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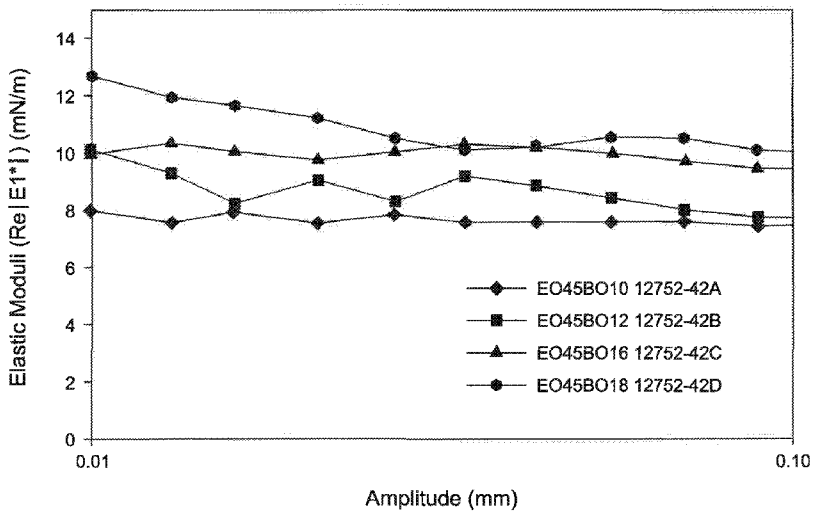
(54) **Title**: ETHYLENEOXIDE BUTYLENEOXIDE BLOCK COPOLYMER COMPOSITIONS

Fig. 1



(57) **Abstract**: The present invention relates to compositions comprising ethyleneoxide butyleneoxide and a galactomannan such as guar. The compositions are particularly well suited for ophthalmic applications such as contact lens disinfection and rewetting. Methods for the treatment of dry eye using the compositions of the present invention are also contemplated.

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IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

ETHYLENEOXIDE BUTYLENEOXIDE BLOCK COPOLYMER COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 61/223,599, filed July 7, 2009, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to ethyleneoxide butyleneoxide block copolymer compositions and specifically to ethyleneoxide butyleneoxide block copolymer compositions comprising a galactomannan such as guar or a guar derivative.

BACKGROUND OF THE INVENTION

The use of polymeric ingredients in compositions, particularly topically administrable ophthalmic compositions, is well known. Polymeric ingredients are typically used in suspension compositions as physical stability aids, helping to keep the insoluble ingredients suspended or easily redispersible. Polymers also impart desirable viscoelastic and rheological characteristics to compositions of which they are a part.

Many polymers have been used in topically administrable ophthalmic compositions. Included among these are cellulosic polymers, such as hydroxypropyl methylcellulose, hydroxyethyl cellulose, and ethylhydroxyethyl cellulose. Also included are synthetic polymers, such as carboxyvinyl polymers and polyvinyl alcohol. Still others include polysaccharides such as xanthan gum, guar gum, and dextran.

Combinations of polymers have also been used in ophthalmic compositions. Certain combinations of polymers are known to provide synergistic effects on viscosity and, in some cases, even a phase transition from a liquid to a gel. For

example, U.S. Pat. No. 4,136,173 discloses ophthalmic compositions containing a combination of xanthan gum and locust bean gum.

BRIEF SUMMARY OF THE INVENTION

The present invention is directed in certain embodiments to ophthalmic compositions comprising an ethyleneoxide butyleneoxide (EO-BO) block copolymer of the formula $(EO)_m(BO)_n$ and a galactomannan such as guar or a guar derivative. The present inventors have unexpectedly discovered that ethyleneoxide butyleneoxide block copolymers interact with galactomannans in aqueous solution. Aqueous compositions comprising EO-BO copolymers are generally Newtonian in behavior, and EO-BO copolymer contributes little to the viscosity of such composition at lower concentrations. However, the galactomannan and EO-BO compositions of the present invention have a synergistic increase in viscosity relative to compositions comprising galactomannan or EO-BO alone. The galactomannan and EO-BO compositions of the present invention have desirable viscoelastic and interfacial properties that make them well suited for ophthalmic applications, and in particular for contact lens disinfection and rewetting.

Ethyleneoxide butyleneoxide block copolymers are very hydrophobic amphiphiles in aqueous solutions. At an air-water interface these nonionic surfactants form elastic layers that can provide a cushioning effect for contact lenses when used in ophthalmic solutions. Furthermore, by modifying the hydrophobicity (changing the butyleneoxide unit) of EO-BO block copolymers in solution, advantageous changes in the elasticity of such solutions can occur.

In a preferred embodiment, the compositions of the present invention comprise a ethyleneoxide butyleneoxide block copolymer of the formula $(EO)_m(BO)_n$ where m is an integer having an average value of 10 to 1000 and n is an integer having an average value of 5 to 1000 and where the galactomannan is a guar derivative such as hydroxypropyl guar, native guar, or hydroxypropyl guar galactomannan.

Embodiments of the present invention also comprise the use of compositions comprising ethyleneoxide butyleneoxide block copolymer and a galactomannan in contact lens disinfection solutions, dry eye and artificial tear compositions. The present invention is also directed to methods of using these compositions to treat various ophthalmic disorders including dry eye, glaucoma, ocular hypertension, infection, allergy and inflammation.

The foregoing brief summary broadly describes the features and technical advantages of certain embodiments of the present invention. Additional features and technical advantages will be described in the detailed description of the invention that follows. Novel features which are believed to be characteristic of the invention will be better understood from the detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGURE 1 shows the amplitude sweep for various EO-BO compositions.

FIGURES 2a–2e show steady state flow curves for EO-BO and HP-guar compositions.

FIGURES 3a–3e show stress sweep curves for EO-BO and HP-guar compositions of TABLE 2.

FIGURES 4a–4e show frequency sweep curves for EO-BO and HP-guar compositions of TABLE 2.

FIGURES 5a–5d show extensional rheology curves for EO-BO and HP-guar compositions of TABLE 2.

FIGURES 6a–6b are amplitude sweep and frequency sweep curves for EO-BO and EO-BO/HP-guar compositions.

FIGURES 7a and 7b are bar charts summarizing experiments examining the ability of EO-BO compositions of the present invention to prevent the uptake of a polar lipid (FITC-DHPE, FIGURE 7a) and a non-polar lipid (NBD-cholesterol, FIGURE 7b) by various silicon hydrogel contact lenses.

FIGURE 8 is a bar chart showing the amount remaining of a non-polar lipid (NBD-cholesterol) on various silicon hydrogel lenses after treatment with compositions containing EO-BO and HP-guar.

FIGURES 9a–9d demonstrate the cleaning efficacy of a EO-BO composition of the present invention compared to vehicle.

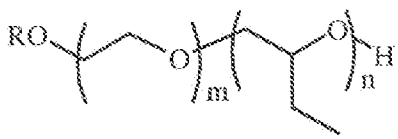
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed in certain embodiments to ophthalmic compositions comprising an ethyleneoxide butyleneoxide (EO-BO) block copolymer and a galactomannan such as guar or a guar derivative. The ethyleneoxide butyleneoxide block copolymers of these compositions have the following general formula:

$$(EO)_m(BO)_n \qquad (I)$$

where m is an integer having an average value of 10 to 1000 and n is an integer having an average value of 5 to 1000. The block copolymers of the present invention are those that include a poly(oxyethylene) block as the hydrophilic component and a poly(oxybutylene) block as the hydrophobic component. These may be in form of a di-block copolymer, denoted as EO-BO, a tri-block copolymer, represented as EO-BO-EO or BO-EO-BO, or other block-type configurations. Unless expressly indicated to the contrary, all references to "EO-BO block copolymers" herein include all of the foregoing forms. These copolymers may also be described in terms of the approximate or average value assigned to the respective repeating group. For example, $(EO)_{20}(BO)_5$, where the average value of the oxyethylene group is 20, and the average value of the oxybutylene group is 5. Compositions of the present invention generally comprise EO-BO copolymer at a concentration of 0.001 to 1.0% w/v. Preferred compositions of the present invention comprise EO-BO copolymer at a concentration of 0.01 to 0.1% w/v.

EO-BO di-block copolymers of the following general formula are particularly preferred:



(II)

wherein R is selected from the group consisting of hydrogen, methyl, ethyl, propyl and butyl; m is an integer having an average value of 10 to 1000; and n is an integer having an average value of 5 to 1000.

Most preferred is a copolymer of formula (II) wherein R is methyl; m has an average value of 45; and n has an average value of 9-18.

The EO-BO block copolymers utilized in the present invention have a molecular weight in the range of 1,000 to about 100,000 Daltons; and more preferably in the range of 1,000 to about 15,000 Daltons.

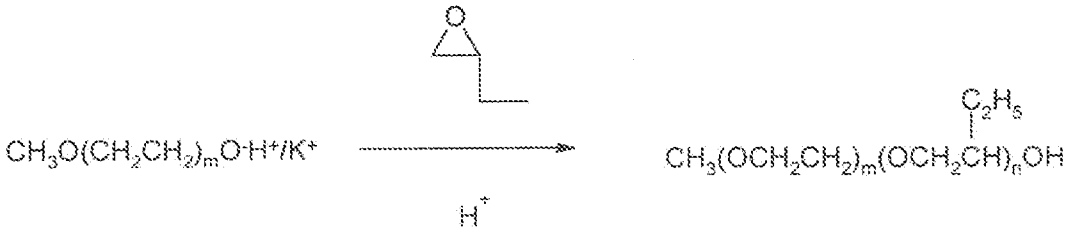
Maintaining a proper hydrophilic-lipophilic balance (HLB) imparts certain properties to the EO-BO block co-polymer compositions of the present invention. For example, the HLB of the block co-polymers utilized in the compositions of the present invention is directly related to the solubility, surface wettability, and interfacial surface activity properties of the compositions of the present invention.

The BO portion of the block copolymer of formula (I) above is hydrophobic and is primarily responsible for the wettability properties of the compositions described herein. The EO portion of the copolymer provides the compositions with hydrophilic properties, but more importantly, it is this portion of the co-polymer that determines the aqueous solubility of the copolymers. Although it is possible to utilize solubilizing agents in the compositions of the present invention, in which case the ratio of the EO to BO segments is somewhat less critical, it is preferred to utilize copolymers that do not require solubilizing agents, as such compounds may disrupt or modify the HLB, which in turn may adversely affect the wettability properties of the compositions, cause ocular irritation, or create other concerns. Therefore, the preferred copolymers of formula (I) above are those wherein there is a predominance of EO to BO segments. That is, the variable "m" in formula (I) and formula (II) above is preferably greater than the variable "n". The EO-BO block co-polymers will preferably have a ratio of EO to BO segments of from about 2:1 to about 10:1, with a ratio of about 3:1 to about 6:1 being most preferred.

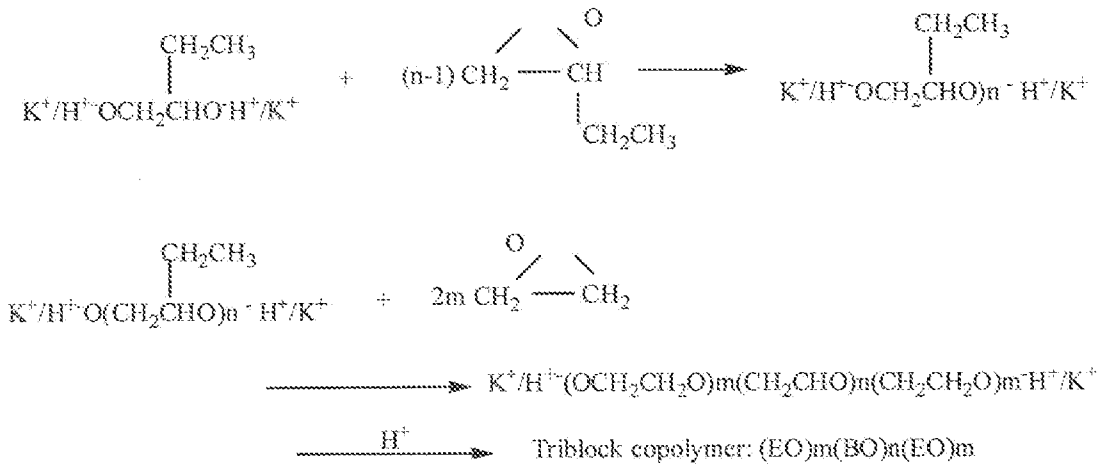
The EO-BO block copolymers of the present invention may be prepared using synthetic methods known to those of skill in the art, for example, as described in Nace, V. M., J. Am. Oil Chem. Soc., Vol. 73(1):1-9, 1996; Yang et al., Macromolecules, Vol. 27:2371-2379, 1994; Yang et al., Langmuir, Vol. 11:4703, 1995; Yu et al., Langmuir, Vol. 12:3404-3412, 1996; Chaibundit et al., Langmuir, Vol. 16:9645-9652, 2000; Bedells et al., J. Chem. Soc., Faraday Trans., Vol. 89:1235-1242, 199; and Kelarakis et al., Macromolecules, Vol. 31:944-946, 1998, the entire contents of each of which are hereby incorporated in the present specification by reference. The foregoing EO-BO block copolymers may also be prepared by the application or adaptation of known methods described in U.S. Patent Nos. 2,828,345 (Spriggs), and 2,174,761 (Schuette et al.), the entire contents of each of which are

hereby incorporated into the present specification by reference. Additional synthetic procedures are taught by Ketelson et al. (U.S. Patent Application Serial No. 11/953654), the contents of which are herein incorporated by reference in its entirety.

Generally, the EO-BO block copolymers described above may be synthesized using a well defined polyethylene glycol (PEG) polymer by controlled addition of oxybutylene to the primary hydroxyl group of the PEG polymer. For example, the EO-BO di-block copolymer $(EO)_{45}(BO)_{10}$ may be prepared according to the following general reaction scheme:



Other variations of the block chemistry structure may also be prepared, using techniques and methods readily available and well-known to those skilled in art. For example, the following reaction process may be utilized for the preparation of tri-block copolymers of the form $(EO)_m(BO)_n(EO)_m$:



The EO-BO block copolymers of the present invention may also be functionalized with specific end groups for specific surface reactions to covalently bind the polymer to a surface or prepare a new polymer material. The EO-BO block copolymers that may be utilized in the present invention are not limited relative to structure or molecular weight, so long as the block copolymers are soluble in aqueous solutions and are non-toxic to ophthalmic tissue at concentrations on the order of those described herein.

As used herein, the term "galactomannan" refers to polysaccharides derived from the above natural gums or similar natural or synthetic gums containing mannose or galactose moieties, or both groups, as the main structural components. Several types of galactomannans that may be used in the present invention are typically derived from guar gum, locust bean gum and tara gum. The galactomannans of the present invention are obtainable from various commercial sources and via synthetic procedures known to those of skill in the art. In preferred embodiments, the galactomannan is hydroxypropyl guar (HP-8A or HP-guar) obtained from Rhodia, Inc. Other galactomannan include, but are not limited to, native guar and hydroxypropyl guar galactomannan produced according to the processes of co-pending U.S. Patent Application Serial Nos. 61/220,859 filed June 26, 2009, and 61/150,215 filed February 5, 2009, the contents of which are herein incorporated by reference in their entirety. Compositions of the present invention generally comprise galactomannan at a concentration of 0.01 to 2.0% w/v. Preferred compositions of the present invention comprise galactomannan at a concentration of 0.05 to 0.25% w/v.

In addition to EO-BO block copolymer and galactomannan, the compositions of the present invention optionally comprise one or more additional components. Such components include, but are not limited to, tonicity agents, preservatives, chelating agents, buffering agents, surfactants, co-solvents, and antioxidants. Other components used in certain embodiments are solubilizing agents, stabilizing agents, comfort-enhancing agents, polymers, emollients, pH-adjusting agents and/or lubricants. Components that may be used in certain compositions of the present invention including water, mixtures of water and water-miscible solvents, such as C1-C7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, and mixtures of those products.

In addition to EO-BO block copolymer and galactomannan, the compositions of the present invention may comprise compounds having antimicrobial or preservative properties. Suitable antimicrobial agents include, but are not limited to those generally used in contact lens care solutions or in other ophthalmic solutions such as polyquaternium-1, which is a polymeric quaternary ammonium compound; myristamidopropyl dimethylamine ("MAPDA"), which is a N,N-dialkyl, N'-alkyl,

ethylene diamine; guanidine derivatives such as polyhexamethylene biguanide ("PHMB") or polyaminopropyl biguanide (PAPB); perborates such as sodium perborate and peroxides such as hydrogen peroxide. The additional antimicrobial agents that may be utilized in the present invention also include the aminobiguanides described in U.S. Patent No. 6,664,294, the entire contents of which are hereby incorporated in the present specification by reference. The preferred additional antimicrobial agents are polyquaternium-1, MAPDA and the amino biguanide identified in U.S. Patent No. 6,664,294 as "Compound Number 1".

Suitable antioxidants include, but are not limited to, sulfites, ascorbates, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

In addition to EO-BO block copolymer and galactomannan, the compositions of the present invention may comprise one or more surfactants. Surfactants utilized in the compositions of the present invention can be cationic, anionic, nonionic or amphoteric. Preferred surfactants are neutral or noninonic surfactants which may present in amounts up to 5 w/v%. Surfactants that may be used with certain embodiments of the present invention include, but are not limited to, polyethylene glycol ethers or esters of fatty acids, polyoxyethylene-polyoxypropylene block copolymers of ethylene diamine (e.g., poloxamines such as Tetronic 1304 or 1107), polyoxypropylene-polyoxyethylene glycol nonionic block copolymers (e.g., poloxamers, such as Pluronic F-127), and p-isooctylpolyethylen phenol formaldehyde polymers (e.g., Tyloxapol).

In certain embodiments of the present invention, suitable cosolvents include glycerin, propylene glycol and polyethylene glycol.

Buffering agents which may be incorporated into compositions of the present invention include, but are not limited to, alkaline metal salts, such as potassium or sodium carbonates, acetates, borates, phosphates and citrates, and weak acids, such as acetic acids and boric acids. The preferred buffering agents are alkaline metal borates, such as sodium or potassium borates. Other pH-adjusting agents, such as inorganic acids and bases, may also be utilized. For example, hydrochloric acid or sodium hydroxide may be employed in concentrations suitable for ophthalmic compositions. The above-described buffering agents are generally present in amounts from about 0.1 to about 2.5 w/v%, preferably from about 0.5 to about 1.5 % w/v%.

The compositions of the present invention are preferably isotonic, or slightly hypotonic, and generally have an osmolality in the range of 210-320 mOsm/kg, and preferably have an osmolality in the range of 235-300 mOsm/kg. This may require a tonicity agent to bring the osmolality of the composition to the desired level. Tonicity-adjusting agents include, but are not limited to, sodium chloride, glycerin, sorbitol, or mannitol.

In contact lens disinfection applications, disinfectants that may be used include, but are not limited to halamines, halogenated amino acids, bis-amines, and certain preservatives listed above. The amount of the disinfectant required to achieve the desired disinfection activity can be determined by persons skilled in the art. The concentration required to achieve the desired activity as a disinfectant while retaining acceptable safety and toxicity properties is referred to herein as "an effective amount". An effective amount will possess antimicrobial activity sufficient to meet generally accepted standards for activity, such as EN ISO 14729:2001 Ophthalmic optics—Contact lens care products—Microbiological requirements and test methods for products and regimens for hygienic management of contact lenses.

