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(54) **Title:** ENCAPSULATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

(57) **Abstract:** The present disclosure provides pharmaceutical compositions with improved mechanical strength and active pharmaceutical ingredients (API) elution properties useful for medical devices such as implants. Also provided are methods of making these compositions, which can include forming sub-micron particles of API and blending with a porous encapsulating material. In one embodiment, the methods can involve forming a solution of the API and precipitating particles thereof such as by adding a nonsolvent to the solution. The precipitated API can be mixing with the encapsulation media to form a blend, which can then be dried, dehydrated and molded to form a desired material, medical device, or implant.

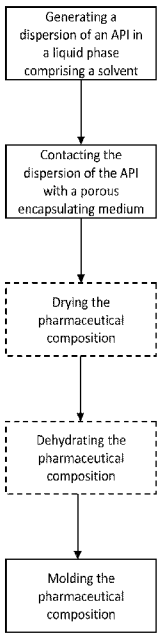


FIG. 1A

WO 2024/250016 A2

ENCAPSULATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional patent application No. 63/506,024, filed June 2, 2023. The content of which is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] Not applicable.

FIELD OF THE INVENTION

[0003] The present disclosure relates to encapsulating compounds in an encapsulating medium, e. g., encapsulating active pharmaceutical ingredients (API) such as antibiotics, non-steroid anti-inflammatory drugs (NSAIDs), analgesics, and other drugs in polyethylene (PE) for the treatment/prevention of infection and/or pain management or encapsulating inactive ingredients such as salts, rubbers, or ceramics in polyethylene to alter its physical and/or chemical characteristics for the fabrication of medical devices.

BACKGROUND

[0004] Total joint replacements (>2 million annual surgeries) are essential in alleviating pain and improving the quality of life for individuals suffering from end-stage joint disease. One of the primary failure modes associated with total joint replacements is prosthetic joint infection (PJI), which can occur through surgical site infection, hematogenous spread, or contiguous infection. While the risk of total joint infection is relatively low—with infection rates typically ranging from 0.6% to 2.4%— the consequences can be severe, leading to significant morbidity and mortality. Infection in a total joint replacement can result in prolonged hospitalization, the need for additional surgeries (such as implant removal or revision), increased pain, functional impairment, and reduced quality of life for the affected individual. PJIs are commonly treated with intravenous or oral antibiotic therapy, surgical debridement, and irrigation with retention of components or revision of the joint components (one- or two-stage). A two-stage revision, which is considered the gold standard for treatment, involves replacing the infected components with an antibiotic spacer and administering a prolonged course of systemic antibiotics before performing a second surgery to implant new components. Antibiotic spacers are typically made of bone cement, which is mixed with high doses of antibiotics, commonly vancomycin and gentamicin/tobramycin. The primary role of spacers is to preserve the joint space and

prevent joint contracture. Also, local antibiotic elution from spacers supports the effect of systemic antibiotics by minimizing the risk of bacteria growth and recolonization on the spacer implants and the local tissues.

[0005] Antibiotic spacers, while moderately valuable in managing PJI, have limitations that can affect their overall success. These include the risk of spacer fracture, dislocation, synovitis caused by spacer implant wear and limited long-term antibiotic release. Ultrahigh molecular weight polyethylene (UHMWPE) was proposed as an alternative material for antibiotic spacers for its therapeutic potential as well as load-bearing properties. Antibiotic-releasing polyethylene offers several advantages that can potentially address limitations associated with traditional bone cement spacers with better mechanical properties, reduced risk of particulate generation (lower wear), and improved long-term antibiotic release.

[0006] Conventional blending methods use solid particles of API mixed with solid particles of ultra-high molecular weight polyethylene followed by compression molding. Mechanical properties of such blends depend on the particle size distribution and the uniformity of blending. However, conventional blending suffers from clustering of API particles and difficulty in uniform distribution of particles, both of which adversely affect mechanical properties. The phase-separated domains of the API can lead to decreased strength and toughness compared to non-drug-loaded (virgin) UHMWPE, limiting its use in longer-term applications. It is also not practical to control particles size distribution with conventional blending.

[0007] Thus, there remains a need for alternative API compositions with improved mechanical strength and toughness as well as API-release properties suitable for long-term use as an implant component.

