 25.19TiO ₂	0.9997	0.9993	0.9958	0.0004	0.45	97.003
	(ppm)	2	+2.05426ZnO - 95.99452La ₂ O ₃ + 46.05426SiO ₂ + 3.65426TiO ₂						

[0086] Table 12 presents a summary of the significant (positive and negative) main, interaction and quadratic compositional factors (ranked highest to lowest) and its effect on producing a chemical shift/peak position towards a negative direction and increasing line width; where ↑ denotes an increase and ↓ a decrease. The data is based on actual component coding.

Table 12.

Ranking of Compositional Factors	Responses	
	A	B
1	↑SiO ₂	↑ SiO ₂
2	↑TiO ₂	↑ TiO ₂
3	↑ZnO	↑ ZnO
4	↑La ₂ O ₃ ²	↓ La ₂ O ₃
5		

[0087] Table 13 presents residuals of the ^{29}Si MAS-NMR chemical shift (a) and line width (b) study for all material compositions synthesized.

Table 13.

Glass	A. ^{29}Si MAS-NMR chemical shift (ppm)			B. ^{29}Si MAS-NMR line width (ppm)		
	Experimental Data	Calculated Data	Residual (Difference)	Experimental Data	Calculated Data	Residual (Difference)
ORP2	-89.803	-89.631	-0.172	26.900	26.927	-0.027
ORP3	-82.336	-82.528	0.192	18.800	18.747	0.053
ORP5	-84.305	-84.650	0.345	19.900	19.847	0.053
ORP7	-83.617	-83.080	-0.537	19.700	19.807	-0.107
ORP9	-85.484	-85.388	-0.096	24.700	24.727	-0.027
ORP11	-86.223	-86.491	0.268	26.900	26.847	0.053

[0088] As shown in the NMR spectra, both NMR peak shift may be increased by decreasing any of the four compositional variants in the order $\text{SiO}_2 > \text{TiO}_2 > \text{ZnO} > \text{La}_2\text{O}_3$, and that the line width follows the same order, except for La_2O_3 . The NMR spectra (FIG. 7)) obtained for ORP2, 9 and 11 appear significantly broader than the other spectra obtained for all other compositions. The difference between the corresponding specimens is that ORP2, 9 and 11 do not contain Lanthanum, while the others do.

[0089] Specimen ORP2 is comprised of more TiO_2 at the cost of ZnO compared to ORP11 and therefore has a higher charge-to-silica ratio, but, the $\text{Q}^n(\text{nSi}, 4-\text{nTi})$ species resonate at lower ppm values than the $\text{Q}^n(\text{nSi}, 4-\text{nZn})$ species. Based on the charge-to-silica ratio and assuming a roughly binary Q-species distribution, ORP11 and 2 should and experimentally do resonate in the Q^3/Q^2 range, specimens ORP9, 7, 5, 3, and 1 in the Q^2/Q^1 range (deconvolutions indicate the presence Q^1 sites) and specimen ORP6 and below in the Q^1/Q^0 range, while specimen ORP10 should only consist of Q^0 and separate metal oxide species. Interestingly, for specimen ORP1 and 6, (*i.e.* where the charge-to-silica ratio comes in the range of Q^0 contributions), separation into glassy and crystalline components already occurs with a higher charge ratio and cannot be made into frits at all. This phase separation in specimen ORP6 is the reason, why its NMR properties fall in between those of the spectra for ORP7 and ORP5, due to the crystals withdrawing cation-oxides and to result in a glass of different composition studied by NMR. La_2O_3 , even at modest concentrations causes a

breakdown of the glasses. This is useful because it adds to the tunability of the degradation of the particulate material.

Quantification of Degradation Products from Glass and Composite

[0090] TRIS-HCl buffer and citric acid buffer solutions with a pH of 7.4 ± 0.1 and pH of 3.0 ± 0.2 respectively, are prepared to simulate normal and extreme physiological conditions (according to ISO10993-14). Both buffer solutions are used for the quantification of degradation products from the glasses. 100mg of each particulate material are immersed in 10 ml of each solution (n=3) in polypropylene tubes maintained at 37°C in a shaking waterbath, agitated at 2 Hz. Specimens are stored for various durations of time - for example, 1, 3, 7, or 30 days. After each time period, specimens are removed and filtered through Grade 5 Whatman filter paper, the filtrate retained for ionic content analysis. The degradation products from the glass are identified and quantified using Inductively Coupled Plasma – Mass Spectrometer. Analysis of each extract are performed in triplicate (n=3 (extracts per condition), 3 analyses performed on each extract).

Analysis of ion release profiles

[0091] The ion release profiles from the embolic agents are described in terms of the ion release concentration (Y) over incubation time (X). Since the incubation time is not an input of the correlation function, the time dependent functions have been fitted to nonlinear regressive polynomial, gaussian, sine waves and exponential models using Prism 5.0 software (GraphPad software Inc.). The best fitting model for the four elements with respect to each embolic agent is the one phase-decay association model:

$$Y = Y_0 + (\text{Plateau} - Y_0) * (1 - \exp(-K * X)) \quad \text{Eq. 7}$$

Wherein:

‘Y’ and ‘X’ are the ion release concentrations in ppm and incubation time in hours, respectively;

‘Y₀’ is the ion release concentration (ppm) at initial ion release; where Y value at X₀=1;

‘Plateau’ is the ion release concentration at an infinite time (ppm), where Y value at X=120 h;

'K' is the rate constant, expressed in reciprocal of the ' t_{au} ' incubation time and unit is inverse days;

' t_{au} ' denotes the time necessary for ion release to reach 63% of the estimated ' y_{max} ' (ppm);

' $t^{1/2}$ ' denotes the half-life (time) to reach 50% of final ' y_{max} ' value, ' $t^{1/2}=t_{au} * \text{LN}(2)$ ';

' t_s ' denotes the difference between Y_0 and Plateau;

' R^2 ' is the sum of the squares of the distances of the points from the best-fit of the exponential nonlinear regression as determined by Prism 5.0 (GraphPad Inc.) software. The value of R^2 is a fraction between 0.0 and 1.0, with the best-fit line with a R^2 equal to 1.0.

Cell Culture testing with Mouse Fibroblast Cell Line L929

[0092] The established mouse fibroblast cell line L929 (American Type Culture Collection CCL 1 fibroblast, NCTC clone 929) is cultured in M199 media supplemented with 10% foetal bovine serum and 1% (2mM) L-glutamine. Cells are grown in T-75 flasks at 37°C in a 5% CO₂ incubator. When the cells reach confluency, they are chemically removed using 0.25% trypsin, centrifuged and re-suspended in fresh culture media to create a new single cell suspension for further inoculation.

Cell Viability Assay

[0093] 3T3 cells are seeded at a density of 1×10^4 /ml in 24 well plates (Sarstedt, Ireland). M199 Culture media is used as a negative control and culture media plus cells used as a positive control. Plates are then incubated for 24 hrs in a cell culture incubator at 37°C (5% CO₂/95% air atmosphere). After 24 hrs, 100 µl of sterile tissue culture water are added to control wells. 100 µl of relevant experimental extracts (containing particles) are added to appropriate wells for testing. The plate is then incubated for 24 hrs in a cell culture incubator at 37°C (5% CO₂/95% air atmosphere). After 24 hrs incubation, each well is exposed to MTT (Sigma Aldrich, Ireland) at an amount equal to 10% of the culture media volume (100µl). Plates are returned to the incubator for 3 hrs. After incubation, MTT solubilisation solution are added to each well at a volume equal to the original culture media volume (1 ml). Each well is titrated using a pipette in order to enhance dissolution of the crystals, after which the absorbance of each well is measured spectrophotometrically at a wavelength of 570

nm. Cell positive control wells were assumed to have metabolic activities of 100% and the percentage metabolic activity of the cells exposed to experimental extracts were calculated relative to this.

Example 9

Preparation of particle extracts for degradation studies

[0094] 0.1g of particles and Contour™ (commercial control) (Lot No.s: 13473927 and 13599201) were immersed in 10 ml⁶ of sterile tissue culture water (Sigma-Aldrich, Canada) for 12, 24, 48, 96 and 120 hours at 37°C in a shaking waterbath (Stuart Sb40, Techne Inc., USA) vibrated rotationally at 2Hz. After each storage period, samples were filtered using a sterile 0.20µm filter (Sarstedt, Canada), and filtrates stored at 7°C prior to *in vitro* evaluation.

[0095] The Si⁴⁺, Na⁺, Ca²⁺, Zn²⁺, Ti⁴⁺, La³⁺, Sr²⁺, and Mg²⁺ concentrations for each extract were analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES, Perkin Elmer Optima 3000, MA, USA). The absorption wavelengths used for the determination of each element is reported in Table 14. Before each cycle of measurement, calibration curves were obtained by preparing standard solutions containing Ti⁴⁺, La³⁺, Sr²⁺, and Mg²⁺ and a separate set of standard solutions containing Si⁴⁺, Na⁺, Ca²⁺ and Zn²⁺ (as obtained from JVA Analytical Ltd, Ireland) at concentrations reported in Tables 15 and 16. Standard sample concentrations were measured periodically to ensure the accuracy of the calibration curve. Triplicates of each extract (from each incubated embolic agent) were measured for each element, with appropriate adjustments in outputs being deployed to balance dilutions of original extracts. The results demonstrate that the complex multi-component system provides for tailored rates of degradability.

Table 14.

Element	Absorption Wavelength	Lower Limit	Upper Limit	Background Correction
Si ⁴⁺	288.158	288.073	288.256	±0.026
Na ⁺	330.237	330.136	330.348	±0.030
Ca ²⁺	396.847	396.679	397.039	±0.072
Zn ²⁺	334.501	334.400	334.614	±0.031

Element	Absorption Wavelength	Lower Limit	Upper Limit	Background Correction
Ti ⁴⁺	337.279	335.188	334.810	±0.031
La ³⁺	407.735	407.971	407.596	±0.075
Mg ²⁺	279.553	279.646	279.399	±0.026
Sr ²⁺	421.552	421.759	421.371	±0.078

[0096] Table 15 provides the standard concentrations used for the ICP measurements (JVA Analytical, Ireland).

Table 15.

Standard	Si ⁴⁺ (mg/L)	Na ⁺ (mg/L)	Ca ²⁺ (mg/L)	Zn ²⁺ (mg/L)
1	2	1	0.5	1
2	4	2	1	2
3	10	4	3	4

[0097] Table 16 provides laboratory standard concentrations used for the ICP measurements.

Table 16.

Standard	Ti ⁴⁺ (mg/L)	La ³⁺ (mg/L)	Mg ²⁺ (mg/L)	Sr ²⁺ (mg/L)
4	0.1	0.1	0.1	0.1
5	1	1	1	1
6	10	10	10	10

[0098] FIG. 11 presents ion release profiles for Si (FIG. 11A) and Na (FIG. 11B) release of the eight embolic particulates with time dependency over 12, 24, 48, 96 and 120 h. Lines are drawn as visual guides. FIG. 12 presents ion release profiles for Ca (FIG. 12A) and Sr (FIG. 12B) release of the eight embolic particulates with time dependency over 12, 24, 48, 96 and 120 h. Lines are drawn as visual guides. FIG. 13 presents ion release profiles for Ti (FIG. 13A) and La (FIG. 13B) release of the eight embolic particulates with time dependency over 12, 24, 48, 96 and 120 h. Lines are drawn as visual guides. Lines are drawn as visual guides (*excluding ambiguous data with $R^2 < 0.6$*). FIG. 14 presents an ion release profile for Mg (FIG. 14A) and mean ($\pm$ SD) release levels for Zn (FIG. 14B) of the eight embolic particulates with time dependency over 12, 24, 48, 96 and 120 h (for Zn (FIG. 14B) only). Lines are drawn

as visual guides. Lines are drawn as visual guides (*excluding ambiguous data with $R^2 < 0.6$*). FIG. 15 presents the effect of embolic material composition on release levels for Si (FIG. 15A) and Na (FIG. 15B) after 120h incubation periods. FIG. 16 presents the effect of embolic material composition on release levels for Ca (FIG. 16A) and Sr (FIG. 16B) after 120h incubation periods. FIG. 17 presents the effect of embolic material composition on release levels for Ti (FIG. 17A); La (FIG. 17B) and Mg (FIG. 17C) after 120h incubation periods.

[0099] Table 16 provides the goodness of fit (in terms of R^2 values) for the non-linear one phase association model formed from Si^{4+} and Na^+ release over 5 time points (12, 24, 48, 96, 120h).

Table 16.

Embolic Composition	Si^{4+}	Na^+
	R^2	R^2
ORP1	0.8219	0.7752
ORP2	0.8115	0.7383
ORP3	0.7195	0.7174
ORP5	0.8691	0.8935
ORP6	0.8123	0.6263
ORP7	0.8672	0.7111
ORP9	0.7839	0.5419
ORP11	0.8697	0.6747

[0100] Table 17 provides the best-fit parameters for the non-linear one phase association model formed from Ca^{2+} release over 5 time points (12, 24, 48, 96, 120h).

Table 17.

Embolic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP1	4.938	7.123	7.948	7.953	0.9808
ORP2	4.003	5.776	3.932	3.936	0.9427
ORP3	4.840	6.982	2.860	2.868	0.9594

Embollic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP5	4.523	6.525	2.663	2.669	0.9660
ORP6	3.926	5.664	2.650	2.653	0.9604
ORP7	3.771	5.440	2.605	2.607	0.9605
ORP9	1.379	1.989	5.515	5.515	0.6575
ORP11	4.044	5.835	3.189	3.193	0.9669

[0101] Table 18 provides the best-fit parameters for the non-linear one phase association model formed from Sr^{2+} release over 5 time points (12, 24, 48, 96, 120h).

Table 18.

Embollic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP1	15.70	22.65	0.3583	0.3706	0.9550
ORP2	14.64	21.12	0.3446	0.3585	0.9181
ORP3	18.28	26.38	0.2980	0.3089	0.9239
ORP5	12.63	18.21	0.2772	0.2828	0.9713
ORP6	16.00	23.08	0.4494	0.4669	0.9645
ORP7	10.20	14.72	0.3201	0.3262	0.9666
ORP9	6.786	9.79	0.4188	0.4202	0.8559
ORP11	9.671	13.95	0.3096	0.3129	0.9749

[0102] Table 19 presents the best-fit parameters for the non-linear one phase association model formed from Ti^{4+} release over 5 time points (12, 24, 48, 96, 120h).

The asterisk (*) represents the models denoted as ambiguous.

Table 19.

Embollic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP1*	~0.233	~0.336	0.1980	0.1980	0.9661
ORP2	2.563	3.698	0.1875	0.1875	0.9815
ORP3	4.300	6.203	0.1861	0.1862	0.9878

Embolitic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP5	2.885	4.162	0.1801	0.1801	0.9876
ORP6	2.885	4.162	0.1801	0.1801	0.9876
ORP7	2.885	4.162	0.1801	0.1801	0.9925
ORP9*	~0.000	~0.000	0.1920	0.1920	0.9867

[0103] Table 20 presents the best-fit parameters for the non-linear one phase association model formed from Mg^{2+} release over 5 time points (12, 24, 48, 96, 120h). The asterisk (*) represents the models denoted as ambiguous.

Table 20.

Embolitic Composition	$t^{1/2}$ (h)	t_{au} (h)	t_s (h)	y_{max} (ppm)	R^2
ORP1	57.52	82.98	0.11	0.1111	0.9639
ORP2	74.21	107.10	0.07	0.0721	0.7802
ORP3	9.50	13.70	0.03	0.0261	0.3176
ORP5*	~0.05	~0.01	0.05	0.0460	0.2356
ORP6	58.01	83.69	0.11	0.1058	0.9656
ORP7*	~0.00	~0.00	0.05	0.0460	0.1572
ORP9	7.71	11.12	0.08	0.0751	0.4458
OR11	3.91	5.64	0.04	0.0372	0.1779

[0104] Surprisingly, Zn^{2+} was only found to initially release after 120 h. All other ions were found to release continuously for all time periods. This is contrary to the expectation that Zn^{2+} would release ions with the immediate onset of its submersion into solution.

[0105] The ion release profiles for both Si^{4+} and Na^{2+} present stable time-dependent increases in ion release (denoted by the goodness of fit values represented by R^2 values ranging from 0.81 to 0.87 with the exception of ORP3 and 9 yielding R^2 values of 0.72 and 0.78, respectively for Si^{4+} and R^2 values ranging from 0.71 to 0.90 with the exception of ORP6, 9 and 11 yielding R^2 values of 0.63, 0.54 and 0.67,

respectively for Na^{2+}) up to 120 h, which potentially indicate the controllable nature for each composition. Full stabilization of ion release is not evident for both ions after 120 h.

[0106] An initial burst of Ca^{2+} released for ORP9 during the first few hours in solution was noted, ending abruptly to maintain a stable release level for the remainder of the study. ORP1 also exhibited an initial burst of Ca^{2+} release to gradually release Ca^{2+} at a stable rate past 24 h. The remaining compositions however, show more gradual initial Ca^{2+} release up to 24 h prior to reach full stabilization. This is likely due to the formation of a hydrogel like layer on the full surface area of the glass particulate as a result of initial Ca^{2+} release (from the particulate) in exchange for H_3O^+ in the incubation media, to precipitate onto the entire surface of the particulate; and further impact upon the rate of ion release from the particulates. Interestingly, the same release profiles were observed for Sr^{2+} and Ti^{4+} .

[0107] Importantly, very slow release levels of Mg^{2+} into the solution were noted, to suggests that it is strongly chelated by the silicate network. The same is reported for La^{2+} with the exception of ORP1 (possibly due to an increase in crystalline species).

Preparation of particle extracts for MTT/Release of LDH Assays

[0108] For this protocol, all particles were sterilized by autoclaving (AMSCO Medallist) at $121^\circ / 25$ bar for a period of 20 mins prior to incubation. Pre-sterilized batches of ContourTM (Lot No.s: 13473927 and 13599201) were used as a control. Subsequently, an equivalent amount (0.1g) of each sterile glass (ORP1-3, ORP5-7, ORP9, ORP11) and ContourTM were immersed in 10mL of sterile tissue culture water (Sigma-Aldrich, Canada) for 24 hours, placed on a roller (rotating at $\sim 2\text{Hz}$.) positioned inside a 37°C incubator. After each storage period, samples were filtered using a sterile $0.20\ \mu\text{m}$ filter (Sarstedt, Canada), and filtrates stored at 7°C prior to *in vitro* evaluation.

Fibroblast Cell Culture

[0109] Immortalized rat fibroblasts (NIH-3T3; American Type Tissue Collection, Manassas, VA) at passages 15–20 were used for experiments. The cells were grown in 75-cm^2 tissue culture flasks in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% fetal calf serum (FCS; heat-inactivated at 56°C for 60 min). Cells were passaged twice weekly at 70% confluence, using 2 mL of 0.25% trypsin-

EDTA to detach cells, and re-suspended in 8 mL of DMEM. Flasks were maintained in a humidified atmosphere at 37°C and 10% CO₂. No antibiotics were used during routine subdivisions or for cell culture experiments to avoid altering cell metabolism. Fibroblasts for use in experiments were harvested at 70% confluence, detached using trypsin-EDTA, suspended at a concentration of 1×10^4 cells/mL, and verified using a Coulter counter.

Assessment of Cell Viability (MTT Assay)

[0110] NIH-3T3 cells (200 µL) were seeded at a density of 1×10^4 cells/mL in 96-nontissue culture-treated polystyrene plates (CoStar, Corning, Canada). DMEM + 5% FCS culture media plus sterile tissue culture water only was used as a negative control and culture media plus cells plus sterile tissue culture water used as a positive control. Serial dilutions were performed on all samples (at 25, 50, 75 and 100%) and performed in triplicate. Hence, 4 plates (corresponding to each dilution) were incubated for 24 h in a cell culture incubator at 37°C (10% CO₂/95% air atmosphere). After 24 h, 5, 10 and 15 µL of sterile tissue culture water were added to each well in their respective plate (corresponding to 75, 50 and 25% dilutions). 20 µL of relevant experimental extracts were then added to appropriate wells for testing. The plate was incubated again for 24 h in a cell culture incubator at 37°C (10% CO₂/95% air atmosphere)⁷. A 5 mg/mL solution of MTT reagent (M2128, Sigma Aldrich Canada) was prepared in phosphate-buffered saline, vortexed and sterile-filtered (0.20µm). Post 24 h incubation of the plates, each well was exposed to the prepared MTT at an amount equal to 10% of the culture media volume. The four plates representing each set of dilutions were then returned to the incubator for 3 h. After incubation, MTT solubilisation solution (Catalog Code: M8910) was added to each well at a volume equal to the original culture media volume. Each well was gently stirred on a rotating table to enhance dissolution of the formazan crystals. Subsequently, the absorbance of each well was spectrophotometrically measured at a wavelength of 570 nm on a multidetection microplate reader (Synergy HT, BIO-TEK). Cell positive control wells were assumed to have 100% metabolic activity corresponding to cellular viability of 100% and the percentage cell viability of the cells exposed to experimental extracts were calculated relative to this.

Assessment of Cell Cytotoxicity (Release of LDH Assay)

[0111] The lactate dehydrogenase (LDH) assay was measured by a colorimetric lactate dehydrogenase (LDH) assay (TOX-7 (Product Code: 050M6079), Sigma Aldrich, Canada), according to instructions from the supplier. The amount of LDH in the medium is proportional to the number of lysed/dead cells present; therefore, this assay can be used to estimate cell death. This assay measures membrane integrity as a function of the amount of cytoplasmic LDH released into the medium. Briefly, assay mixture was prepared by mixing equal amounts of LDH assay substrate (Catalog Number: L2402), cofactor (Catalog Number: L2527) and dye solutions (Catalog Number: L2277). For all cultures (70 μ L), assay mixture was added to the medium in a proportion of two to one in 4 x 96-well tissue culture-treated polystyrene plates (CoStar, Corning, Canada). Each plate corresponds to medium dilutions of 25, 50, 75 and 100%, respectively. After incubation at room temperature in the dark (each plate covered with Al foil) and through gentle rotation on a roller, the color reaction was stopped by 1 N HCl. Similar to the MTT assay, DMEM + 5% FCS culture media plus sterile tissue culture water only was used as a negative control and culture media plus cells plus sterile tissue culture water used as a positive control. Absorbance was determined at 490 nm using a multidetection microplate reader (Synergy HT, BIO-TEK), with the background correction performed at 650 nm.

Statistical Analysis

[0112] Each experiment was performed in triplicate and analysed using Prism 5.0 software (GraphPad software, Inc.) Results are expressed as mean $\pm$ standard deviation of the triplicate determinations. One way analysis of variance (ANOVA) was carried out followed by a Tukey's post hoc test for comparisons between groups. The level of significance was set at $p < 0.05$. FIG. 18A presents cell viability in the presence of ORP1-3, ORP5-7, ORP9 and ORP11 and ContourTM for 24 h embolic particulate extracts at 25, 50 and 100% serial dilutions. Results represent mean $\pm$ SD (no significant statistical differences ($p < 0.05$) were observed between any of the extracts tested). FIG. 18B presents cell toxicity in the presence of ORP1-3, ORP5-7, ORP9 and ORP11 and ContourTM for 24 h embolic particulate extracts at 25, 50, 75 and 100% serial dilutions. Results represent mean $\pm$ SD (no significant statistical differences ($p < 0.05$) were observed between any of the extracts tested). FIG. 19

presents contour plots' showing the compositional-interaction effects on the experimental embolic materials cell viability (%) at four various additions of Ti (0.017 (FIG. 19A), 0.033 (FIG. 19B), 0.042 (FIG. 19C) and 0.05 mol. (FIG. 19D)) in actual component coding.

[0113] Table 21 provides the final regression equations in terms of L_Pseudo (1); Actual components (2) and R^2 values; and summarized ANOVA for cell viability. The ANOVA data demonstrates that the model adequately predicts the cell viability response of the particulate material.

Table 21.

Response	Regression Models	Summarized ANOVA					
		R^2	$R^2_{adj.}$	$R^2_{pred.}$	Prob > F	CV (%)	Adeq. Prec.
Cell Viability (%)	1 +66.63ZnO – 145.51La ₂ O ₃ + 338.30SiO ₂ + 815.98TiO ₂ + 265.33ZnO * La ₂ O ₃ – 365.03ZnO * SiO ₂ – 913.28ZnO * TiO ₂	0.9999	0.9994	0.9817	0.0179	0.36	123.770
	2 +1236.37607ZnO – 1029.59161La ₂ O ₃ + 393.36925SiO ₂ + 1798.32577TiO ₂ + 2295.21826ZnO * La ₂ O ₃ – 3157.72134ZnO * SiO ₂ – 7900.33004ZnO * TiO ₂						

[0114] Table 22 provides the residuals of the cell viability study for all material compositions synthesized.

Table 22.

Cell Viability (%)				
Glass	Experimental Data	SD	Calculated Data	Residual (Difference)
ORP1	73.790	°19.77	73.954	-0.164
ORP2	84.120	°17.23	84.087	-0.033

Cell Viability (%)				
Glass	Experimental Data	SD	Calculated Data	Residual (Difference)
ORP3	81.270	°16.15	81.153	0.117
ORP5	91.790	°18.74	91.885	-0.095
ORP6	72.370	°17.05	72.301	0.069
ORP7	71.440	°10.90	71.323	0.117
ORP9	62.240	°22.03	62.278	-0.038
ORP11	60.760	°03.49	60.798	-0.038

[0115] Table 23 provides the summary of the significant (positive and negative) main, interaction and quadratic compositional factors (ranked highest to lowest) and its effect on increasing cytocompatibility; where ↑ denotes an increase and ↓ a decrease. The data is based on actual component coding.

Table 23.

Ranking of Compositional Factors	Cell Viability Response
1	↓ZnO*TiO ₂
2	↑TiO ₂
3	↓ZnO*SiO ₂
4	↑SiO ₂
5	↑ZnO*La ₂ O ₃

[0116] The data demonstrates that the most significant ‘main’ compositional variants which impact upon cell viability at 75% are on the order TiO₂>SiO₂. An interesting feature is that, counter to what would be expected, ZnO in its own right does not contribute to a reduction in cell viability. Rather, ZnO is dependant on interactions with TiO₂ (Table 23 G; ZnO*TiO₂ is the 1st most significant factor with respect to the MTT assay) to reduce cell viability; whereby a decrease in ZnO for an increase in TiO₂ may enhance cell viability. Similarly, the interactions between ZnO and SiO₂ indicates that decreased ratio of ZnO:SiO₂ will allow for enhanced

cytocompatibility. Other surprising relationships shown in the data are described below.

[0117] It also would not have been predicted that increasing the ratio of ZnO:La₂O₃ provides for increased levels of cell viabilities. This interaction effect deems La₂O₃ more cytotoxic than ZnO. To the contrary, it would have been expected that the Zn containing materials described herein would demonstrate a cytotoxicity profile counter to requirements. However, it is clearly demonstrated that the complex multi-component system provides for tailored (equivalent or superior) cytocompatibility versus conventional embolic materials (Contour).

Evaluation of Radiopacity

[0118] Radiopacity of OccluRad versus PVA (Contour) was determined using computed tomography scans of Gammex Tissue Characterization phantom inserts filled with each product. FIG. 20 is a comparison of radiopacity for ORP vs. PVA in various dilutions of saline/contrast agent. Results are provided in terms of the materials Hounsfield Unit (HU) values.

[0119] Due to the complexity of the multi-component systems (compositions) disclosed, one could not predict the response for each, with respect to its inherent radiopacity. It is noted that the HU values for ORP5 representative for all sets of compositions disclosed) demonstrates far superior levels to Contour in the absence of any contrast agent.

In vivo Evaluation of Safety and Efficacy

[0120] Animal units (New Zealand White Rabbits) were used for a pilot examination of local effects after implantation in the uterine artery. Material (ORP 5) was delivered to the relevant vasculature, using a 25G butterfly cannulae, in a suspension of saline (8mg/mL). 8 animals were utilized; 4 treated with ORP5 and 4 with Contour. Animals were euthanized after 21 days, using Isoflurane and KCl (the latter administered *via* IV at 2mg/kg). Laparotomy was performed, and the uterus, including both ovaries, was removed. The left and right uterine horns were dissected, fixed in 10% formaldehyde solution and sectioned appropriately for histological evaluation. Histological samples were taken at four to six different levels (depending on size) along the uterine horn; routine hematoxylin and eosin staining was performed thereafter.

[0121] FIG. 21 presents histological data, derived from one animal in each group, with respect to the performance of Contour (FIG. 21A), ORP5 (FIG. 21B) and Control (FIG. 21C).

[0122] That ORP5 worked as well as and in some measures, out performed, the Contour could not have been predicted. Gross examination of the pathology specimens from all 8 rabbits showed a necrotic uterus at the embolization site, with no obvious changes in any of the untreated uterine horns. No adverse reactions were observed for any of the H&E stained tissues examined (in both experimental and commercial groups) with comparable data to untreated (normal) uterine tissues. In the intracutaneous irritation test, there was no evidence of irritation in both the polar (normal saline) and non-polar (sesame oil) vehicles (the mean score difference less than 1 in all observations), to demonstrate equivalency for ORP5 to the embolic predicate Contour.

Intracutaneous Irritation Test

[0123] This study was conducted according to ISO 10993-10. The potential of the test article (extract of particle ORP5) producing irritation was evaluated after intracutaneous injection of the test article. Three New Zealand White rabbits were used in this study. Each rabbit was injected intracutaneously with 0.2 mL of test article or vehicles. The polar vehicle was normal saline, and the nonpolar vehicle was sesame oil. The treatment designs of each animal are presented in FIG. 22. Table 24 provides the Draize grading system for the experiment.

Table 24.

Reaction	Numerical Grading
1. Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet-redness) to escher formation preventing grading of erythema	4
2. Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined edema (edges of area well-defined by definite raising)	2

Reaction	Numerical Grading
Moderate edema (raised approximately 1mm)	3
Severe erythema (raised approximately 1mm and extending beyond exposure area)	4

[0124] The appearance of each injection site was noted and marked immediately after injection. Observation of the tissue reaction at 0 hours (immediately after injection), 24 hours, 48 hours, and 72 hours after injection were graded. Any reaction at the injection site was recorded accordingly. FIG. 23 provides images of the intradermal injection sites for the three NZW rabbits after 24, 48 and 72h observations.

Conformation of Fibrinogen in embolic extracts containing degradation products

[0125] Far-ultraviolet (UV) Circular Dichroism (CD) spectra were recorded using a Jasco J-810 spectropolarimeter (Easton, MD) with temperature control capability. A 6.4 mg/mL solution of fibrinogen from human plasma (F4883, plasminogen free, containing 58% protein, 96% clottable protein; Sigma Aldrich, ON) in 25 mM sodium phosphate buffer adjusted to pH 7.4 ± 0.05 using NaOH and H₂SO₄ was diluted to a concentration of 0.2 mg/mL with the solutions of embolic extracts (containing the ion degradation products, as prepared in **Example 9** at n=3 for each extract)). The concentration of the stock fibrinogen solution was determined by UV spectroscopy at 280 nm using the manufacturer's molar extinction coefficient. All spectra were collected at 37°C (controlled with a NESLAB RTE-111 bath, Thermo Scientific, Newington, NH) in three repetitions (260-190 nm, 1 nm steps, 50 nm/min) in a 0.5 mm pathlength quartz cuvette (Hellma, Müllheim, Germany). The triplicate spectra for each ion degradation solution were averaged, blank subtracted with phosphate buffer (25 mM; pH 7.4 ± 0.05), and converted to mean residue ellipticity ([θ]). Relative fibrinogen conformation between samples was monitored by comparing [θ] at the minima corresponding to the α -helical bands at ~208 and 222 nm. FIG. 24 illustrates changes in Fg conformation monitored by far-ultraviolet circular dichroism (CD) spectroscopy as a function of the ionic dissolution products with respect to time. FIG. 24A is an example of CD spectra for ORP5 over time. FIGS. 24B and C are intensity (mean of 3 replicates, blank subtracted; average deviation shown) at the minima at ~208 and 222 nm of Fg CD spectra for each ionic dissolution product. All

data is reported in mean residue ellipticity $[\theta]$. The provided legend applies for all three panels.