For ophthalmic applications of the present invention, the pH of the compositions may be in an ophthalmic acceptable range of 3.0 to 8.0. Preferred ophthalmic compositions are prepared using a buffering system that maintains the composition at a pH of about 3.0 to a pH of about 8.0.

In particular embodiments, compositions of the present invention are suitable for topical application to mammalian eyes. For example, for ophthalmic administration, the composition may be a solution, a suspension, a gel, water-in-oil and oil-in-water emulsions, or an ointment. Preferred compositions for ophthalmic administration will be aqueous solution in the form of drops. The term "aqueous" typically denotes an aqueous composition wherein the excipient is >50%, more preferably >75% and in particular >90% by weight water. These drops may be delivered from a single dose ampoule which may preferably be sterile and thus render bacteriostatic components of the composition unnecessary. Alternatively, the drops may be delivered from a multi-dose bottle which may preferably comprise a device which extracts preservative from the composition as it is delivered, such devices being known in the art.

In certain topical ophthalmic applications, the compositions of the present invention may comprise one or more tear substitutes. A variety of tear substitutes are known in the art and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, and ethylene glycol; polymeric polyols such as polyethylene glycol; cellulose esters such hydroxypropylmethyl cellulose, carboxy methylcellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; vinyl polymers, such as polyvinyl alcohol; and carbomers, such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P. Topical ophthalmic compositions of the present invention generally have a viscosity of 0.5-100 cps, preferably 0.5-50 cps, and most preferably 1-20 cps. This relatively low viscosity insures that the product is comfortable, does not cause blurring, and is easily processed during manufacturing, transfer and filling operations.

Compositions of the present invention can also be used to deliver a pharmaceutical agent to the eye. Such pharmaceutical agents include, but are not limited to anti-glaucoma agents, anti-angiogenesis agents; anti-infective agents; anti-inflammatory agents; growth factors; immunosuppressant agents; and anti-allergic agents. Anti-glaucoma agents include, but are not limited to, beta-blockers, such as betaxolol and levobetaxolol; carbonic anhydrase inhibitors, such as brinzolamide and dorzolamide; prostaglandins, such as travoprost, bimatoprost, and latanoprost; seretonergics; muscarinics; dopaminergic agonists. Anti-angiogenesis agents include, but are not limited to, anecortave acetate (RETAANE™, Alcon™ Laboratories, Inc. of Fort Worth, Tex.) and receptor tyrosine kinase inhibitors (RTKi). Anti-inflammatory agents include, but are not limited to, non-steroidal and steroidal anti-inflammatory agents, such as triamcinolone actinide, suprofen, diclofenac, ketorolac, nepafenac, rimexolone, and tetrahydrocortisol. Growth factors include EGF or VEGF. Anti-allergic agents include, but are not limited to, olopatadine and epinastine, H1 and H4 receptor antagonists (such as those disclosed in WO 2010/030785 to Borchardt et al., herein incorporated by reference in its entirety).

Examples

The following examples are presented to further illustrate selected embodiments of the present invention.

EXAMPLE 1

Ingredient	% w/v
$EO_{45}BO_{14}$	0.2
HP-Guar	0.15
Boric Acid	0.35
Sodium Borate	0.11
Sodium Chloride	0.7
Sodium Chlorite	0.006
Sodium Hydroxide/Hydrochloric Acid	pH adjust to 7.0
Purified Water	QS

EXAMPLE 2

Experiments were performed to examine the rheology of EO-BO and guar compositions of the present invention. These experiments included bulk rheology experiments including steady state flow, and frequency and stress sweeps. Extensional and interfacial rheology characterization was also performed.

Bulk rheology experiments were conducted using a controlled stress rheometer (AR 2000ex, TA Instruments, Inc.). The measurement system was a 40mm acrylic 2° cone and plate with a sample volume of 0.58mL. A temperature of 25°C +/- 0.1°C was maintained and a cover was placed over the measurement system to prevent evaporation of the solutions. For steady state flow (SSF) experiments, the instrument applies a controlled stress which in turn gives the result as viscosity vs. shear rate. Two dynamic tests were conducted: oscillation stress sweep and oscillation frequency sweep. The oscillation stress sweep holds the frequency of the solution constant while measuring a range of stresses. The oscillation stress sweep measures G' (elastic/storage modulus) and G" (viscous, loss modulus). From this information the linear viscoelastic region (LVR) can be determined. The LVR is a region in the stress sweep, obtained from G', where the solution holds its elasticity, G', over a range of stresses. A measure of relative elasticity, $\tan(\delta)=G"/G'$, is obtained from these experiments. The oscillation frequency sweep holds the stress constant within the LVR while measuring a range of frequencies. This measurement

can determine G', G" and tan(δ) as well. The oscillation frequency sweep shows how well a solution maintains its structure.

Interfacial rheology experiments were conducted using an optical oscillating drop generator device (OCA20, Dataphysics Instruments) equipped with a piezoelectric device and amplifier that controlled the oscillations of the drop. The drop, suspended in a temperature and humidity controlled cell at the tip of a stainless steel needle of 1.65mm external diameter, was observed with a CCD camera (768 x576 pixels) at 500 images per second. The oscillating drop generator (ODG) technique characterizes the mechanical strength of the films formed by analyzing the drop shape at a set frequency over a range of amplitudes. The amplitude changes the volume and shape of the drop and therefore the surface area.

The controlled parameters for the steady state flow experiments are as follows:

- All solutions prior to experiment had the same rheological history
- 40mm 2° Acrylic Cone.
  - 0.75 mL volume
  - 60 μm gap
- Double Concentric Cylinder
  - 6.8 mL volume
  - 500 μm gap
- Temperature was set at 25°C
- Equilibration was set for 10 minutes after the geometry was set
  - Pre-Shear of 10 s-1 for 10 sec
- Torque was set from 0.1 μNm to 100 μNm
  - 0.1 μNm is the lowest limit
  - 100 μNm and beyond is not accounted for
- 5 points per decade; 5 min equilibrium at each point; triple measurements at 5% tolerance
- A 60 mm plate cover was placed over the geometry to prevent evaporation.

Oscillation parameters:

- Stress(Torque) Sweep
  - 0.1 dyne.cm to 100 dyne.cm is within the raw phase for all solutions tested
  - Frequency set at 0.1 Hz
- Frequency Sweep
  - 0.01 Hz to 10 Hz
  - Torque set at 100 dyne.cm
- Time Sweep
  - Pre shear of 100 s-1 for 10seconds
  - Frequency at 0.1 Hz and torque at 100 dyne.cm used

Extensional Parameters:

- Geometry

Plate Diameter	6.00 mm
Sample Initial Height	3.01 mm
Sample Final Height	13.32 mm
Sample Volume	80 µL
System Hencky Strain	1.49
Initial Aspect Ratio	1.00
Final Aspect Ratio	4.44

- Stretch Profile

Type	**Linear**
Effective Velocity	0.21 mm/s
Strike Time	50 ms
Strike Distance	10.31 mm

- Measurement Options

Method	**High Speed Digital Mode**
Sample Rate	10,000 Hz
Sample Duration	1.0 s

Note: For sample duration longer than 1.0sec, the sample rate was adjusted for optimal measurement.

The following is a description of the parameters and equipment used for the interfacial rheology experiment utilizing an oscillating bubble. The OCA 20 with the

oscillating drop generator was used for the oscillating bubble experiment. The following are the parameters used in the experiment for each composition:

Method	Pendant Drop Oscillating Volume
Needle	1.65mm
Bubble Equilibration Time	3.5 Hours
Iteration Step	20 (logarithmic)
Frequency	0.1 s-1
Amplitude	0.003mm-0.3mm
Duration per Step	40 sec
Images per Step	1000
Temperature	25˚C

Prior to each run the system was checked and standardized by confirming the surface tension of water at 72.5mN/m at 25˚C in air. A quartz cuvete was filled half full with purified water and placed below the drops while out of the view of the camera. This was to prevent water loss of the drop during equilibration and throughout the experiment. Before the each oscillating bubble experiment began, the bubbles equilibrated for a time of not less than 3.5 hours.

TABLES 1 and 2 below detail compositions tested in the EO-BO interfacial rheology and EO-BO/guar rheology experiments, respectively. All compositions of TABLE 2 also comprise 1.0% boric acid, 0.35% NaCl, and 0.001% polyquaternium-1, and have a pH of 7.5.

TABLE 1

Composition Chemical (% wt/% vol.)	12752-42A	12752-42B	12752-42C	12752-42D
$EO_{45}BO_{10}$	0.05	-	-	-
$EO_{45}BO_{12}$	-	0.05	-	-
$EO_{45}BO_{16}$	-	-	0.05	-
$EO_{45}BO_{18}$	-	-	-	0.05
pH	7.5	7.5	7.5	7.5
Purified Water (QS = 100mL)	QS	QS	QS	QS

TABLE 2

Composition Chemical (% wt/% vol.)	134346-31A	134346-31B	134346-31C	134346-31D	134346-31E	134346-31F	134346-31G	134346-31H	134346-31I	134346-31J	134346-31K
HP-Guar	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
$EO_{45}BO_9$	-	0.2	0.5	-	-	-	-	-	-	-	-
$EO_{45}BO_{11}$	-	-	-	0.2	0.5	-	-	-	-	-	-
$EO_{45}BO_{14}$	-	-	-	-	-	0.2	0.5	-	-	-	-
$EO_{45}BO_{16}$	-	-	-	-	-	-	-	0.2	0.5	-	-
$EO_{45}BO_{18}$	-	-	-	-	-	-	-	-	-	0.2	0.5
Break up Times (s)	0.131	0.247	0.323	0.361	0.342	0.118	0.146	0.140	0.180	0.104	0.138
Visc.(cPs) @ 10.0s-1	10.54	10.59	11.00	12.70	11.22	6.80	5.20	6.12	6.09	4.80	4.64

FIGURE 1 shows the amplitude sweep for the EO-BO compositions of TABLE 1. The graphs demonstrate that the elastic contribution at the air-water interface for these EO-BO compositions increases as the BO unit size increases from BO_{10} to BO_{18}.

FIGURES 2a-2e show steady state slow curves for EO-BO and HP-Guar compositions of TABLE 2. The graphs show that shear thinning is reduced as the EO-BO block copolymer concentration increases. $EO_{45}BO_{9-11}$ compositions have similar viscosity profiles compared to the composition containing only HP-guar. $EO_{45}BO_{14-18}$ compositions have shear thinning profiles which are similar that of the composition containing only HP-guar; however, their viscosities are lower than the composition containing only HP-guar.

FIGURES 3a-3e show stress sweep curves for EO-BO and HP-Guar compositions of TABLE 2. The curves demonstrate that all compositions tested are viscous (G") dominant solutions with elasticity (G', structure). $EO_{45}BO_{9-11}$ compositions have a similar structure to the composition containing only HP-guar, with similar linear viscoelastic regions. $EO_{45}BO_{14-18}$ compositions have some structure, but have linear viscoelastic regions that drop off rapidly as the shear rate increases.

FIGURES 4a-4e show frequency sweep curves for EO-BO and HP-Guar compositions of TABLE 2. $EO_{45}BO_{9-11}$ compositions have a similar structure to the composition containing only HP-guar throughout the frequency sweep. $EO_{45}BO_{14-18}$ compositions have some structure, which drops off rapidly at higher frequency.

FIGURES 5a-5d show extensional rheology curves for the EO-BO and HP-guar compositions of TABLE 2. The curves demonstrate that $EO_{45}BO_{9-11}$ compositions have longer break up times than the composition containing only HP-guar. $EO_{45}BO_{14-18}$ compositions have similar break up times compared to the composition containing only HP-guar. $EO_{45}BO_{9-11}$ compositions also have higher extensional viscosities relative to the composition containing only HP-guar. $EO_{45}BO_{14-18}$ compositions have similar extensional viscosities relative to the composition containing only HP-guar. The effect of EO-BO compositions was seen in other galactomannans such as native guar. As shown in TABLE 3 below, EO-BO increased the break up times for compositions comprising both HP-guar and native guar.

TABLE 3

Sample	Concentration	pH	Break Up Time
A	0.2% HP8A/0.04% EOBO	7.5	0.09264
B	0.2% HP8A	7.5	0.09922
C	0.2% Native Guar/ 0.04% EOBO	7.5	0.10002
D	0.2% Native Guar/0.04% EOBO	7.5	0.08642
E	0.2% Native Guar/0.2% EOBO	7.5	0.09602
F	0.2% Native Guar	7.5	0.09042
A	0.2% HP8A/0.04% EOBO	8.0	0.21142
B	0.2% HP8A	8.0	0.27863
C	0.2% Native Guar/ 0.04% EOBO	8.0	0.32863
D	0.2% Native Guar/0.04% EOBO	8.0	1.39927
E	0.2% Native Guar/0.2% EOBO	8.0	2.12335
F	0.2% Native Guar	8.0	1.67517

FIGURES 6a-6b show amplitude sweep and frequency sweep curves for EO-BO and HP-guar compositions of TABLE 2. For the amplitude and frequency sweeps, both $EO_{45}BO_{11}$ and $EO_{45}BO_{16}$ compositions are elastic dominant at the air-water interface. However, $EO_{45}BO_{16}$ has more structure relative to $EO_{45}BO_{11}$. EO-

BO dominates the structure at the air-water interface at the tested concentrations compared to guar.

The above rheology characterizations demonstrate the compositions of the present invention are well suited for ophthalmic applications and particularly topical ophthalmic applications. In particular, EO-BO and guar compositions may provide additional tear film stability when used in dry eye compositions.

EXAMPLE 3

Compositions of the present invention were tested for their ability to (i) prevent deposition of lipids and proteins on silicon hydrogel lenses and (ii) to clean lenses of lipid and protein deposits. TABLE 4 is a summary of the lenses tested, and TABLES 5 and 6 list compositions that were tested.

TABLE 4

Brand Name	Manufacturer
Acuvue® Advance™	Vistakon®
PureVision™	Bausch and Lomb®
Focus Night&Day™	Ciba Vision®
Biofinity®	Cooper Vision

TABLE 5

Composition Chemical (% wt/vol.)	14336-11A	14336-11B	14336-11C
Polyquaternium-1	0.001	0.001	0.001
N[3-dimethylamino propyl] tetra decanamide	0.0006	0.0006	0.0006
$EO_{45}BO_{11}$	-	-	0.04
Tetronic 1304	-	0.04	0.04
Sorbitol	1.2	1.2	1.2
Boric Acid	0.6	0.6	0.6
Sodium Citrate	0.65	0.65	0.65
Sodium Chloride	0.1	0.1	0.1
EDTA	0.05	0.05	0.05
2-amino-2-methyl-1-propanol	0.42	0.42	0.42
Purified Water	QS	QS	QS
pH	7.8	7.8	7.8

TABLE 6

Composition Chemical (% wt/% vol)	13990-23A	13990-23B	13990-23C	13990-23D
Polyquaternium-1	0.001	0.001	0.001	0.001
N[3-dimethylamino propyl] tetra decanamide	0.0007	0.0008	0.0007	0.0008
$EO_{45}BO_9$	0.05	0.05	-	-
$EO_{45}BO_{11}$	-	-	0.05	0.05
Tetronic 1304	0.05	0.05	0.05	0.05
Sorbitol	1.2	1.2	1.2	1.2
Boric Acid	0.6	0.6	0.6	0.6
Sodium Citrate	0.65	0.65	0.65	0.65
Sodium Chloride	0.1	0.1	0.1	0.1
EDTA	0.05	0.05	0.05	0.05
2-amino-2-methyl-1-propanol	0.42	0.42	0.42	0.42
Purified Water	QS	QS	QS	QS
pH	7.8	7.8	7.8	7.8

The bar charts of FIGURES 7a and 7b summarize experiments examining the ability of EO-BO compositions of the present invention to prevent the uptake of a polar lipid (FITC-DHPE, FIGURE 7a) and a non-polar lipid (NBD-cholesterol, FIGURE 7b) by the silicon hydrogel lenses of TABLE 4. The results illustrate that the compositions (Lot 13990-23A and 23C, TABLE 6) are particularly effective at preventing the uptake of the non-polar lipid by all lenses tested.

FIGURE 8 shows a bar chart showing the amount remaining of a non-polar lipid (NBD-cholesterol) on the lenses of TABLE 4 after cleaning with various test compositions. The chart illustrates that a composition of the present invention (14336-11C, TABLE 5) tested removes non-polar lipid deposits from silicone hydrogel contact lenses better than the other tested compositions in 3 out of 4 lenses.

FIGURES 9a – 9d demonstrate that a composition of the present invention (14336-11C, TABLE 5) is effective at cleaning various proteins (lysozyme, lactoferrin, beta-lactoglobulin) from the tested lenses of TABLE 4.

In summary, the results of the experiments demonstrate that compositions of the present invention are effective lens cleaners and can prevent the uptake of non-polar lipids. The compositions are also particularly effective at removing non-polar lipid deposits from lenses.

The present invention and its embodiments have been described in detail. However, the scope of the present invention is not intended to be limited to the particular embodiments of any process, manufacture, composition of matter, compounds, means, methods, and/or steps described in the specification. Various modifications, substitutions, and variations can be made to the disclosed material without departing from the spirit and/or essential characteristics of the present invention. Accordingly, one of ordinary skill in the art will readily appreciate from the disclosure that later modifications, substitutions, and/or variations performing substantially the same function or achieving substantially the same result as embodiments described herein may be utilized according to such related embodiments of the present invention. Thus, the following claims are intended to encompass within their scope modifications, substitutions, and variations to processes, manufactures, compositions of matter, compounds, means, methods, and/or steps disclosed herein.

CLAIMS

What is claimed is:

1. A sterile, aqueous ophthalmic composition comprising an ethyleneoxide butyleneoxide (EO-BO) block copolymer of the formula $(EO)_m(BO)_n$ and a galactomannan.

2. A composition according to claim 1 wherein m has an average value of 45 and n has an average value of 9 to 18.

3. A composition according to claim 1 wherein m has an average value of 45 and n has an average value of 9 to 11.

4. A composition according to claim 1 wherein said galactomannan is guar or a derivative thereof.

5. A composition according to claim 4 wherein said guar or guar derivative is selected from the group consisting of:
native guar, hydroxypropyl guar, and hydroxypropyl guar galactomannan.

6. A composition according to claim 1 wherein said EO-BO block copolymer is present at a concentration of 0.001 to 1.0% w/v.

7. A composition according to claim 1 wherein said EO-BO block copolymer is present at a concentration of 0.01 to 0.1% w/v.

8. A composition according to claim 1 wherein said galactomannan is present at a concentration of 0.01 to 2.0% w/v.

9. A composition according to claim 1 wherein said galactomannan is present at a concentration of 0.05 to 0.25% w/v.

10. A method for treating dry eye comprising administering a topical ophthalmic composition, said composition comprising an ethyleneoxide butyleneoxide (EO-BO) block copolymer of the formula $(EO)_m(BO)_n$ and a galactomannan.

11. A method according to claim 10 wherein m has an average value of 45 and n has an average value of 9 to 18.

12. A method according to claim 10 wherein m has an average value of 45 and n has an average value of 9 to 11.

13. A method according to claim 10 wherein said galactomannan is guar or a derivative thereof.

14. A method according to claim 13 wherein said guar or guar derivative is selected from the group consisting of:
native guar, hydroxypropyl guar, and hydroxypropyl guar galactomannan.

15. A method according to claim 10 wherein said EO-BO block copolymer is present at a concentration of 0.001 to 1.0% w/v.