SUMMARY

[0008] The present disclosure provides pharmaceutical compositions and methods that overcome the aforementioned drawbacks by providing a blending process that offers enhanced mechanical properties. Incorporation of UHMWPE with sub-micron API particles provides enhanced mechanical properties and drug release profiles relative to traditional blending techniques.

[0009] In one aspect of the present disclosure, a pharmaceutical composition is described. The pharmaceutical composition comprises a porous encapsulating medium and particles of an active pharmaceutical ingredient encapsulated in the pores of the porous encapsulating medium. In some embodiments, the particles of the active pharmaceutical ingredient have an average size of less than 1 μm. The encapsulating medium can include a polymeric material, such as ultra-high molecular weight

polyethylene (UHMWPE). The active pharmaceutical ingredient can comprise an antibiotic, such as gentamicin sulfate. The pharmaceutical composition can be in a solid form, such as a molded solid. The pharmaceutical composition may have improved mechanical properties and/or API elution profile. As a nonlimiting example, the pharmaceutical composition can have an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa. As a nonlimiting example, the pharmaceutical composition can comprise at least 6% by weight the active pharmaceutical ingredient, and the active pharmaceutical ingredient can have a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

[0010] In another aspect of the present disclosure, a method of preparing a pharmaceutical composition is described. The method can comprise generating a dispersion of an active pharmaceutical ingredient in a liquid phase comprising a solvent. The method can further comprise contacting the dispersion of the active pharmaceutical ingredient with a porous encapsulating medium, thereby producing the pharmaceutical composition, wherein particles of the active pharmaceutical ingredient are encapsulated in the pores of the porous encapsulating medium. For example, the active pharmaceutical ingredient can include an antibiotic, such as gentamicin sulfate. In some embodiments, the method comprises generating a dispersion of gentamicin sulfate in a liquid phase comprising about 30% (v/v) water and about 70% (v/v) ethanol. The method can further comprise drying and/or dehydrating the pharmaceutical composition to produce a dried pharmaceutical composition. The method can further comprise molding the dried pharmaceutical composition by a heat molding process.

[0011] In another aspect, the present disclosure provides a pharmaceutical composition produced by the preparation method as described herein.

[0012] In another aspect, the present disclosure provides a medical device comprising a pharmaceutical composition as described herein or a pharmaceutical composition produced by the preparation method as described herein. The medical device can be, for example, an implant such as a joint replacement implant.

[0013] In another aspect of the present disclosure, a joint replacement implant is described. The joint replacement implant comprises a heat molded polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE) and gentamicin sulfate, wherein particles of gentamicin sulfate are encapsulated in pores of the heat molded polymeric material.

[0014] In another aspect of the present disclosure, a method of preparing an implant is described. The method comprises: generating a dispersion of a gentamicin sulfate in a liquid phase comprising a solvent and a non-solvent; contacting the dispersion of gentamicin sulfate with a porous polymeric

material comprising ultra-high molecular weight polyethylene (UHMWPE), thereby producing an implant composition, wherein particles of gentamicin sulfate are encapsulated in the pores of the porous polymeric material; and heat molding the implant composition to produce the implant.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Some embodiments of the disclosure are described herein with reference to the accompanying figures. The description, together with the figures, make apparent to a person having ordinary skill in the art how some embodiments of the disclosure may be practiced. The figures are for the purpose of illustrative discussion and no attempt is made to show structural details of an embodiment in more detail than is necessary for a fundamental understanding of the teachings of the disclosure. Any figures herein are not shown to scale. Where dimensions are given in the text or figures, these dimensions are merely exemplary and do not limit the scope or spirit of the disclosed invention.

[0016] FIG. 1A is a flow chart of a method for preparing a pharmaceutical composition, according to aspects of the present disclosure.

[0017] FIG. 1B is a flow chart of a method of preparing an implant, according to aspects of the present disclosure.

[0018] FIG. 2 is a set of elemental analysis images of polyethylene blocks prepared with API particles UHMWPE blends and cold molding cycle. Top Left: Electron image. Top Right: Overlapped C, O, and S Kα1 image. Bottom Left: S Kα1 image. Bottom Middle: O Kα1 image. Bottom Right: C Kα1 image.