[0126] The effect of the degradation by-products from such complex multi-component systems on the secondary structure of fibrinogen, Fg (an essential precursor protein for clot formation) could not have been predicted. Interestingly, no significant conformational changes to Fg structure were observed by CD (FIG. 24), despite previous literature reports of this possibility. The response of platelets in contact with ORP5 and Contour using LDH assays could not have been predicted.

Platelet lactate dehydrogenase (LDH) assay studies

[0127] All protocols pertaining to the use of whole blood and platelets were approved by the Capital Health Research Ethics Board. The blood (31.5 mL) was collected *via* venipuncture from healthy, aspirin-free human volunteers at the Laboratory Blood Collection facility at the Victoria General Hospital in seven 4.5 mL glass BD Vacutainer tubes (Catalog No. 364606, Becton-Dickinson, Franklin Lakes, NJ) containing an acid-citrated dextrose (ACD) anticoagulant. It is important to note that the first tube (4.5 mL) of blood was discarded, as it is rich in clotting factors, and then the remaining 27 mL was collected. Platelet rich plasma (PRP) was generated by centrifuging the ACD-anticoagulated blood (1500rpm, 8 min, 25 °C) using an Eppendorf 5702 centrifuge. Careful transfer of the PRP to individual centrifuge tubes was completed using sterile plastic pasteur pipettes.

[0128] Platelet concentration was measured using a LH 785 CBC analyzer. The platelet concentration was recorded for each patient but not adjusted. The platelet suspension was then added to the preferred particles (ORP5 and ContourTM) at a final concentration of 0.1cc per mL of platelet suspension (3 mL of patient PRP for each embolic agent with the exception of patient 1006 which only had enough PRP to add 2.5 ml of PRP per embolic agent) and allowed to adhere for 1 h at 37 °C under static conditions.

[0129] At the end of this step, the suspension was aspirated from each well, and the non-adherent platelets were rinsed away by filling and aspirating the wells ten times with 2.5 mL of PBS. The entire duration from blood collection to the conclusion of this step was less than 4 h. Platelet LDH was quantified by measuring the lactate dehydrogenase (LDH) released when the adherent platelets were lysed with a Triton-

PSB buffer. A calibration curve was constructed using a known number of platelets and the platelet adhesion on the embolic agents was determined from this calibration curve. FIG. 25 illustrates results for platelet LDH assay (ORP5 vs. PVA) with (FIG. 25A) and without (FIG. 25B) outlier.

[0130] Given the complexity of the disclosed compositions, one could not have predicted the response of platelets to the material using the LDH assay. It is noted that performance of the multi-component systems in this assay demonstrate equivalent compatibility to Contour.

[0131]

[0132] The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

References.

1. Zhang XF, Kehoe S, Adhi SK, Ajithkumar TG, Moane S, O'Shea H, Boyd D, Composition-structure-property (Zn^{2+} and Ca^{2+} ion release) evaluation of Si-Na-Ca-Zn-Ce glasses: Potential components for nerve guidance conduits. *Materials Science and Engineering C* 2011; doi:10.1016/j.msec.2010.12.016
2. Murphy S, Boyd D, Moane S, and Bennett M. The effect of composition on ion release from Ca-Sr-Na-Zn-Si glass bone grafts. *J Mater Sci Mater Med* 2009; 20: 2207-2214.
3. Duee, C., et al., *Mixture designs applied to glass bioactivity evaluation in the Si-Ca-Na system*. *Journal of Non-Crystalline Solids*, 2009. **355**(16-17): p. 943-950.
4. Akalin, O., et al., *Optimization of chemical admixture for concrete on mortar performance tests using mixture experiments*. *Chemometrics and Intelligent Laboratory Systems*, 2010. **104**(2): p. 233-242.
5. Papelis C, Um W, Russell CE, and Chapman JB. Measuring the specific surface

area of natural and manmade glasses: effects of formation process, morphology, and particle size. *Colloids and Surfaces a-Physicochemical and Engineering Aspects* 2003; 215: 221-239.

6. Ning J, Yao A, Wang DP, Huang WH, Fu HL, Liu X, Jiang XQ, and Zhang XL. Synthesis and in vitro bioactivity of a borate-based bioglass. *Materials Letters* 2007; 61: 5223-5226.
7. Cheung S, Gauthier M, Lefebvre LP, Dunbar M, and Filiaggi M. Fibroblastic interactions with high-porosity Ti-6Al-4V metal foam. *Journal of Biomedical Materials Research Part B-Applied Biomaterials* 2007; 82B: 440-449.

Table 2. 177 glass compositions (mol. fraction) formulated using design of experiments. The NM components are varied between 0 to 0.140 mol. fraction.

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
78	1	0.000	0.150	0.520	0.050	0.140	0.000	0.140	0.000
4	2	0.290	0.000	0.570	0.000	0.000	0.140	0.000	0.000
17	3	0.290	0.140	0.520	0.050	0.000	0.000	0.000	0.000
132	4	0.000	0.000	0.570	0.050	0.100	0.140	0.000	0.140
150	5	0.000	0.150	0.520	0.050	0.000	0.000	0.140	0.140
73	6	0.200	0.000	0.520	0.000	0.140	0.000	0.140	0.000
6	7	0.290	0.000	0.570	0.000	0.000	0.000	0.000	0.140
43	8	0.290	0.000	0.520	0.000	0.000	0.140	0.050	0.000
10	9	0.000	0.290	0.570	0.000	0.000	0.000	0.140	0.000
125	10	0.000	0.200	0.520	0.000	0.000	0.140	0.000	0.140
14	11	0.290	0.000	0.520	0.050	0.000	0.140	0.000	0.000
142	12	0.000	0.010	0.520	0.050	0.140	0.140	0.000	0.140
121	13	0.000	0.100	0.570	0.050	0.140	0.000	0.000	0.140
20	14	0.000	0.290	0.520	0.050	0.000	0.000	0.140	0.000
144	15	0.000	0.000	0.520	0.050	0.140	0.140	0.010	0.140
171	16	0.000	0.000	0.570	0.010	0.000	0.140	0.140	0.140
62	17	0.000	0.100	0.570	0.050	0.140	0.140	0.000	0.000
152	18	0.000	0.100	0.570	0.050	0.000	0.000	0.140	0.140
151	19	0.100	0.000	0.570	0.050	0.000	0.000	0.140	0.140
15	20	0.290	0.000	0.520	0.050	0.000	0.000	0.140	0.000
153	21	0.000	0.000	0.570	0.050	0.100	0.000	0.140	0.140
27	22	0.290	0.090	0.570	0.050	0.000	0.000	0.000	0.000
8	23	0.000	0.290	0.570	0.000	0.140	0.000	0.000	0.000
145	24	0.200	0.000	0.520	0.000	0.000	0.000	0.140	0.140

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
63	25	0.290	0.000	0.520	0.000	0.000	0.000	0.140	0.050
134	26	0.060	0.000	0.520	0.000	0.140	0.140	0.000	0.140
107	27	0.290	0.000	0.520	0.000	0.000	0.000	0.050	0.140
148	28	0.000	0.150	0.570	0.000	0.000	0.000	0.140	0.140
160	29	0.000	0.000	0.570	0.010	0.140	0.000	0.140	0.140
120	30	0.100	0.000	0.570	0.050	0.140	0.000	0.000	0.140
75	31	0.150	0.000	0.570	0.000	0.140	0.000	0.140	0.000
128	32	0.150	0.000	0.520	0.050	0.000	0.140	0.000	0.140
108	33	0.050	0.290	0.520	0.000	0.000	0.000	0.000	0.140
159	34	0.000	0.010	0.570	0.000	0.140	0.000	0.140	0.140
24	35	0.290	0.000	0.570	0.050	0.000	0.090	0.000	0.000
164	36	0.000	0.000	0.530	0.050	0.140	0.000	0.140	0.140
9	37	0.000	0.290	0.570	0.000	0.000	0.140	0.000	0.000
124	38	0.200	0.000	0.520	0.000	0.000	0.140	0.000	0.140
90	39	0.100	0.000	0.570	0.050	0.000	0.140	0.140	0.000
126	40	0.150	0.000	0.570	0.000	0.000	0.140	0.000	0.140
174	41	0.000	0.010	0.520	0.050	0.000	0.140	0.140	0.140
141	42	0.010	0.000	0.520	0.050	0.140	0.140	0.000	0.140
7	43	0.290	0.140	0.570	0.000	0.000	0.000	0.000	0.000
92	44	0.000	0.000	0.570	0.050	0.100	0.140	0.140	0.000
74	45	0.000	0.200	0.520	0.000	0.140	0.000	0.140	0.000
122	46	0.000	0.000	0.570	0.050	0.140	0.100	0.000	0.140
135	47	0.000	0.060	0.520	0.000	0.140	0.140	0.000	0.140
64	48	0.290	0.050	0.520	0.000	0.000	0.000	0.140	0.000
93	49	0.000	0.000	0.520	0.000	0.140	0.140	0.140	0.060
12	50	0.140	0.290	0.570	0.000	0.000	0.000	0.000	0.000
95	51	0.000	0.060	0.520	0.000	0.140	0.140	0.140	0.000

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
119	52	0.000	0.150	0.520	0.050	0.140	0.000	0.000	0.140
162	53	0.010	0.000	0.520	0.050	0.140	0.000	0.140	0.140
69	54	0.000	0.290	0.520	0.000	0.050	0.000	0.140	0.000
80	55	0.100	0.000	0.570	0.050	0.140	0.000	0.140	0.000
112	56	0.240	0.000	0.570	0.050	0.000	0.000	0.000	0.140
49	57	0.050	0.290	0.520	0.000	0.000	0.140	0.000	0.000
157	58	0.000	0.000	0.520	0.000	0.140	0.060	0.140	0.140
133	59	0.000	0.000	0.570	0.050	0.000	0.140	0.100	0.140
23	60	0.290	0.000	0.570	0.050	0.090	0.000	0.000	0.000
86	61	0.000	0.150	0.570	0.000	0.000	0.140	0.140	0.000
47	62	0.000	0.290	0.520	0.000	0.000	0.140	0.050	0.000
21	63	0.000	0.290	0.520	0.050	0.000	0.000	0.000	0.140
19	64	0.000	0.290	0.520	0.050	0.000	0.140	0.000	0.000
71	65	0.240	0.000	0.570	0.050	0.000	0.000	0.140	0.000
56	66	0.000	0.150	0.570	0.000	0.140	0.140	0.000	0.000
176	67	0.000	0.000	0.520	0.050	0.010	0.140	0.140	0.140
102	68	0.000	0.000	0.520	0.050	0.140	0.140	0.140	0.010
67	69	0.000	0.290	0.520	0.000	0.000	0.000	0.140	0.050
76	70	0.000	0.150	0.570	0.000	0.140	0.000	0.140	0.000
99	71	0.000	0.000	0.570	0.010	0.140	0.140	0.140	0.000
115	72	0.000	0.200	0.520	0.000	0.140	0.000	0.000	0.140
58	73	0.000	0.150	0.520	0.050	0.140	0.140	0.000	0.000
34	74	0.290	0.000	0.520	0.000	0.140	0.000	0.050	0.000
29	75	0.000	0.290	0.570	0.050	0.000	0.090	0.000	0.000
41	76	0.240	0.000	0.570	0.050	0.140	0.000	0.000	0.000
163	77	0.000	0.010	0.520	0.050	0.140	0.000	0.140	0.140
87	78	0.150	0.000	0.520	0.050	0.000	0.140	0.140	0.000

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
139	79	0.000	0.000	0.570	0.010	0.140	0.140	0.000	0.140
167	80	0.000	0.060	0.520	0.000	0.000	0.140	0.140	0.140
48	81	0.000	0.290	0.520	0.000	0.000	0.140	0.000	0.050
65	82	0.290	0.000	0.520	0.000	0.050	0.000	0.140	0.000
5	83	0.290	0.000	0.570	0.000	0.000	0.000	0.140	0.000
156	84	0.000	0.060	0.520	0.000	0.140	0.000	0.140	0.140
88	85	0.000	0.150	0.520	0.050	0.000	0.140	0.140	0.000
45	86	0.290	0.050	0.520	0.000	0.000	0.140	0.000	0.000
83	87	0.200	0.000	0.520	0.000	0.000	0.140	0.140	0.000
40	88	0.050	0.290	0.520	0.000	0.140	0.000	0.000	0.000
173	89	0.010	0.000	0.520	0.050	0.000	0.140	0.140	0.140
51	90	0.240	0.000	0.570	0.050	0.000	0.140	0.000	0.000
165	91	0.000	0.000	0.520	0.050	0.140	0.010	0.140	0.140
28	92	0.000	0.290	0.570	0.050	0.090	0.000	0.000	0.000
113	93	0.000	0.240	0.570	0.050	0.000	0.000	0.000	0.140
44	94	0.290	0.000	0.520	0.000	0.000	0.140	0.000	0.050
118	95	0.150	0.000	0.520	0.050	0.140	0.000	0.000	0.140
131	96	0.000	0.100	0.570	0.050	0.000	0.140	0.000	0.140
66	97	0.290	0.000	0.520	0.000	0.000	0.050	0.140	0.000
26	98	0.290	0.000	0.570	0.050	0.000	0.000	0.000	0.090
170	99	0.000	0.010	0.570	0.000	0.000	0.140	0.140	0.140
52	100	0.000	0.240	0.570	0.050	0.000	0.140	0.000	0.000
104	101	0.290	0.050	0.520	0.000	0.000	0.000	0.000	0.140
46	102	0.290	0.000	0.520	0.000	0.050	0.140	0.000	0.000
37	103	0.000	0.290	0.520	0.000	0.140	0.050	0.000	0.000
36	104	0.290	0.050	0.520	0.000	0.140	0.000	0.000	0.000
146	105	0.000	0.200	0.520	0.000	0.000	0.000	0.140	0.140

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
158	106	0.010	0.000	0.570	0.000	0.140	0.000	0.140	0.140
89	107	0.000	0.000	0.570	0.050	0.000	0.140	0.140	0.100
109	108	0.000	0.290	0.520	0.000	0.050	0.000	0.000	0.140
96	109	0.010	0.000	0.570	0.000	0.140	0.140	0.140	0.000
18	110	0.000	0.290	0.520	0.050	0.140	0.000	0.000	0.000
25	111	0.290	0.000	0.570	0.050	0.000	0.000	0.090	0.000
42	112	0.000	0.240	0.570	0.050	0.140	0.000	0.000	0.000
32	113	0.090	0.290	0.570	0.050	0.000	0.000	0.000	0.000
116	114	0.150	0.000	0.570	0.000	0.140	0.000	0.000	0.140
149	115	0.150	0.000	0.520	0.050	0.000	0.000	0.140	0.140
129	116	0.000	0.150	0.520	0.050	0.000	0.140	0.000	0.140
117	117	0.000	0.150	0.570	0.000	0.140	0.000	0.000	0.140
101	118	0.000	0.010	0.520	0.050	0.140	0.140	0.140	0.000
82	119	0.000	0.000	0.570	0.050	0.140	0.100	0.140	0.000
84	120	0.000	0.200	0.520	0.000	0.000	0.140	0.140	0.000
2	121	0.190	0.290	0.520	0.000	0.000	0.000	0.000	0.000
61	122	0.100	0.000	0.570	0.050	0.140	0.140	0.000	0.000
175	123	0.000	0.000	0.530	0.050	0.000	0.140	0.140	0.140
166	124	0.060	0.000	0.520	0.000	0.000	0.140	0.140	0.140
11	125	0.000	0.290	0.570	0.000	0.000	0.000	0.000	0.140
97	126	0.000	0.010	0.570	0.000	0.140	0.140	0.140	0.000
168	127	0.000	0.000	0.520	0.000	0.060	0.140	0.140	0.140
13	128	0.290	0.000	0.520	0.050	0.140	0.000	0.000	0.000
22	129	0.140	0.290	0.520	0.050	0.000	0.000	0.000	0.000
147	130	0.150	0.000	0.570	0.000	0.000	0.000	0.140	0.140
68	131	0.050	0.290	0.520	0.000	0.000	0.000	0.140	0.000
39	132	0.000	0.290	0.520	0.000	0.140	0.000	0.000	0.050

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
1	133	0.290	0.190	0.520	0.000	0.000	0.000	0.000	0.000
81	134	0.000	0.100	0.570	0.050	0.140	0.000	0.140	0.000
54	135	0.000	0.200	0.520	0.000	0.140	0.140	0.000	0.000
94	136	0.060	0.000	0.520	0.000	0.140	0.140	0.140	0.000
31	137	0.000	0.290	0.570	0.050	0.000	0.000	0.000	0.090
50	138	0.000	0.290	0.520	0.000	0.050	0.140	0.000	0.000
53	139	0.200	0.000	0.520	0.000	0.140	0.140	0.000	0.000
138	140	0.000	0.010	0.570	0.000	0.140	0.140	0.000	0.140
114	141	0.200	0.000	0.520	0.000	0.140	0.000	0.000	0.140
127	142	0.000	0.150	0.570	0.000	0.000	0.140	0.000	0.140
143	143	0.000	0.000	0.530	0.050	0.140	0.140	0.000	0.140
91	144	0.000	0.100	0.570	0.050	0.000	0.140	0.140	0.000
38	145	0.000	0.290	0.520	0.000	0.140	0.000	0.050	0.000
123	146	0.000	0.000	0.570	0.050	0.140	0.000	0.100	0.140
155	147	0.060	0.000	0.520	0.000	0.140	0.000	0.140	0.140
16	148	0.290	0.000	0.520	0.050	0.000	0.000	0.000	0.140
55	149	0.150	0.000	0.570	0.000	0.140	0.140	0.000	0.000
161	150	0.000	0.000	0.570	0.000	0.140	0.010	0.140	0.140
105	151	0.290	0.000	0.520	0.000	0.050	0.000	0.000	0.140
59	152	0.000	0.000	0.570	0.050	0.140	0.140	0.100	0.000
33	153	0.290	0.000	0.520	0.000	0.140	0.050	0.000	0.000
172	154	0.000	0.000	0.570	0.000	0.010	0.140	0.140	0.140
72	155	0.000	0.240	0.570	0.050	0.000	0.000	0.140	0.000
3	156	0.290	0.000	0.570	0.000	0.140	0.000	0.000	0.000
77	157	0.150	0.000	0.520	0.050	0.140	0.000	0.140	0.000
177	158	0.085	0.085	0.543	0.023	0.066	0.066	0.066	0.066
35	159	0.290	0.000	0.520	0.000	0.140	0.000	0.000	0.050

Std.	Run	Si	Ca	Zn	Mg	La	Sr	Ti	Na
ORP#									
57	160	0.150	0.000	0.520	0.050	0.140	0.140	0.000	0.000
100	161	0.010	0.000	0.520	0.050	0.140	0.140	0.140	0.000
169	162	0.010	0.000	0.570	0.000	0.000	0.140	0.140	0.140
60	163	0.000	0.000	0.570	0.050	0.140	0.140	0.000	0.100
111	164	0.000	0.290	0.520	0.000	0.000	0.000	0.050	0.140
70	165	0.000	0.290	0.520	0.000	0.000	0.050	0.140	0.000
140	166	0.000	0.000	0.570	0.000	0.140	0.140	0.010	0.140
154	167	0.000	0.000	0.570	0.050	0.000	0.100	0.140	0.140
137	168	0.010	0.000	0.570	0.000	0.140	0.140	0.000	0.140
106	169	0.290	0.000	0.520	0.000	0.000	0.050	0.000	0.140
98	170	0.000	0.000	0.570	0.000	0.140	0.140	0.140	0.010
79	171	0.000	0.000	0.570	0.050	0.140	0.000	0.140	0.100
30	172	0.000	0.290	0.570	0.050	0.000	0.000	0.090	0.000
85	173	0.150	0.000	0.570	0.000	0.000	0.140	0.140	0.000
103	174	0.000	0.000	0.530	0.050	0.140	0.140	0.140	0.000
110	175	0.000	0.290	0.520	0.000	0.000	0.050	0.000	0.140
130	176	0.100	0.000	0.570	0.050	0.000	0.140	0.000	0.140
136	177	0.000	0.000	0.520	0.000	0.140	0.140	0.060	0.140

WHAT IS CLAIMED IS:

1. A particulate material comprising:
0.4 - 0.6 mole fraction SiO_2 ;
0.00 - 0.1 mole fraction TiO_2 ;
0.04 - 0.188 mole fraction La_2O_3 ;
0.03 - 0.3 mole fraction MgO ;
0.03 - 0.3 mole fraction Na_2O ; and
0.068 - 0.290 mole fraction ZnO .
2. The particulate material of claim 1 wherein MgO is present at 0.03 to 0.2 mole fraction.
3. The particulate material of claim 1 further comprising SrO .
4. The particulate matter of claim 3 wherein the SrO is present at 0.035 mole fraction.
5. The particulate material of claim 3 wherein the MgO and the SrO together are present at 0.03 - 0.3 mole fraction.
6. The particulate material of claim 5 wherein the MgO and the SrO together are present at 0.05 - 0.2 mole fraction.
7. The particulate matter of any one of claims 1-6, further comprising CaO .
8. The particulate matter of claim 7, wherein the CaO is present at 0.035 mole fraction.
9. The particulate material of any one of claims 1-8 wherein the La_2O_3 is present at 0.04 to 0.1 mole fraction.
10. The particulate material of claim 9 wherein the La_2O_3 is present at 0.04 to 0.07 mole fraction.

11. The particulate material of any one of claims 1-10 wherein the TiO_2 is present at 0.017 to 0.05 mole fraction.
12. The particulate material of any one of claims 1-11 wherein the SiO_2 is present at 0.5 - 0.57 mole fraction.
13. The particulate material of any one of claims 1-12 wherein the Na_2O is present at 0.03 - 0.2 mole fraction.
14. The particulate material of claim 13 wherein the Na_2O is present at 0.03 - 0.15 mole fraction.
15. The particulate material of any one of claims 1-14, comprising no more than 0.1 mole fraction aluminosilicates, phosphates or a combination thereof.
16. The particulate matter according to claim 1, wherein the particulate matter consists of:
 - 0.562 mole fraction SiO_2 ;
 - 0.042 mole fraction TiO_2 ;
 - 0.068 mole fraction La_2O_3 ;
 - 0.035 mole fraction MgO ;
 - 0.035 mole fraction Na_2O ;
 - 0.188 mole fraction ZnO ;
 - 0.035 mole fraction CaO ; and
 - 0.035 mole fraction SrO .
17. The particulate material of any one of claims 1-16 wherein the particulate material is radiopaque.
18. The particulate material any one of claims 1-17 wherein the particulate material is biocompatible.

19. The particulate material of any one of claims 1-18 wherein said particulate material is degradable in vivo.
20. The particulate material of claim 19 wherein said particulate material degrades substantially in more than six months.
21. The particulate material of any one of claims 1-20 further comprising a therapeutic component.
22. The particulate material of claim 21 wherein said therapeutic component is released under physiological conditions.
23. The particulate material of any one of claims 1-22 having a Q-speciation of $Q^1 - Q^3$.
24. The particulate material of claim 23 having a Q-speciation of Q_1 .
25. The particulate material of any one of claims 1-24 having an average diameter of 45-1180 μm .
26. The particulate material of claim 25 having an average diameter of 200-1000 μm .
27. The particulate material of claim 26 having an average diameter of 300-500 μm .
28. The particulate material of claim 26 having an average diameter of 500-710 μm .
29. The particulate material of any one of claims 1-28 further comprising a polymeric coating.
30. The particulate material of claim 29 wherein said polymeric coating comprises poly(lactic-co-glycolic acid).
31. The particulate material of claim 30 wherein said polymeric coating comprises a poloxamer.

32. The particulate material of claim 31 wherein said polymeric coating comprises Pluronic F-127.
33. The particulate material of claim 29 further comprising a therapeutic component.
34. The particulate material of claim 33 wherein said therapeutic component is released under physiological conditions.
35. The particulate material of any one of claims 1-34 for use in vascular occlusion.
36. The particulate material of claim 35 for treatment of a vascular malformation.
37. The particulate material of claim 35 for organ ablation.
38. The particulate material of claim 35 for chemoembolization.
39. The particulate material of claim 35 for treatment of a hemorrhage.
40. The particulate material of any one of claims 1-34 for use in vascular occlusion for uterine fibroid embolization.
41. A particulate material comprising:
 - 0.4 - 0.6 mole fraction SiO_2 ;
 - 0 - 0.1 mole fraction TiO_2 ;
 - 0.04 - 0.188 mole fraction La_2O_3 ;
 - 0.068 - 0.29 mole fraction ZnO ; and
 - Na_2O , MgO , SrO , CaO , or any combination thereof,
 wherein the Na_2O , MgO , SrO , CaO , or combination thereof is present at 0.14 mole fraction.
42. The particulate material of claim 41 wherein the MgO is present at 0.035 mole fraction.

43. The particulate material of claim 41 wherein the SrO is present at 0.035 mole fraction.
44. The particulate material of claim 41, wherein the Na₂O is present at 0.035 mole fraction.
45. The particulate material of claim 41, wherein the CaO is present at 0.035 mole fraction.
46. The particulate material of claim 41, wherein the Na₂O, MgO, SrO, and CaO are each present at 0.035 mole fraction.
47. The particulate material of any one of claims 41-46 wherein the La₂O₃ is present at 0.04 to 0.07 mole fraction.
48. The particulate material of any one of claims 41-47 wherein the TiO₂ is present at 0 to 0.05 mole fraction.
49. The particulate material of any one of claims 41-47 wherein the TiO₂ is present at 0.017 to 0.05 mole fraction.
50. The particulate material of any one of claims 41-49, wherein the SiO₂ is present at 0.4 - 0.57 mole fraction.
51. The particulate material of any one of claims 41-50, wherein the particulate material comprises no more than 0.1 mole fraction aluminosilicates, phosphates or a combination thereof.
52. The particulate material of claim any one of claims 41-51 further comprising a therapeutic component.
53. The particulate material of claim 52 wherein said therapeutic component is released under physiological conditions.
54. The particulate material of any one of claims 41-51 having a Q-speciation of Q¹ – Q³.

55. The particulate material of claim 54 having a Q-speciation of $Q^2 - Q^3$.
56. The particulate material of any one of claims 41-55 having an average diameter of 45-1180 μm .
57. The particulate material of claim 56 having an average diameter of 200-1000 μm .
58. The particulate material of claim 57 having an average diameter of 300-500 μm .
59. The particulate material of claim 57 having an average diameter of 500-710 μm .
60. A composition comprising:
the particulate material of any one of claims 41-59; and
a polymer coating the particulate material, or a polymer matrix suspending the particulate material therein.
61. The composition of claim 60 wherein the polymer comprises poly(lactic-co-glycolic acid).
62. The composition of claim 60 wherein the polymer comprises a poloxamer.
63. The composition of claim 62 wherein the polymer comprises Pluronic F-127.
64. The composition of claim 60 further comprising a therapeutic component.
65. The composition of claim 64 wherein said therapeutic component is released under physiological conditions.
66. The particulate material of any one of claims 41-59, or the composition of any one of claims 60-65, for use in vascular occlusion.

67. The particulate material or composition of claim 66 for treatment of vascular malformations.
68. The particulate material or composition of claim 66 for organ ablation.
69. The particulate material or composition of claim 66 for chemoembolization.
70. The particulate material or composition of claim 66 for treatment of hemorrhage.
71. The particulate material of any one of claims 41-59, or the composition of any one of claims 60-65, for use in vascular occlusion for uterine fibroid embolization.