16. A method according to claim 10 wherein said EO-BO block copolymer is present at a concentration of 0.01 to 0.1% w/v.

17. A method according to claim 10 wherein said galactomannan is present at a concentration of 0.01 to 2.0% w/v.

18. A method according to claim 10 wherein said galactomannan is present at a concentration of 0.05 to 0.25% w/v.

19. A method of disinfecting a contact lens which comprises immersing the lens in an antimicrobial composition comprising an ethyleneoxide butyleneoxide block copolymer of the formula $(EO)_m(BO)_n$ and a galactomannan for a time sufficient to disinfect the lens.

20. A method of delivering a pharmaceutical agent to the eye which comprises topically administering to the eye a composition comprising one or more pharmaceutically active agent(s), an ethyleneoxide butyleneoxide block copolymer of the formula $(EO)_m(BO)_n$ and a galactomannan.

5

21. A composition according to claim 20, wherein the pharmaceutically active agent(s) is/are selected from the group consisting of: anti-glaucoma agents, anti-angiogenesis agents; anti-infective agents; anti-inflammatory agents; growth factors; immunosuppressant agents; and anti-allergic agents.

Fig. 1

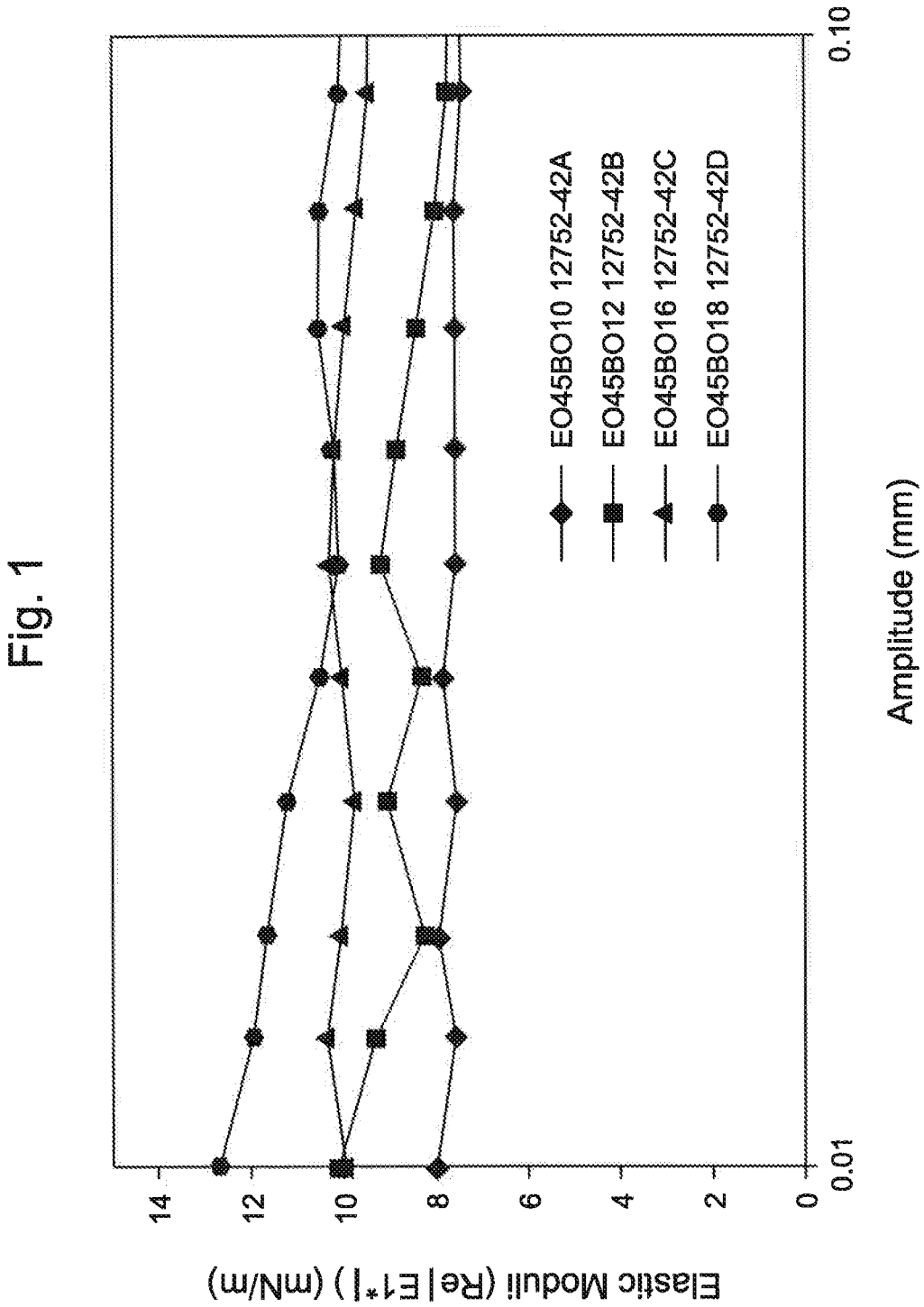

Elastic Moduli (Re|E1*|) (mN/m)
0
2
4
6
8
10
12
14
0.01
0.10
Amplitude (mm)
EO45BO10 12752-42A
EO45BO12 12752-42B
EO45BO16 12752-42C
EO45BO18 12752-42D

Fig. 2a

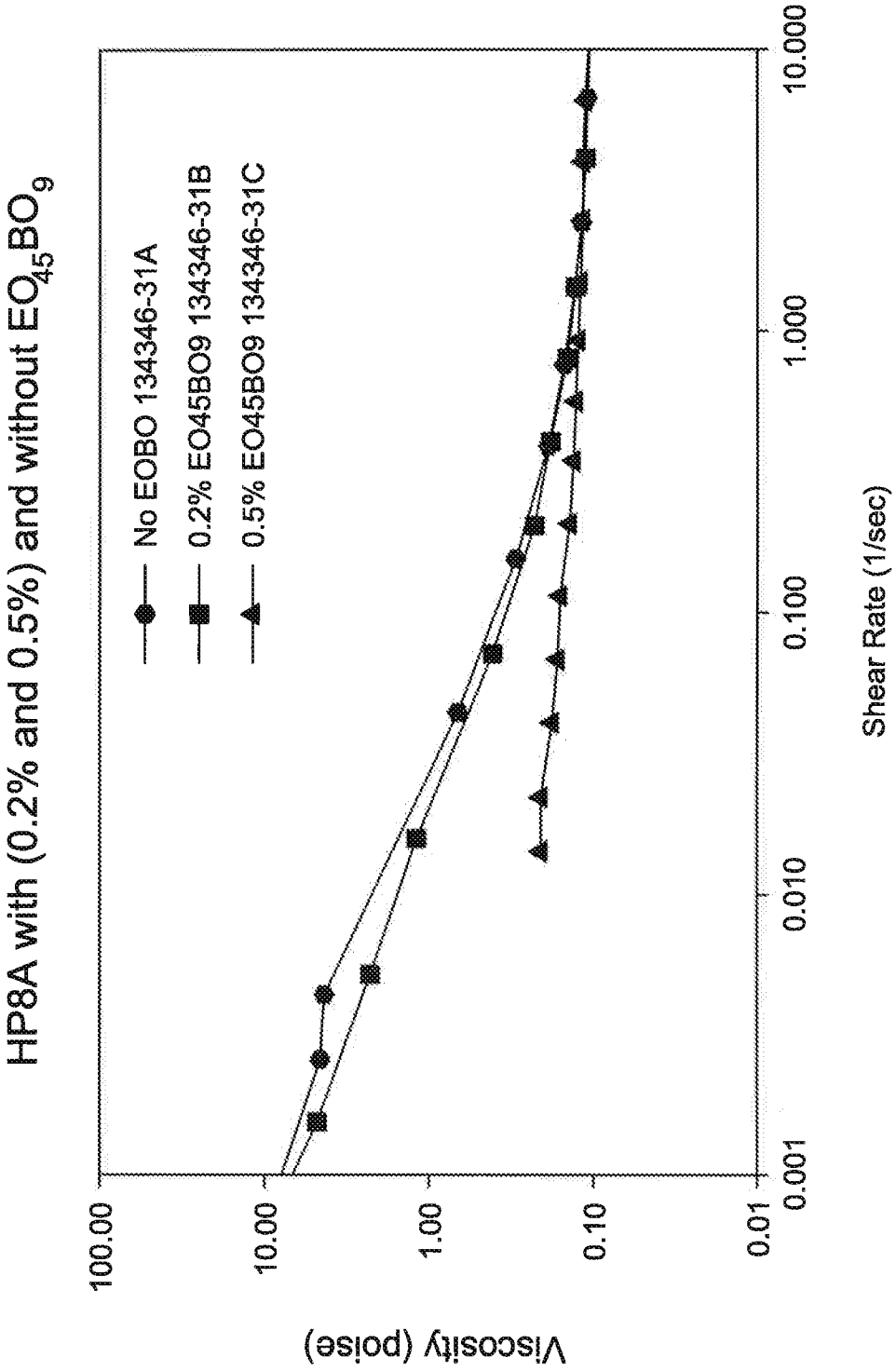

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_9$
No EOBO 134346-31A
0.2% EO45BO9 134346-31B
0.5% EO45BO9 134346-31C
Viscosity (poise)
100.00
10.00
1.00
0.10
0.01
0.001
0.010
0.100
1.000
10.000
Shear Rate (1/sec)

Fig. 2b

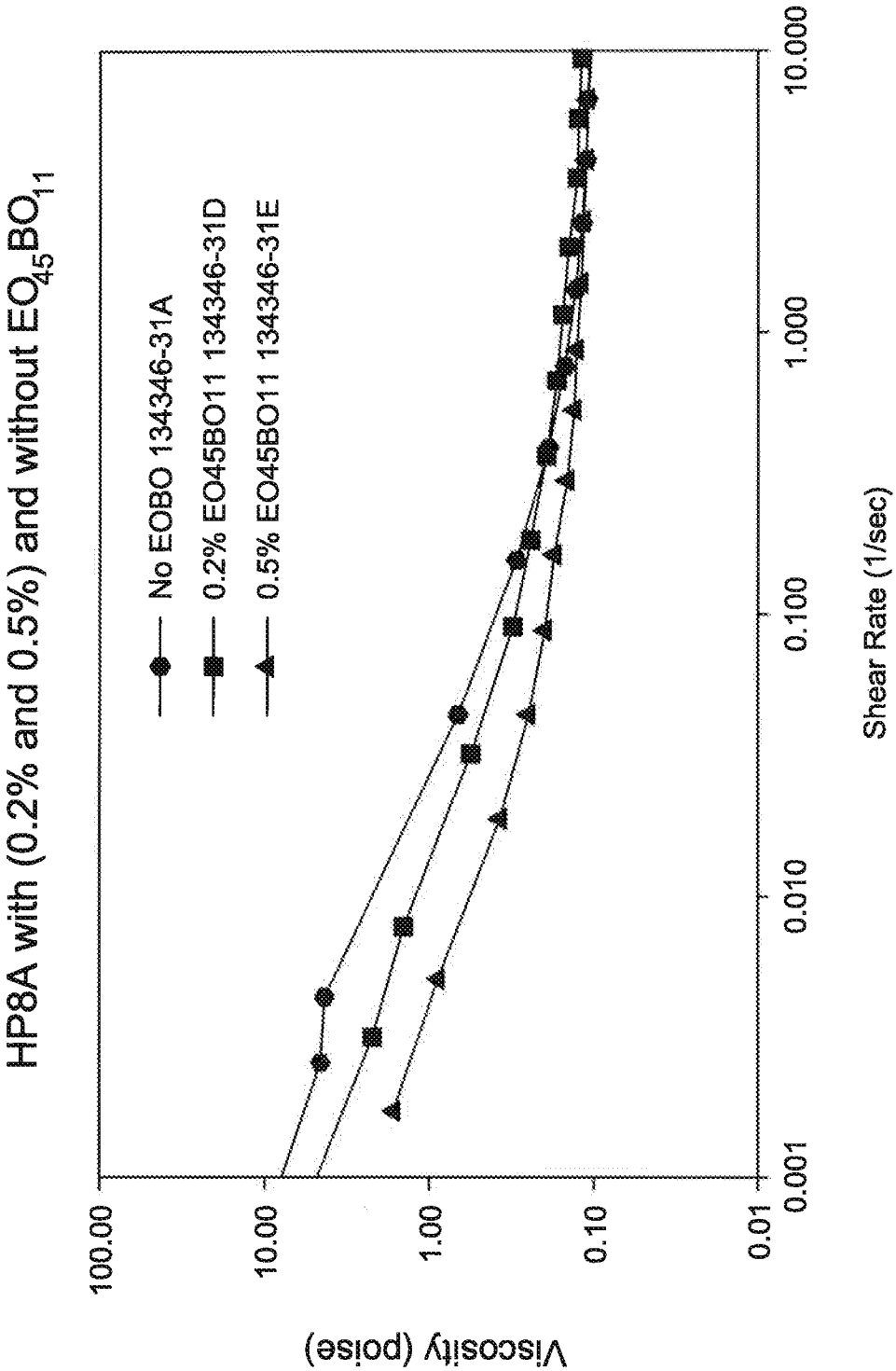

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{11}$
No EOBO 134346-31A
0.2% EO45BO11 134346-31D
0.5% EO45BO11 134346-31E
Viscosity (poise)
100.00
10.00
1.00
0.10
0.01
Shear Rate (1/sec)
0.001
0.010
0.100
1.000
10.000

Fig. 2c

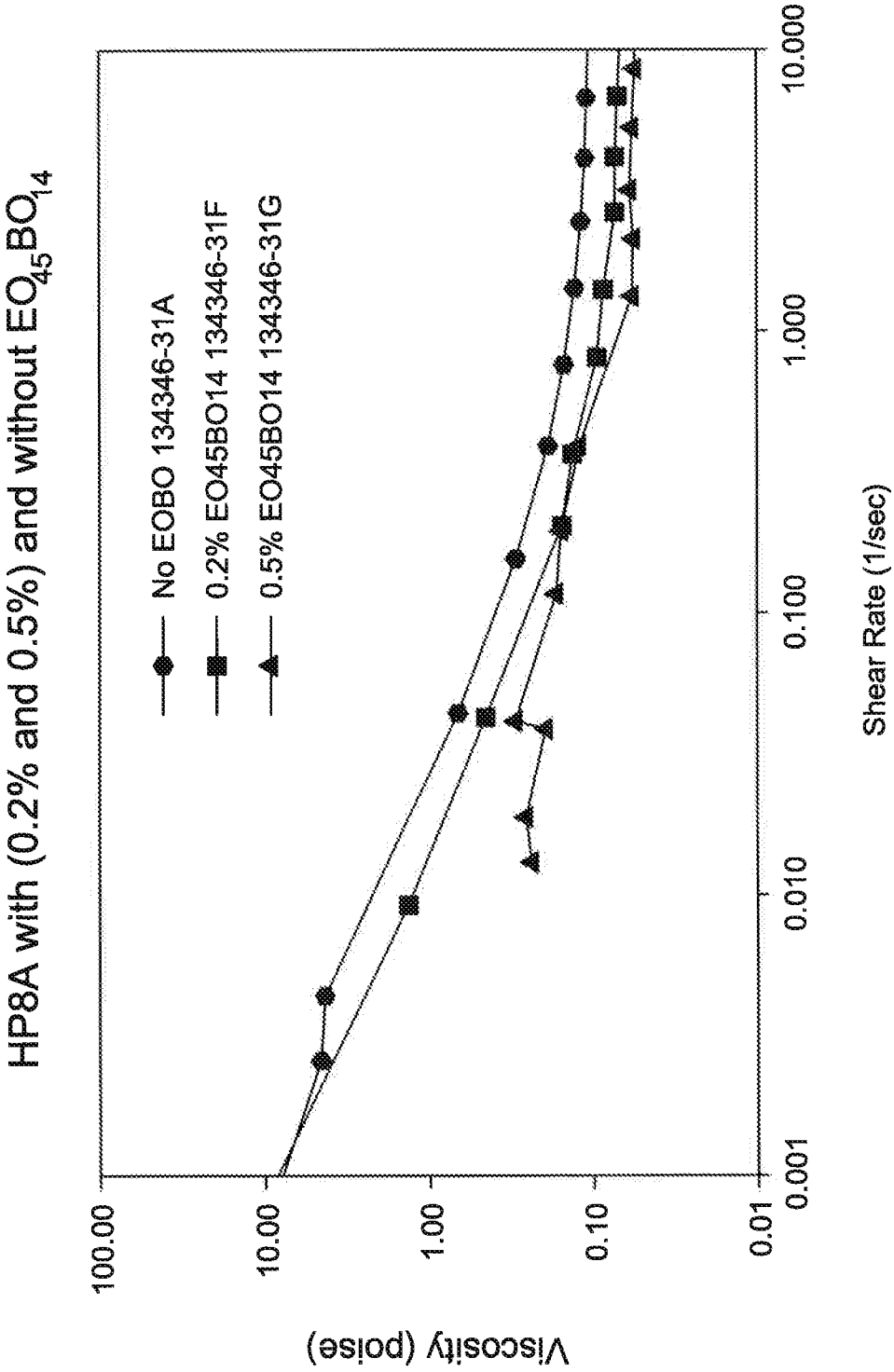

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{14}$
No EOBO 134346-31A
0.2% EO45BO14 134346-31F
0.5% EO45BO14 134346-31G
Viscosity (poise)
100.00
10.00
1.00
0.10
0.01
Shear Rate (1/sec)
0.001
0.010
0.100
1.000
10.000