[0019] FIG. 3 is a set of elemental analysis images of polyethylene blocks prepared with API particles UHMWPE blends and hot molding cycle. Top Left: Electron image. Top Right: EDS layered image. Bottom Left: S Kα1 image. Bottom Middle: O Kα1 image. Bottom Right: C Kα1 image.

[0020] FIG. 4A is a light microscopy image of polyethylene blocks prepared with API particles UHMWPE blends and hot molding cycle.

[0021] FIG. 4B is a light microscopy image of polyethylene blocks prepared with conventional blending and cold molding cycle.

[0022] FIG. 5A is a plot of the gentamicin release rate from UHMWPE prepared with GSWE-140 powder and tablets.

[0023] FIG. 5B is a plot of the gentamicin percent cumulative release from UHMWPE prepared with GSWE-140 powder and tablets.

[0024] FIG. 6A is a plot of gentamicin release rate from UHMWPE prepared with WGSE -140 powder and tablets.

[0025] FIG. 6B is a plot of gentamicin percent cumulative release from UHMWPE prepared with WGSE -140 powder and tablets.

[0026] FIG. 7A is a plot of the tensile test results of GSWE -140 Powder.

[0027] FIG. 7B is a plot of the tensile test result of GSWE-140 Tablet.

[0028] FIG. 8A is a plot of the ultimate tensile strength of WGSE -140 with different gentamicin loading ratios.

[0029] FIG. 8B is a plot of the elongation at break of WGSE -140 with different gentamicin loading ratios.

[0030] FIG. 9 is a plot of IZOD test results of WGSE -140 with different gentamicin loading ratios.

[0031] FIG. 10A is a micrograph of resolidified UHMWPE blends. Scale bar = 100 μm.

[0032] FIG. 10B is a micrograph of as received UHMWPE blends. Scale bar = 100 μm.

[0033] FIG. 10C is a micrograph of sub-micron GS UHWMPE blends. Scale bar = 100 μm.

[0034] FIG. 10D is micrograph showing sub-micron GS particles appearing as clusters on either side of fusion lines within the UHMWPE matrix (scale bar = 50 μm).

[0035] FIG. 10E is a SEM micrograph of sub-micron GS particle clusters on either side of the fusion lines (scale bar = 100 μm).

[0036] FIG. 10F is a SEM EDX nitrogen elemental map (N in green) of sub-micron GS particle clusters on either side of the fusion lines (scale bar = 100 μm).

[0037] FIG. 10G is a SEM EDX sulfur elemental map (S in orange) of sub-micron GS particle clusters on either side of the fusion lines (scale bar = 100 μm).

[0038] FIG. 10H is a SEM EDX combined elemental map of FIGS. 9E-9G.

[0039] FIG. 10I is a FIB-SEM micrograph. FIB-SEM revealed subsurface pore sizes of 0.060-0.350 μm (scale bar = 5 μm):,

[0040] FIG. 10J is a FIB-SEM EDX nitrogen elemental map (N in green).

[0041] FIG. 10K is a FIB-SEM EDX nitrogen sulfur elemental map (S in orange).

[0042] FIG. 10L is a FIB-SEM image with combined map of FIGS. 9I-9K.

[0043] FIG. 10M is a schematic of boundaries of the UHMWPE flakes in resolidified (left), as-received (middle), and sub-micron GS UHMWPE blends (right).

[0044] FIG. 11A is a plot of the ultimate tensile strength (UTS) for 10% GS UHMWPE blend showed varying mechanical properties among resolidified, as-received, and sub-micron GS UHMWPE blends. Sub-micron GS UHMWPE blend showed the highest UTS (A).

[0045] FIG. 11B is a plot of the elongation at break (EAB) for 10% GS UHMWPE blend showed varying mechanical properties among resolidified, as-received, and sub-micron GS UHMWPE blends. EAB measurements were lower only for the resolidified particles among the three blends studied.

[0046] FIG. 11C is a plot of the yield strength (YS) for 10% GS UHMWPE blend showed varying mechanical properties among resolidified, as-received, and sub-micron GS UHMWPE blends. YS of the sub-micron blend was higher than those of as-received and resolidified blends (C).