1 / 31

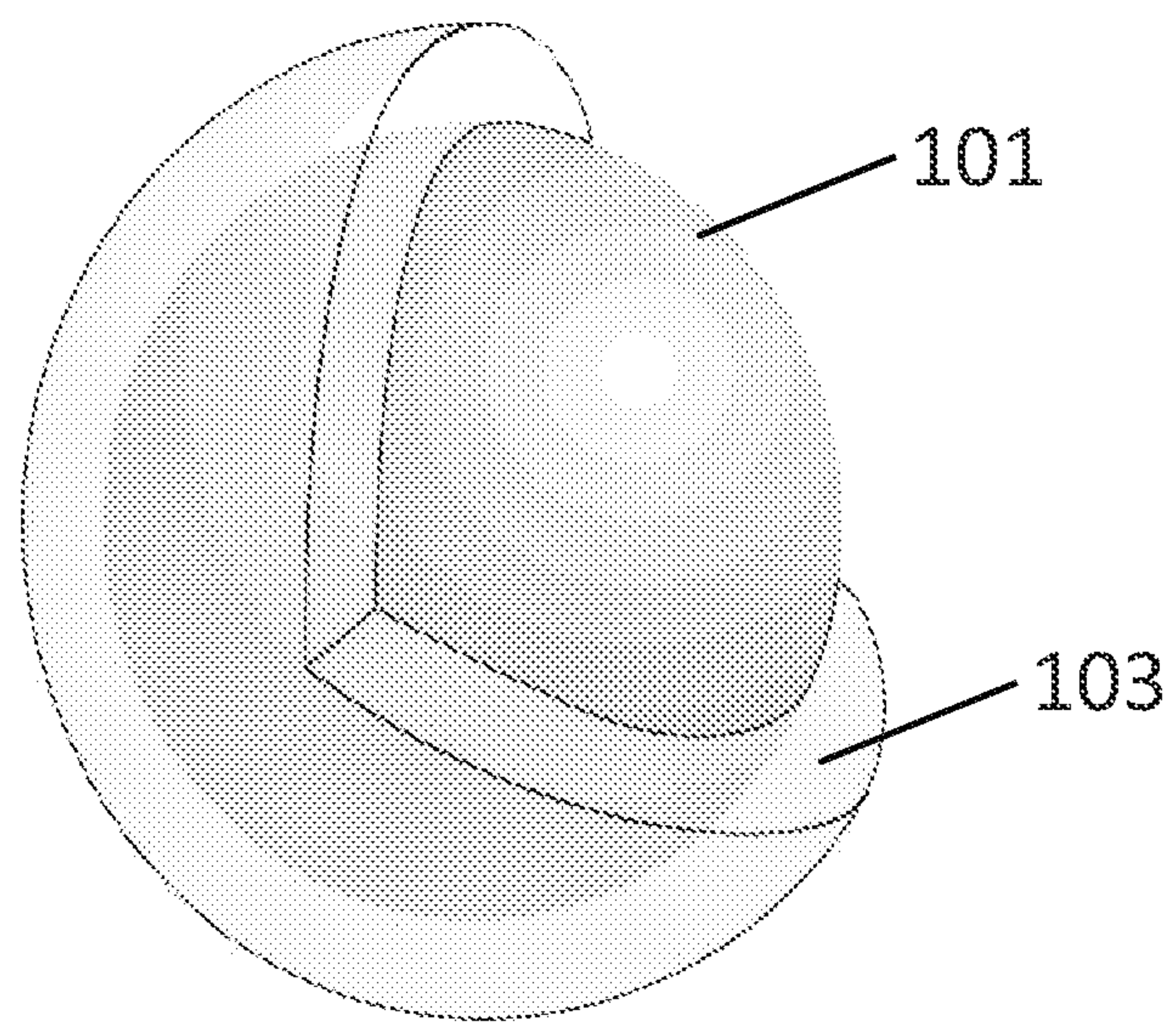


FIG. 1

2 / 31

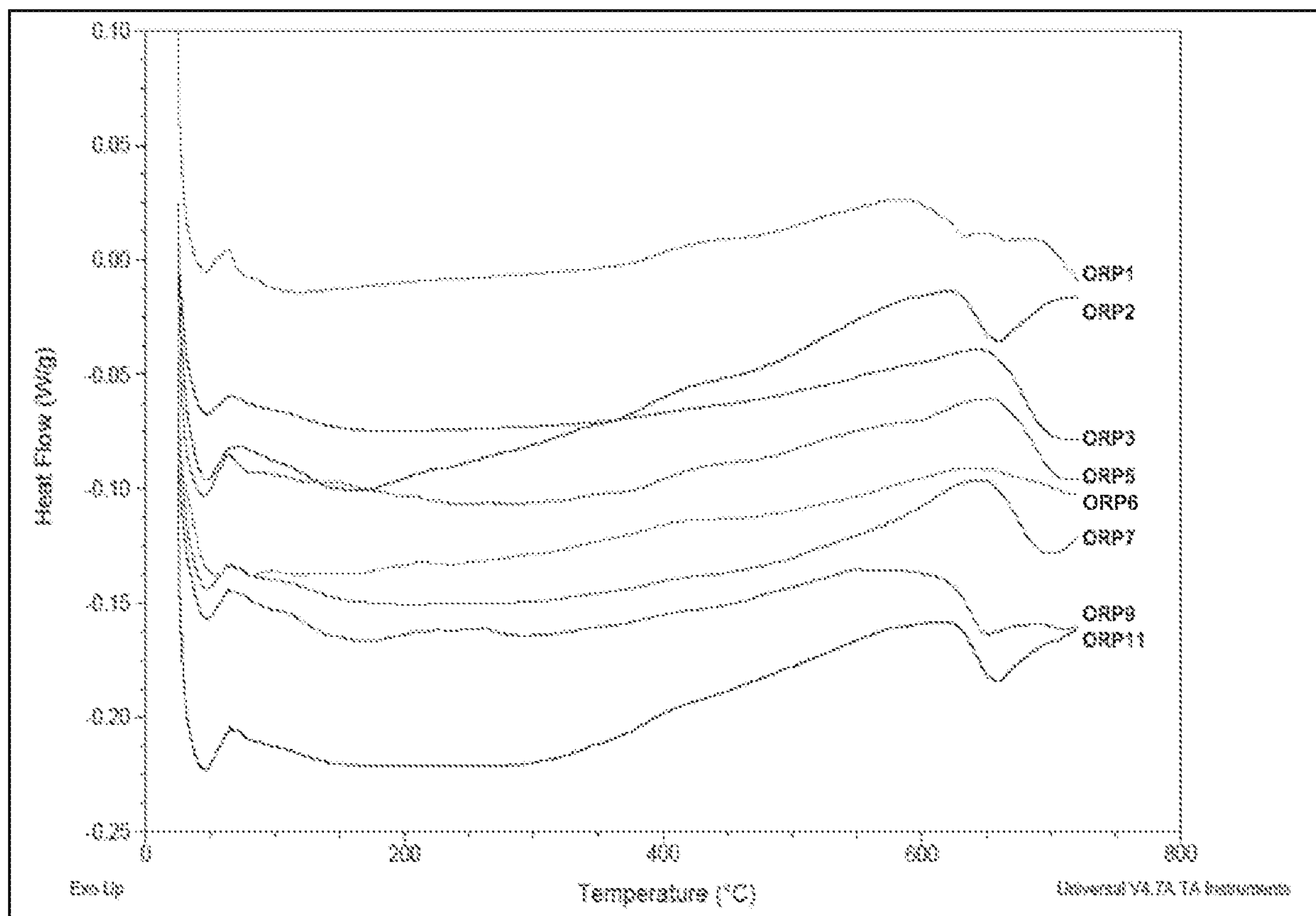


FIG. 2

3 / 31

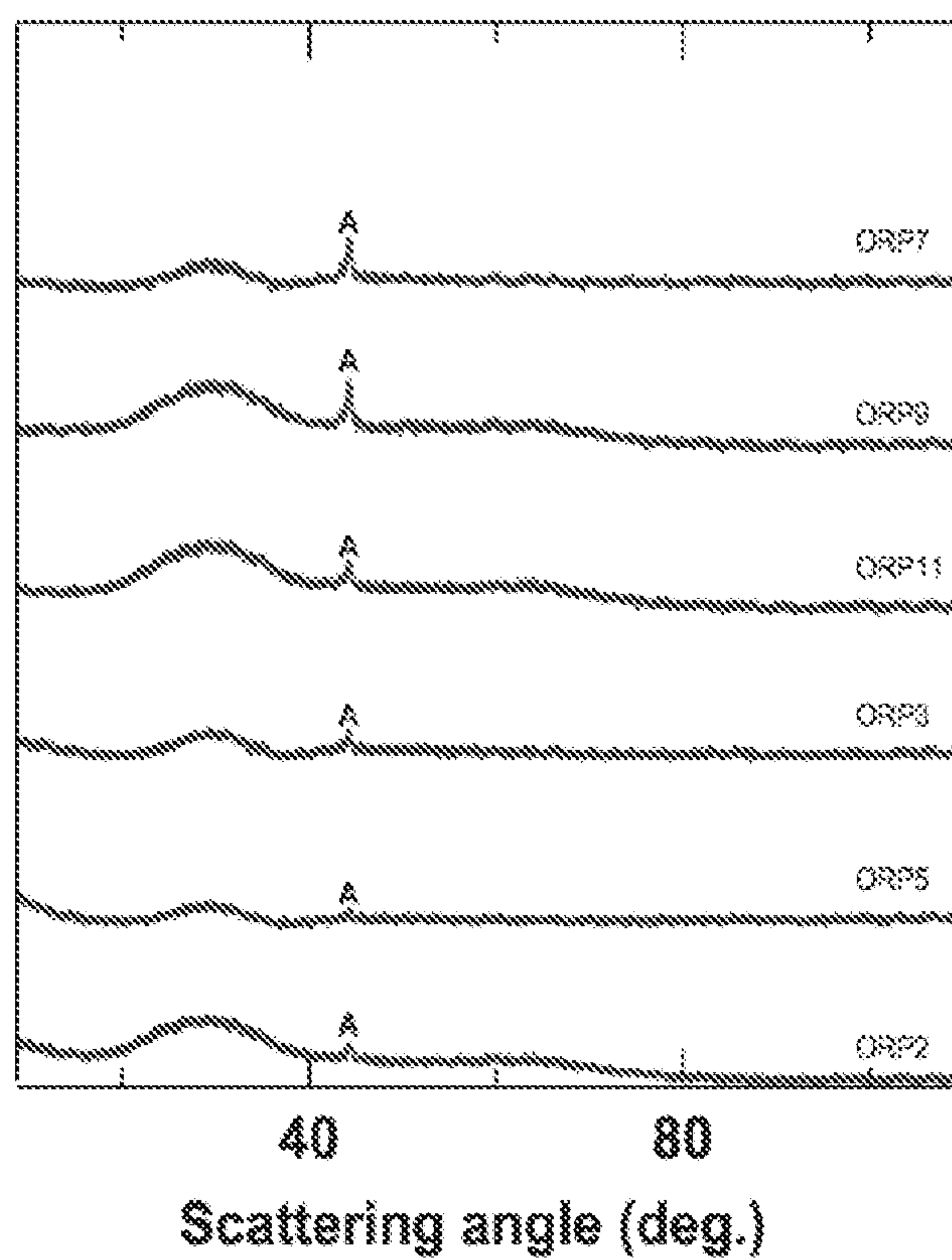


FIG. 3A

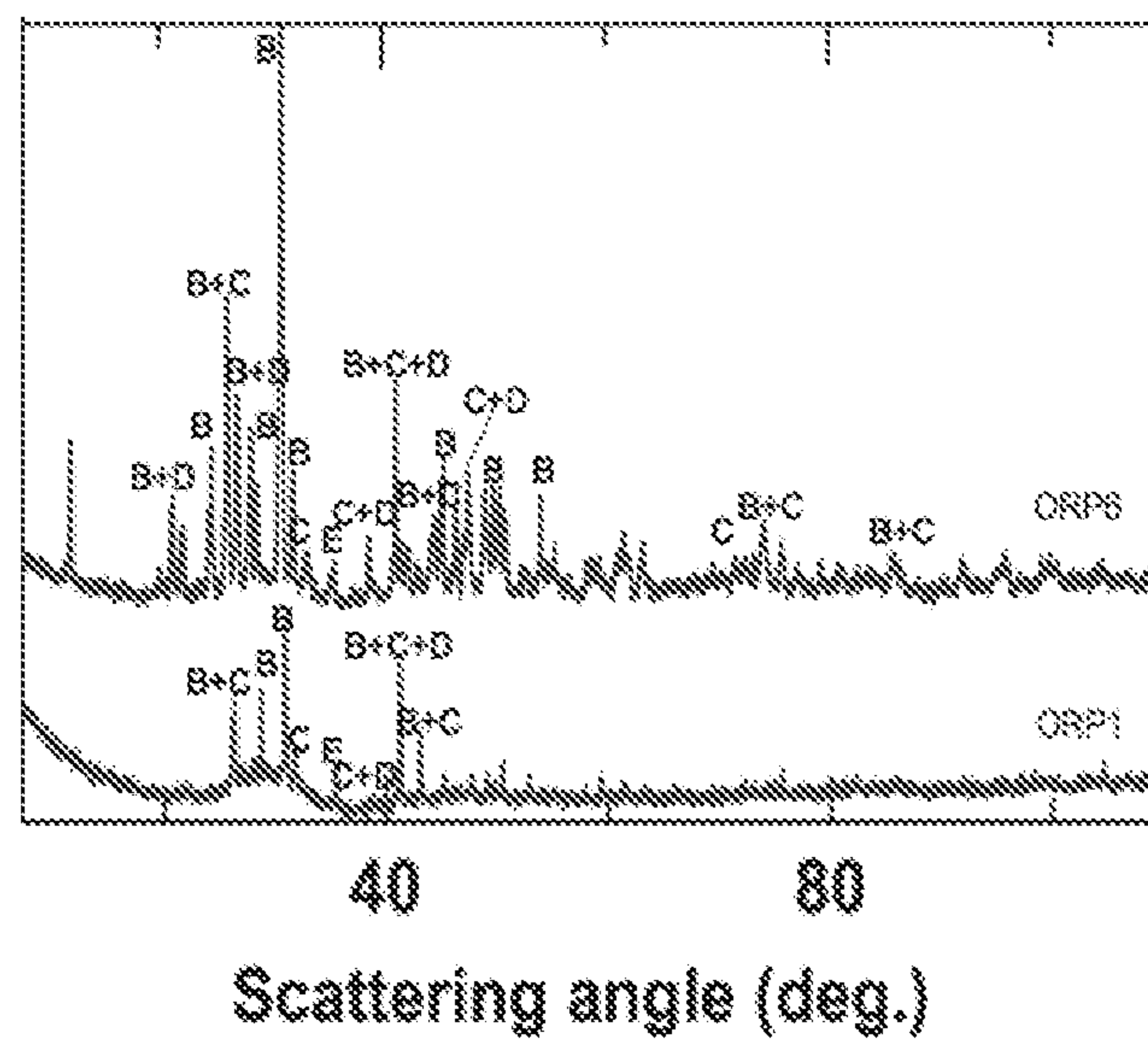
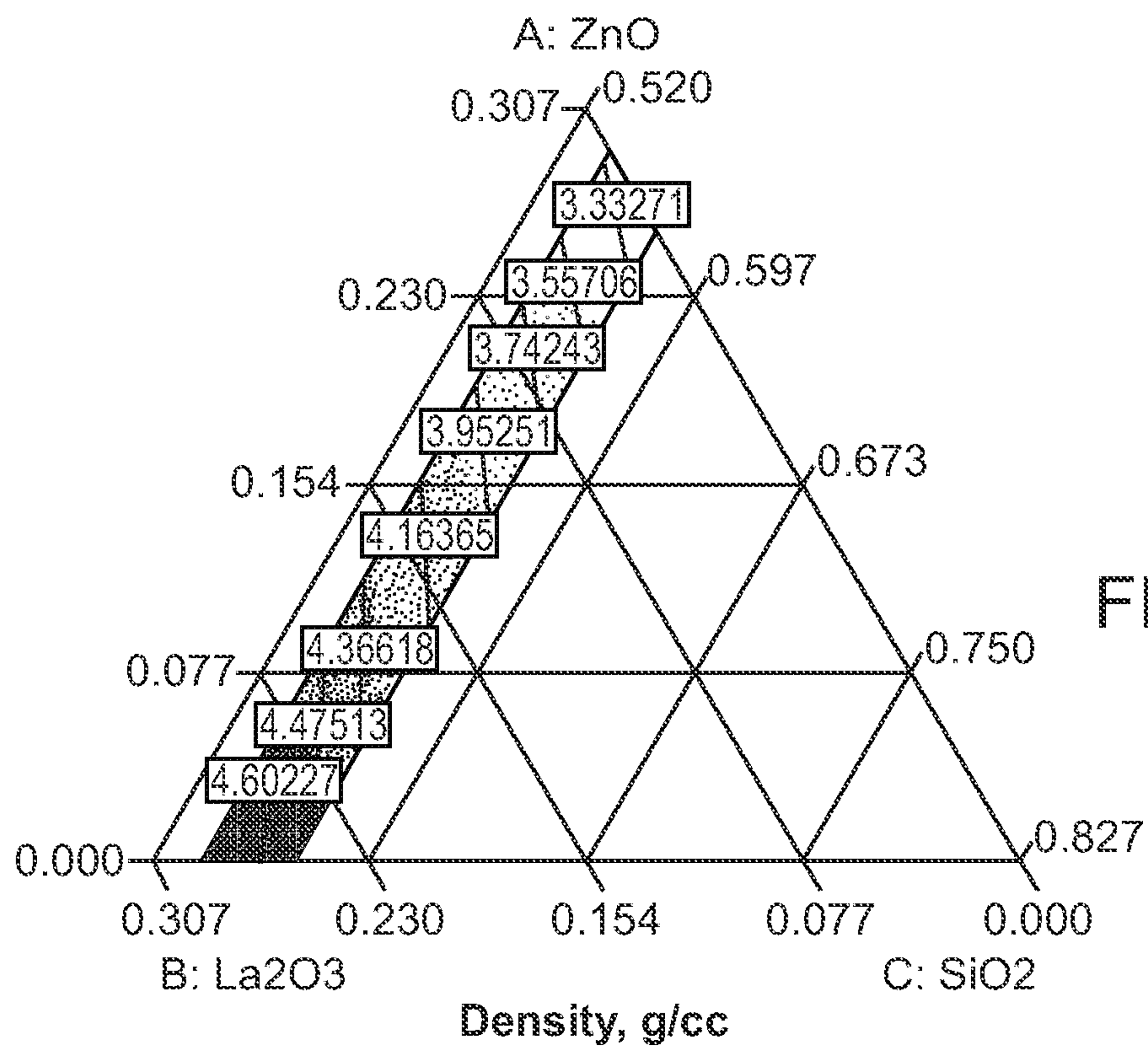
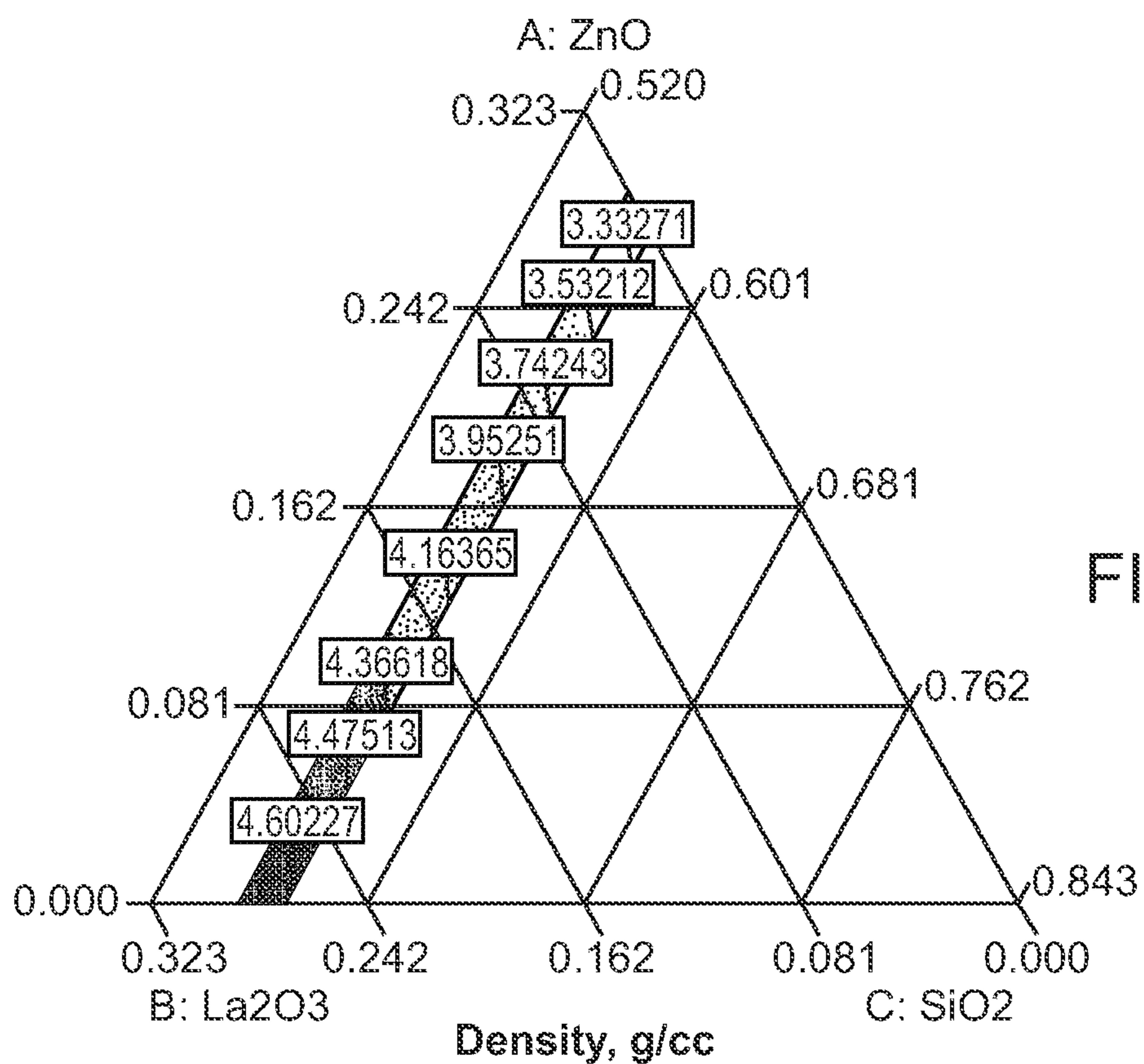
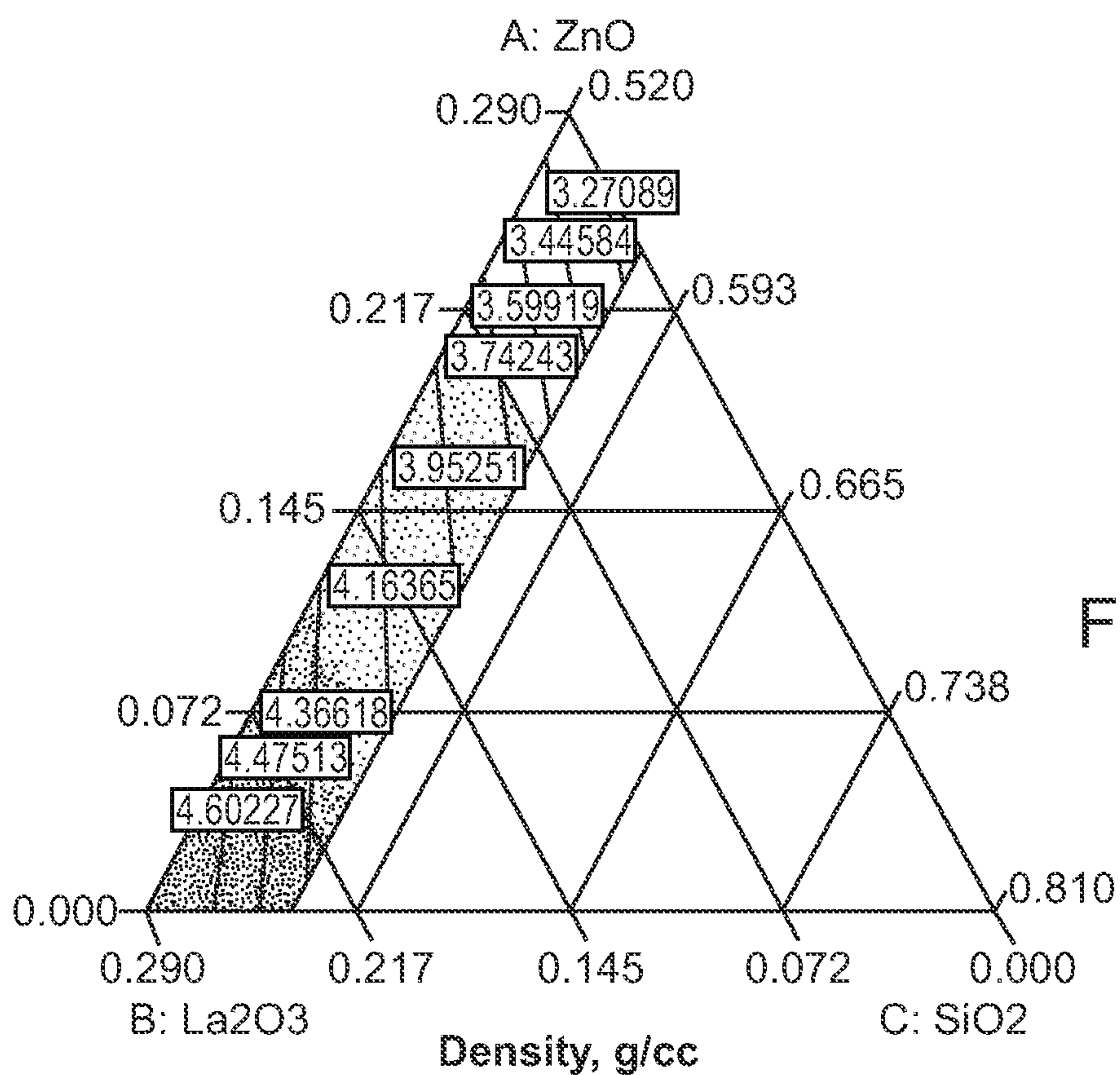
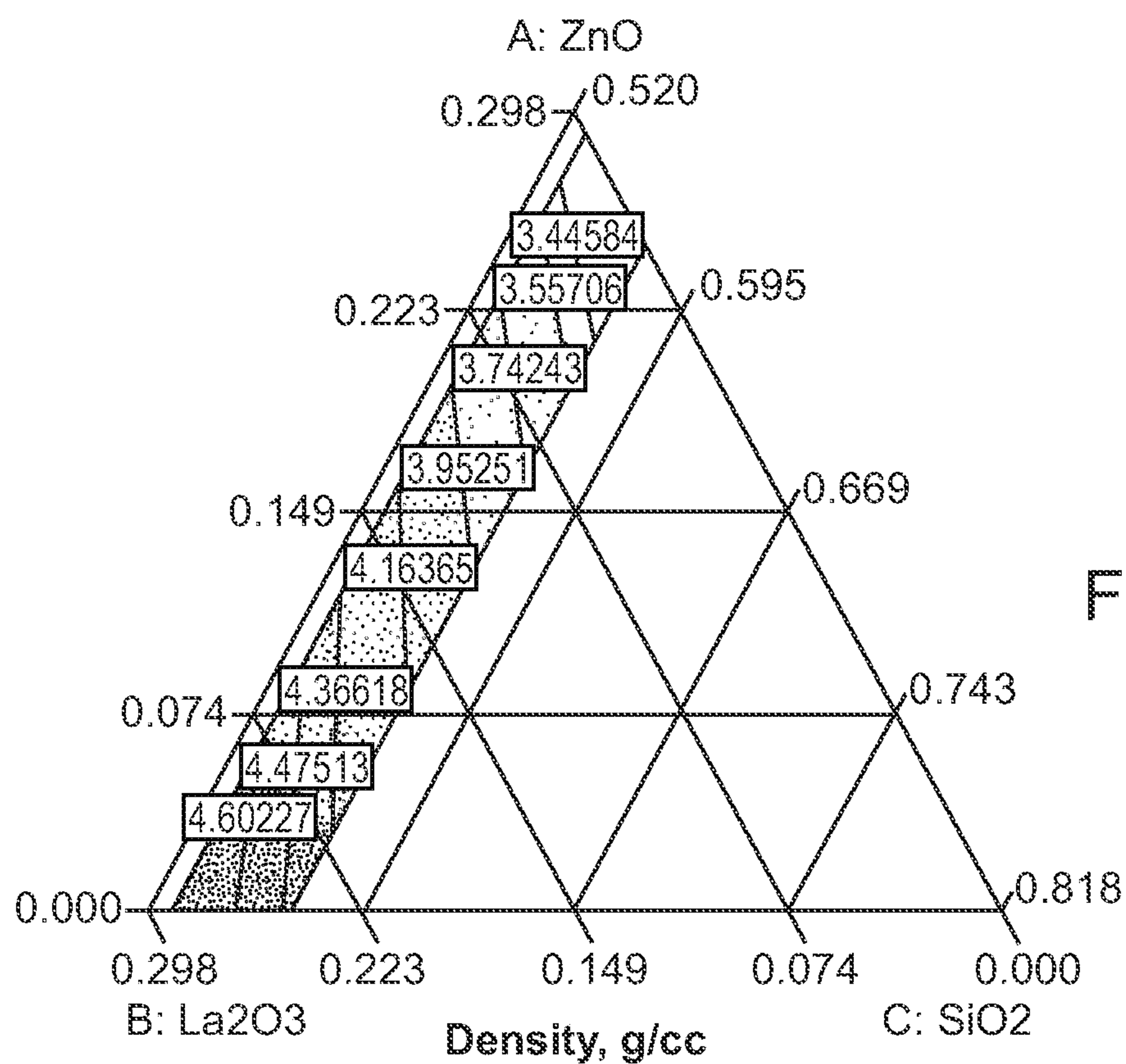