Fig. 2d

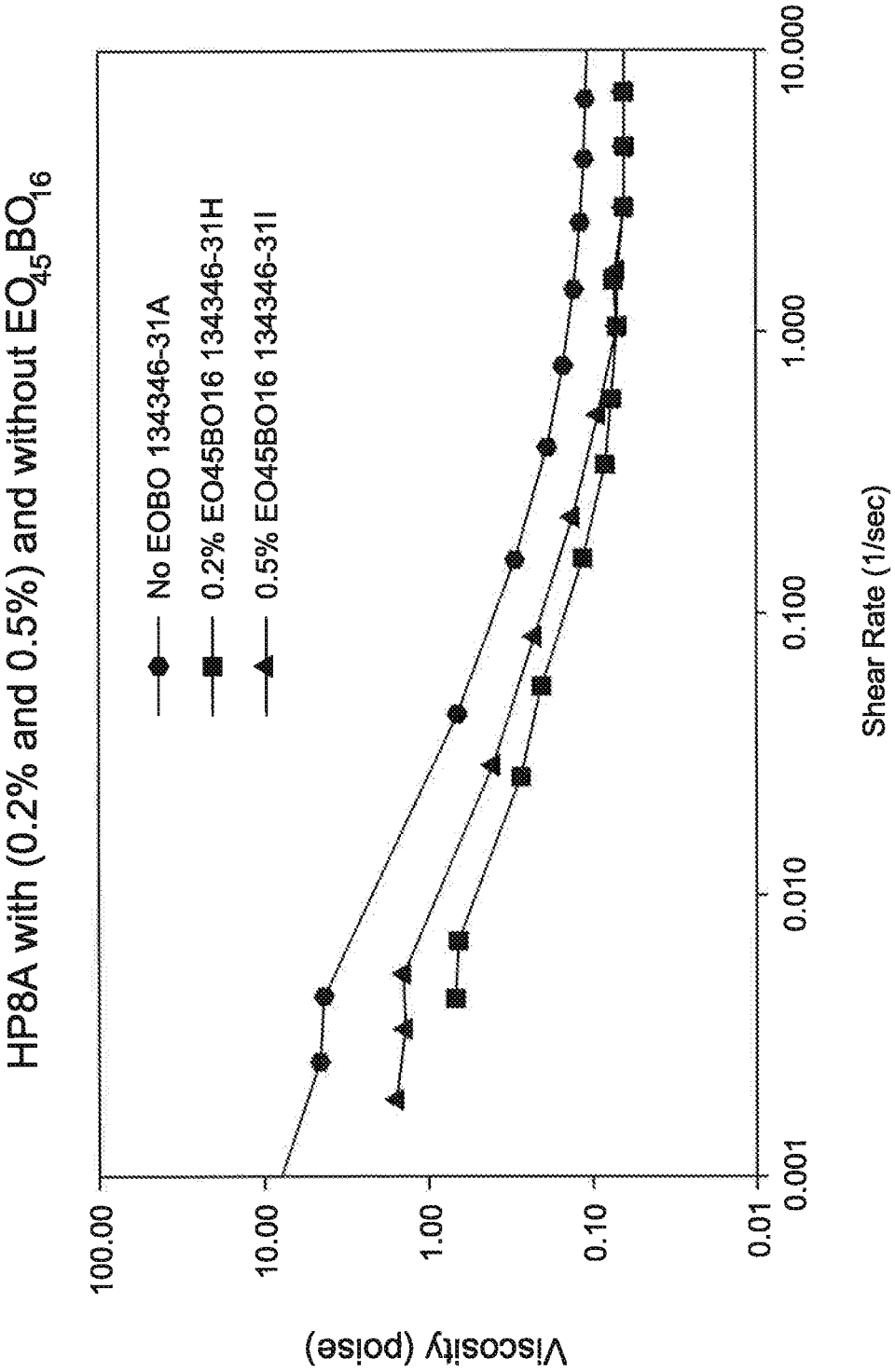

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{16}$
No EOBO 134346-31A
0.2% EO45BO16 134346-31H
0.5% EO45BO16 134346-31I
Viscosity (poise)
100.00
10.00
1.00
0.10
0.01
Shear Rate (1/sec)
0.001
0.010
0.100
1.000
10.000

Fig. 2e

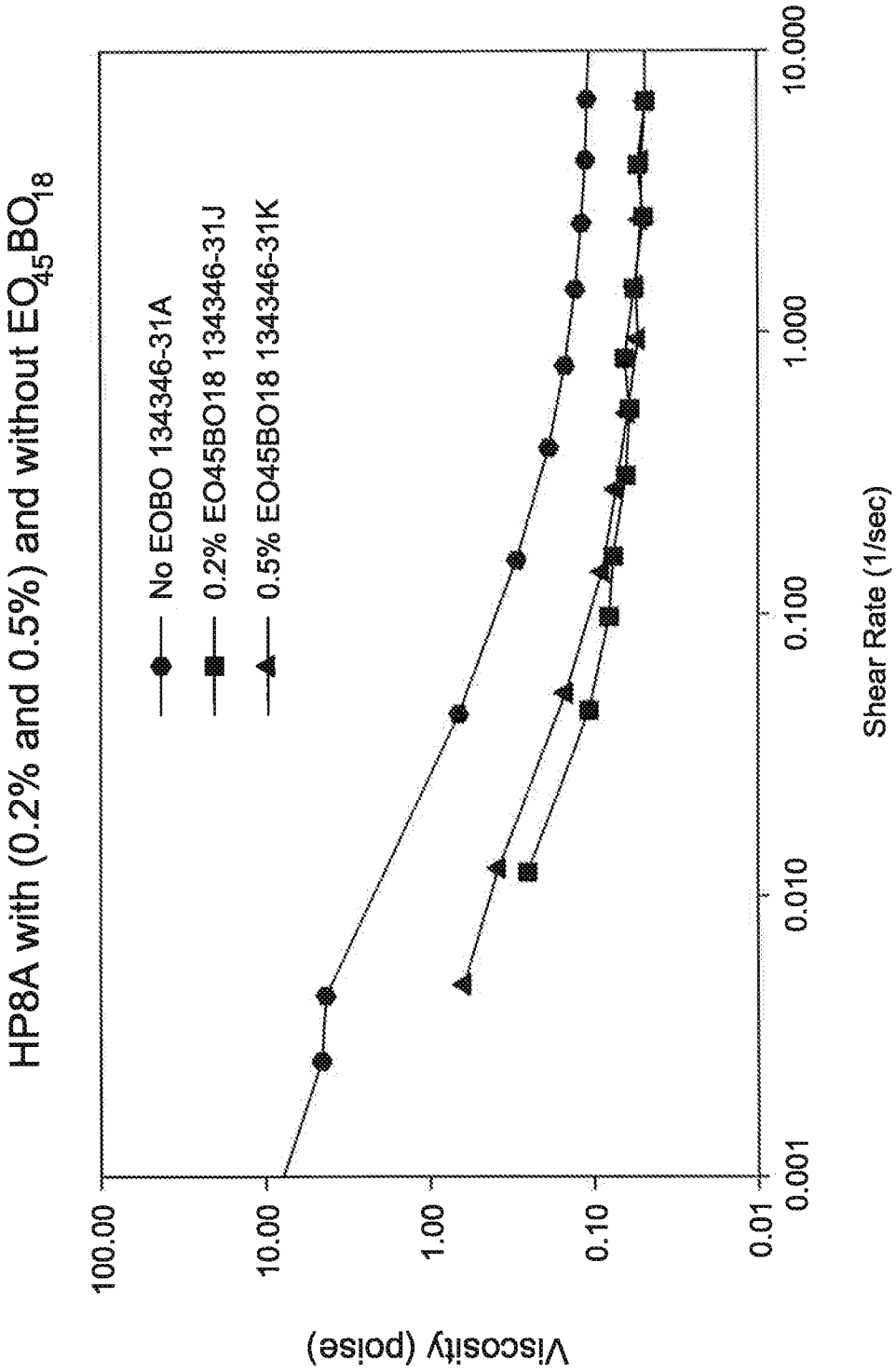

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{18}$
No EOBO 134346-31A
0.2% EO45BO18 134346-31J
0.5% EO45BO18 134346-31K
Viscosity (poise)
100.00
10.00
1.00
0.10
0.01
Shear Rate (1/sec)
0.001
0.010
0.100
1.000
10.000

Fig. 3a

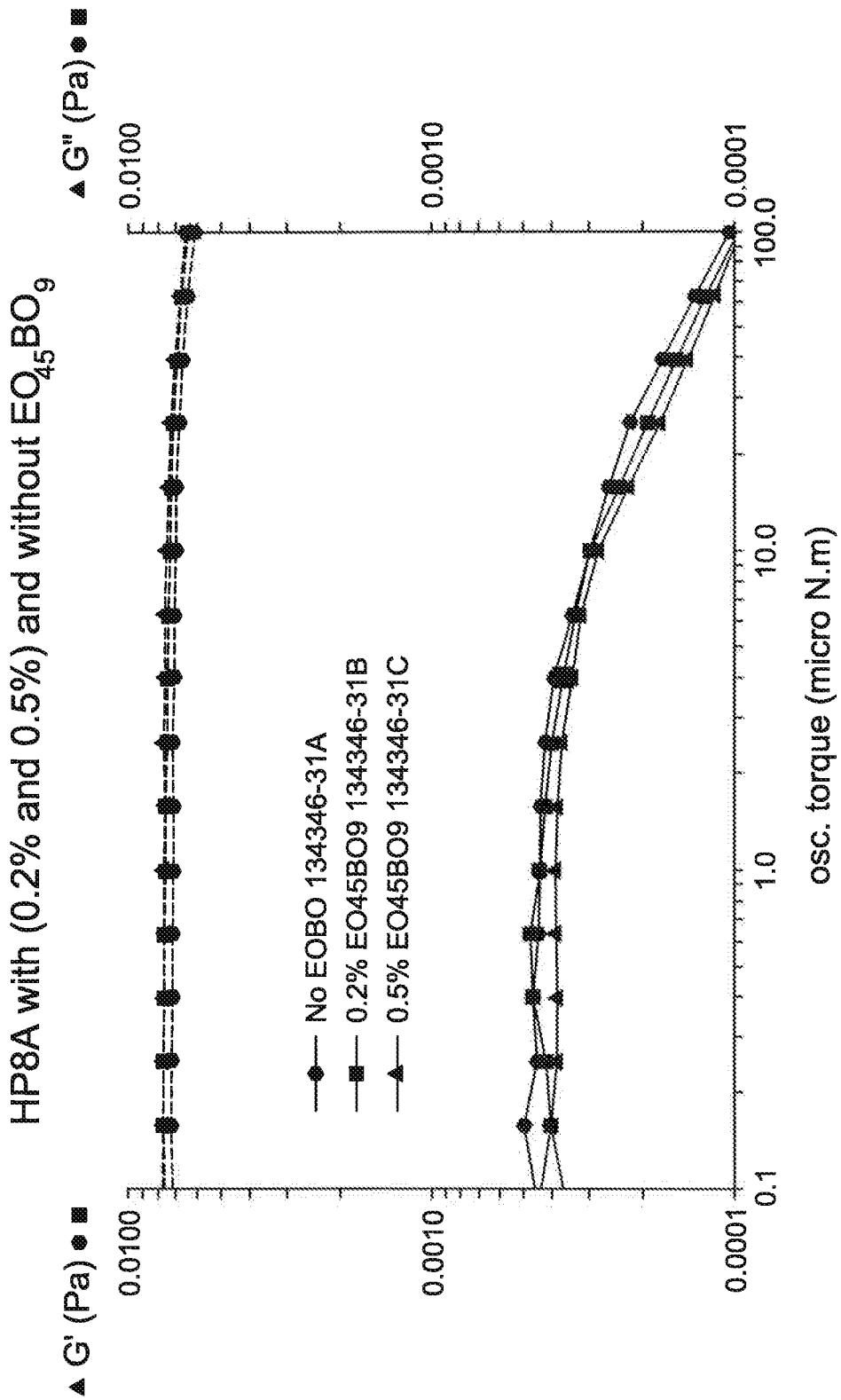

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_9$
▲ G' (Pa) ● ■
▲ G" (Pa) ● ■
0.0100
0.0010
0.0001
100.0
10.0
1.0
0.1
osc. torque (micro N.m)
No EOBO 134346-31A
0.2% EO45BO9 134346-31B
0.5% EO45BO9 134346-31C

Fig. 3b

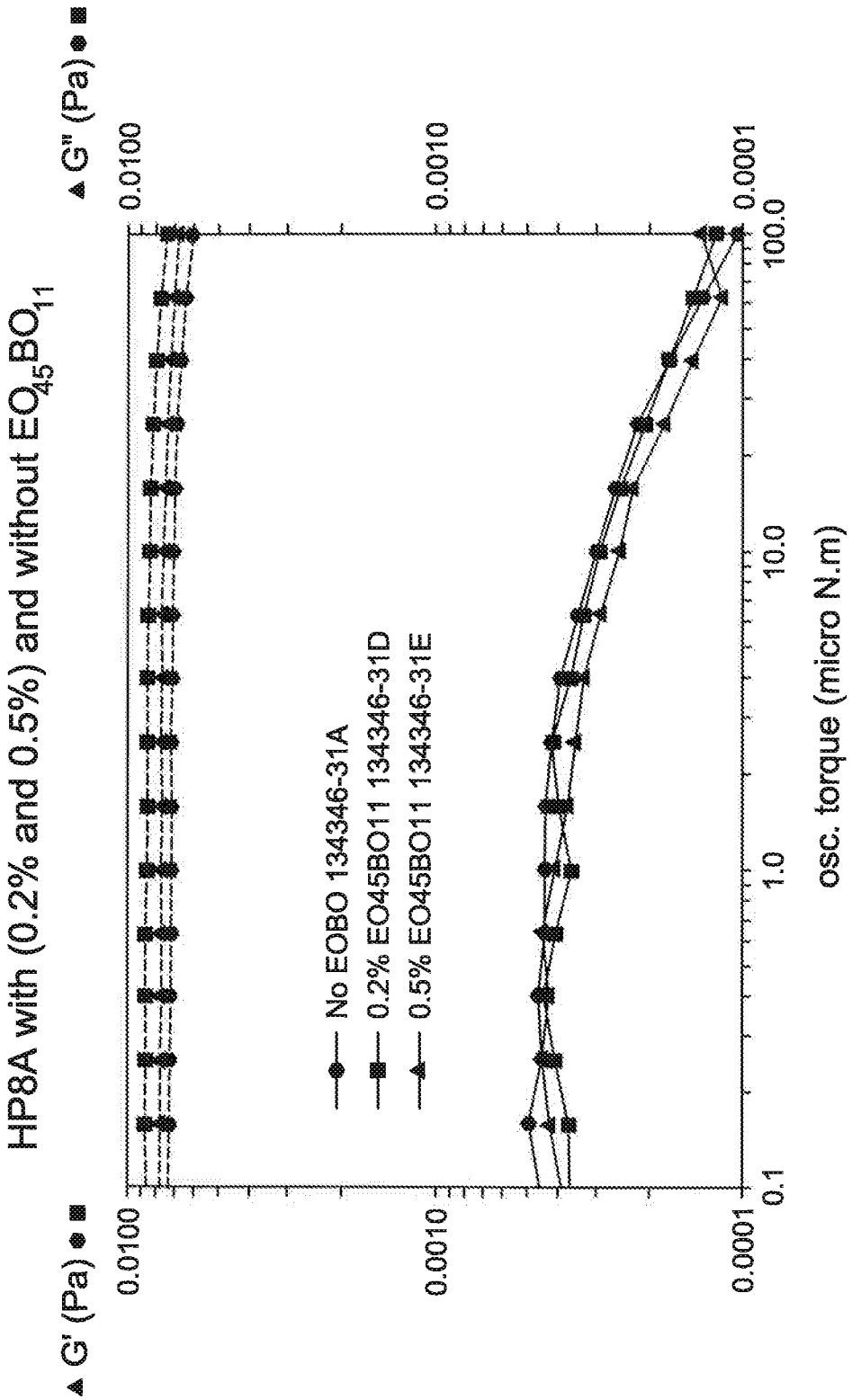

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{11}$
▲ G' (Pa) ● ■
▲ G" (Pa) ● ■
0.0100
0.0010
0.0001
0.1
1.0
10.0
100.0
osc. torque (micro N.m)
No EOBO 134346-31A
0.2% EO45BO11 134346-31D
0.5% EO45BO11 134346-31E

Fig. 3c

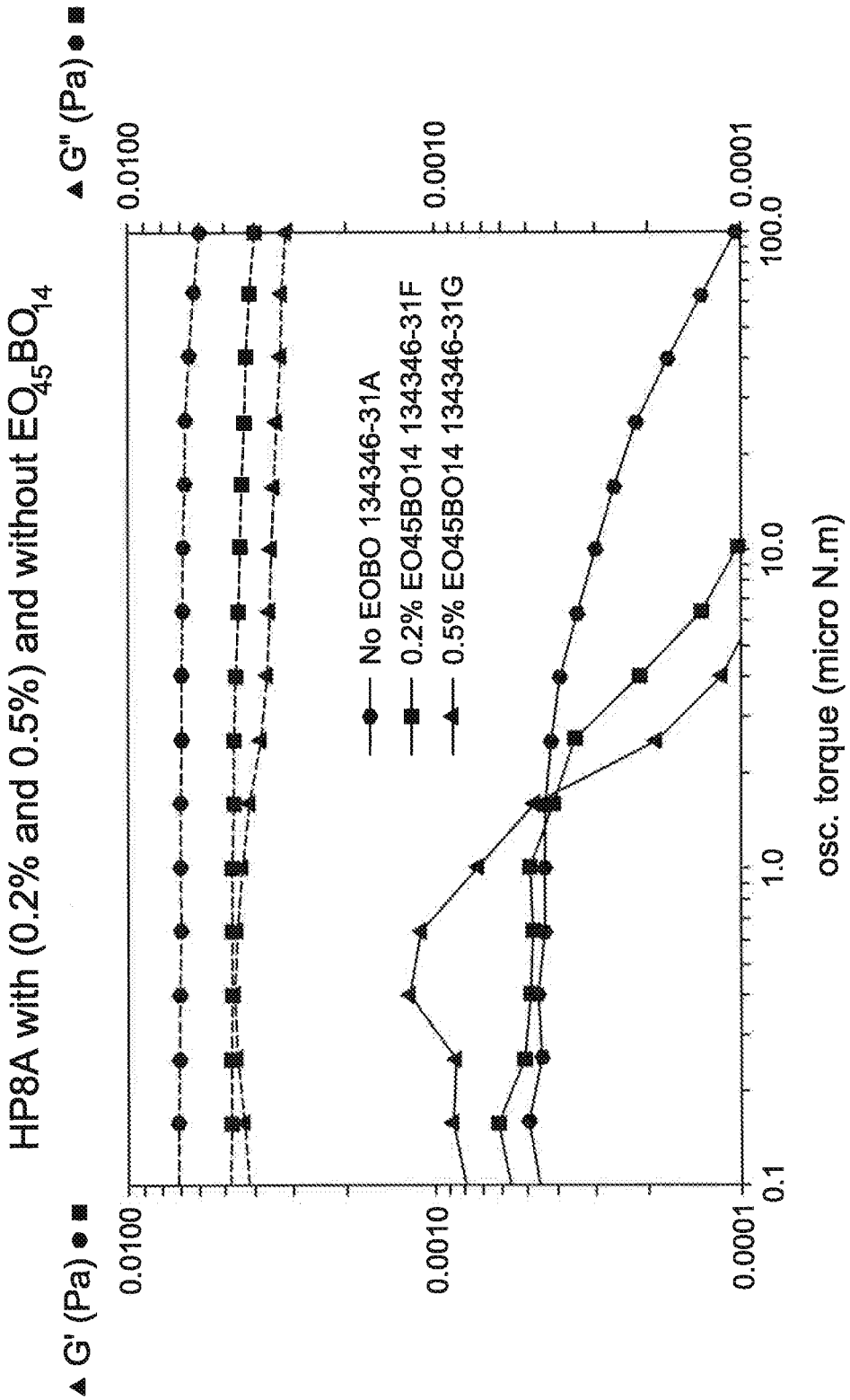

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{14}$
▲G' (Pa) ● ■
▲G" (Pa) ● ■
0.0100
0.0010
0.0001
0.1
1.0
10.0
100.0
osc. torque (micro N.m)
No EOBO 134346-31A
0.2% EO45BO14 134346-31F
0.5% EO45BO14 134346-31G