[0047] FIG. 11D is a plot of the EAB for varying GS UHMWPE blend percentages. Increased GS content led to reductions in EAB.

[0048] FIG. 11E is a plot of the UTS for varying GS UHMWPE blend percentages. Increased GS content led to reductions in UTS.

[0049] FIG. 11F is a plot of IZOD impact strength for varying GS UHMWPE blend percentages. Increased GS content led to reductions in IZOD impact strength.

[0050] FIG. 12A is a plot comparing the normalized release rate of resolidified GS UHMWPE, as-received GS UHMWPE, and sub-micron GS UHMWPE blend of GS eluted from varying size GS UHMWPE blends as a function of time. The release rate did not vary between resolidified and as-received GS UHMWPE blends after the 6-hour burst, while that of sub-micron GS UHMWPE blend was significantly higher than those of the other two blends. After the 6-hour and 1-day burst releases, the release rate stayed constant for 6% and 8% GS loading in sub-micron GS UHMWPE blends.

[0051] FIG. 12B is a plot comparing the fractional cumulative release of resolidified GS UHMWPE, as-received GS UHMWPE, and sub-micron GS UHMWPE blend of GS eluted from varying size GS UHMWPE blends as a function of time.

[0052] FIG. 12C is a plot comparing the normalized cumulative release of resolidified GS UHMWPE, as-received GS UHMWPE, and sub-micron GS UHMWPE blend of GS eluted from varying size GS UHMWPE blends as a function of time.

[0053] FIG. 12D is a plot comparing the normalized release rate of GS eluted from sub-micron GS UHMWPE blends with different loadings (10%, 8%, and 6%) as a function of time. Release rate of 10% sub-micron GS UHMWPE was significantly higher than those of the other two blends for 28 days.

[0054] FIG. 12E is a plot comparing the fractional cumulative release of GS eluted from sub-micron GS UHMWPE blends with different loadings (10%, 8%, and 6%) as a function of time.

[0055] FIG. 12F is a plot comparing the normalized cumulative release of GS eluted from sub-micron GS UHMWPE blends with different loadings (10%, 8%, and 6%) as a function of time.

[0056] FIG. 12G is a plot of the predicted in-vivo concentrations resulting from gentamicin release from the 6%, 8%, and 10% sub-micron GS UHMWPE blends. Sub-micron GS UHMWPE blends with both 8% and 10% loading could maintain intra-articular concentrations for 100×MIC levels at 28 days.

[0057] FIG. 12H is a plot of the predicted in-vivo concentrations resulting from gentamicin release from sub-micron GS UHMWPE blends, solidified GS UHMWPE blends, and as-received GS

UHMWPE blends. While 6% sub-micron GS UHMWPE blend and 10% resolidified GS UHMWPE blend could maintain 10× MIC for the same duration, that of as-received GS UHMWPE blend stayed only above 1× MIC value for predicted intra-articular GS concentration.

[0058] FIG. 13A is a plot of the predicted intraarticular GS concentration resulting from gentamicin release from 6%, 8%, and 10% sub-micron GS UHMWPE blends (3-hour half-life scenario).

[0059] FIG. 13B is a plot of the predicted intraarticular GS concentration resulting from gentamicin release from 6%, 8%, and 10% sub-micron GS UHMWPE blends (6-hour half-life scenario). The predictive models indicated a discernible difference in intraarticular GS concentration between the 3-hour (FIG. 12A) and 6-hour half-life scenarios. Notably, in the 3-hour half-life model, the GS concentration for an 8% loading fell below the 100× MIC threshold but remained significantly above the 10× MIC limit. Conversely, the 6-hour half-life model exhibited sustained concentrations above both MIC thresholds for a longer duration.

[0060] FIG. 14A is a plot of the predicted GS concentration in joint spaces resulting from gentamicin release from different sizes of GS UHMWPE blends, including resolidified, as-received, and sub-micron GS (3-hour half-life scenario).

[0061] FIG. 14B is a plot of the predicted GS concentration in joint spaces resulting from gentamicin release from different sizes of GS UHMWPE blends, including resolidified, as-received, and sub-micron GS (6-hour half-life scenario).