FIG. 3A

4 / 31



5 / 31



6 / 31

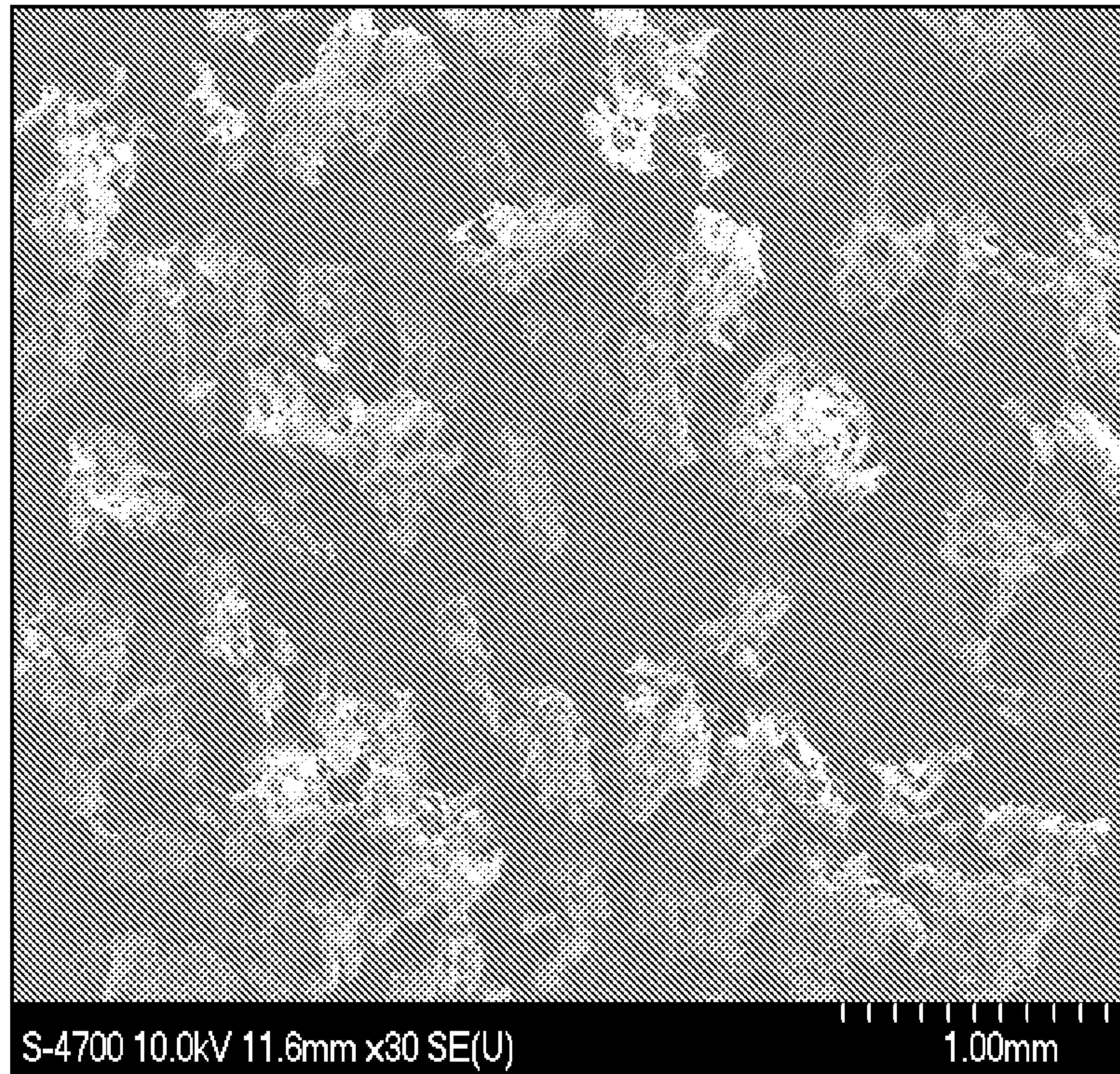


FIG. 5A

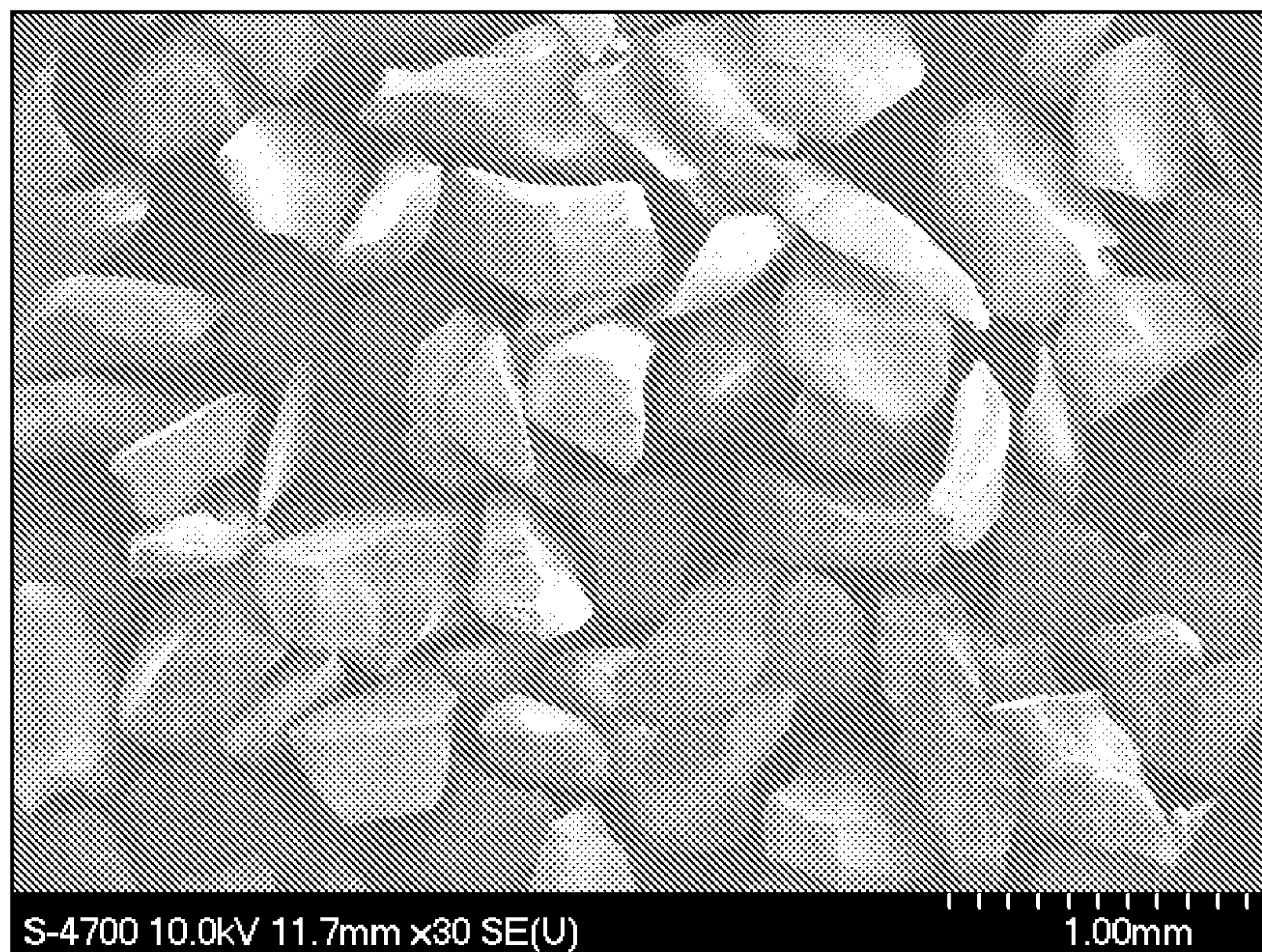


FIG. 5B

7 / 31

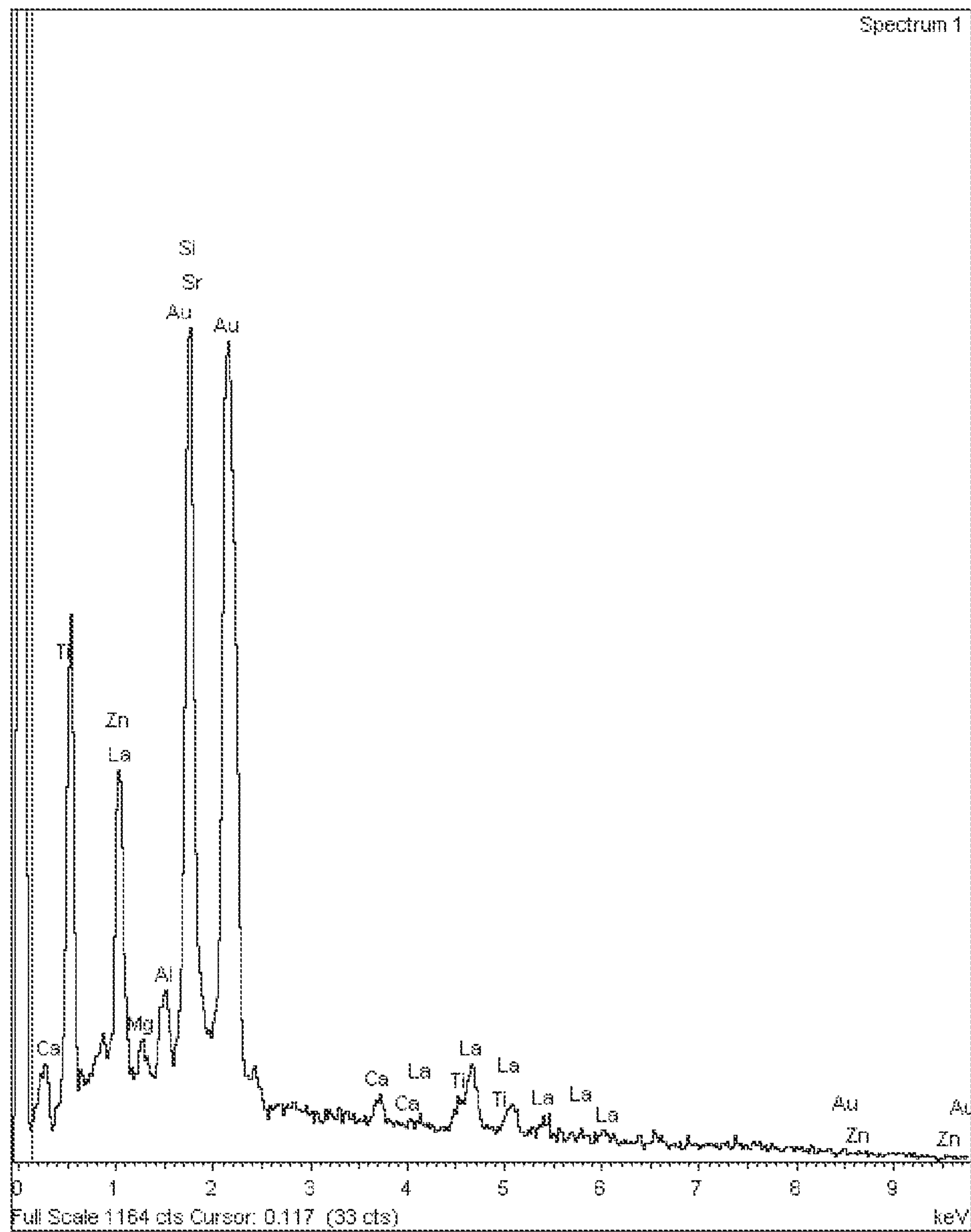


FIG. 6

8 / 31

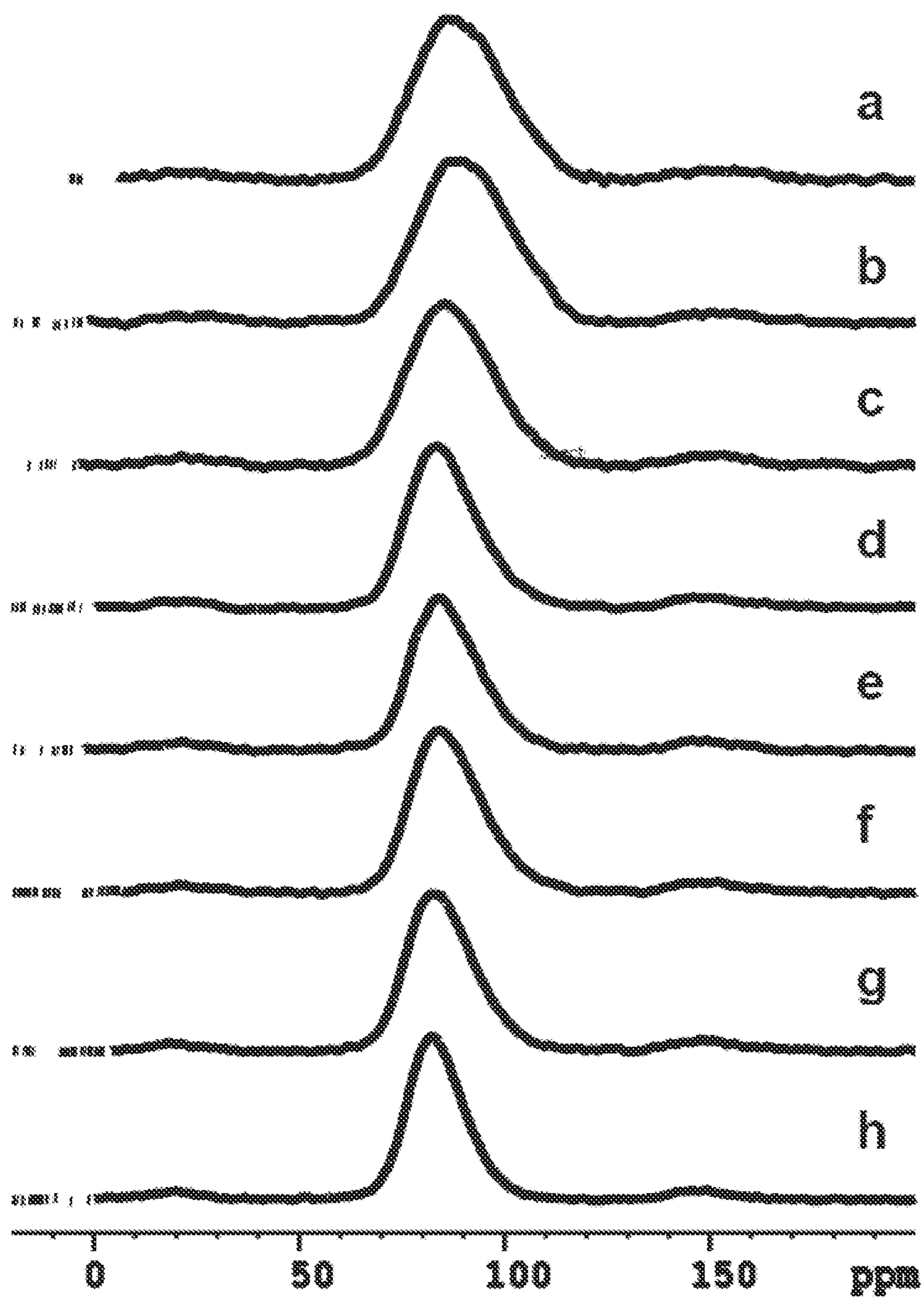


FIG. 7

9 / 31

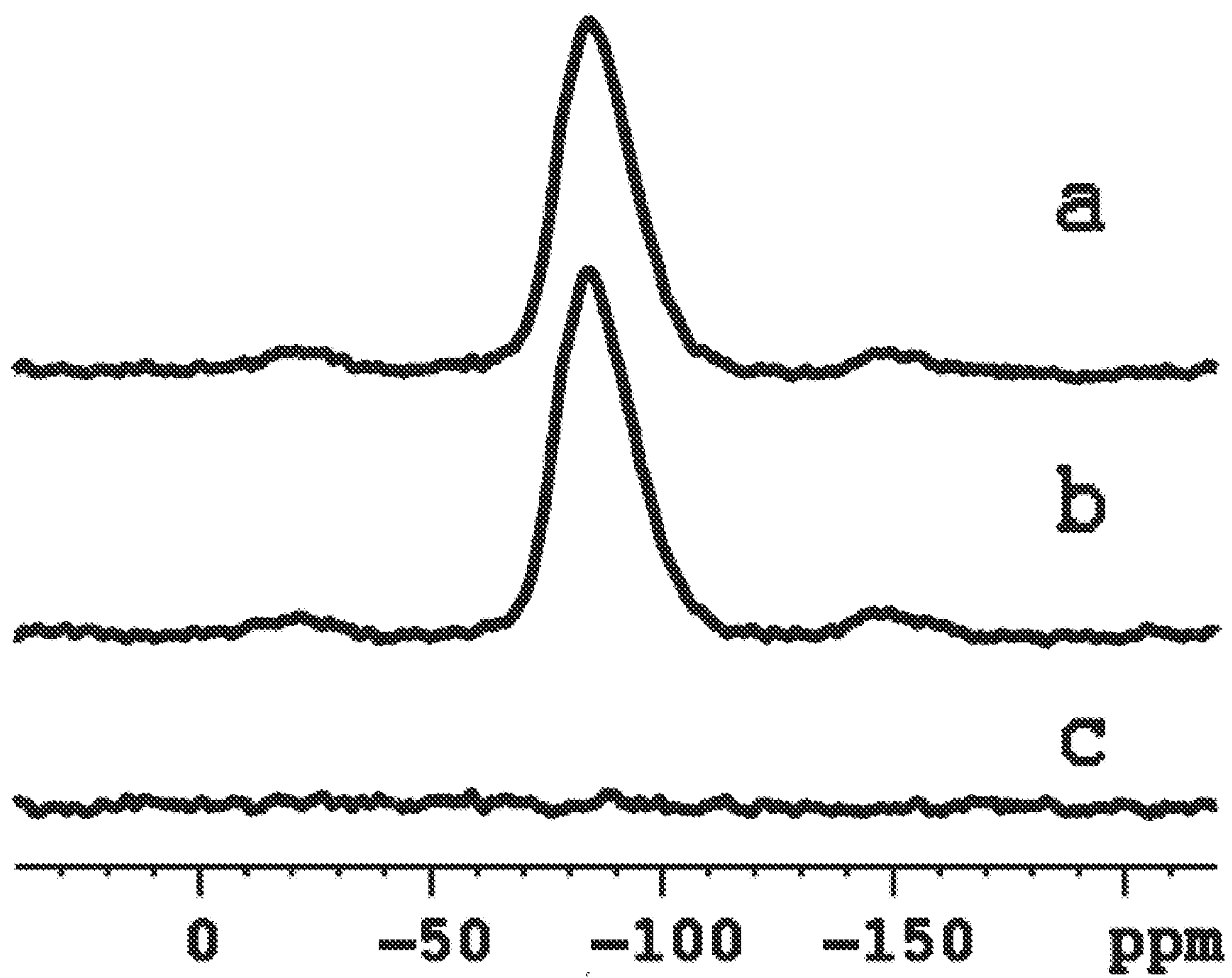


FIG. 8

10 / 31

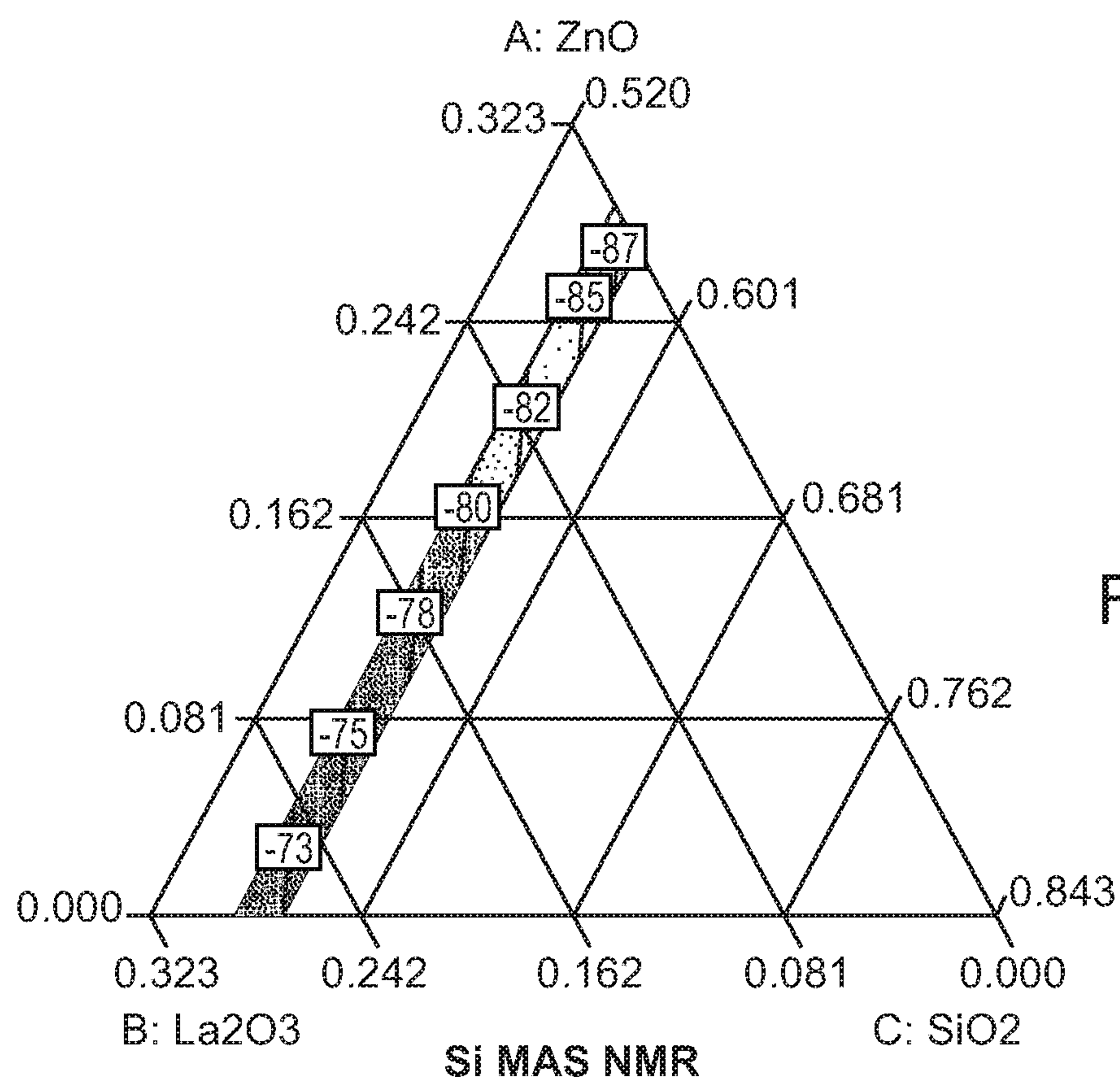


FIG. 9A

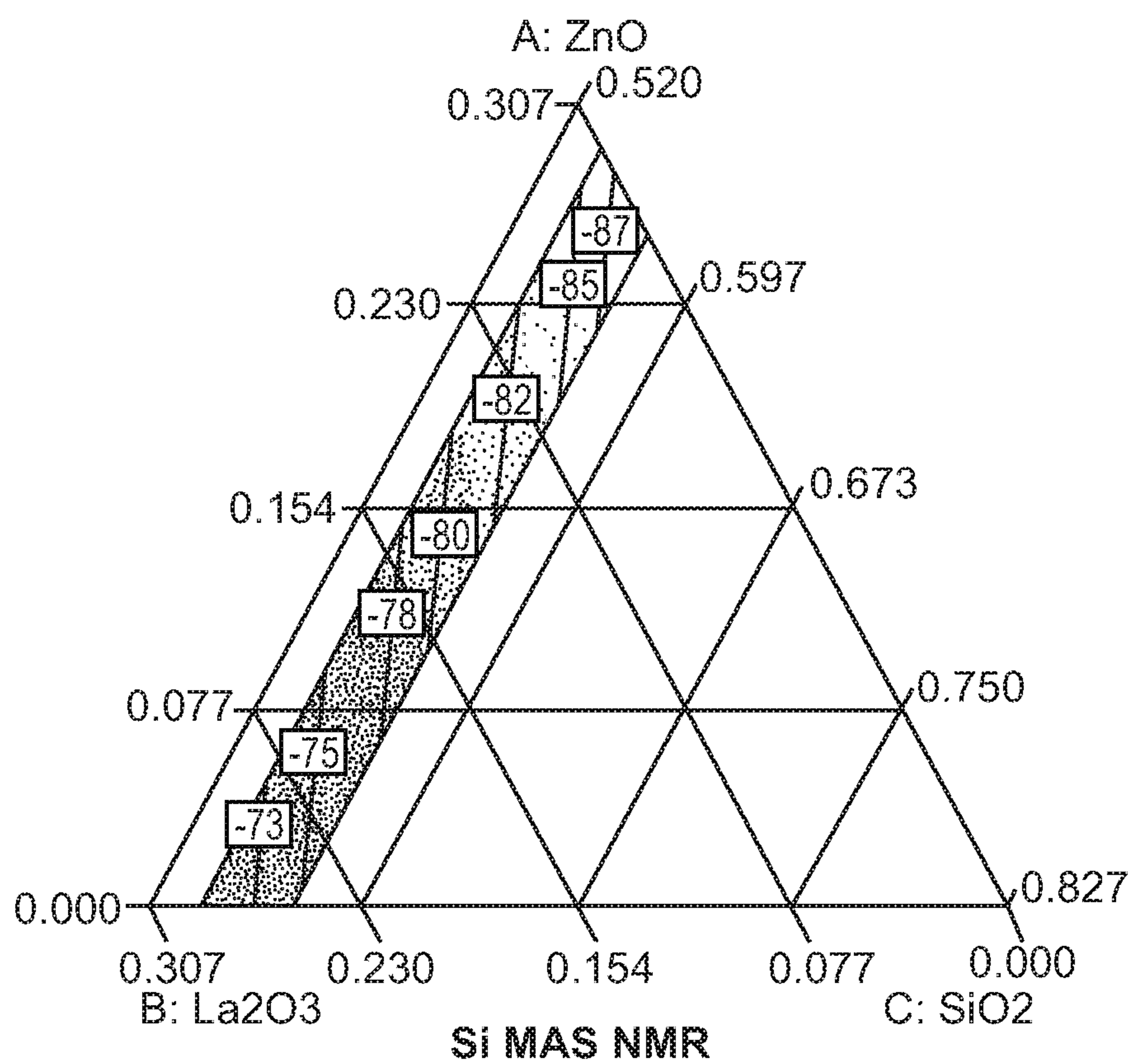
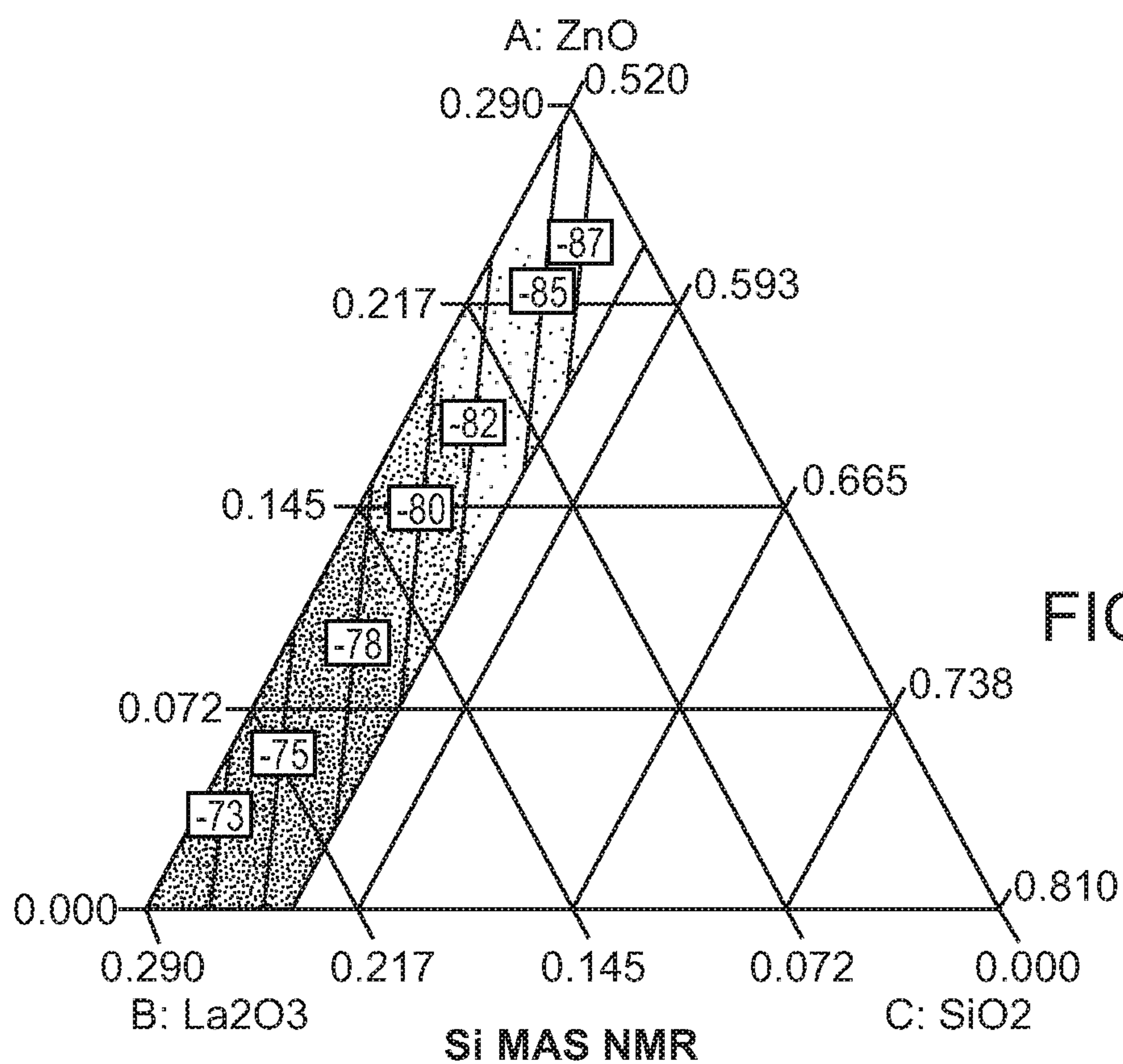
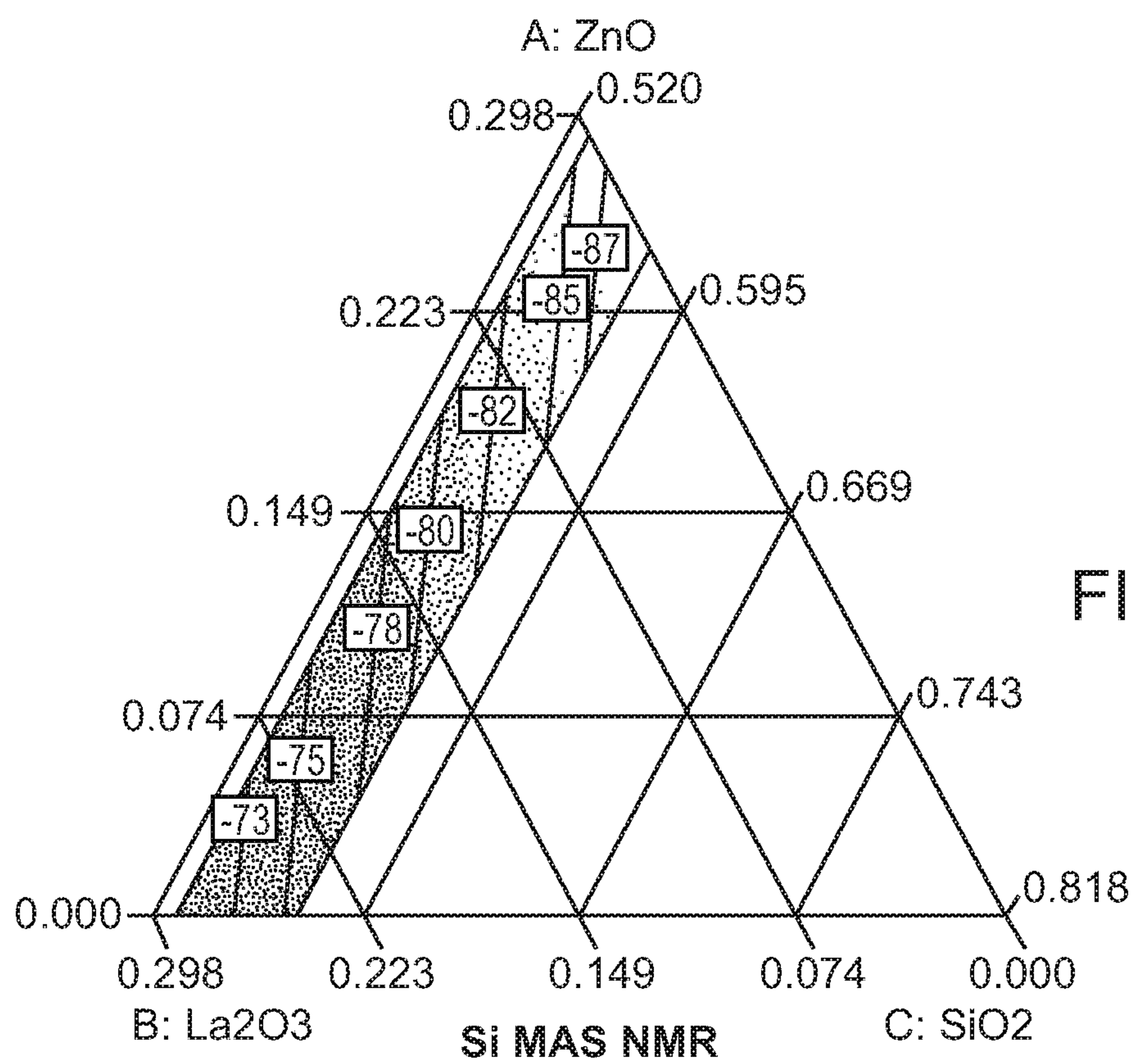