Fig. 3d

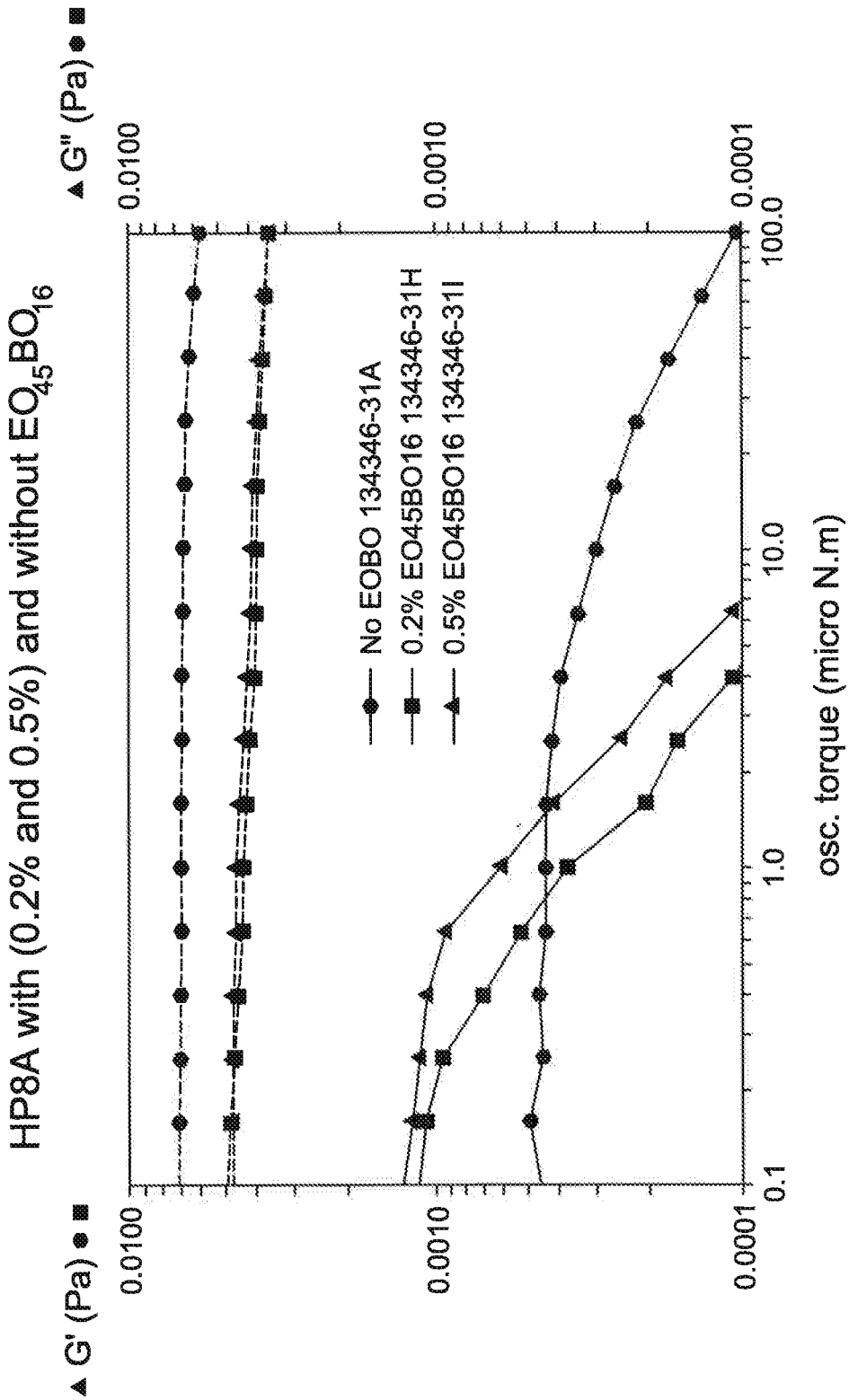

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{16}$
▲ G' (Pa) ● ■
▲ G" (Pa) ● ■
0.0100
0.0010
0.0001
0.0100
0.0010
0.0001
No EOBO 134346-31A
0.2% EO45BO16 134346-31H
0.5% EO45BO16 134346-31I
0.1
1.0
10.0
100.0
osc. torque (micro N.m)

Fig. 3e

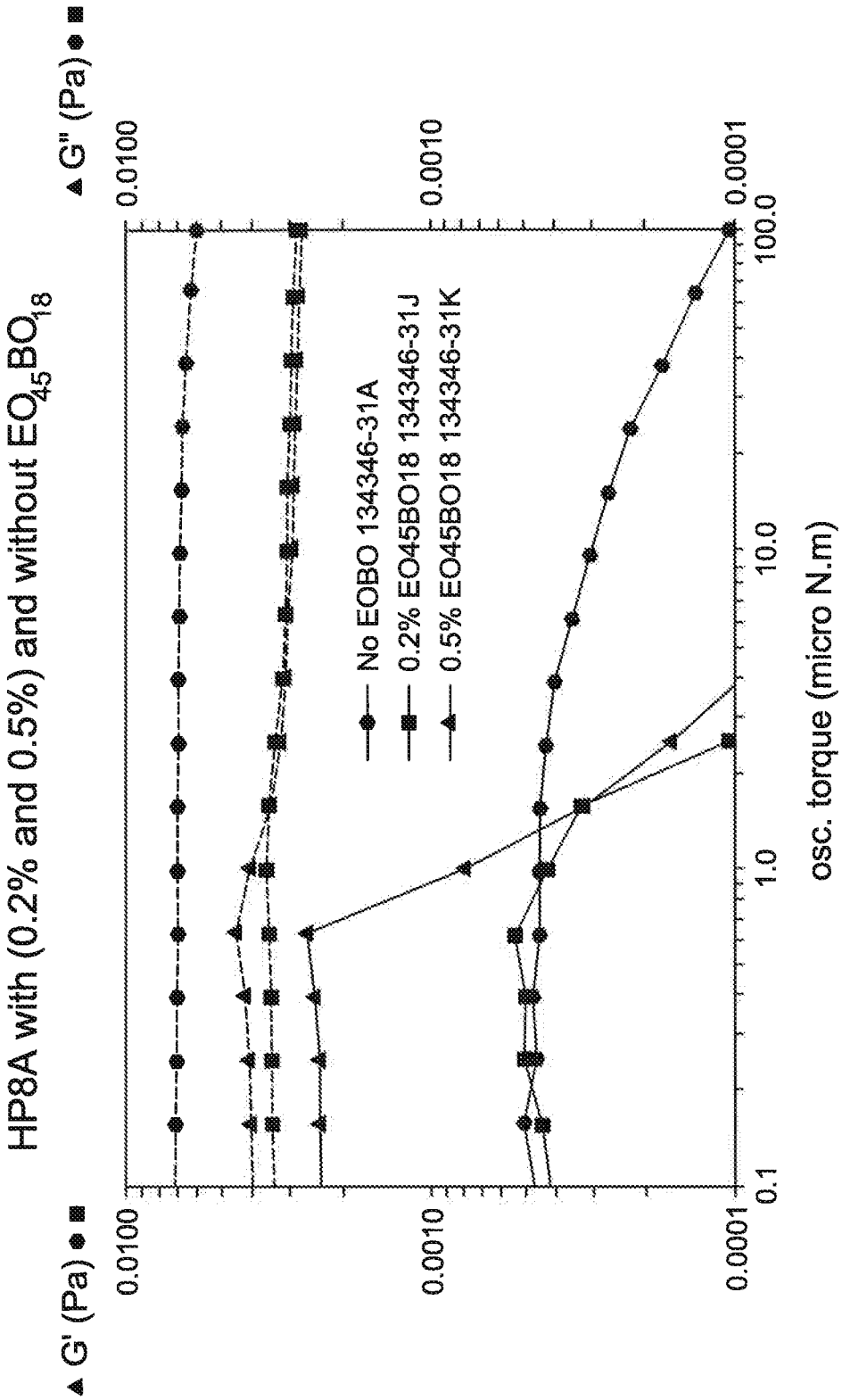

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{18}$
▲ G' (Pa) ● ■
▲ G" (Pa) ● ■
0.0100
0.0010
0.0001
0.0100
0.0010
0.0001
0.1
1.0
10.0
100.0
osc. torque (micro N.m)
No EOBO 134346-31A
0.2% EO45BO18 134346-31J
0.5% EO45BO18 134346-31K