[0062] FIG. 15 is a ^{1}H NMR spectra of GS (panel A) and GS eluted from the sub-micron GS UHMWPE blend (panel B). The spectra exhibited a high degree of structural similarity. Both spectra displayed characteristic peaks at specific chemical shift values, suggesting the preservation of key functional groups in GS after its integration with the UHMWPE matrix. The consistency in the intensity and multiplicity of these peaks further supported the notion that the chemical environment of the hydrogen atoms in GS remained largely unchanged after blending and high temperature (170 °C molding). This was particularly evident in the overlapping regions of the spectra, where the alignment of peaks indicated a similar distribution of chemical environments. Additionally, the absence of new or shifted peaks in the spectrum of eluted GS (B) suggested that the blending and molding processes did not significantly alter the molecular structure of GS.

[0063] FIG. 16 is a ^{1}H NMR spectra of GS (tope spectra) and GS eluted from sub-micron GS UHMWPE blend (bottom spectra). Assigned Multiples of GS: 1H NMR (D2O, 500 MHz) δ 5.91 – 5.81 (1H, m), 5.09 (1H, d, J = 3.7 Hz), 4.21 – 4.09 (2H, m), 4.07 – 3.95 (2H, m), 3.80 (3H, qd, J = 8.9, 5.2 Hz), 3.61 – 3.49 (1H, m), 3.49 – 3.39 (3H, m), 2.88 (4H, s), 2.71 (1H, s), 2.49 (1H, s), 2.56 – 2.46 (1H, m), 2.10 – 1.97 (2H, m), 1.88 (1H, s), 1.59 – 1.49 (1H, m), 1.32 – 1.22 (7H, m).

[0064] FIG. 17 is a comparison of ^{1}H NMR spectra ranges of GS (black line) and GS eluted from sub-micron GS UHMWPE blend (red line). The specific chemical shift ranges examined were: 4.18-4.04 (top left panel), 3.61-3.38 (top right panel), 2.52 -1.9 (bottom left panel), and 1.32-1.22 ppm (bottom right panel). A key observation was the variation in peak heights, attributable to concentration differences between the control GS and the eluted GS. Despite these differences, the overall peak patterns appeared comparable across all ranges. This similarity suggests that the elution process does not significantly alter the fundamental molecular structure of GS.

DETAILED DESCRIPTION

[0065] Traditionally, commercially available API particles are dry blended with an encapsulation media, dehydrated, and molded. For instance, gentamicin sulfate particles are dry blended with UHMWPE powder flakes, dehydrated, and molded. With this method, the particle size of the API remains unchanged during the blending and molding process. The molded articles typically have domains of clustered API articles within the encapsulation media, for example, gentamicin sulfate particles clustered within the UHMWPE matrix. These clusters adversely affect the mechanical properties of UHMWPE. In medical device applications, implant performance depends on many factors, especially on the mechanical properties of the implant, some of which could be fabricated with UHMWPE/API blends. Aspects of the present disclosure allow for control of the particle size of the API within the encapsulation media by precipitating the API from a solution by using precipitation agents, such as solvents, in which the API has low solubility to control the particle size of the API domains. Smaller API particles in the encapsulation media, polyethylene, in this case, would result in better mechanical properties and in better control of API elution characteristics. The present methods and compositions result in a much smaller API particle size in the encapsulation media and hence results in better mechanical properties and better wear resistance of the consolidated blend. The present method and compositions also allow for better control of the burst release and long-term elution rate of the API from the encapsulating media.

[0066] API(s) encapsulated within encapsulation media with tailored mechanical properties and/or API elution characteristics can be administered to achieve desired therapeutic outcomes. For instance, a medical device fabricated from UHMWPE encapsulated with antibiotics with high strength, high wear resistance, antibiotic elution at therapeutic levels can be used to treat periprosthetic joint infection in total joint patients or can be used to prevent infection or can be used to provide an implant that decreases the extent of bacterial colonization on implant surfaces. Another example is a medical device

fabricated from UHMWPE encapsulated with analgesics with desirable mechanical properties and/or wear resistance that can be used as an implant to help in pain management.