FIG. 9B

11 / 31



12 / 31

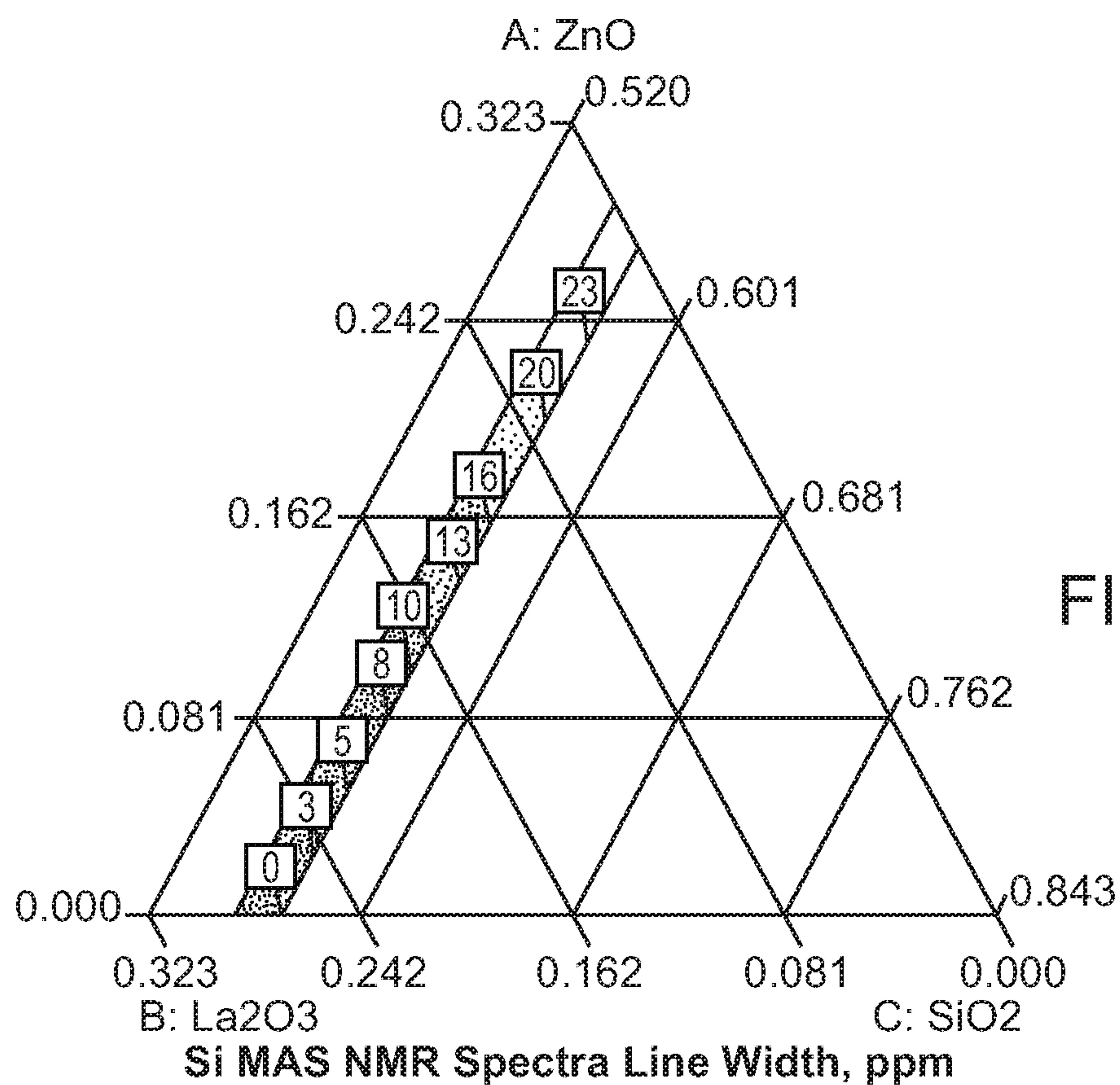


FIG. 10A

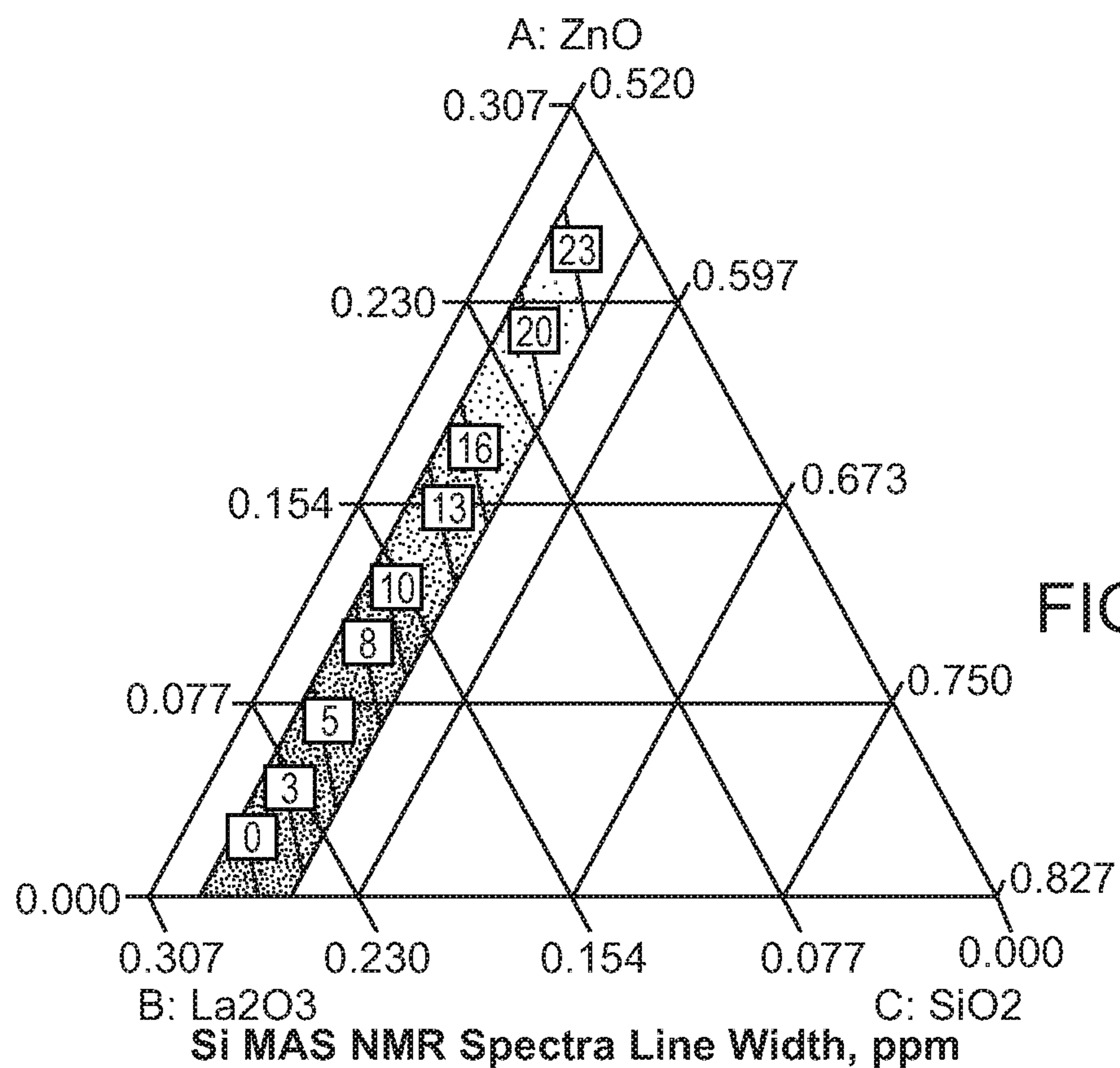
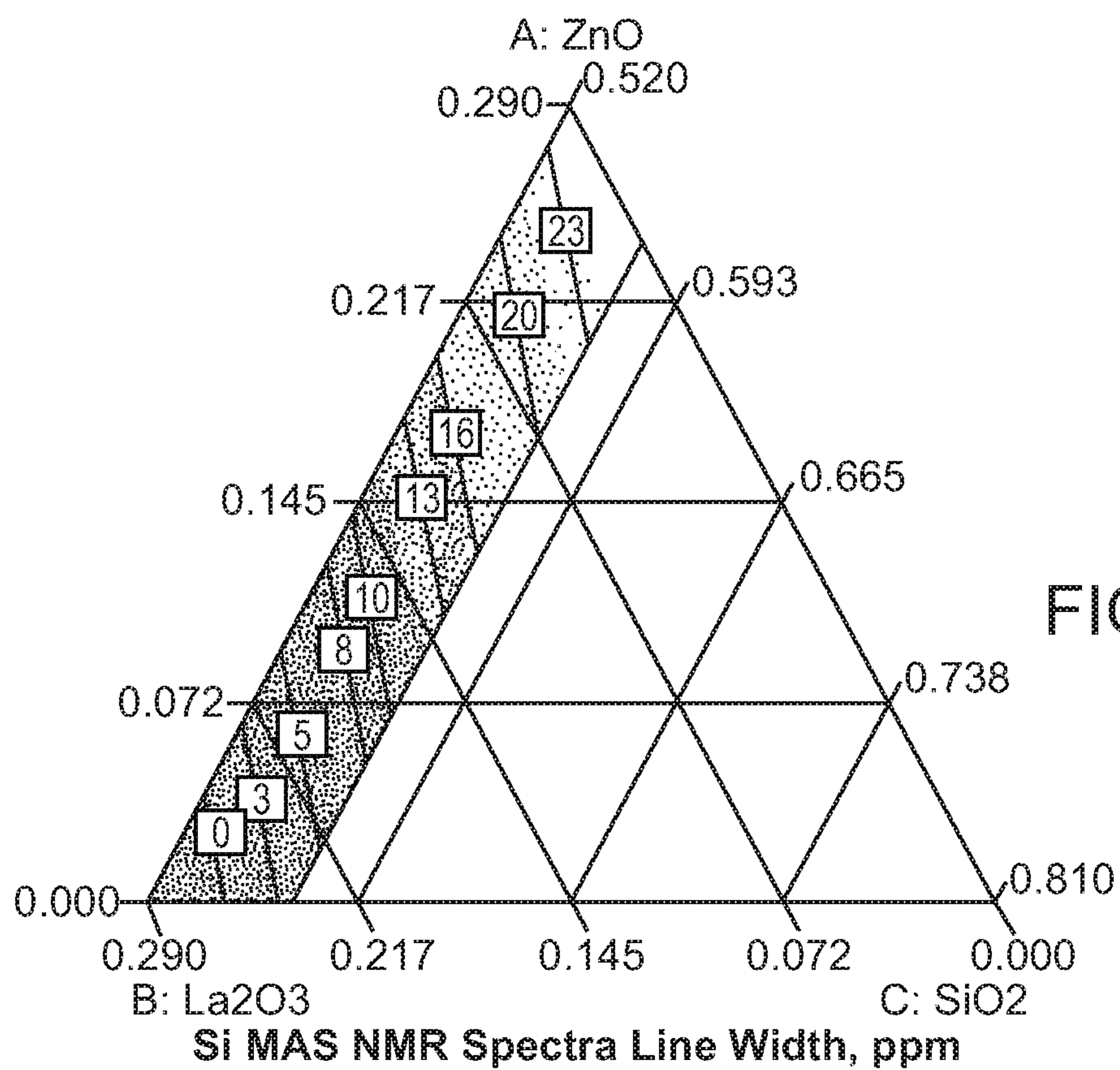
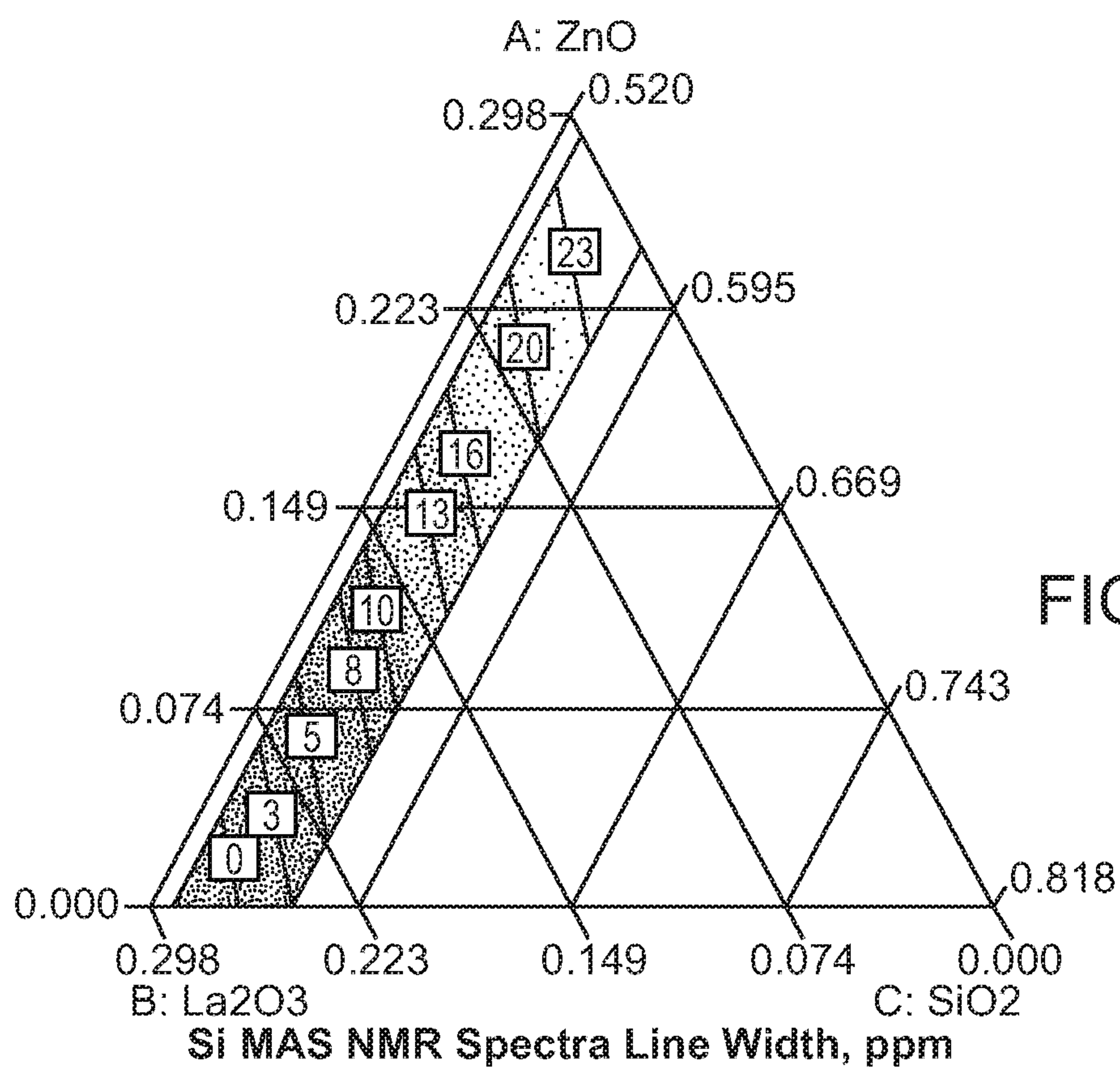