Fig. 4a

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_9$

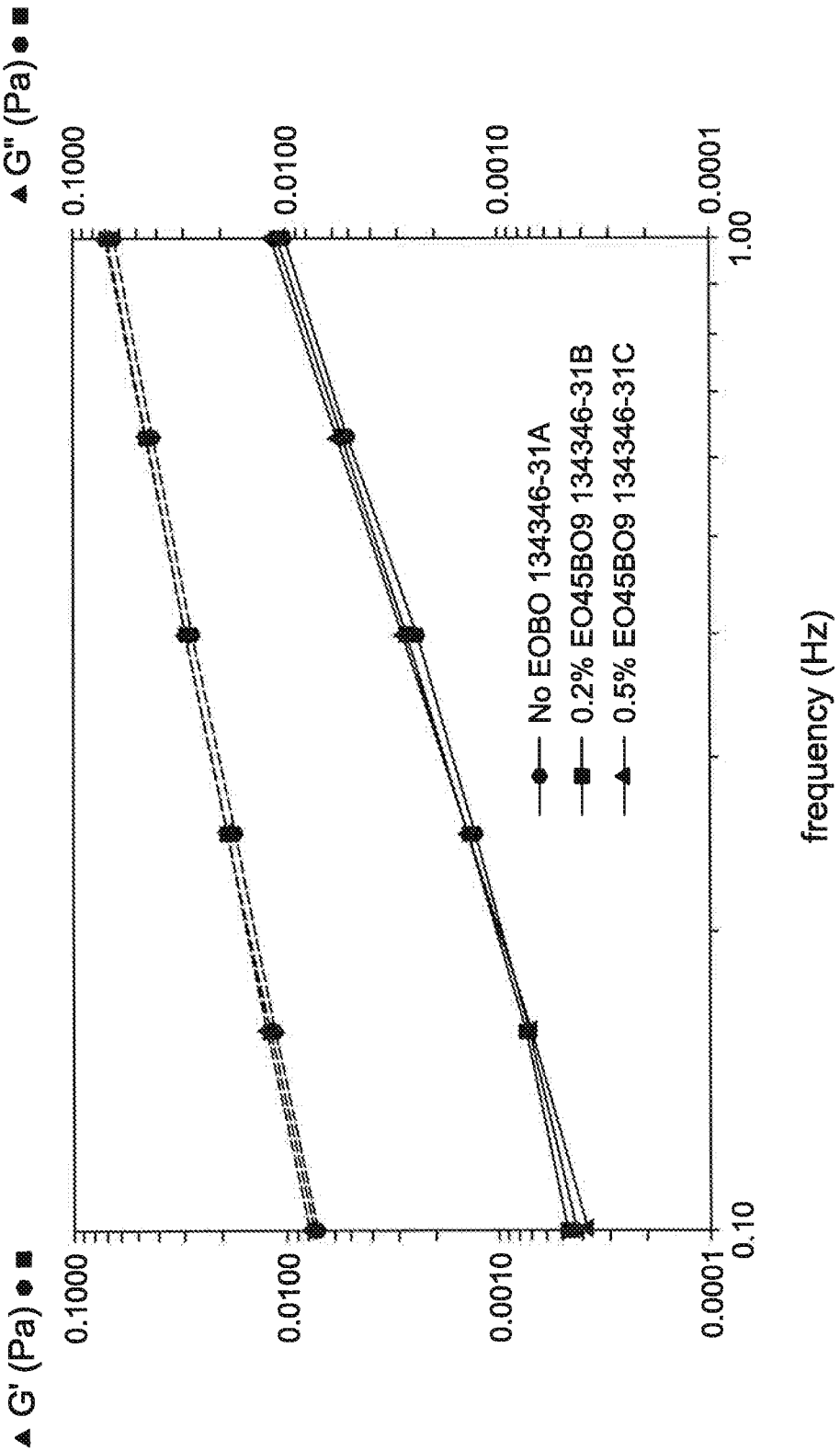


Fig. 4b

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{11}$

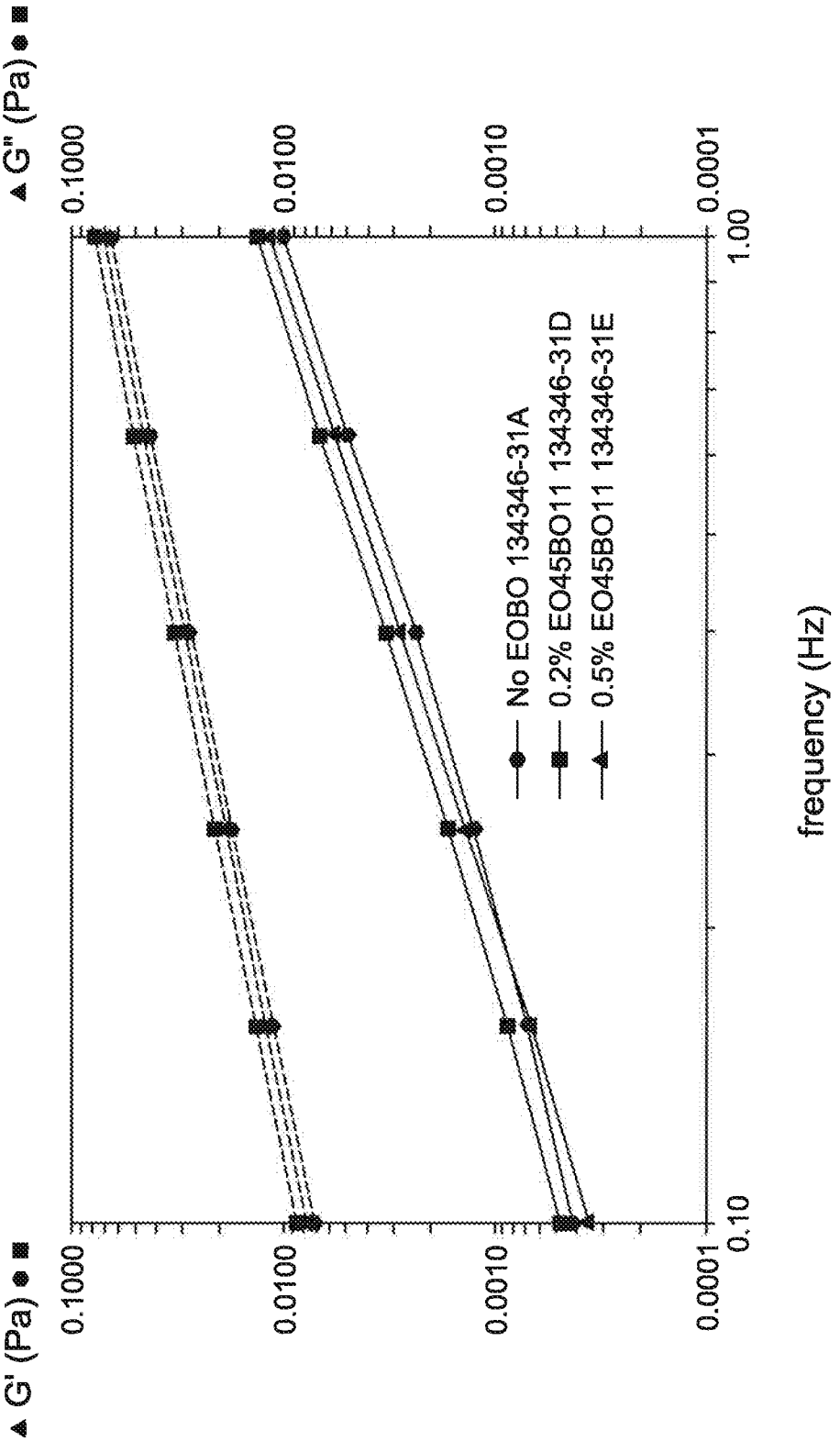


Fig. 4c

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{14}$

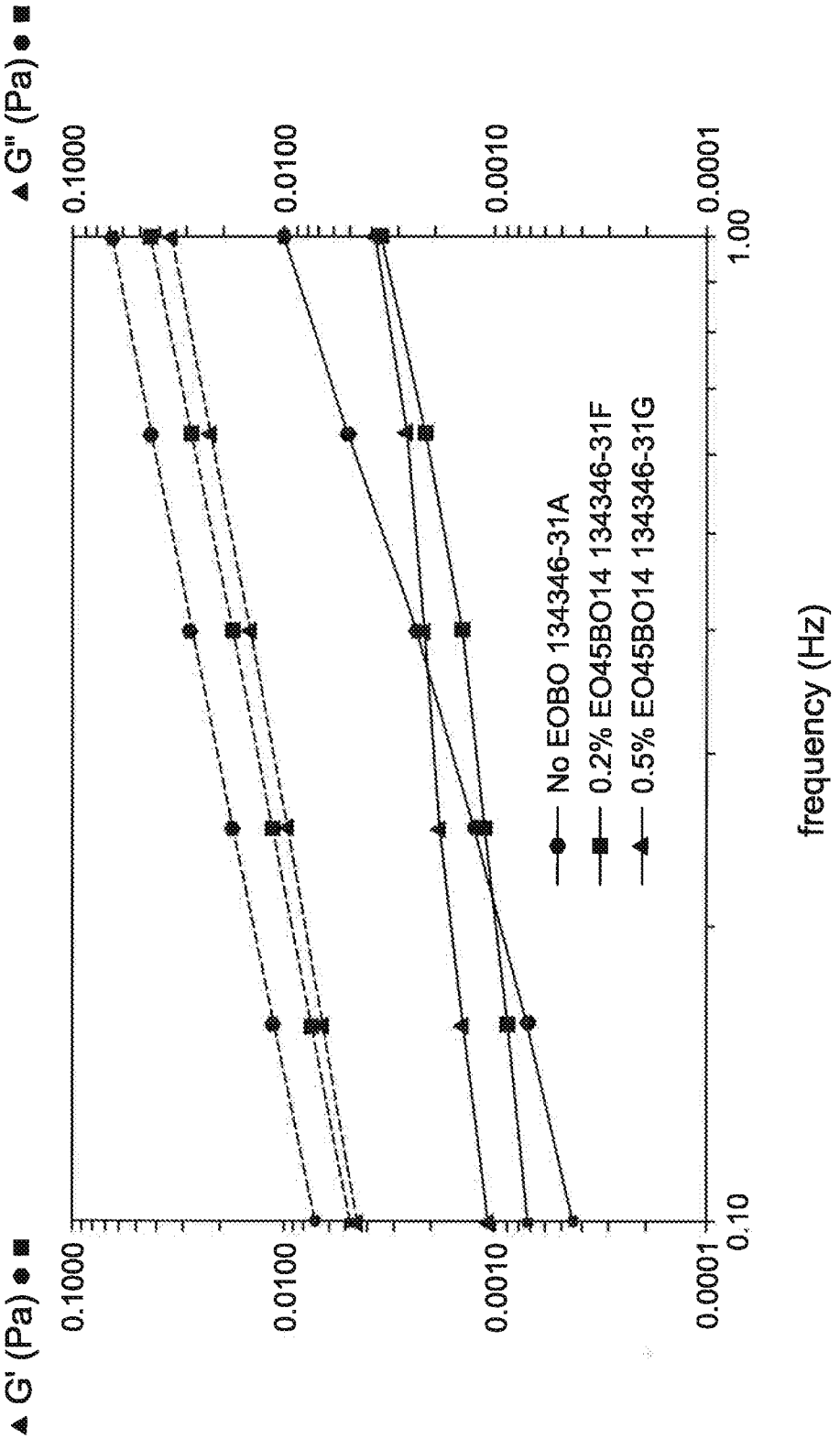


Fig. 4d

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{16}$

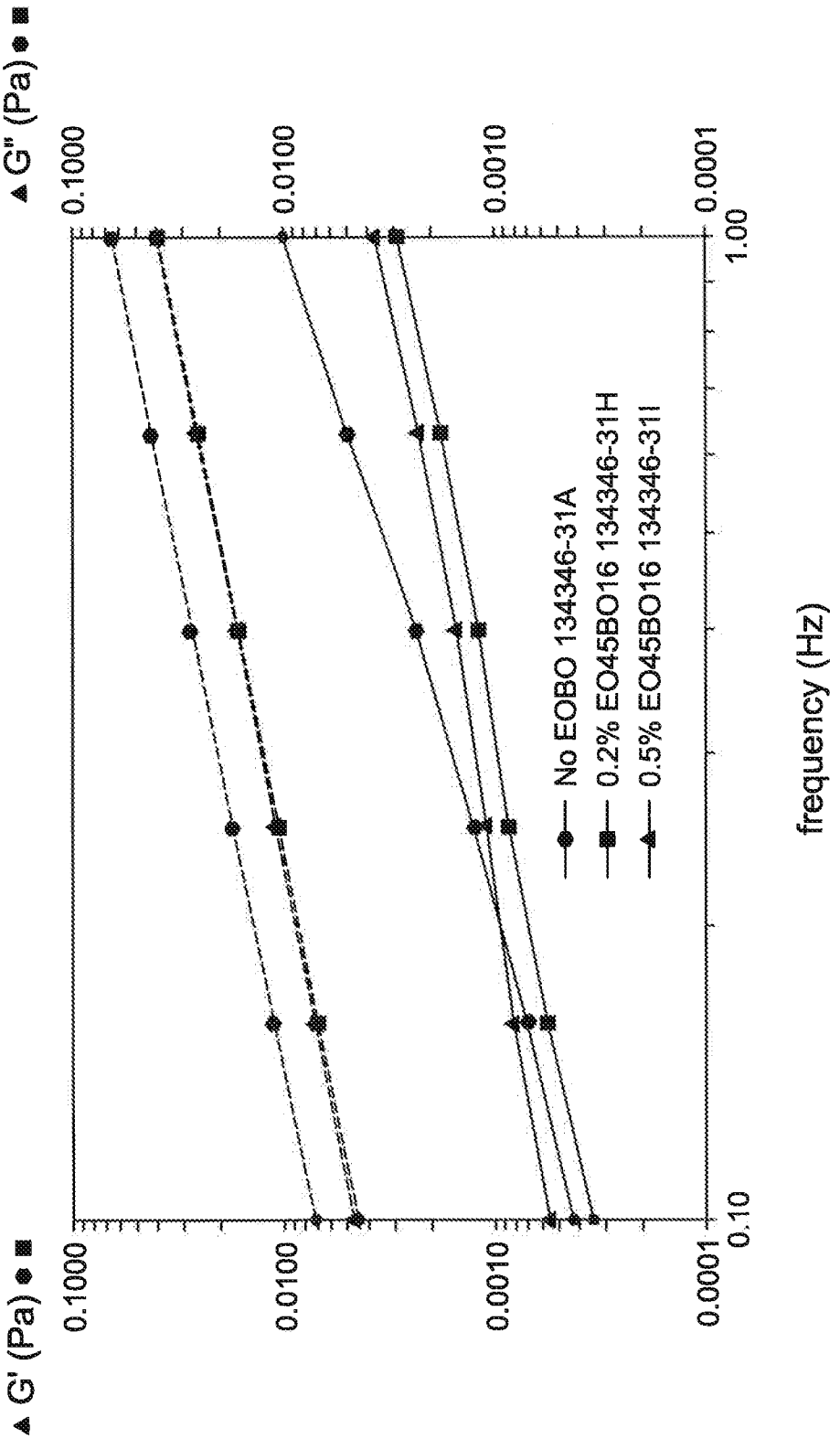


Fig. 4e

HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{18}$

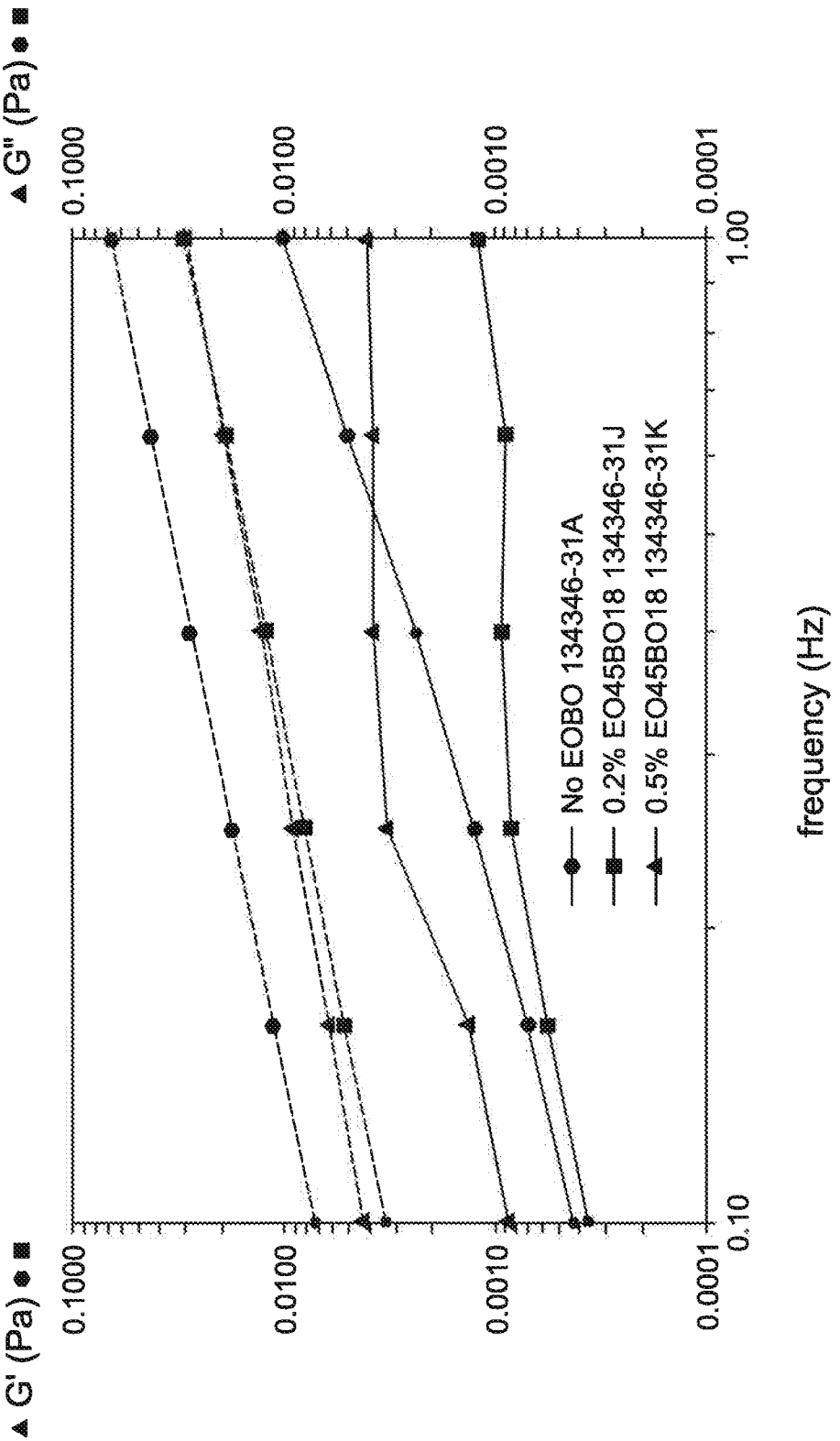


Fig. 5a

Break Up Time for HP8A with (0.2% and 0.5%) and without $EO_{45}BO_9$ and $EO_{45}BO_{11}$

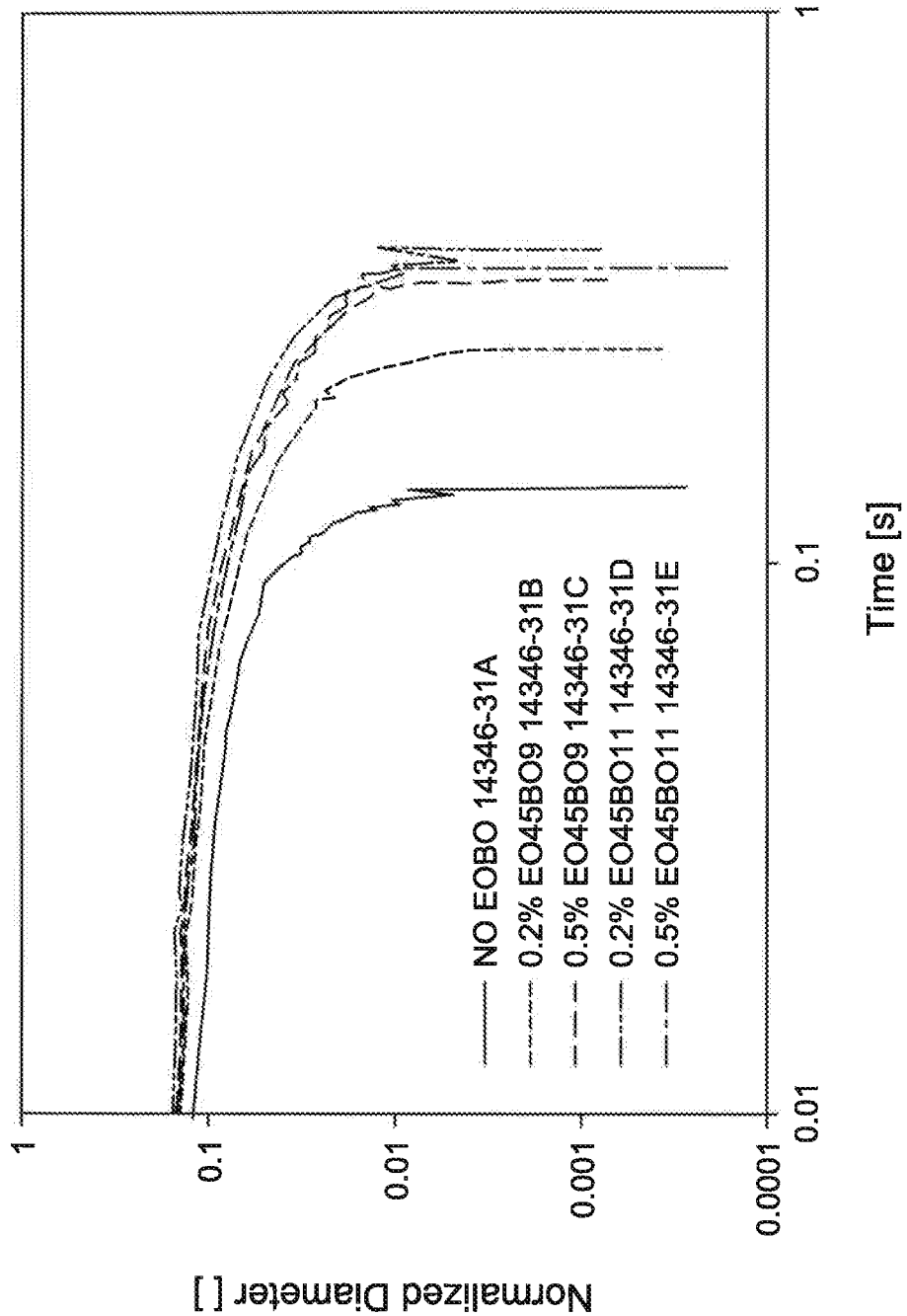


Fig. 5b

Extensional Viscosity for HP8A with (0.2% and 0.5%) and without $EO_{45}BO_9$ and $EO_{45}BO_{11}$

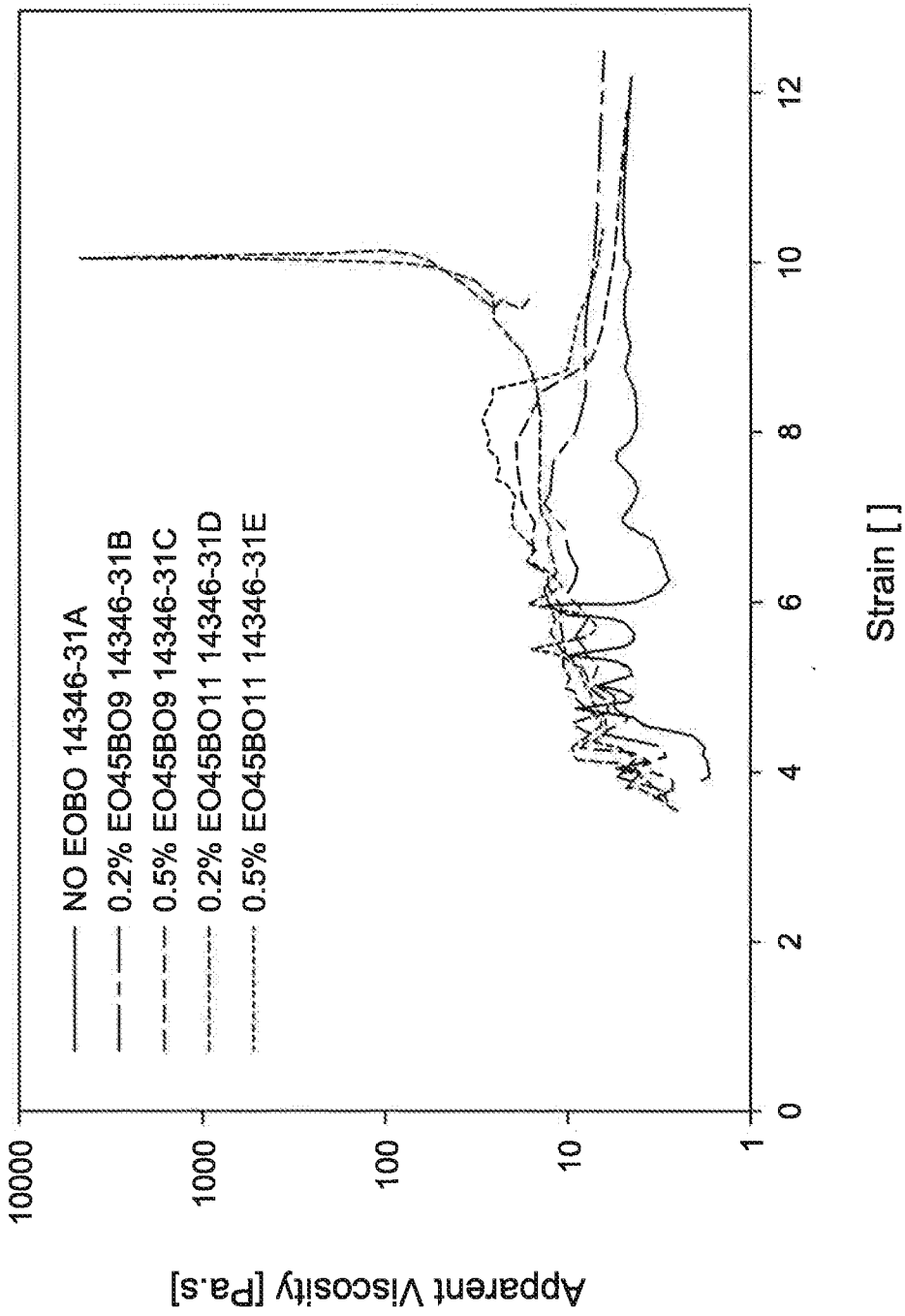


Fig. 5c

Break Up Time for HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{14}$, $EO_{45}BO_{16}$, and $EO_{45}BO_{18}$

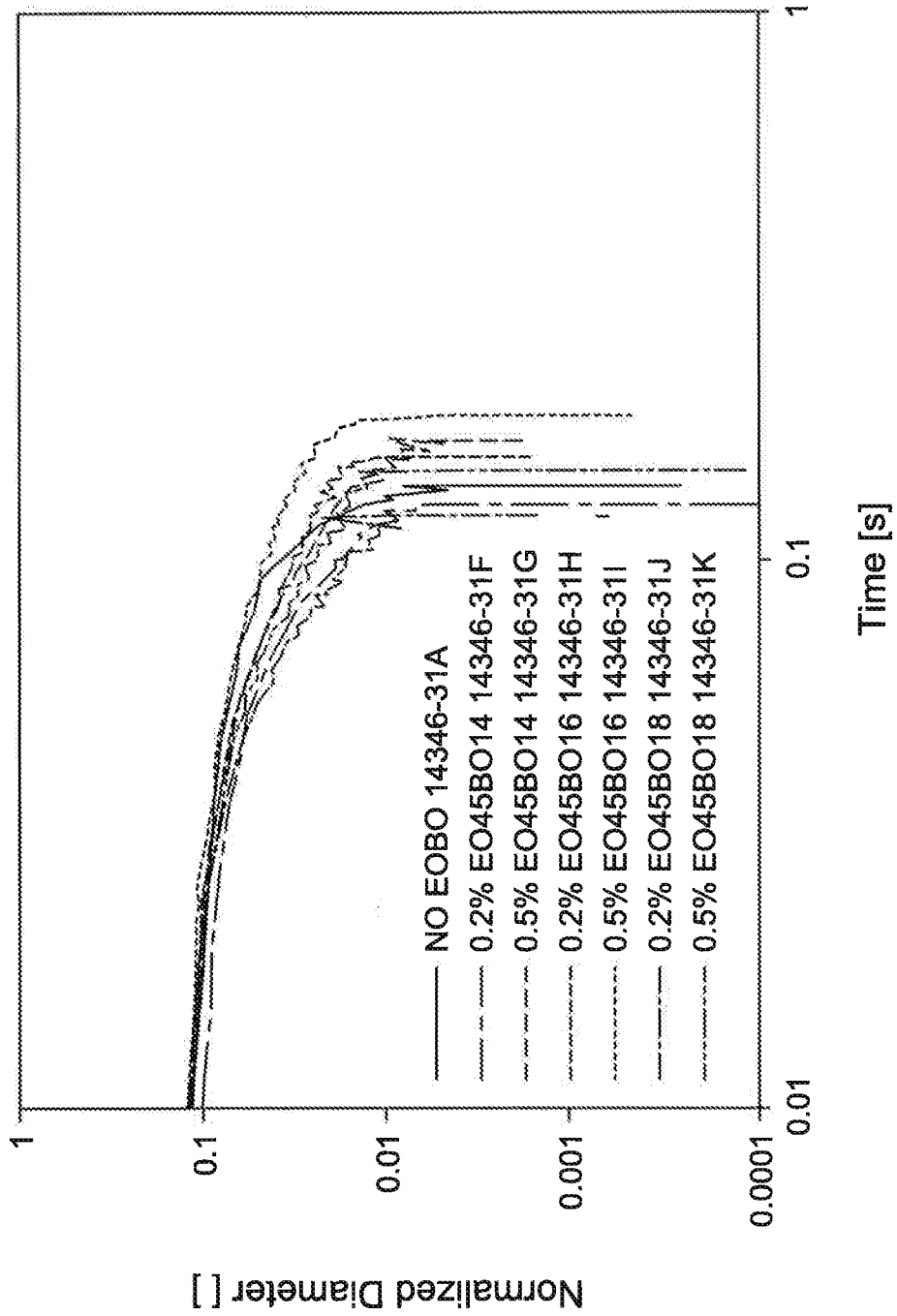


Fig. 5d

Extensional Viscosity for HP8A with (0.2% and 0.5%) and without $EO_{45}BO_{14}$, $EO_{45}BO_{16}$, and $EO_{45}BO_{18}$