[0067] As described in a non-limiting example herein, in-situ formed active pharmaceutical ingredient (API) particles can be encapsulated in an encapsulation media for instance UHMWPE, PLGA, bone cement by: (i) Adding the API into a solvent or a mixture of solvents whereby creating a solution, (ii) precipitating particles of API in said solution by a variety of methods, for instance by adding a non-solvent, (iii) mixing said API particles with an encapsulation media forming a blend, (iv) drying said blend, (v) optionally dehydrating the dried blend, and (vi) molding the blend. In the present disclosure, several techniques for manufacturing API-doped encapsulation media blocks and encapsulating active and/or inactive ingredients are described. This novel method can be used to encapsulate any compound in an encapsulating medium to create a composite material and tailor its properties for a variety of applications, such as delivery of a therapeutic agent, a medical implant, a fixation method to fix implants to bone, or a load bearing component.

[0068] The present disclosure describes decreasing antibiotic particle size encapsulated in UHMWPE to improve mechanical strength. GS is typically a loose powder in its as-received form, and particle sizes are usually under 100 μm. Resolidification from solution is one method to fabricate larger GS particles, which are commonly used in GS-containing bone cement. Smaller particles can be obtained by solvent/non-solvent precipitation. As described herein, UHMWPE samples are blended with gentamicin sulfate of different particle sizes and the effect of particle size and content on mechanical properties, elution characteristics, and morphological attributes are assessed.

[0069] A GS UHMWPE spacer that offers enhanced mechanical properties can be critical for patients with PJI. Additionally, a GS UHMWPE implant that combines high strength, superior wear resistance, and effective antibiotic elution at therapeutic levels could be a pivotal advancement: It has the potential to prevent periprosthetic joint infections not just in high-risk revision cases but also in primary total joint arthroplasty procedures. The compositions and methods could significantly reduce the high morbidity and mortality associated with PJIs and potentially save the US healthcare system over a billion dollars every year.

[0070] The invention comprises, consists of, or consists essentially of the following features, in any combination.

[0071] Composition

[0072] In one aspect, the present disclosure provides a pharmaceutical composition comprising a porous encapsulating medium and particles of an active pharmaceutical ingredient encapsulated in the pores of the porous encapsulating medium.

[0073] As used herein, the encapsulating medium can be polymeric, metallic, ceramic, wood, fabric, composite material, or mixtures thereof. In some embodiments, the encapsulating medium comprises a polymeric material. In some embodiments, the encapsulating medium can be high density polyethylene, low density polyethylene, linear low density polyethylene, ultra-high molecular weight polyethylene (for example GUR 1020, GUR 1050), or radiation or chemical crosslinked polyethylene. For example, the polymeric material can comprise ultra-high molecular weight polyethylene (UHMWPE). Preferably the encapsulating medium has a porous surface. As an example, a polymeric encapsulating medium may be UHMWPE in the form of powder flakes. These flakes can have surface porosity and bulk porosity to facilitate encapsulation of API particles.

[0074] In some embodiments the encapsulating medium contains antioxidants, for example vitamin-E, Irganox 1010 or other similar compounds as listed in US Patents Methods for Making Oxidation Resistant Material. US Patent 12/904,481, Highly Crystalline Cross-linked Oxidation Resistant Polyethylene, US Patent 9,168,683, Oxidation Resistant Homogenized Polymeric Material. US Patent 8,461,225.

[0075] The term "pore," "porous," or "porosity" as used herein in connection with the encapsulating medium can include any opening, void space, or hollow structure on the surface or inside of the material, such as surface pores, holes, and channels. The encapsulating medium can have a porous surface and/or a porous bulk structure. In some embodiments, the encapsulating medium has a porous surface.

[0076] The pores of the porous encapsulating medium can have an average size of at least 0.010 μm, at least 0.1 μm, at least 0.5 μm, at least 1 μm, at least 5 μm, at least 10 μm, at least 50 μm, at least 100 μm, at least 500 μm, or at least 1000 μm.