FIG. 10B

13 / 31



14 / 31

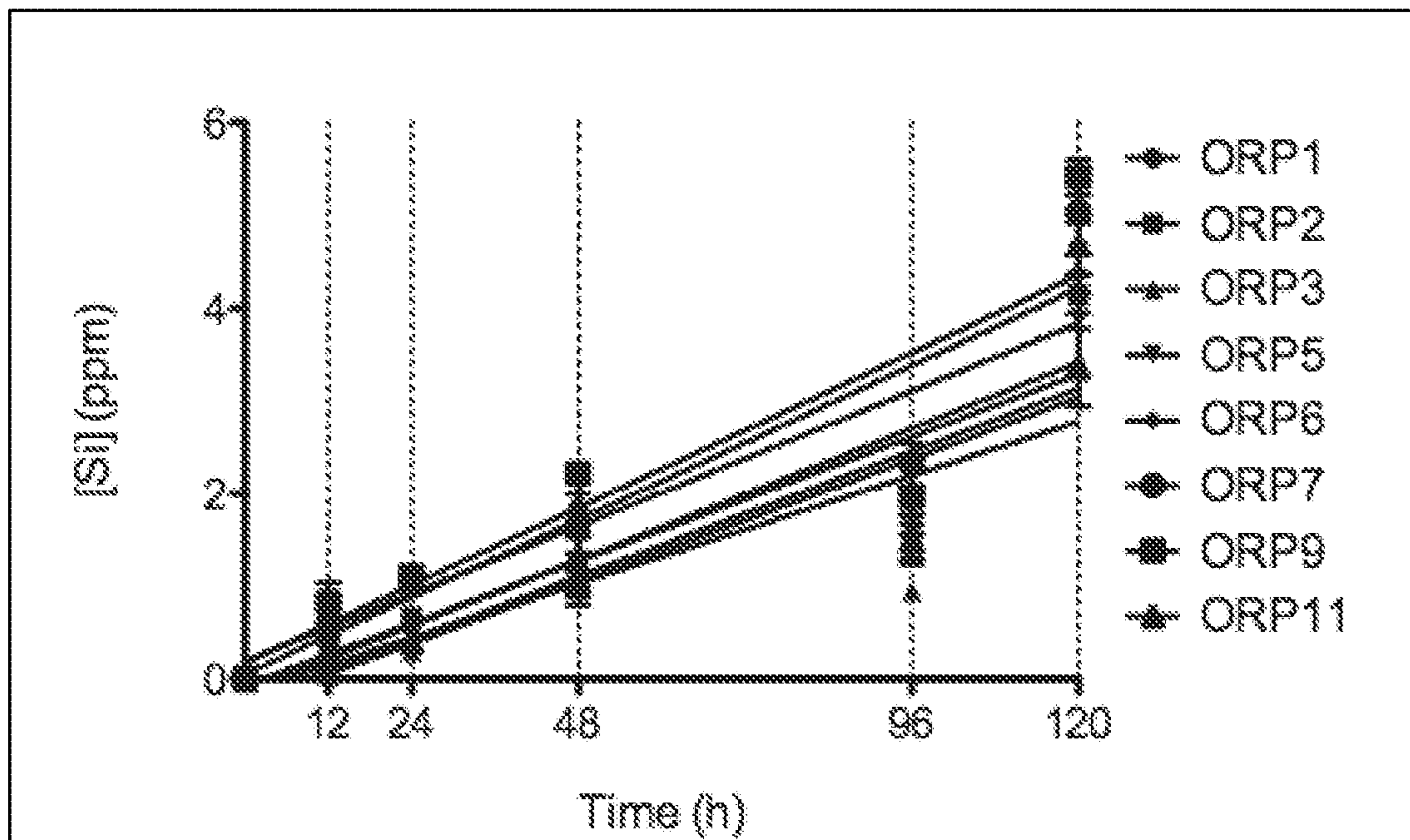


FIG. 11A

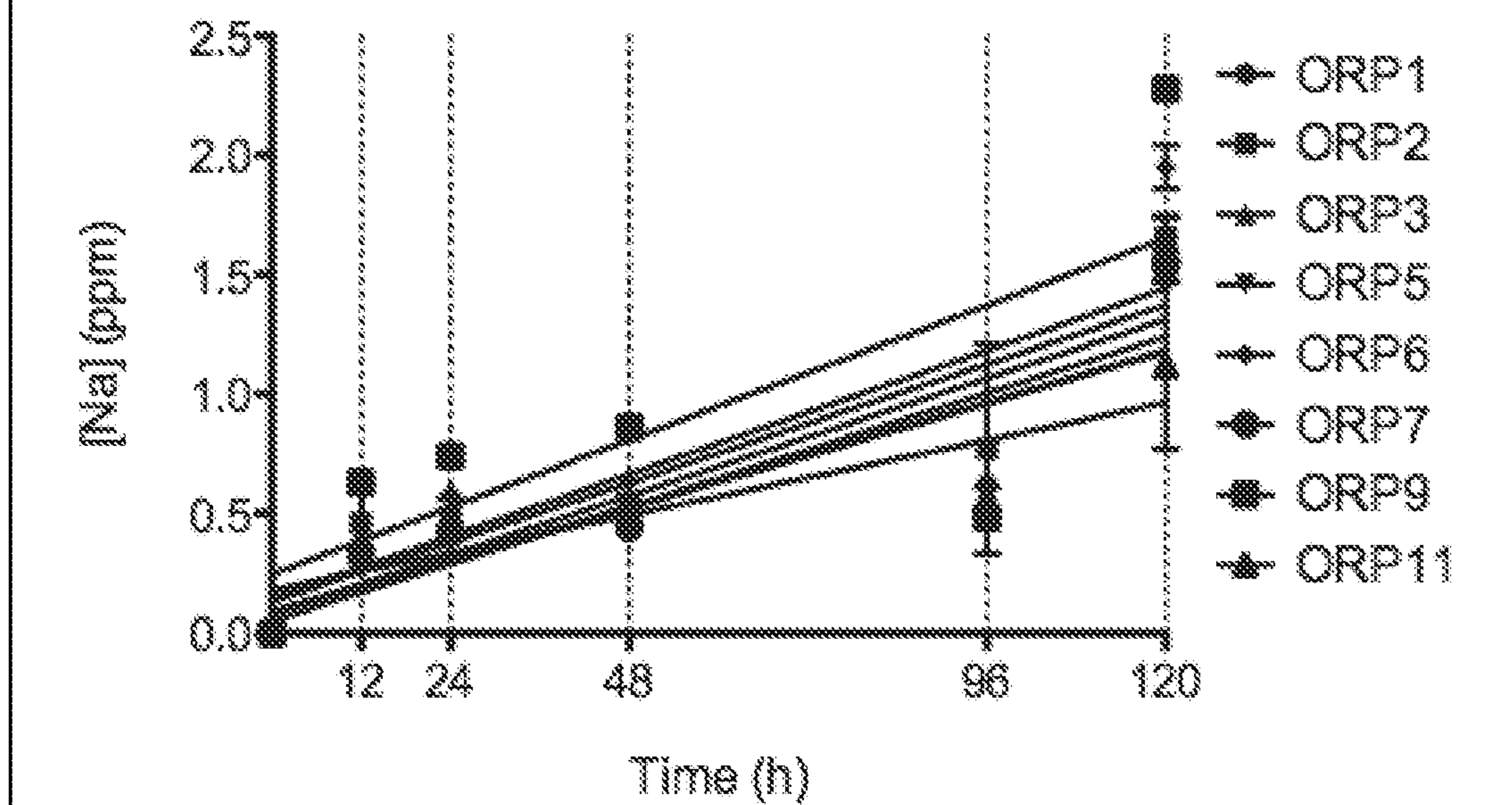


FIG. 11B

15 / 31

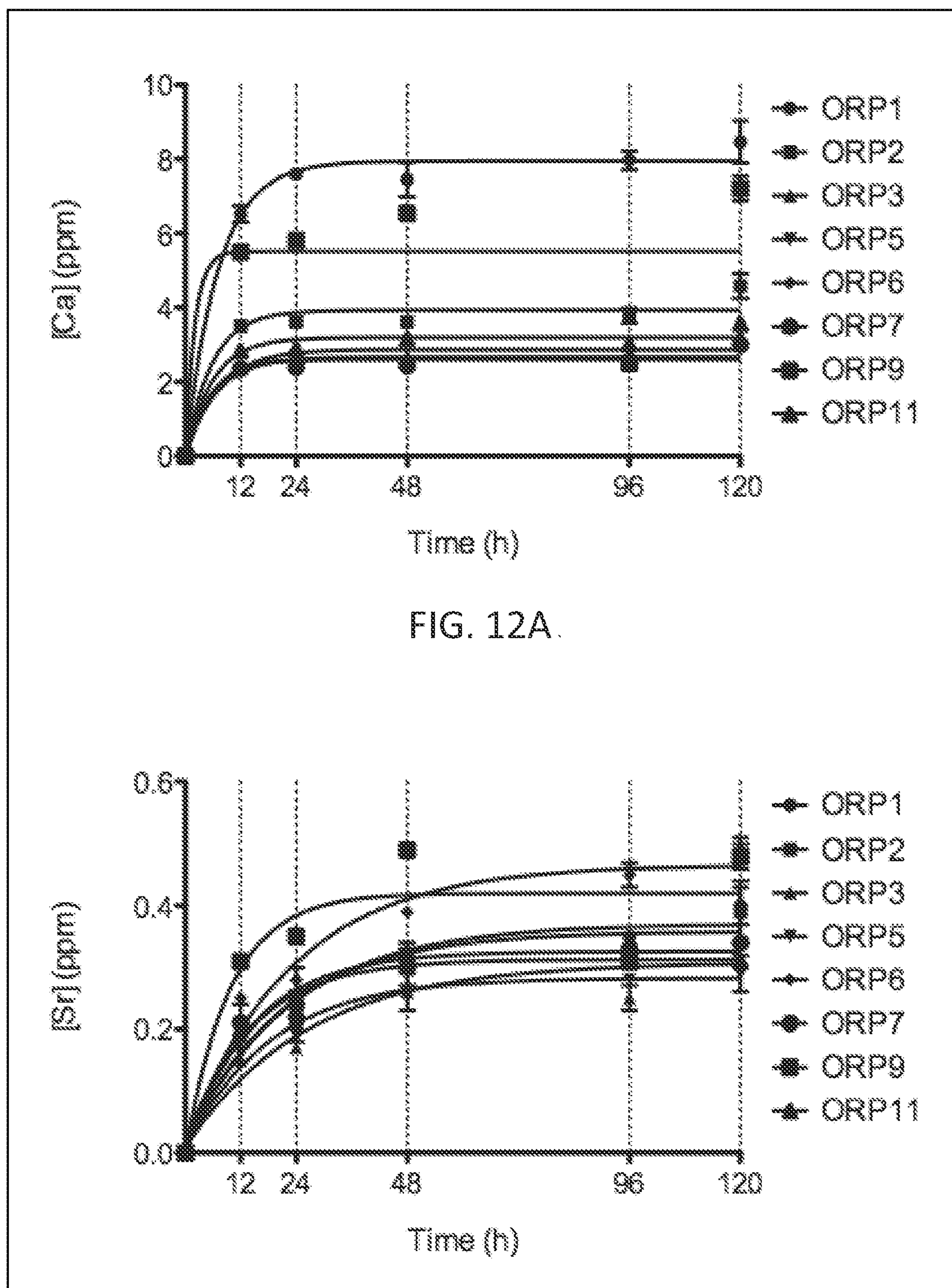


FIG. 12B

16 / 31

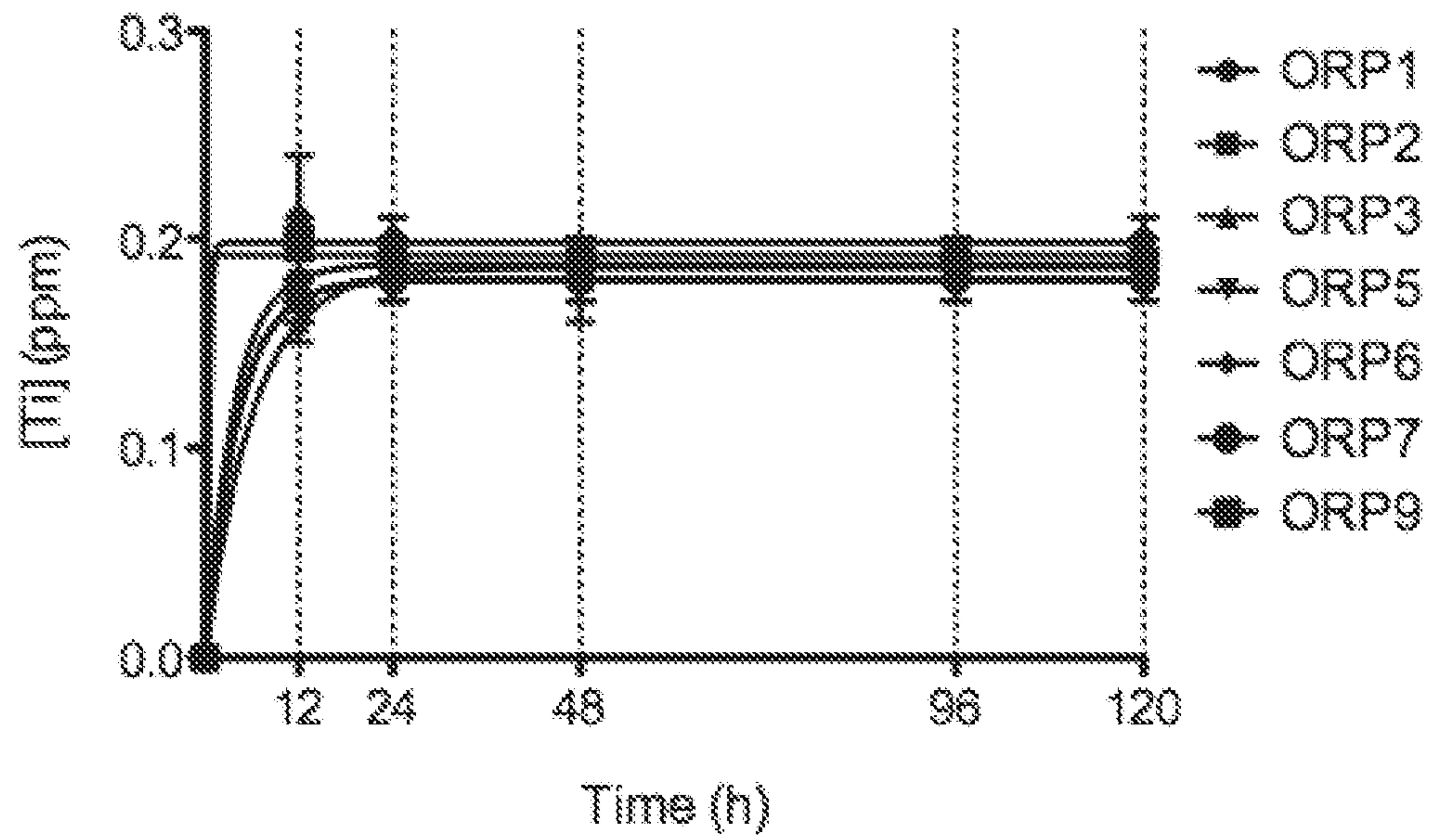


FIG. 13A

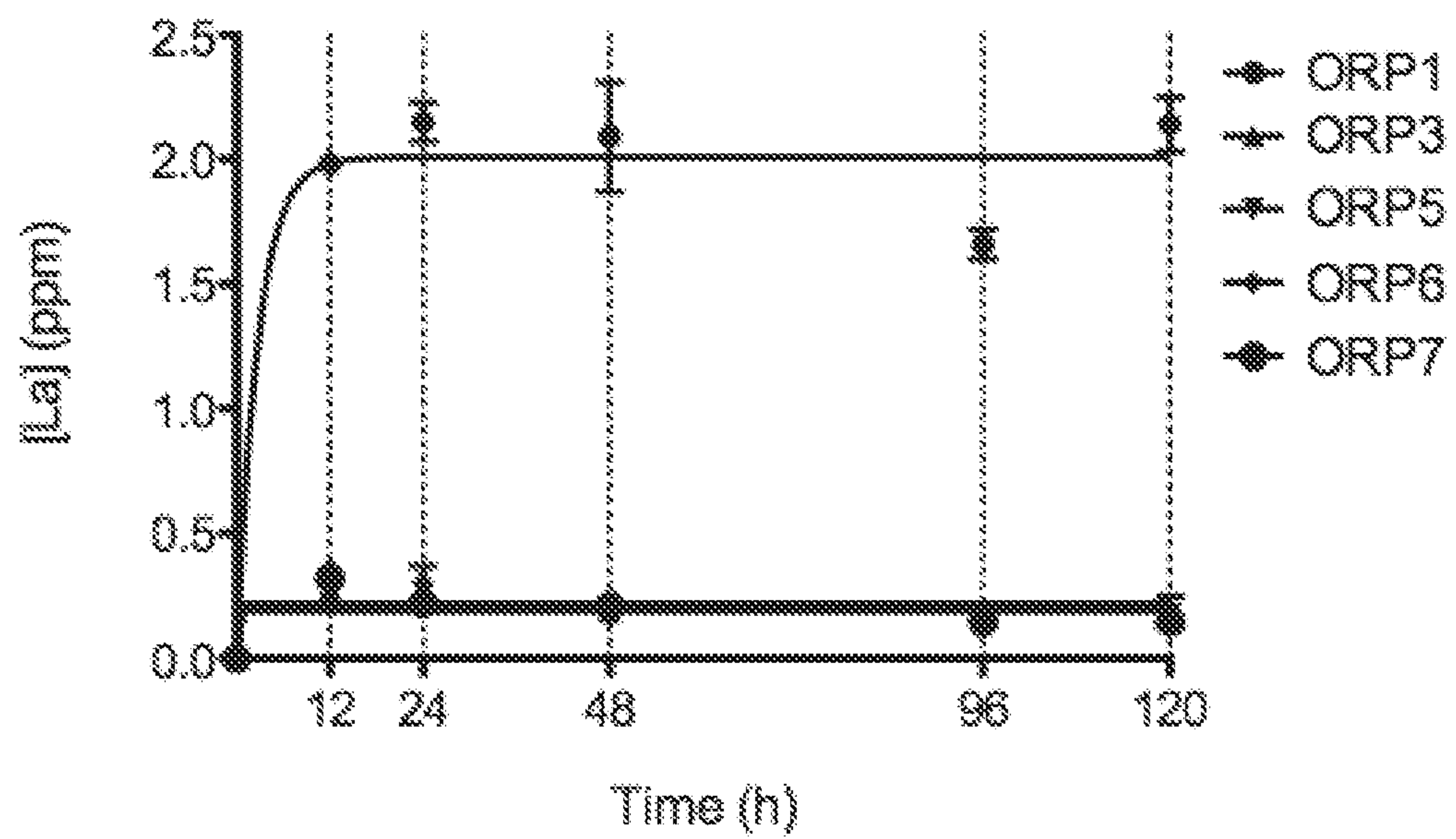


FIG. 13B

17 / 31

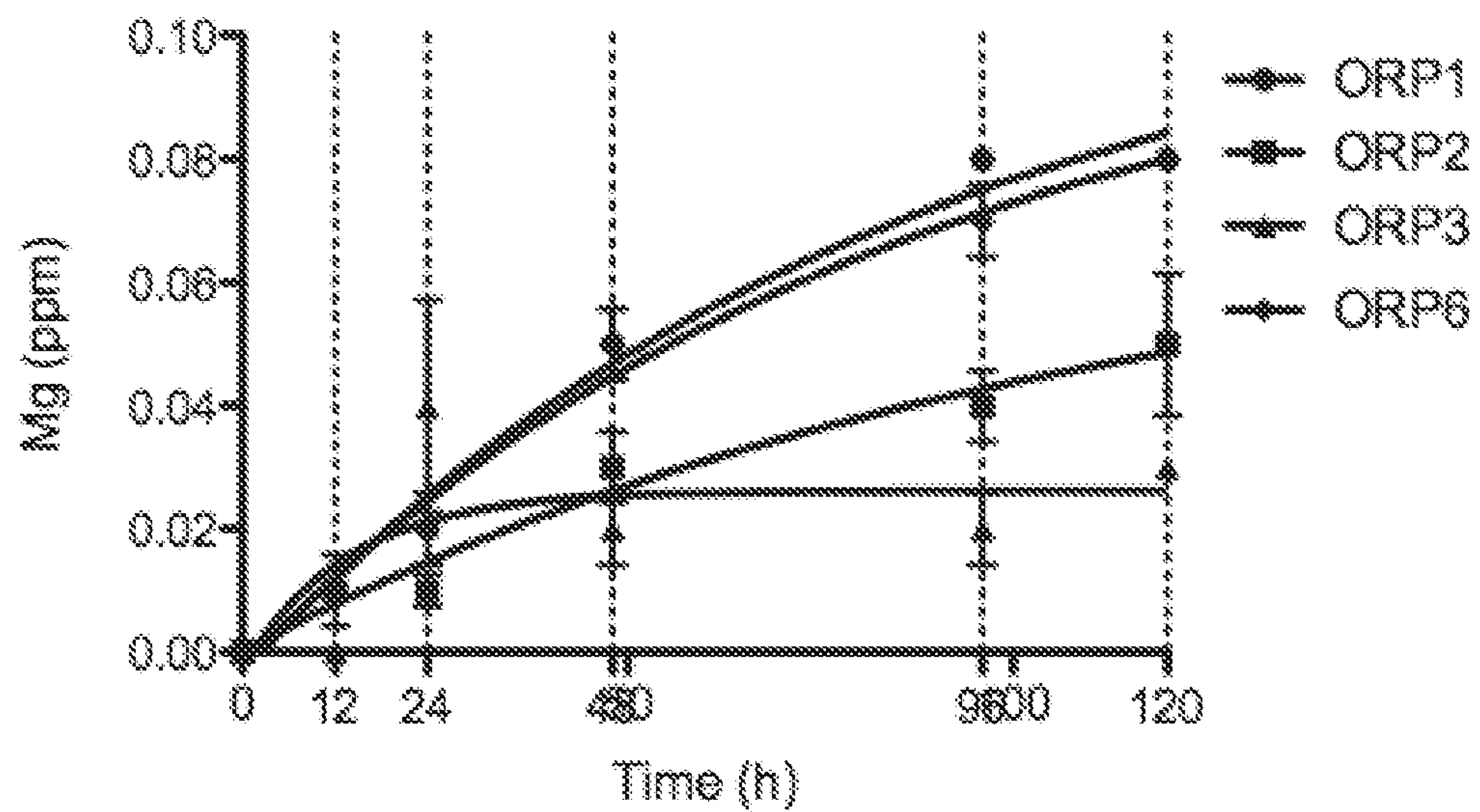


FIG. 14A

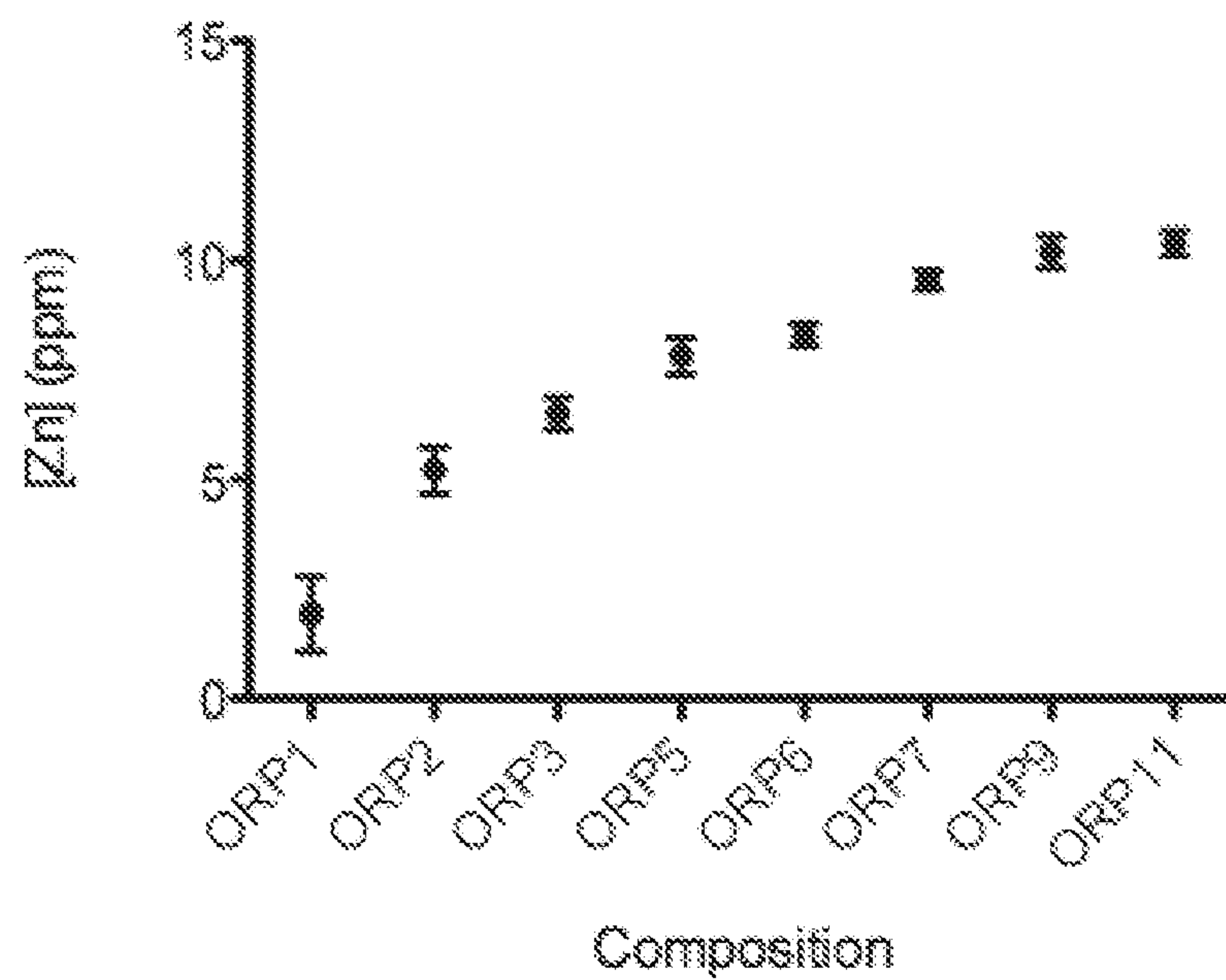


FIG. 14B

18 / 31

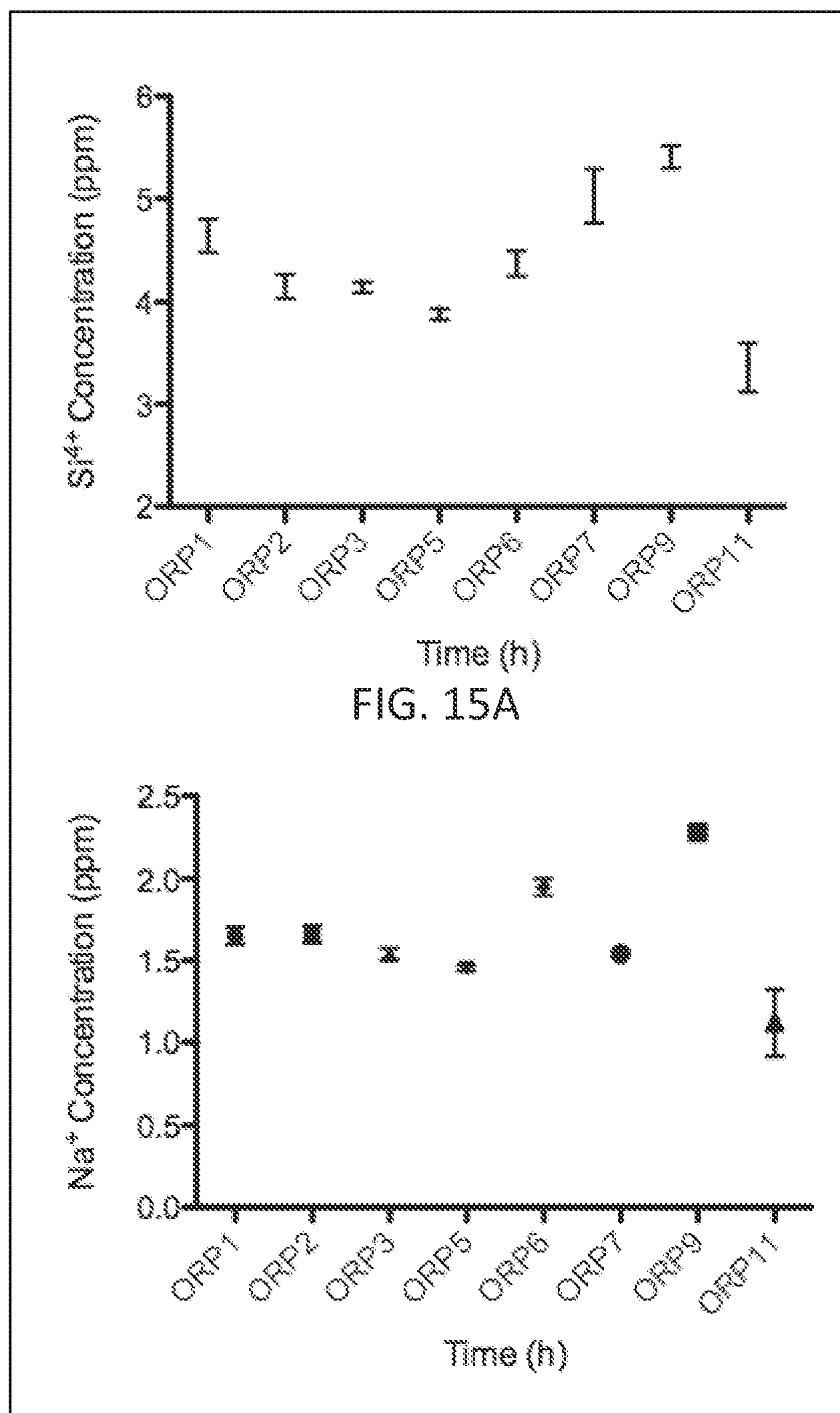


FIG. 15B

19 / 31

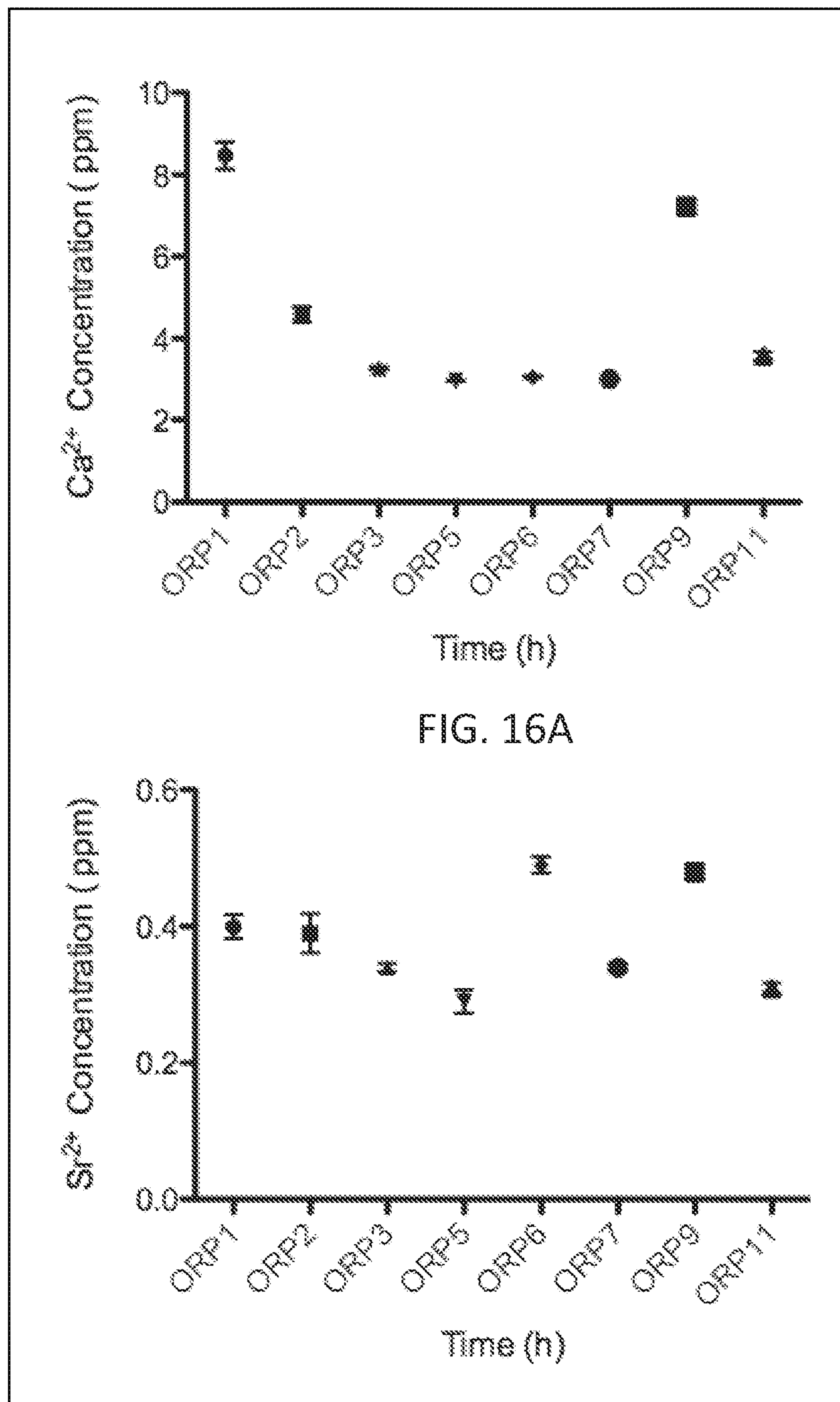


FIG. 16B

20 / 31

FIG. 17A

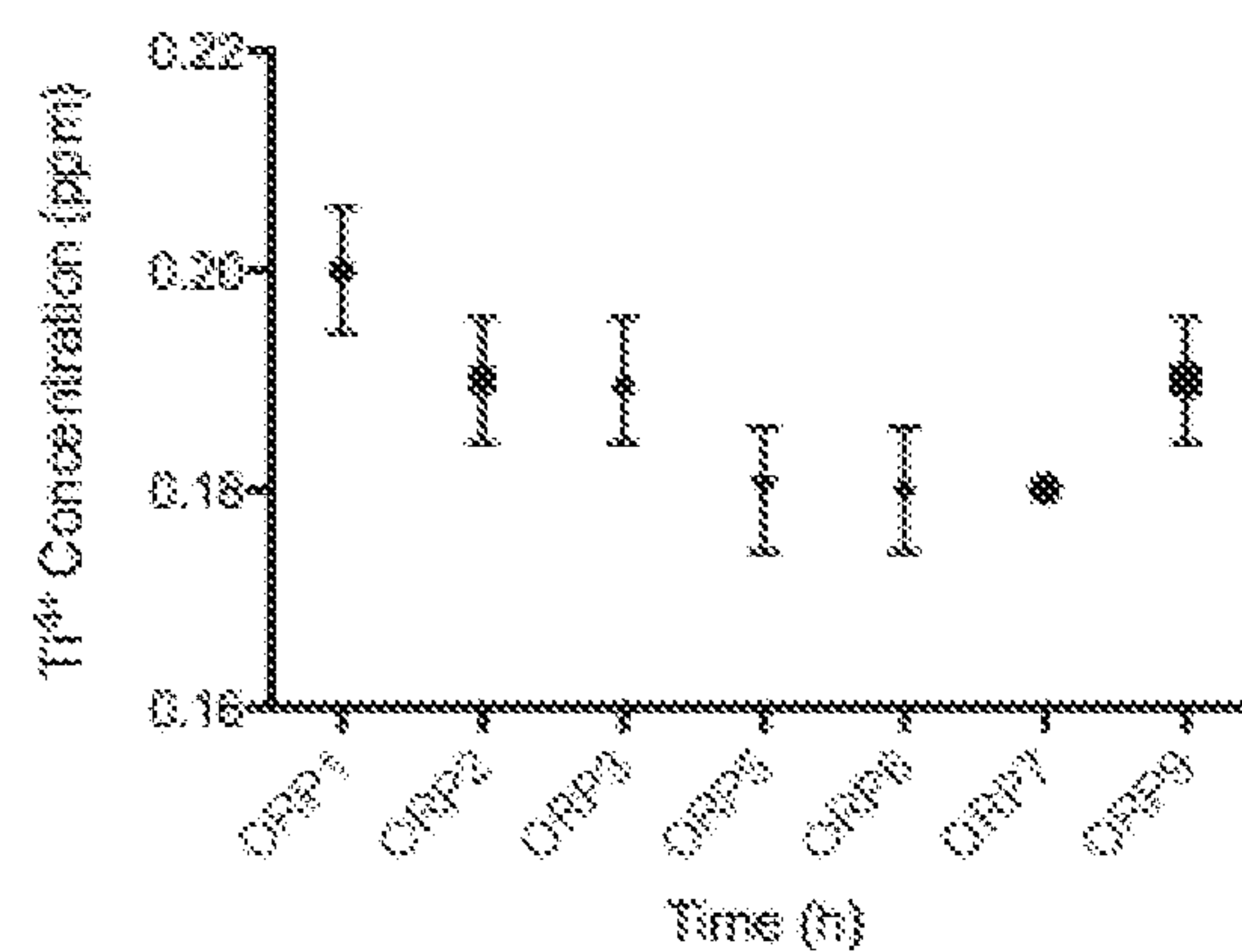


FIG. 17B

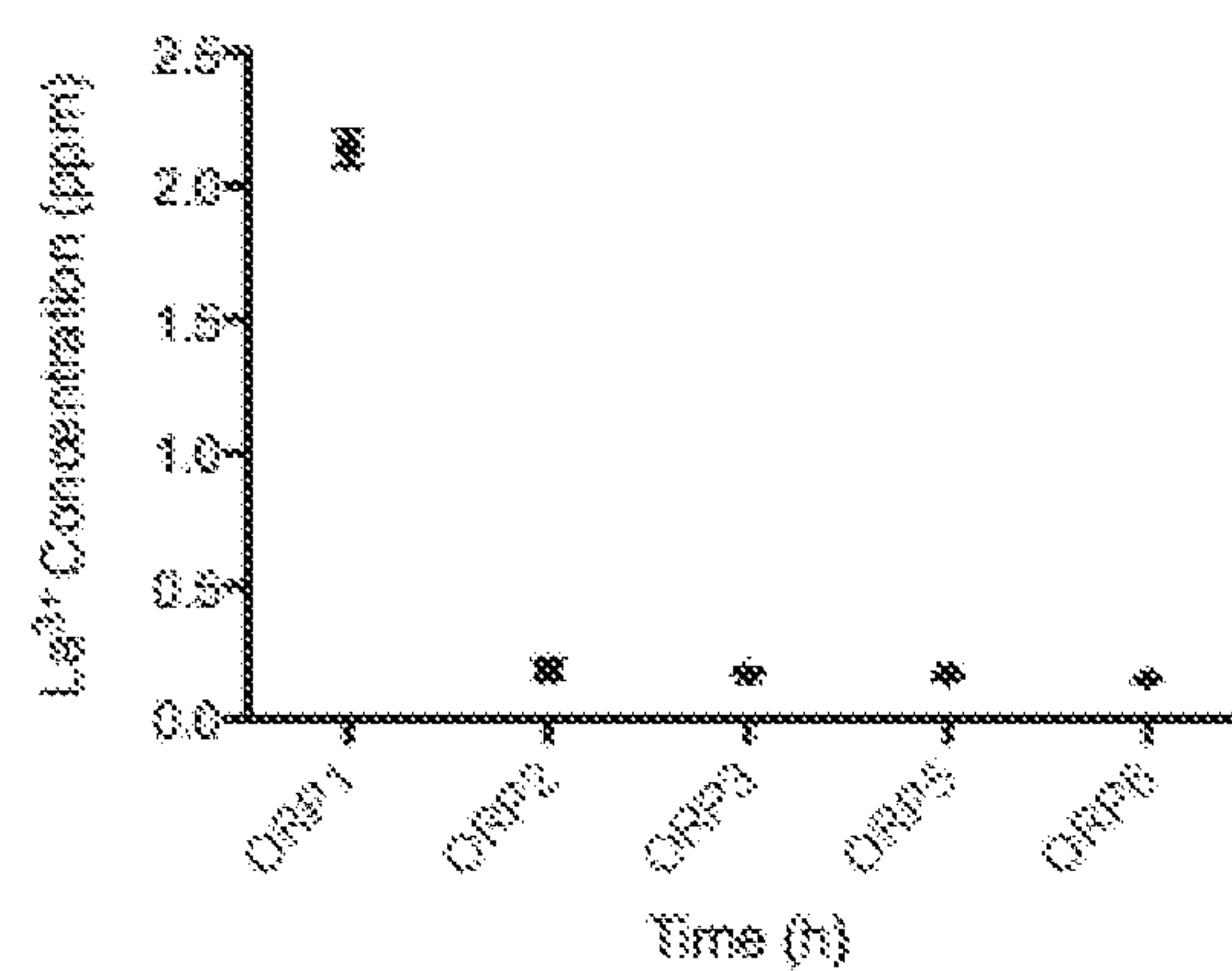
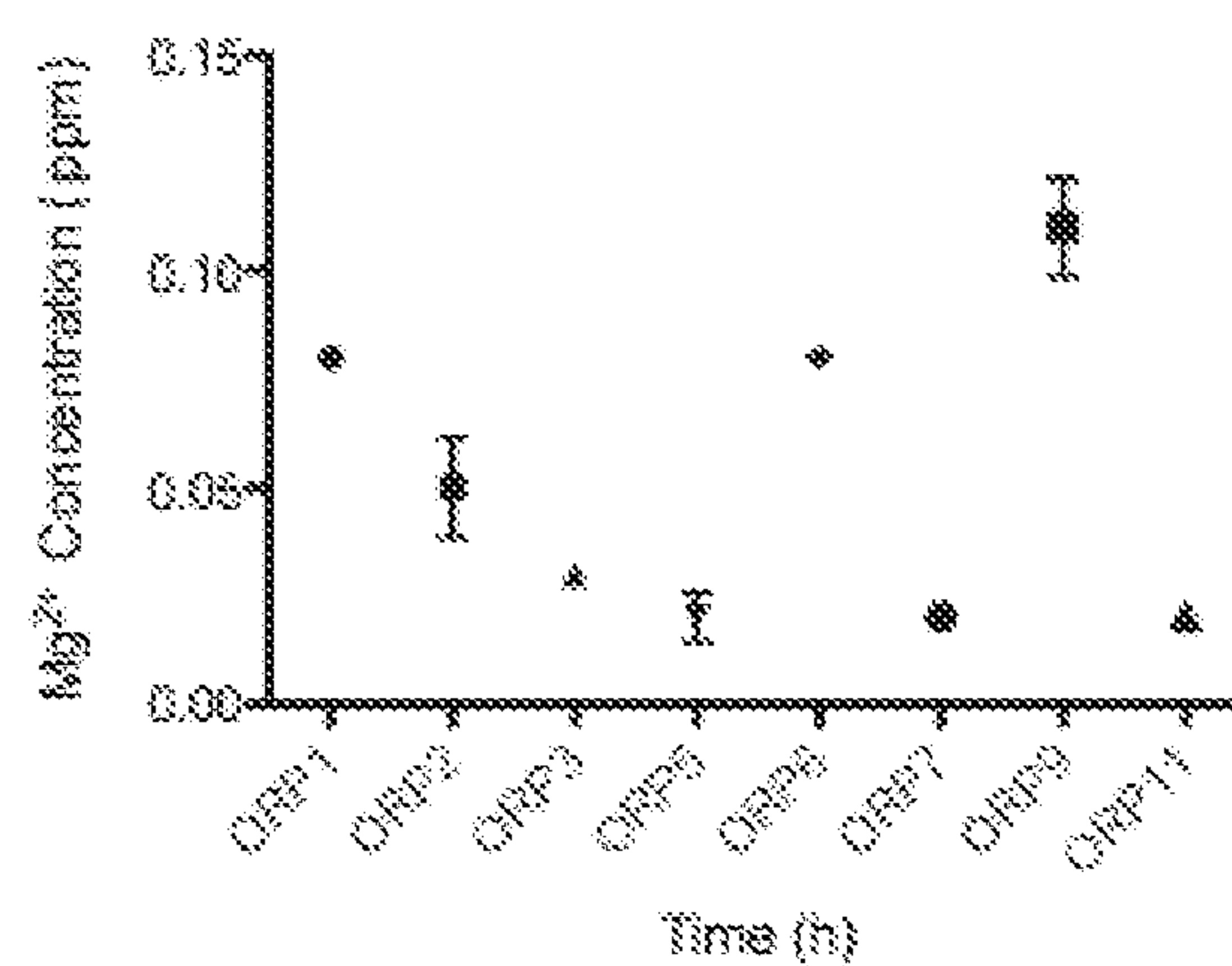