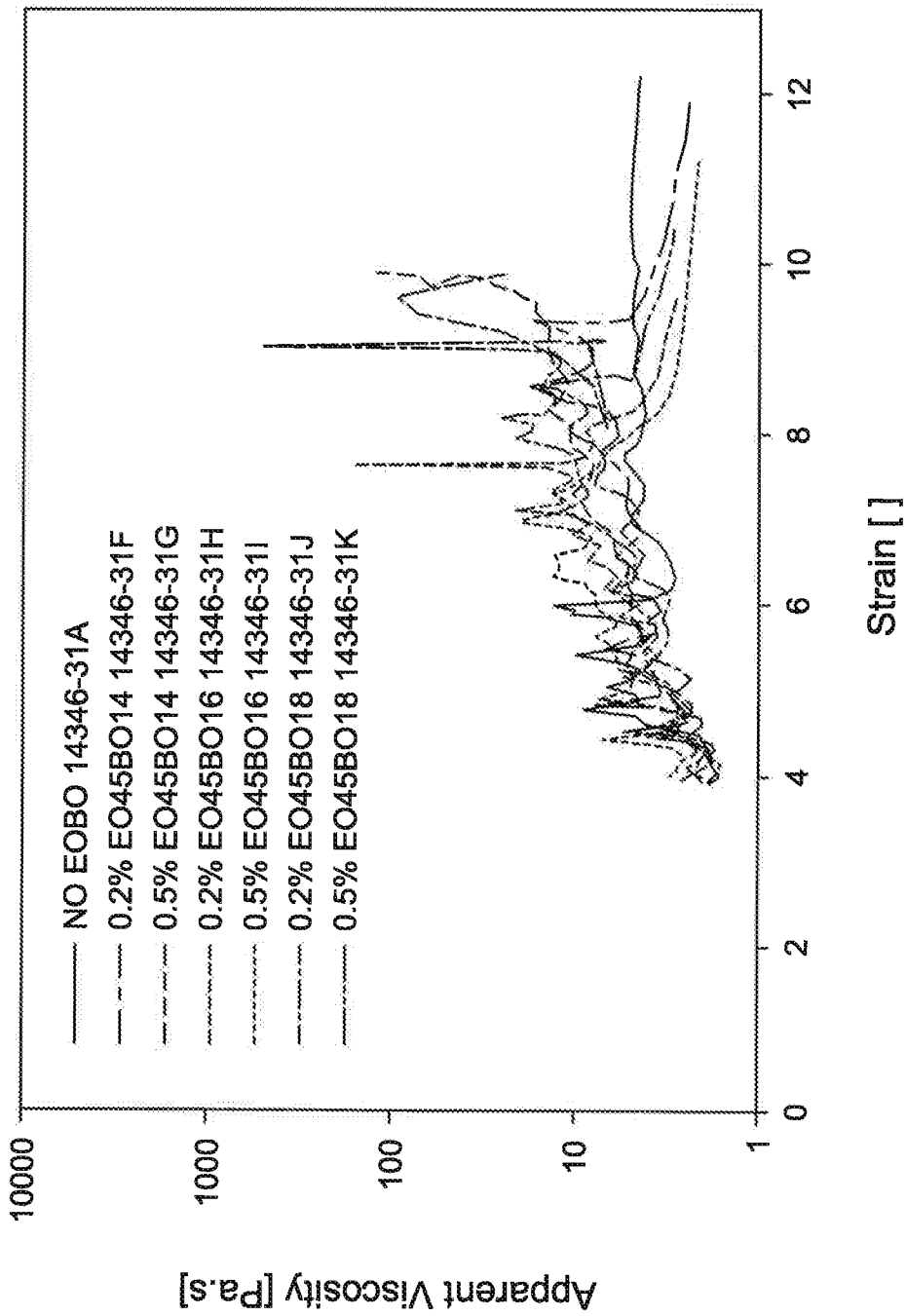


Fig. 6a
Frequency Sweep For $EO_{45}BO_{11}$ and $EO_{45}BO_{16}$ with HP Guar

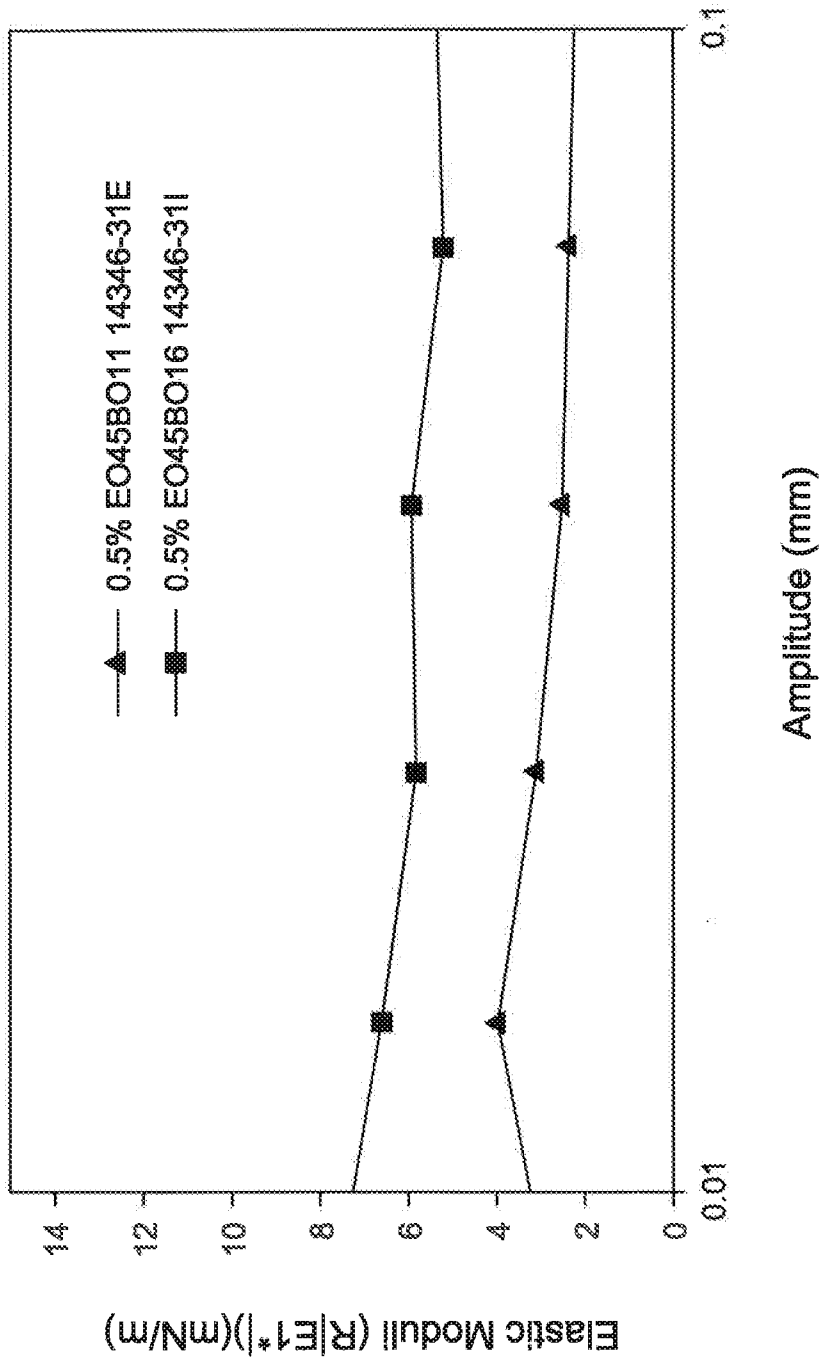


Fig. 6b

Frequency Sweep For $EO_{45}BO_{11}$ and $EO_{45}BO_{16}$ with HP Guar

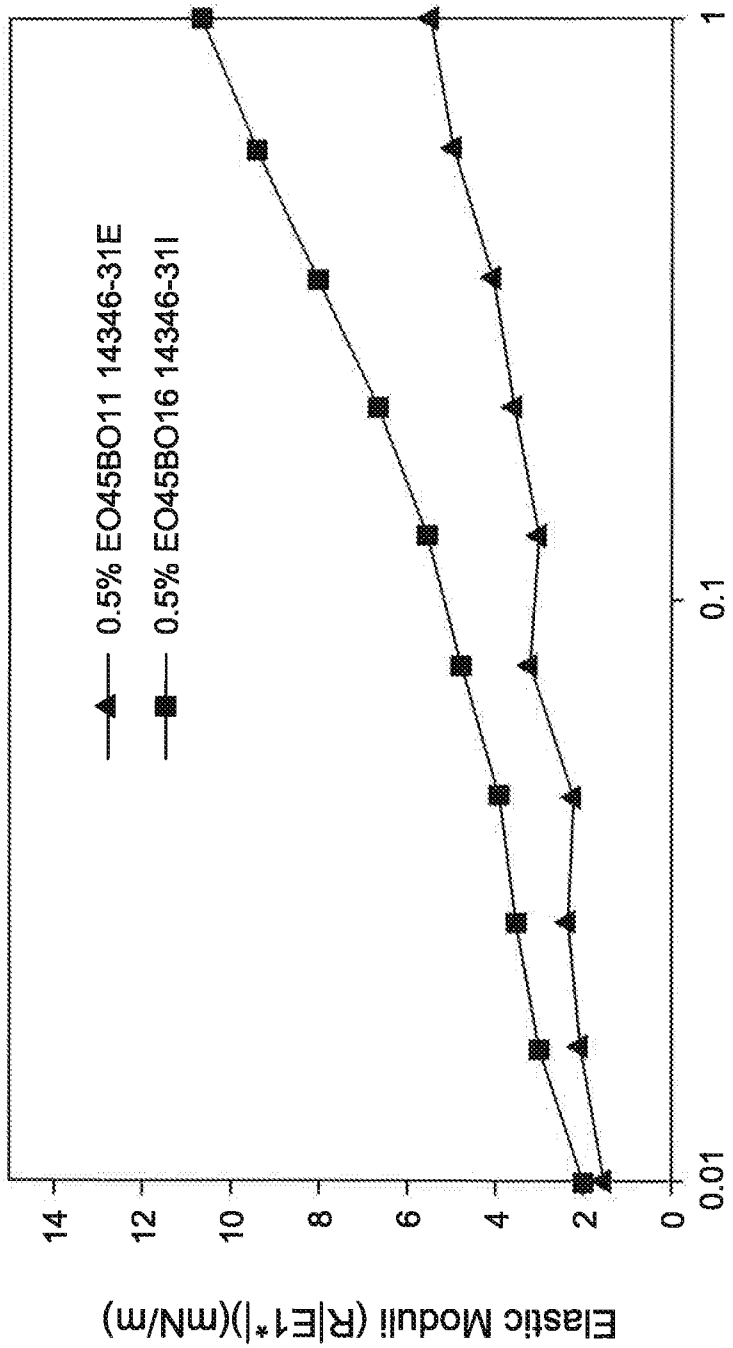


Fig. 7a

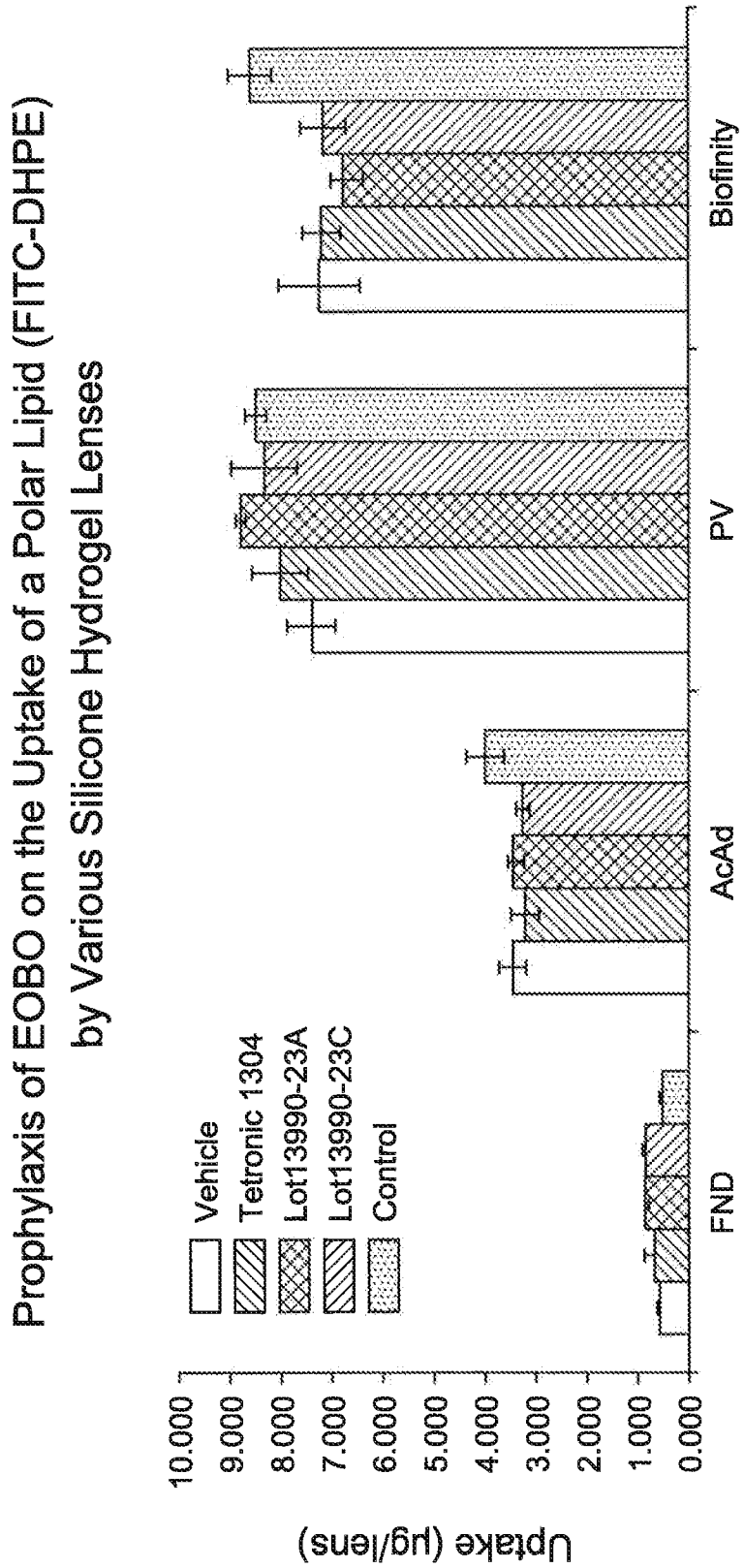

Prophylaxis of EOBO on the Uptake of a Polar Lipid (FITC-DHPE)
by Various Silicone Hydrogel Lenses
Uptake (µg/lens)
10.000
9.000
8.000
7.000
6.000
5.000
4.000
3.000
2.000
1.000
0.000
Vehicle
Tetronic 1304
Lot13990-23A
Lot13990-23C
Control
FND
AcAd
PV
Biofinity

Fig. 7b

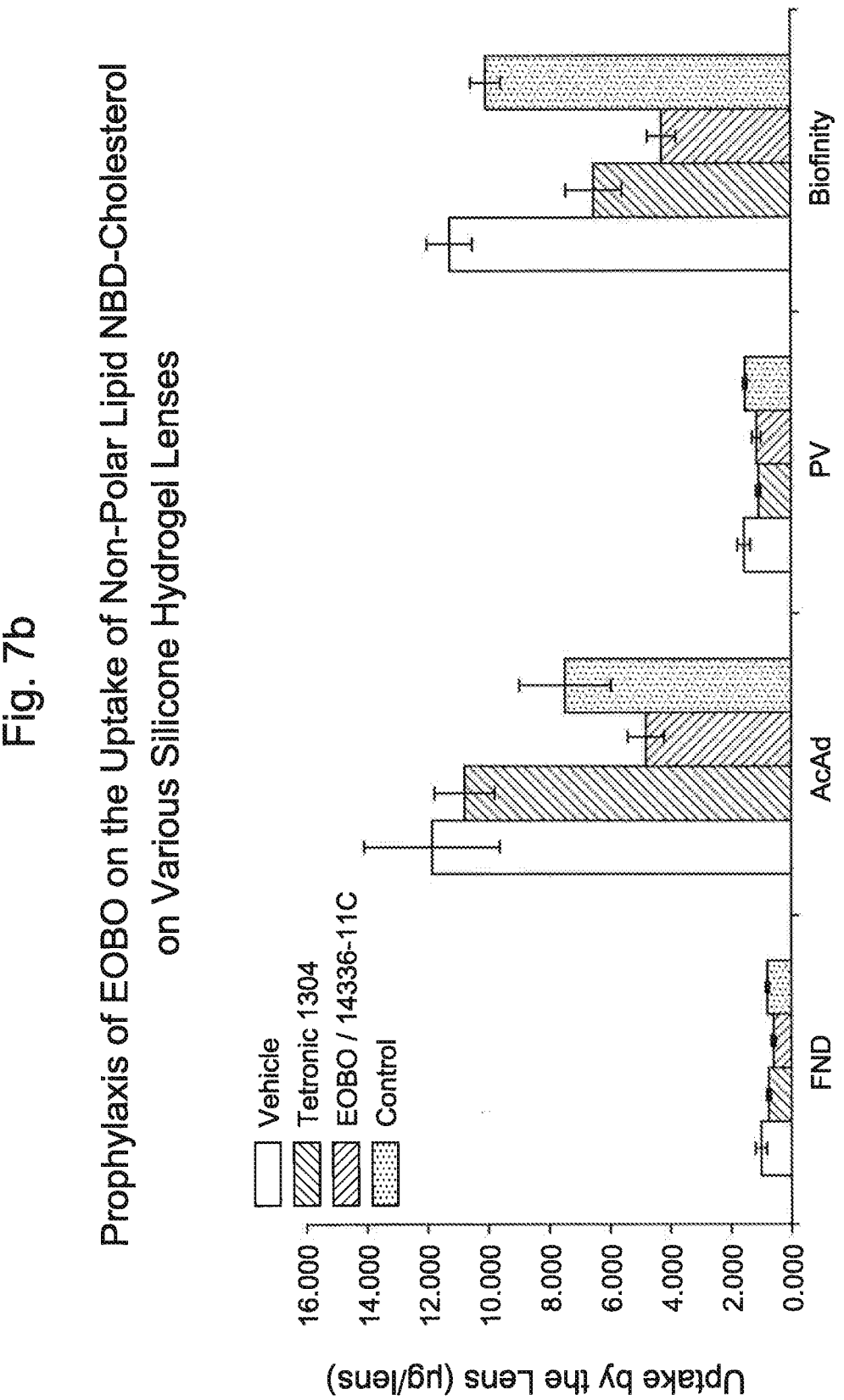

Prophylaxis of EOBO on the Uptake of Non-Polar Lipid NBD-Cholesterol
on Various Silicone Hydrogel Lenses
Vehicle
Tetronic 1304
EOBO / 14336-11C
Control
Uptake by the Lens (µg/lens)
16.000
14.000
12.000
10.000
8.000
6.000
4.000
2.000
0.000
FND
AcAd
PV
Biofinity

Fig. 8

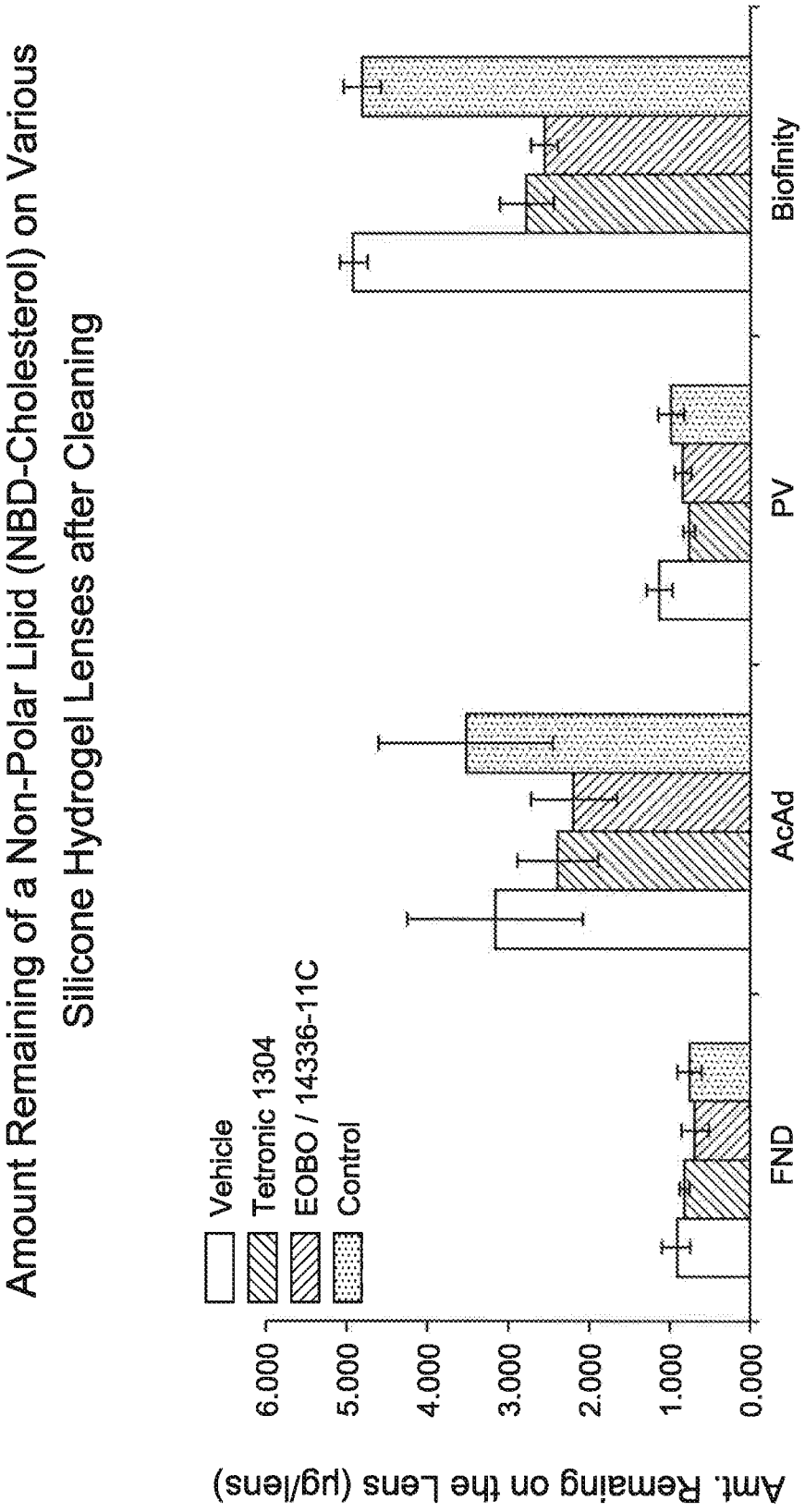

Amount Remaining of a Non-Polar Lipid (NBD-Cholesterol) on Various Silicone Hydrogel Lenses after Cleaning
Vehicle
Tetronic 1304
EOBO / 14336-11C
Control
Amt. Remaining on the Lens (µg/lens)
6.000
5.000
4.000
3.000
2.000
1.000
0.000
FND
AcAd
PV
Biofinity

Fig. 9a

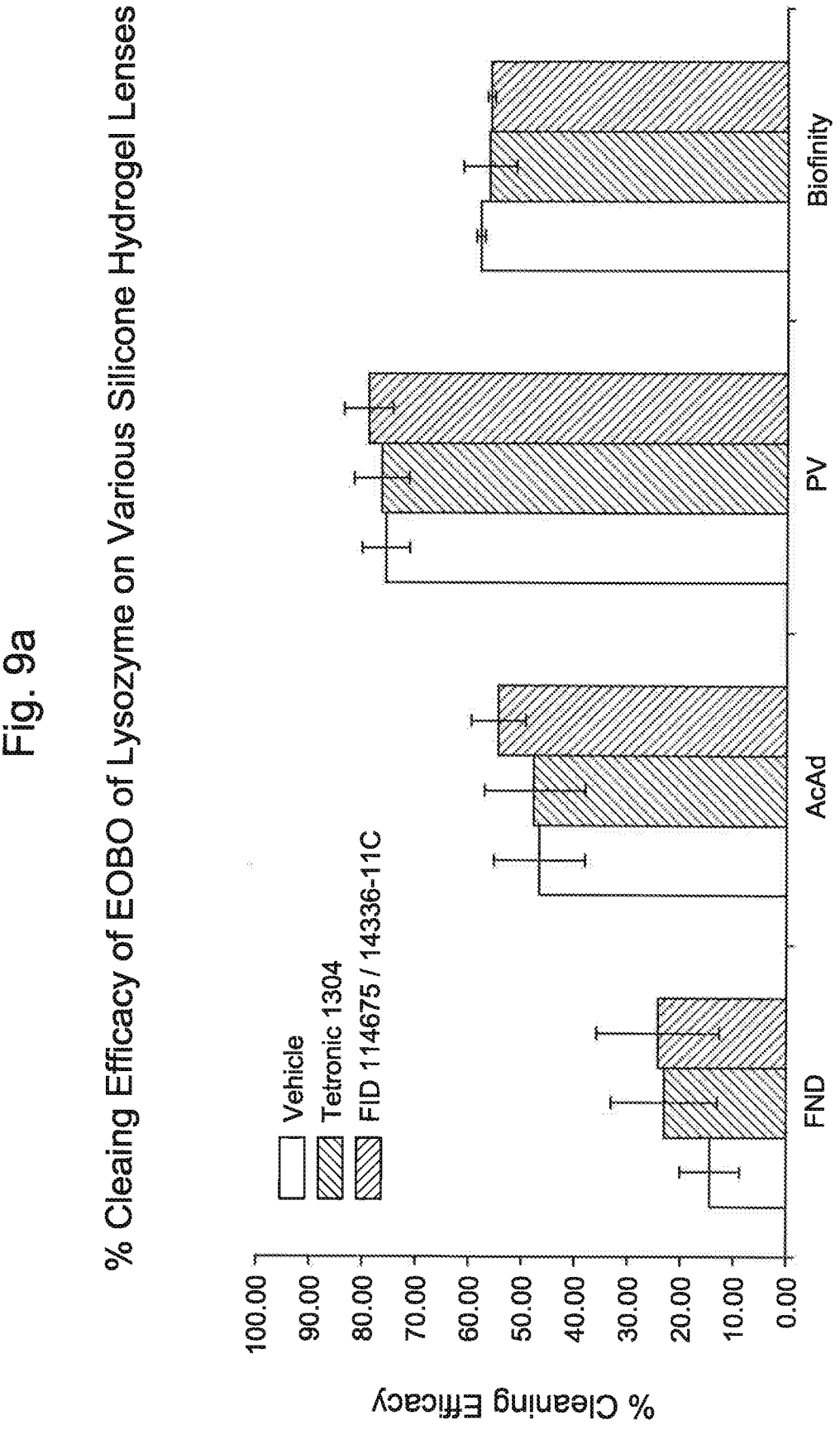

% Cleaing Efficacy of EOBO of Lysozyme on Various Silicone Hydrogel Lenses
% Cleaning Efficacy
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Vehicle
Tetronic 1304
FID 114675 / 14336-11C
FND
AcAd
PV
Biofinity

Fig. 9b

Amount Remaining of Lactoferrin on Various Silicone Hydrogel Lenses after Cleaning

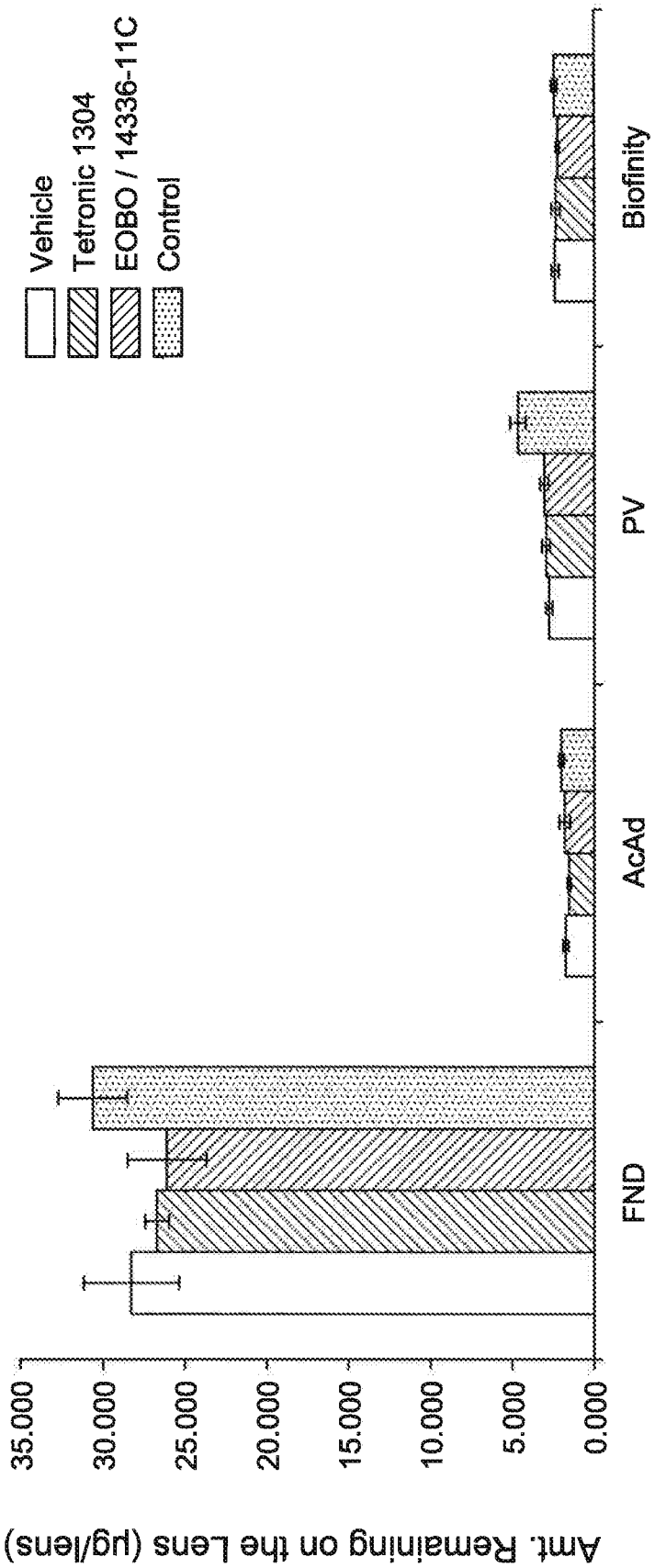


Fig. 9c

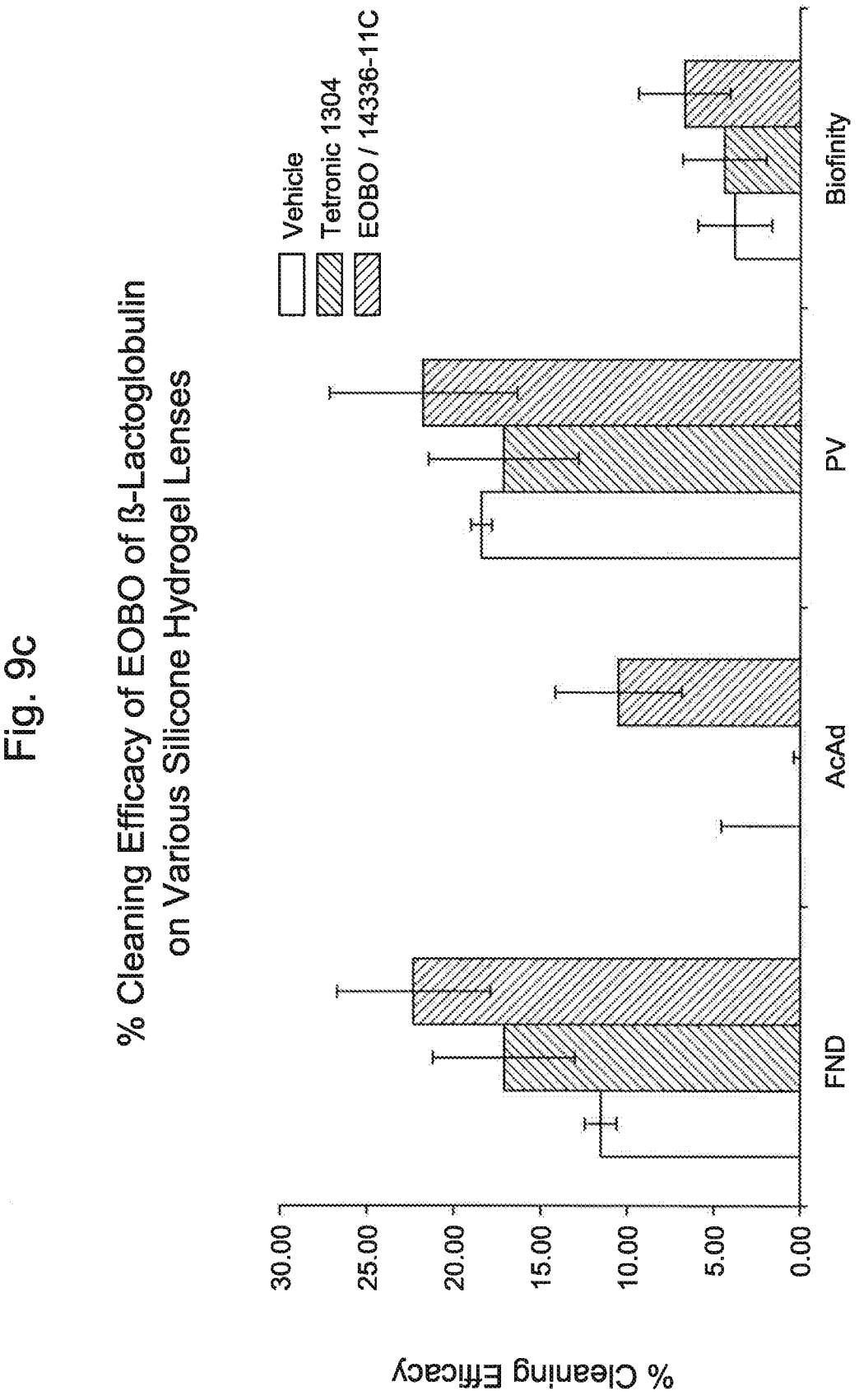
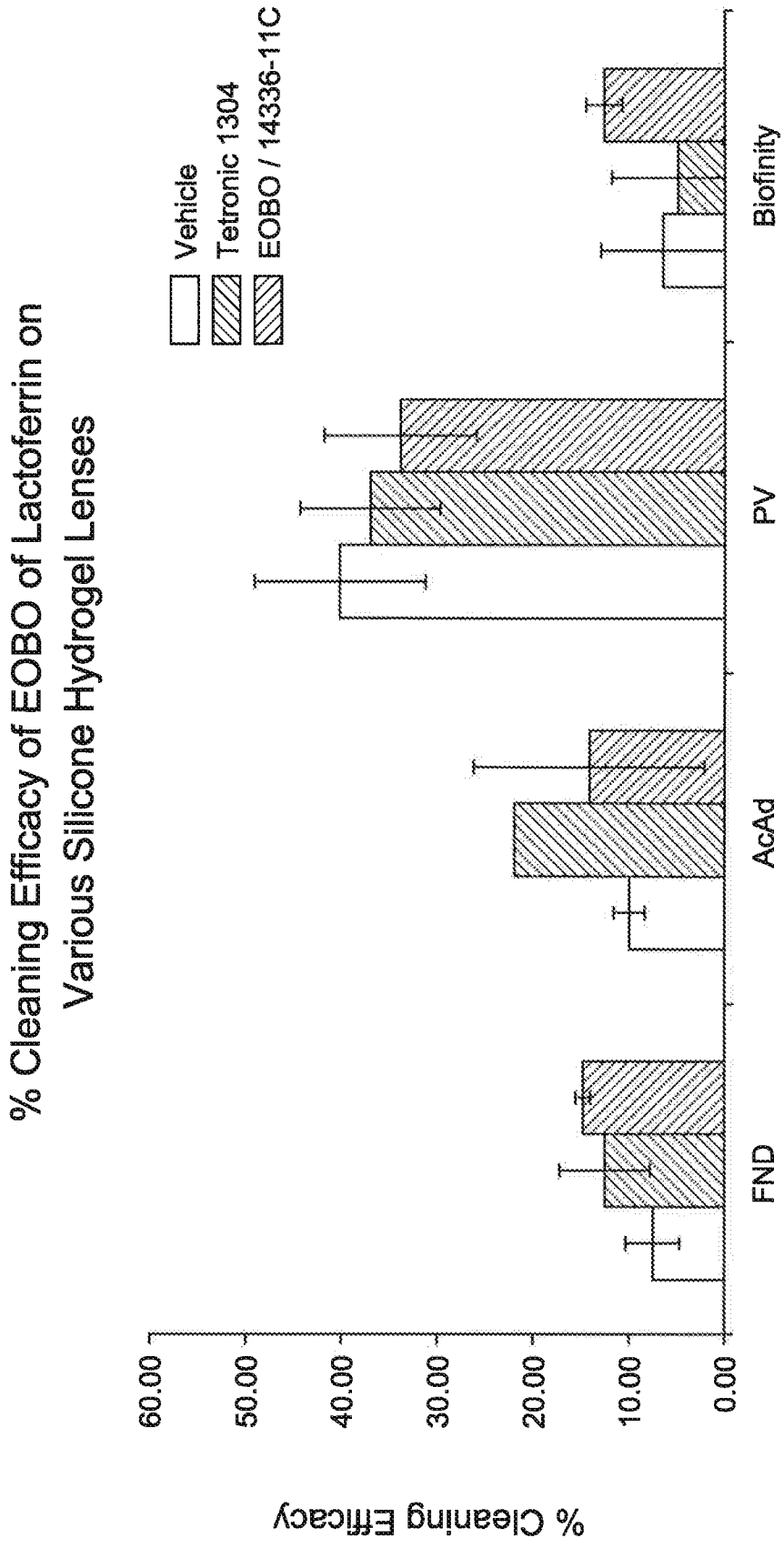

% Cleaning Efficacy of EOBO of ß-Lactoglobulin on Various Silicone Hydrogel Lenses
Vehicle
Tetronic 1304
EOBO / 14336-11C
% Cleaning Efficacy
30.00
25.00
20.00
15.00
10.00
5.00
0.00
FND
AcAd
PV
Biofinity

Fig. 9d


% Cleaning Efficacy of EOBO of Lactoferrin on Various Silicone Hydrogel Lenses
Vehicle
Tetronic 1304
EOBO / 14336-11C
% Cleaning Efficacy
60.00
50.00
40.00
30.00
20.00
10.00
0.00
FND
AcAd
PV
Biofinity