FIG. 17B



21 / 31

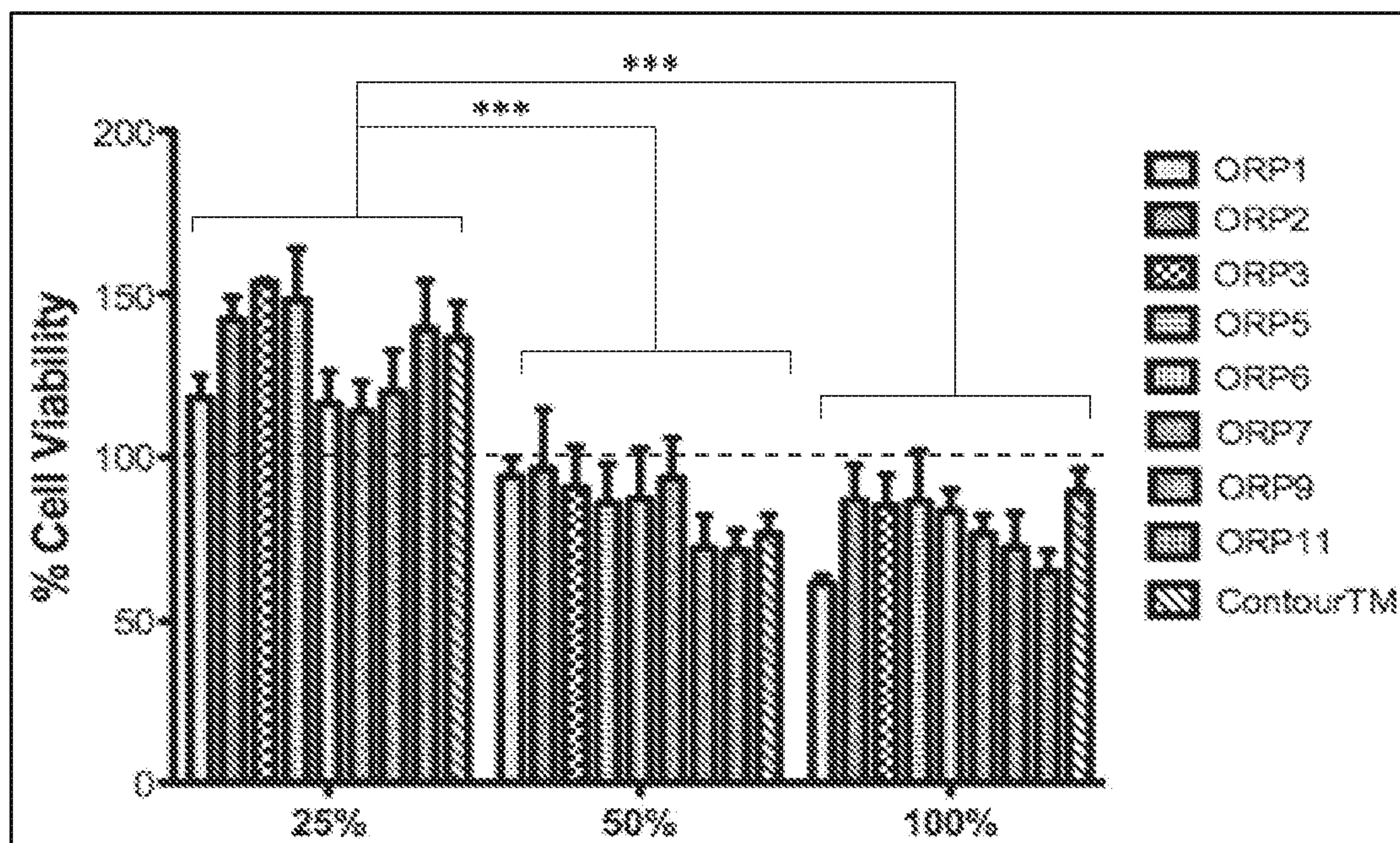


FIG. 18A

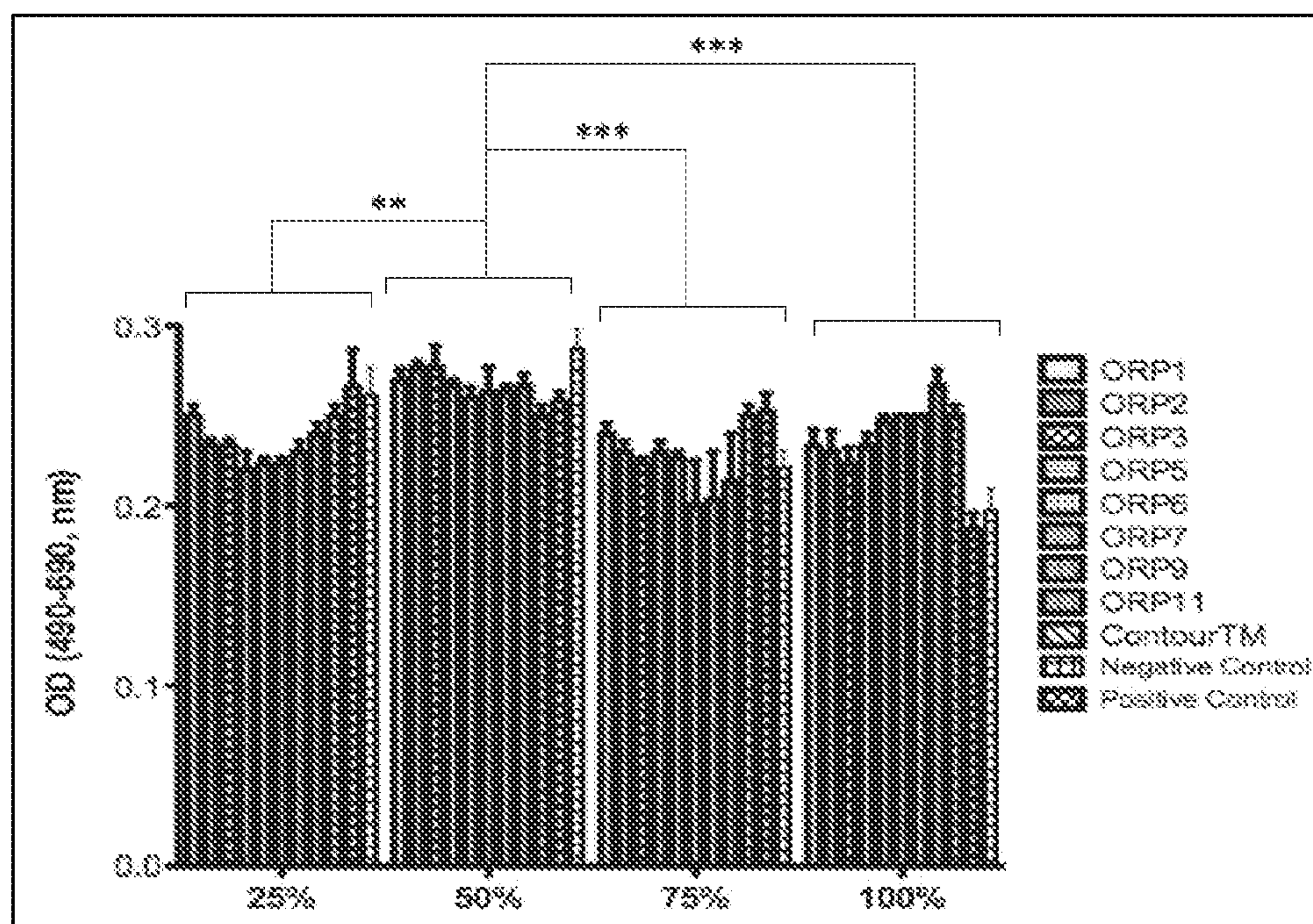
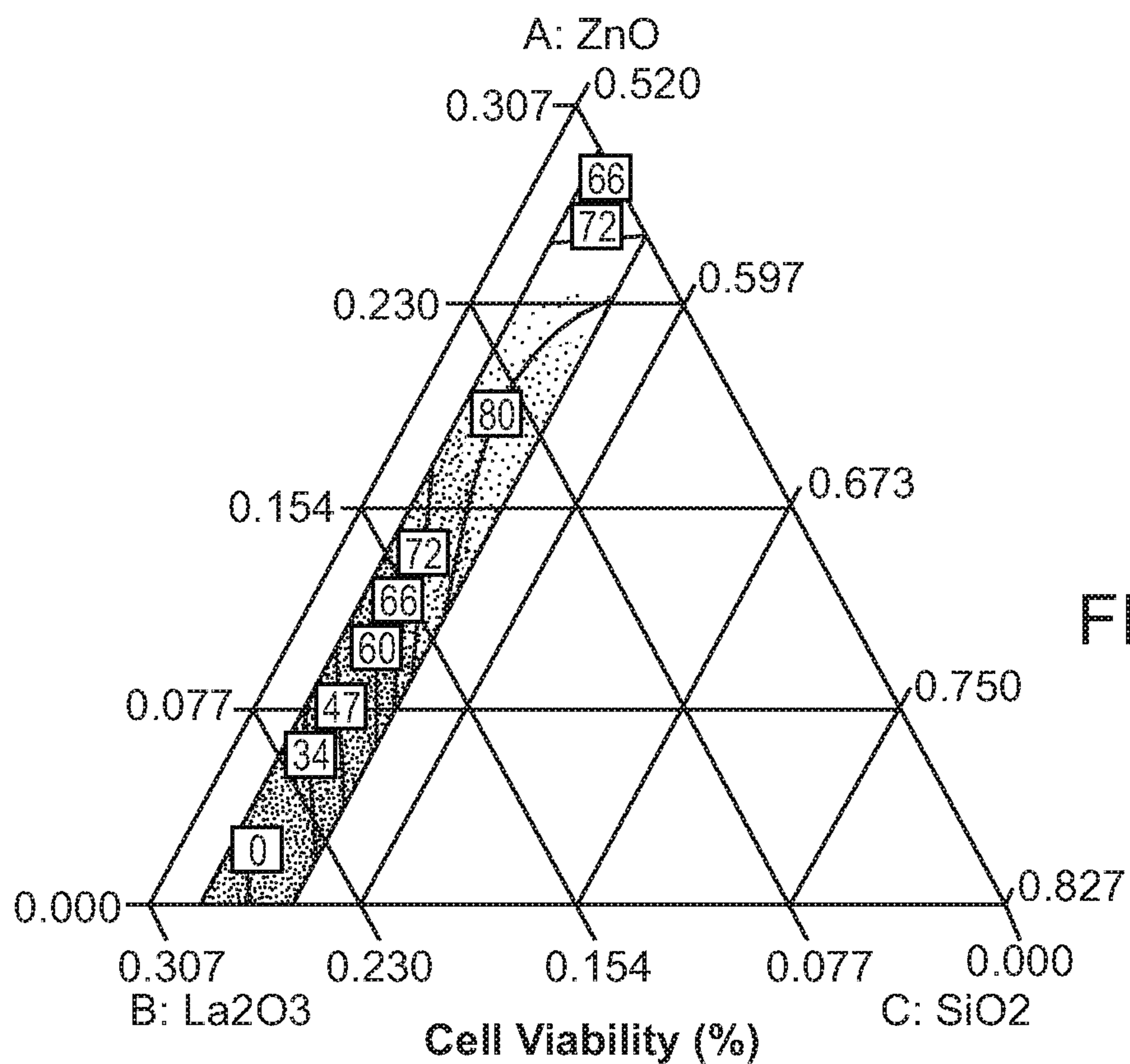
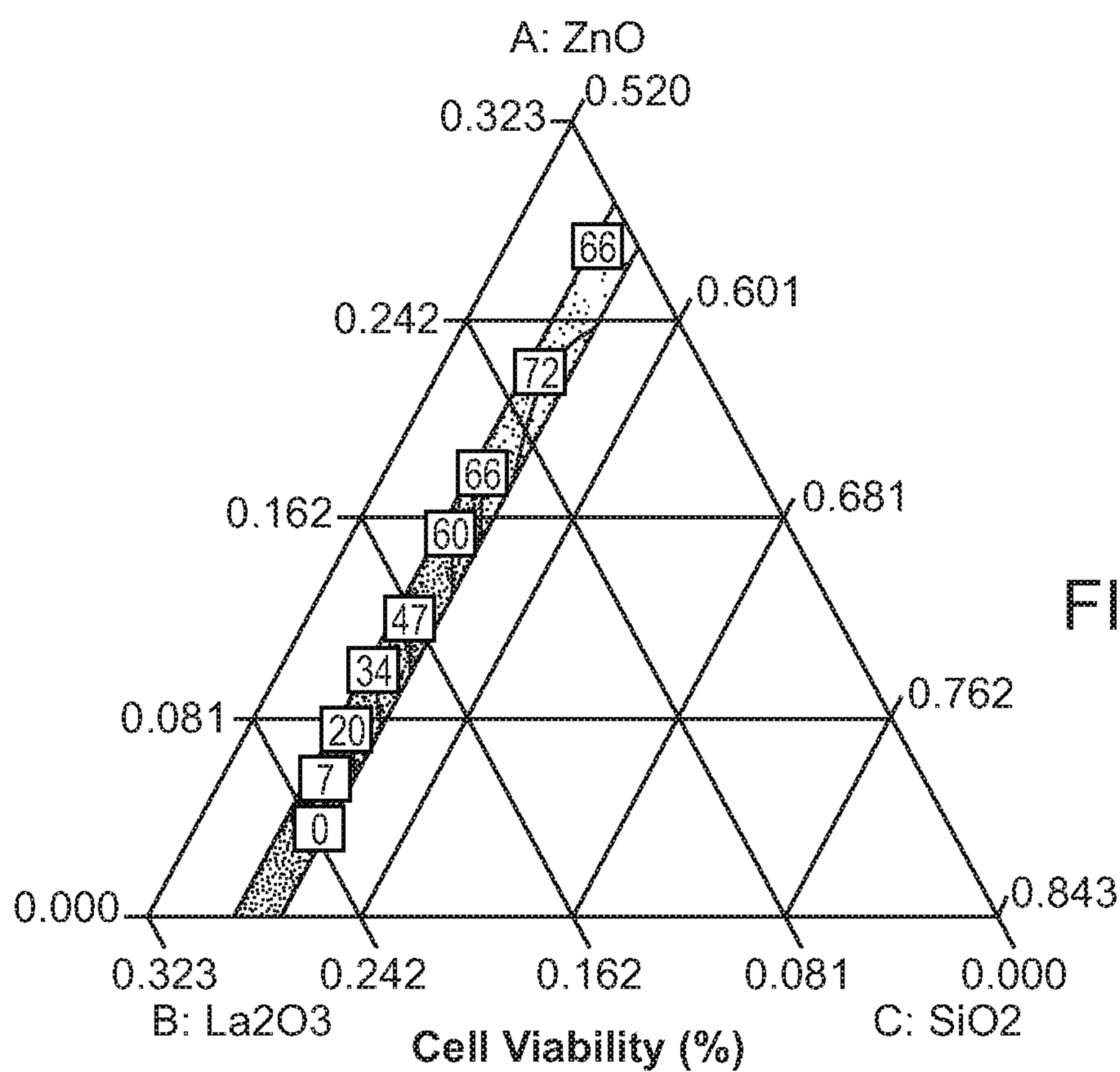
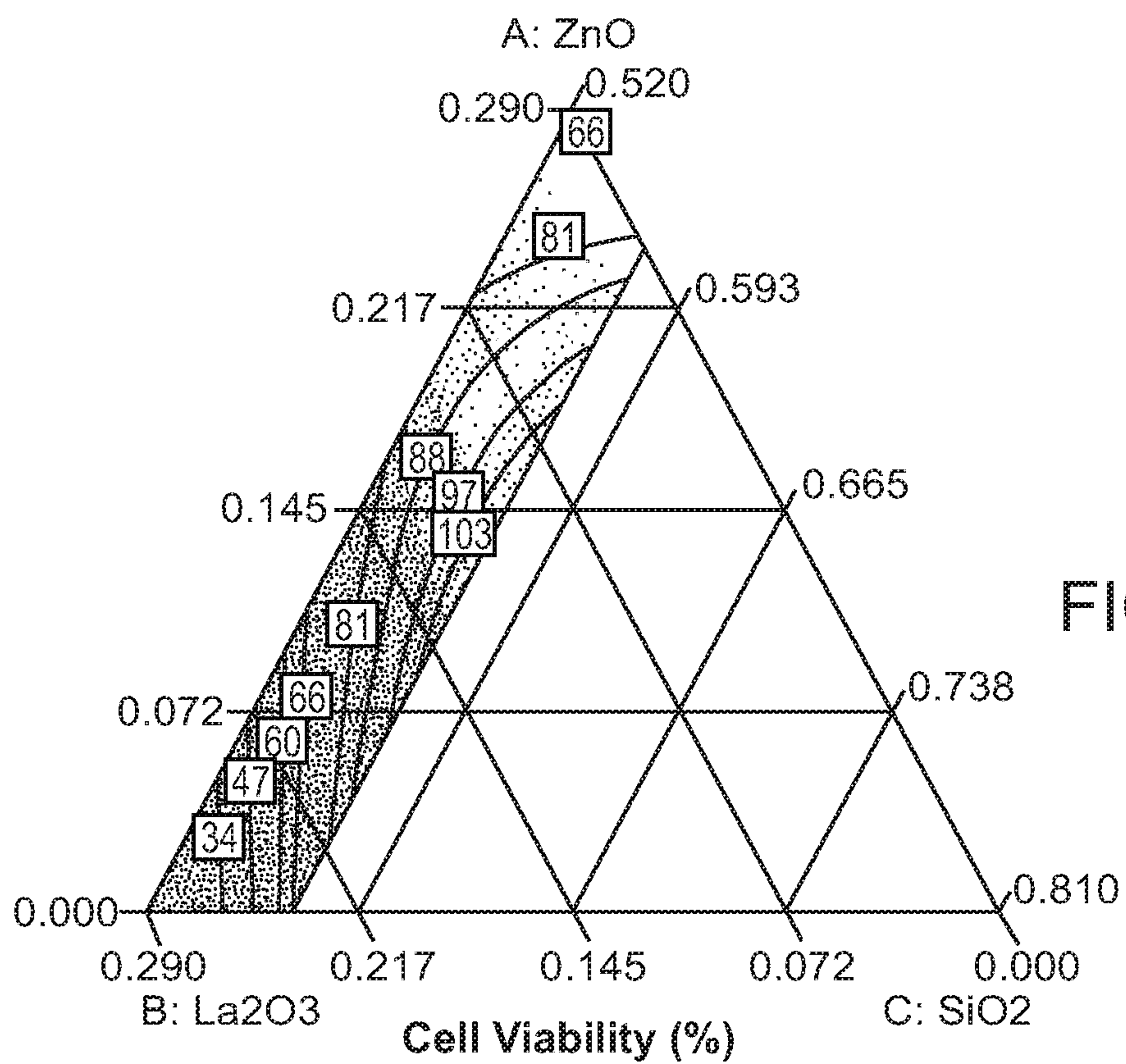
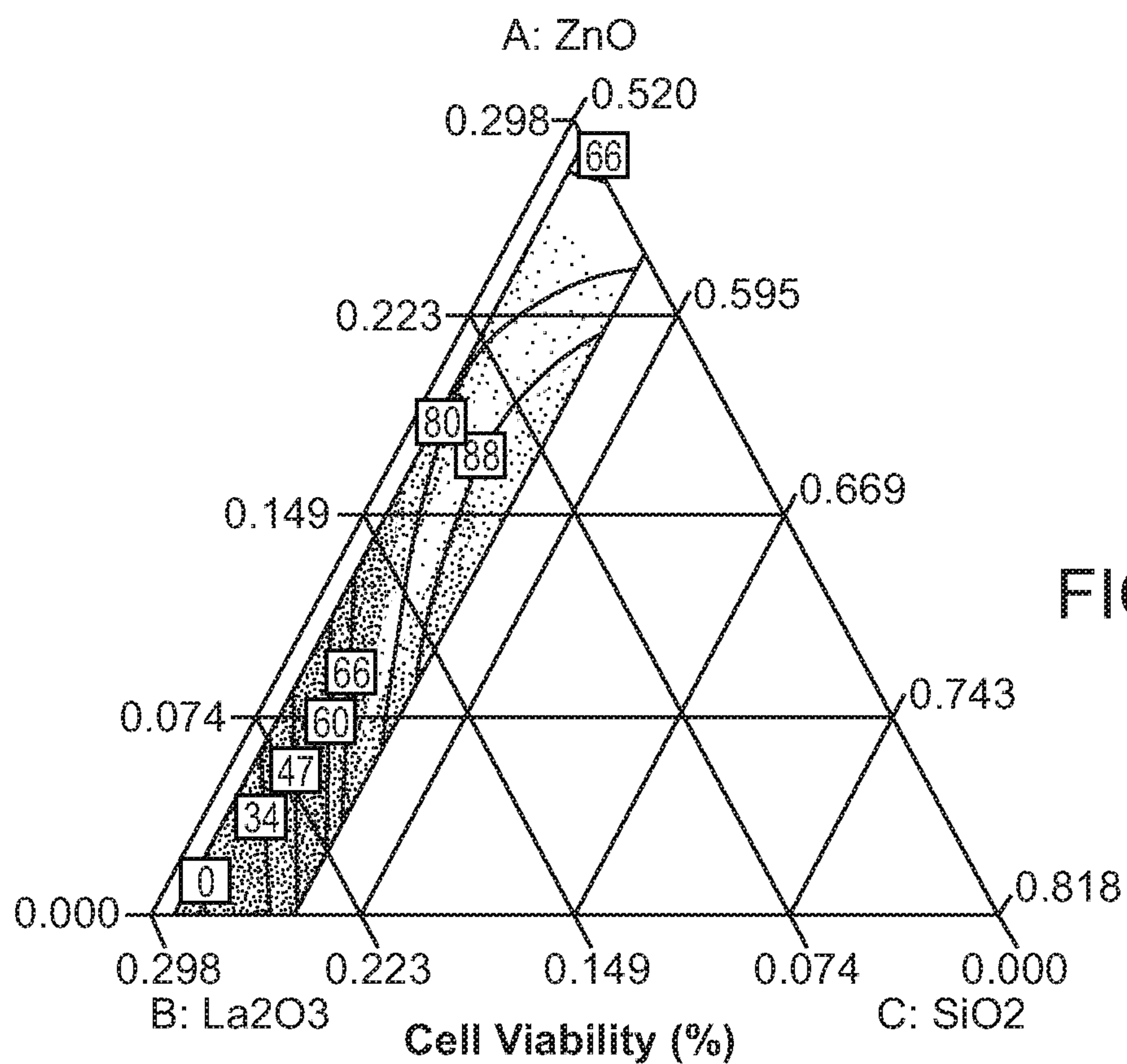


FIG. 18B

22 / 31



23 / 31



24 / 31

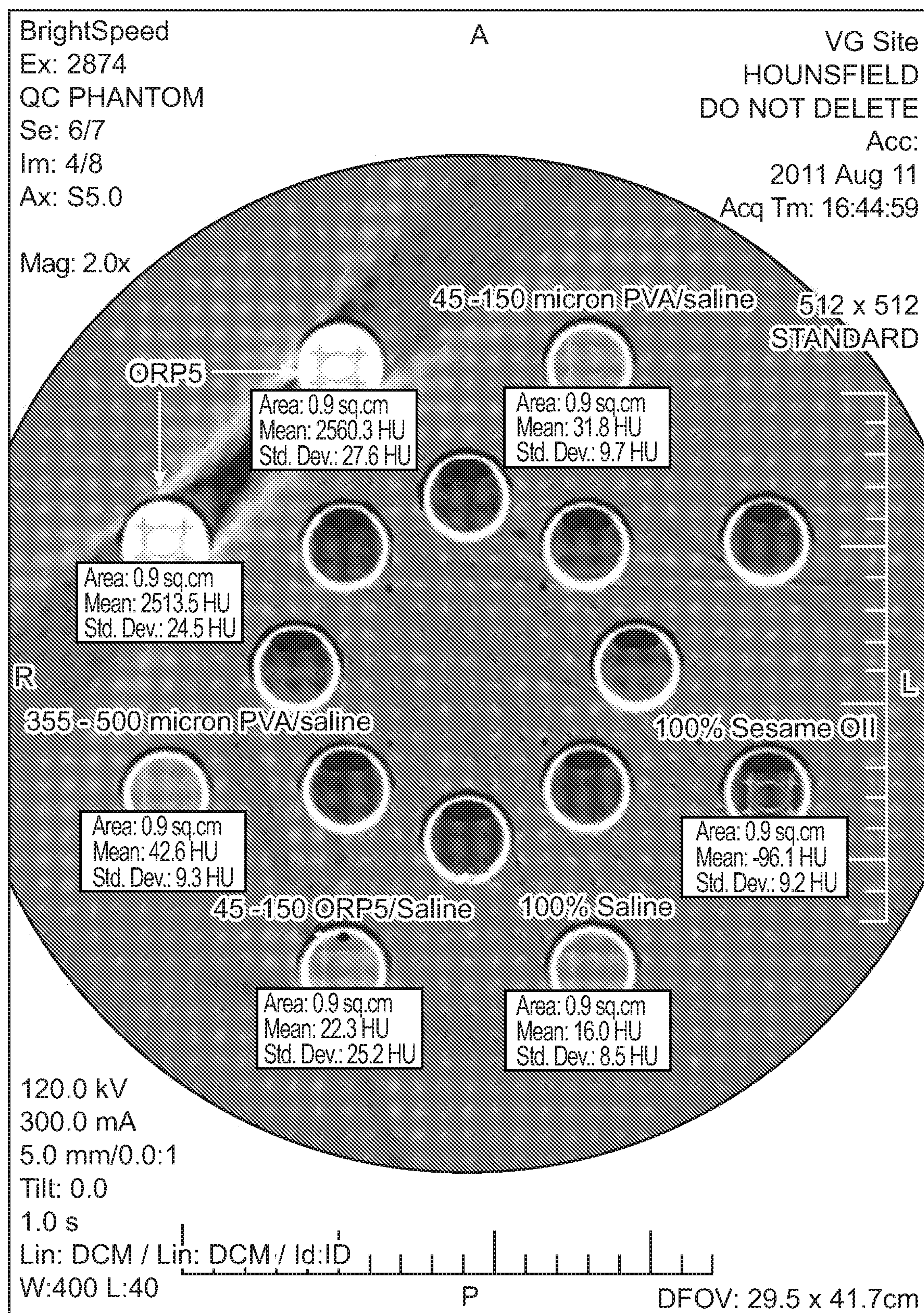


FIG. 20

25 / 31

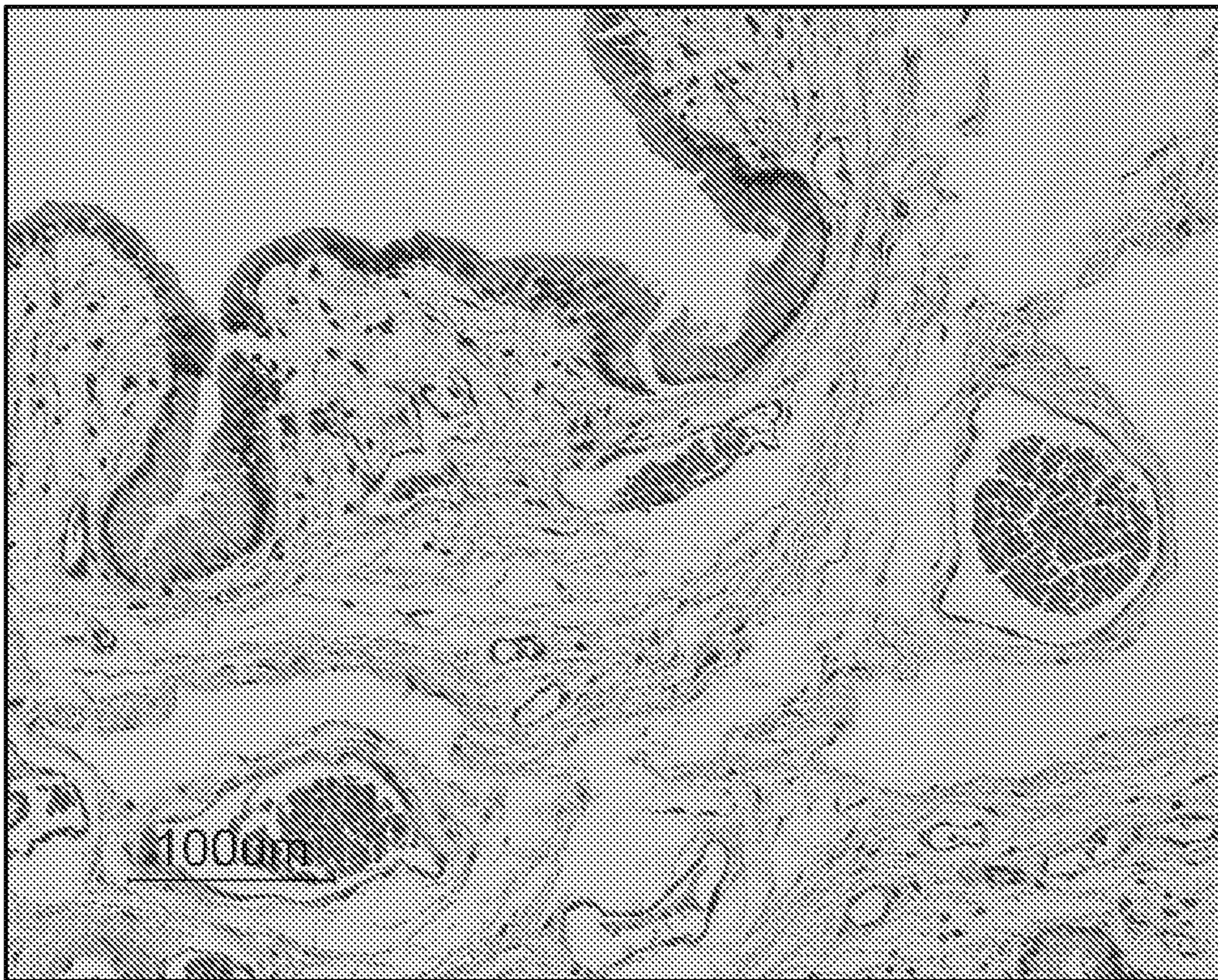
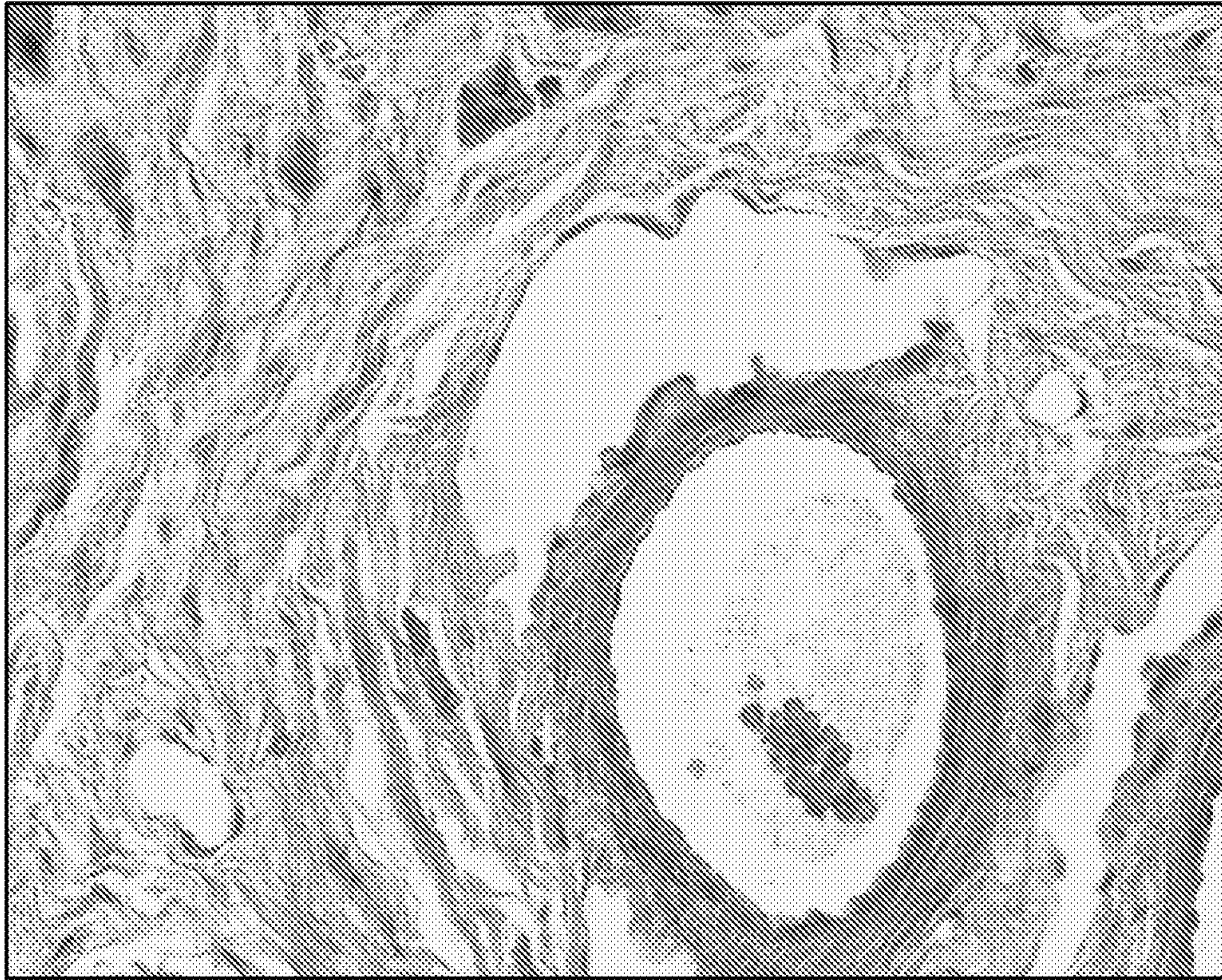


FIG. 21A

26 / 31

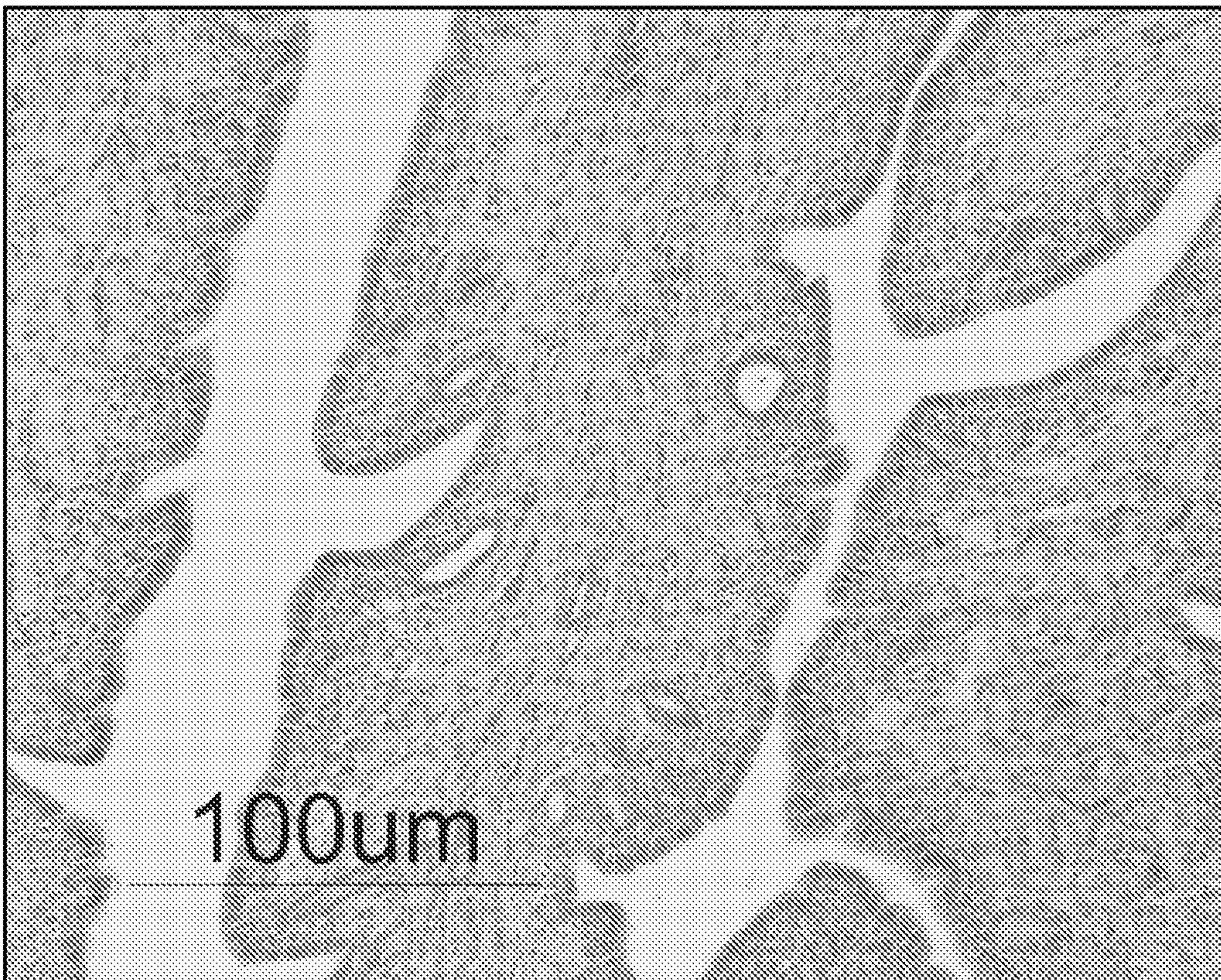
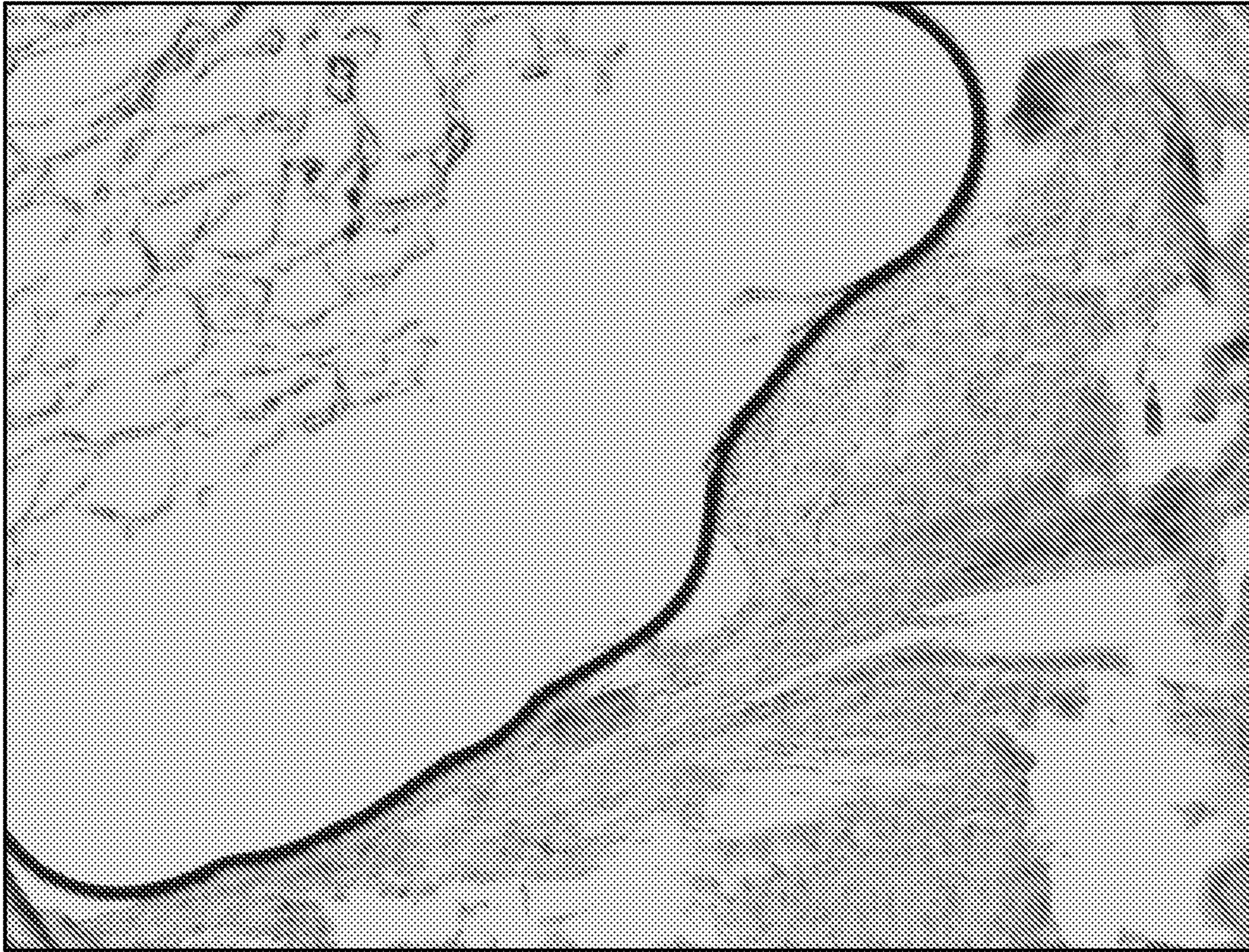


FIG. 21B

27 / 31

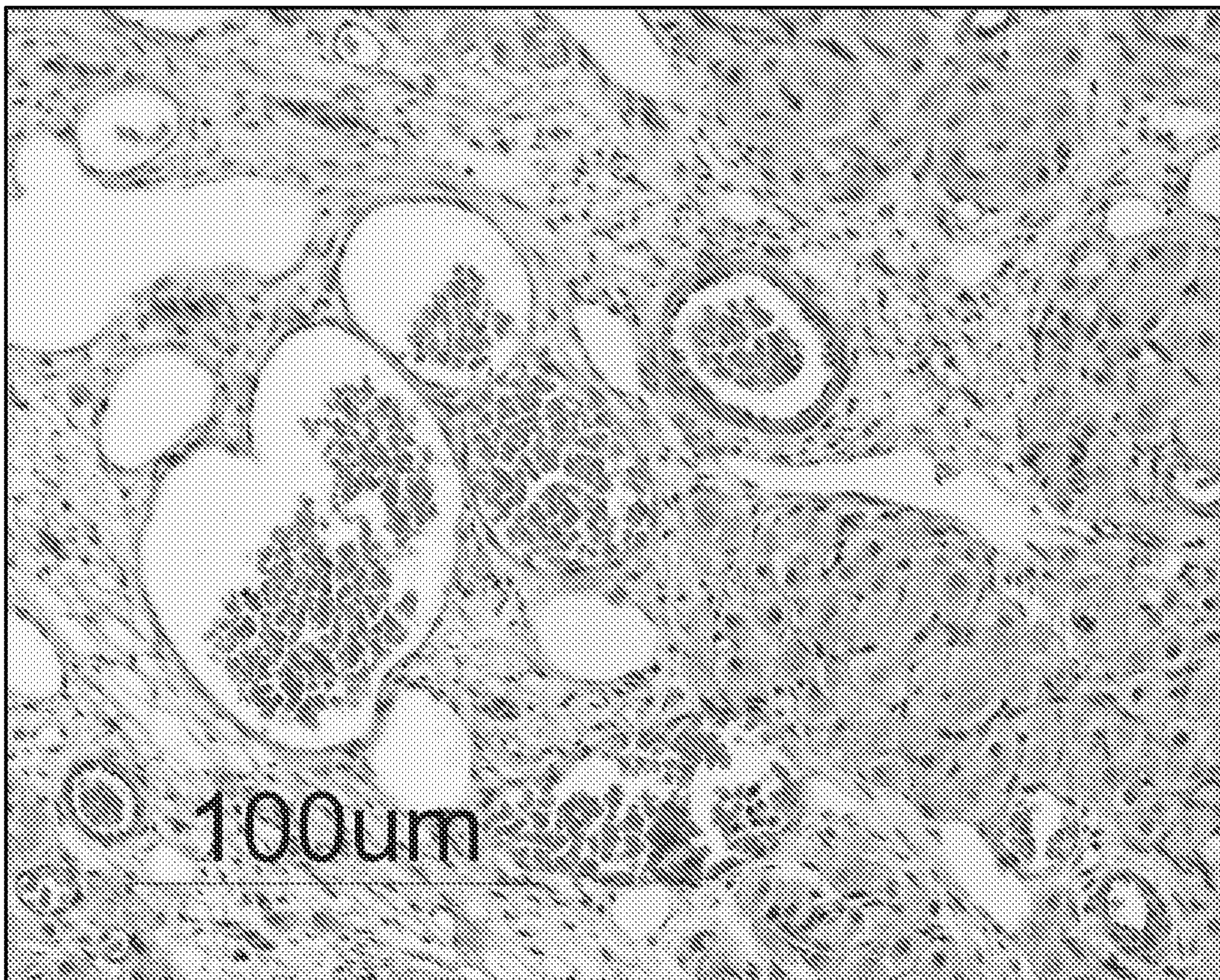
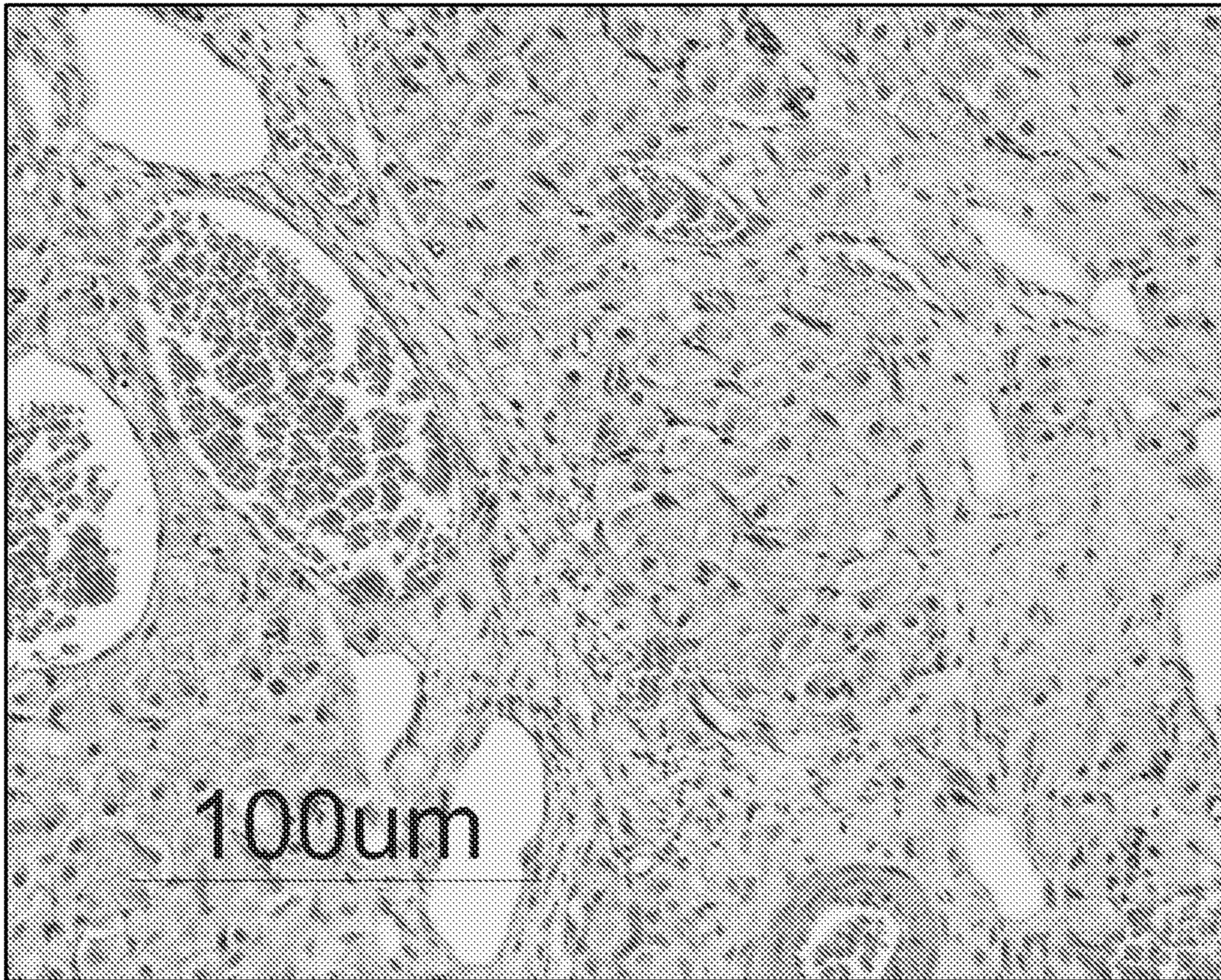
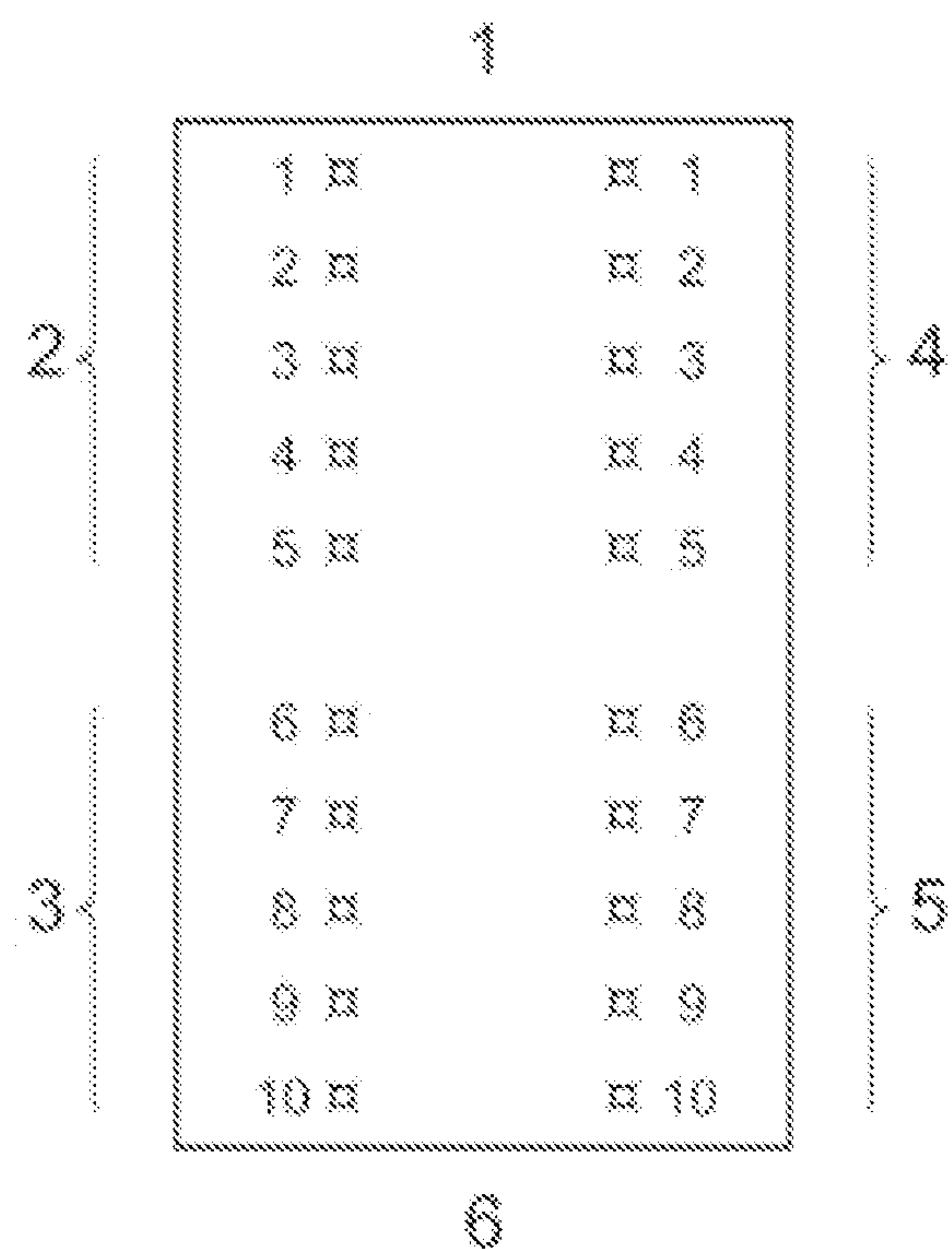


FIG. 21C

28 / 31

**Key**

- 1 cranial end
- 2 0,2 ml injections of polar extract
- 3 0,2 ml injections of non-polar extract
- 4 0,2 ml injections of polar solvent control
- 5 0,2 ml injections of non-polar solvent control
- 6 caudal end

FIG. 22

29 / 31

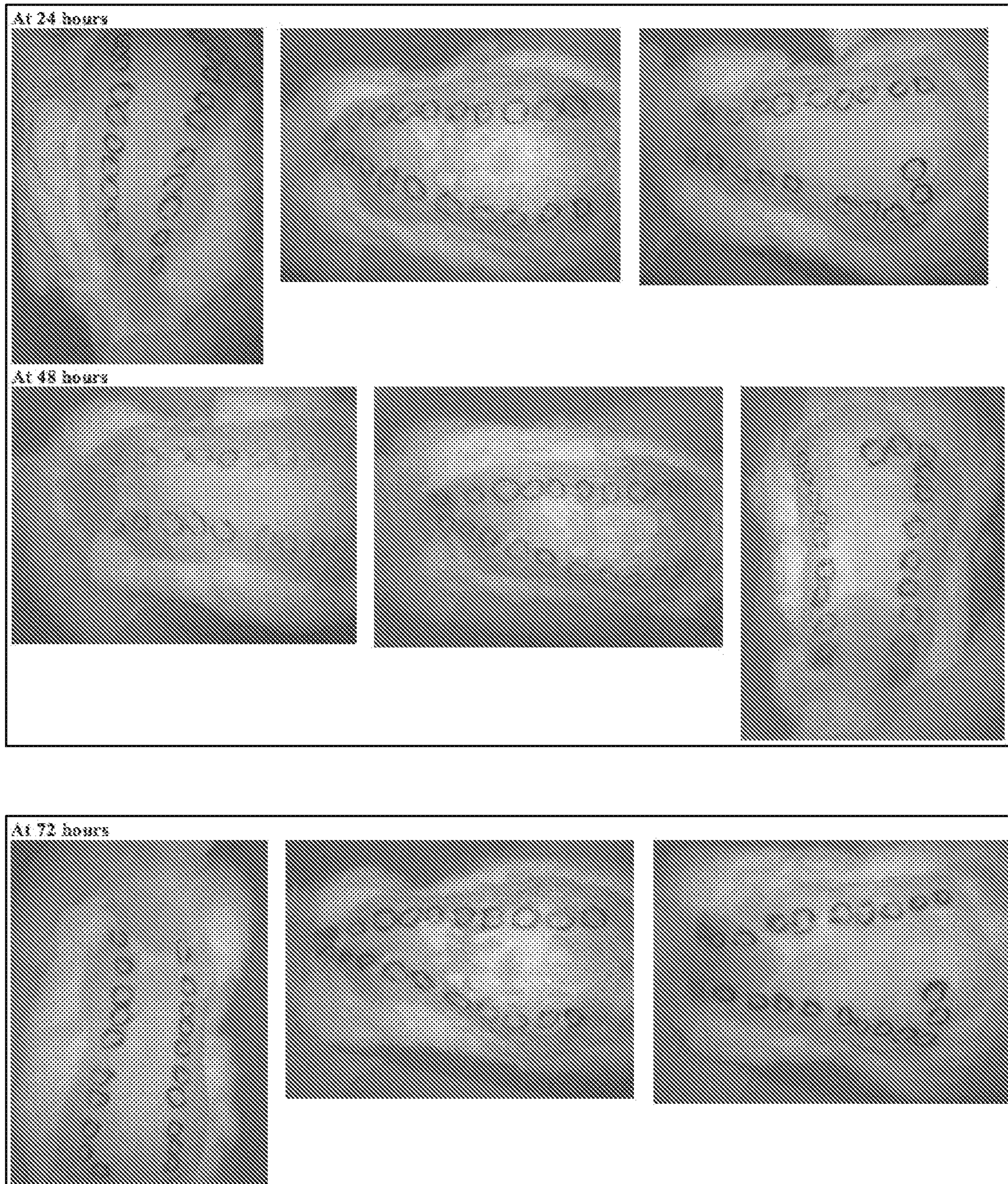


FIG. 23

30 / 31

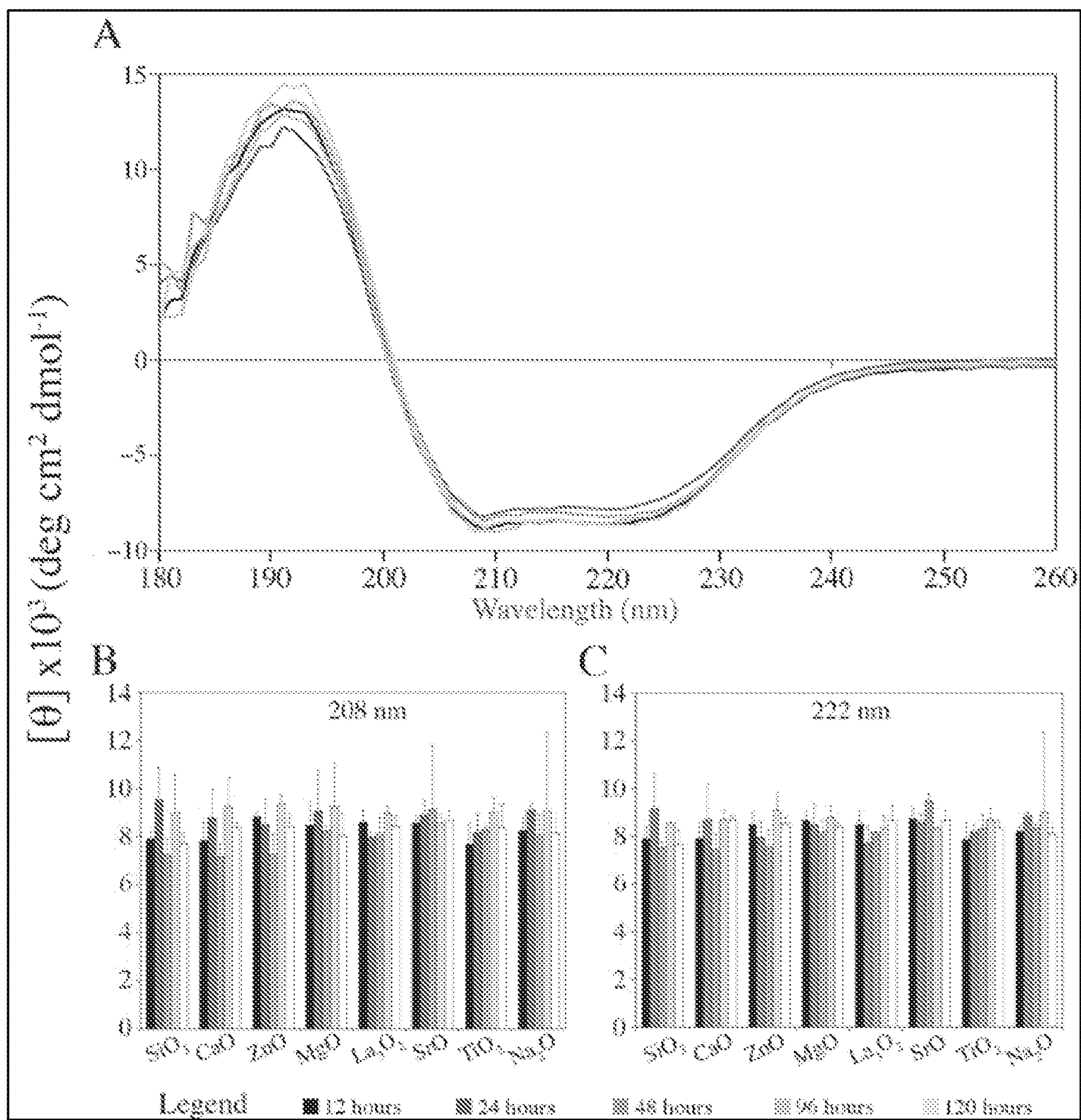


FIG. 24

31 / 31

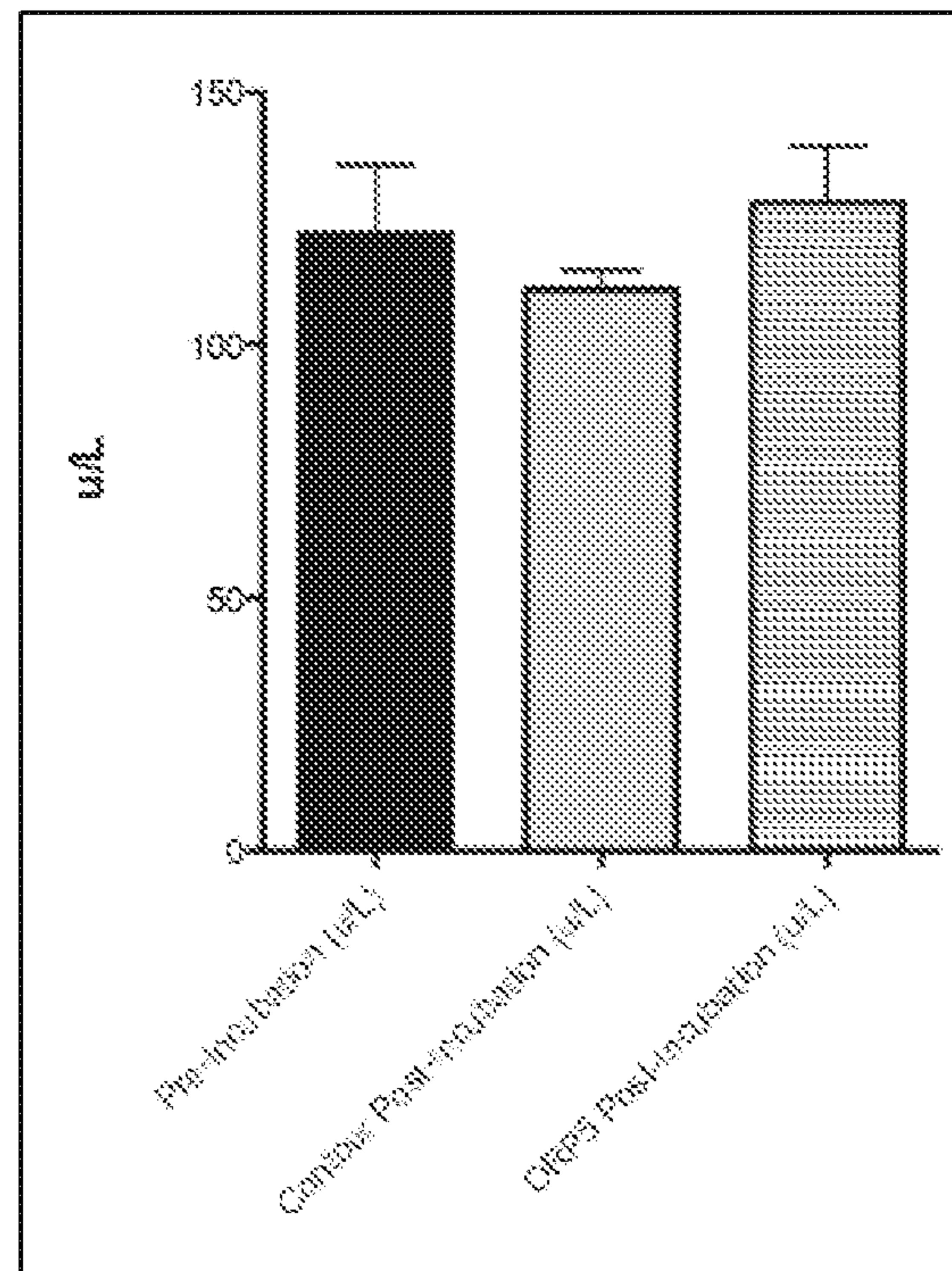


FIG. 25A

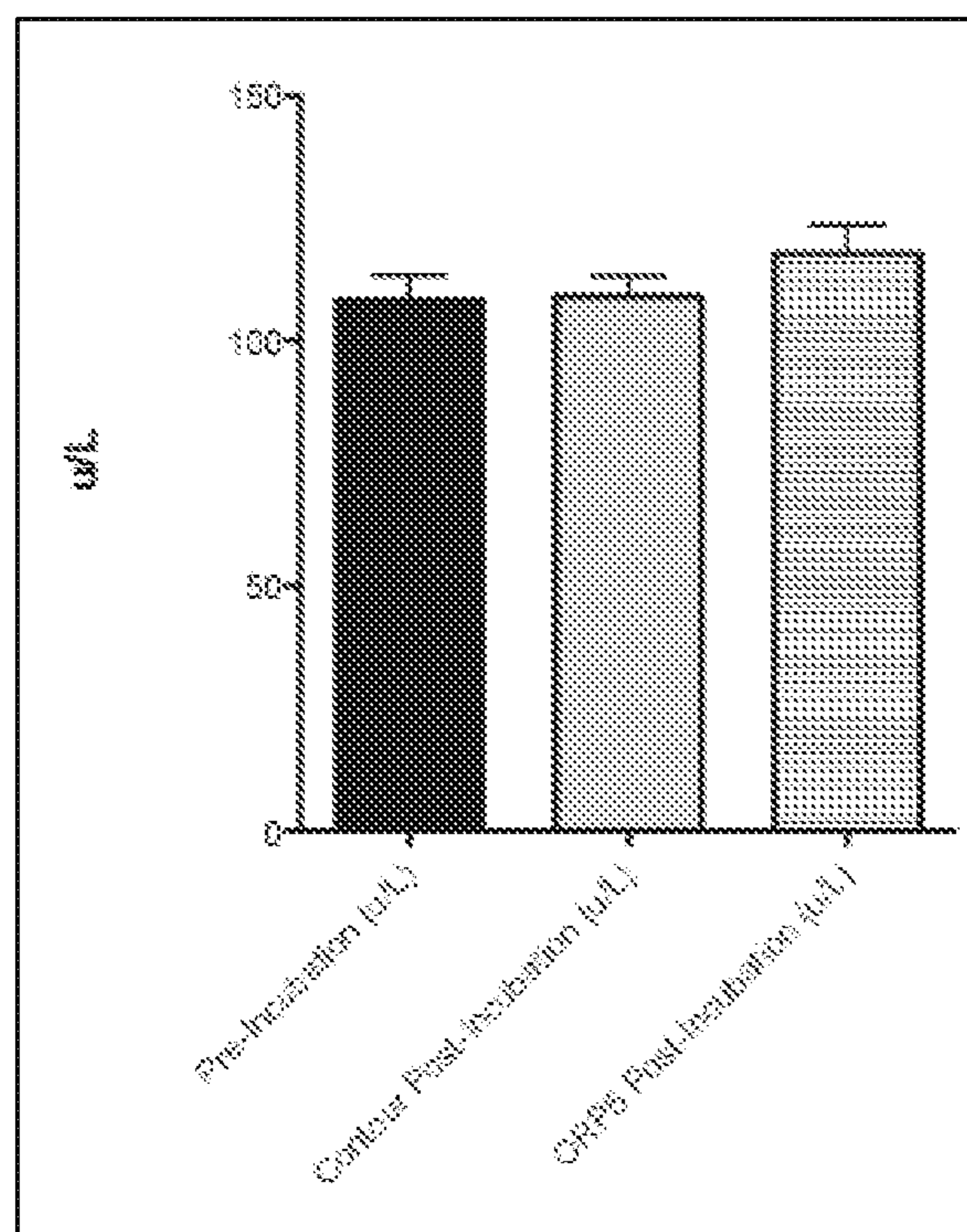


FIG. 25B