[0077] The active pharmaceutical ingredient as used herein can include an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof. In some embodiments, the active pharmaceutical ingredient comprises an antibiotic. Examples of API are vancomycin, tobramycin, gentamicin, cefadroxil, cefazolin, cephalexin, cefaclor, cefotetan, cefoxitin, cefprozil, cefuroxime, loracarbef, cefdinir, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftozoxime, ceftriaxone, cefepime, amikacin, streptomycin, doxycycline, erythromycin, gentamicin, isoniazid, rifampin, and ethambutol. Sulfonamides, beta-lactams including penicillin, cephalosporin, and carbepenems, aminoglycosides, quinolones, and oxazolidinones, and metals such as copper, iron, aluminum, zinc, gold, compound, and ions thereof, and various combinations thereof. Nonsteroid anti-inflammatory drugs, including but not limited to salicylate, indomethacin, flubiprofen, diclofenac, ketorolac, naproxen, piroxicam, tabferon, ibuprofen,

etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenyl Butazone, Clofezone, Oxyphenbutazone, Plexazone, Apazone, Benzidoamine, Bucolome, Cinchopen, Clonixin, Ditrazol, Epilizol, Fenoprofen, Floctafenil, Flufenamic acid, Graphenin, Indoprofen, Ketoprofen, Meclofenamic acid, Mephenamine Acid, niflumic acid, phenacetin, salidifamide, sulindac, suprofen, tolmetin and their salts. Salicylates include acetylsalicylic acid, sodium acetylsalicylate, calcium acetylsalicylate, salicylic acid and sodium salicylate. In some embodiments, the active pharmaceutical ingredient comprises an antibiotic, which comprises gentamicin sulfate. In some embodiments, the antibiotic is gentamicin sulfate.

[0078] Analgesics include opioid agonist and antagonists. The opioid agonists include but are not limited to alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitrnmide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

[0079] The opioid antagonists include but are not limited to naloxone (U.S. 3,254,088, which is incorporated herein by reference in its entirety), naltrexone (U.S. 3,332,950, which is incorporated herein by reference in its entirety) and mixtures thereof; or a pharmaceutically acceptable salt thereof. In still another embodiment, the opioid analgesic or the analgesic is a combination of an opioid agonist and opioid antagonist (examples include, but are not limited to, suboxone which is a combination of buprenorphine and naloxone).

[0080] For a more detailed description of the analgesics, see "Chapter 23 - Opioid Analgesics" by Gutstein et al. (pages 569-619) and "Chapter 27 - Analgesic- Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout" by Roberts et al. (pages 687-731), both from Goodman & Gilman's The Pharmacological Basis of Therapeutics, Joel G. Hardman and Lee E. Limbird, eds., 10th Ed., pages 569-619, (2001)) and Glen R. Hanson, "Analgesic, Antipyretic and Anti-Inflammatory Drugs" in Remington: The Science and Practice of Pharmacy, A. R. Gennaro ed. 19th ed., vol. II: 1196-1221(1995).

[0081] Other APIs include lipopolysaccharides (LPS), polyguanidines (CPG), bacterial lysates, defensins and their salts such as hydrochloride sodium, sulfate, acetate, phosphate or diphosphate, chloride, potassium, maleate, calcium, citrate, mesylate, nitrate, tartrate, aluminum, and/or gluconate. For instance, vancomycin hydrochloride, gentamicin sulfate, tobramycin sulfate, and/or polyhexamethylene guanidine phosphate or mixtures thereof.

[0082] Other APIs are local anesthetic agents, for example bupivacaine, ropivacaine, dibucaine, procaine, chloroprocaine, prilocaine, mepivacaine, etidocaine, tetracaine, lidocaine, xylocaine, and mixtures thereof. The local anesthetic can be in the form of a salt, for example, hydrochloride, bromide, acetate, citrate, carbonate or sulfate.

[0083] APIs also comprise therapeutic biomolecules, for example polypeptides, proteins, amino acids, polysaccharides, disaccharides, lipids, natural and synthetic nucleic acids, including but not limited to modified ribonucleic acids (RNA), mRNAs, microRNAs, siRNAs, shRNAs, and other RNAi types, double strand linear deoxyribonucleic acids (DNA), double strand circular DNA, single strand linear DNA and mixtures thereof.

[0084] In some embodiments, the API particles include or are replaced with a compound (or particles of the compound) comprising of chemicals such as salts, metals, ceramics, composites, rubbers and any reinforcing agents such as calcium chloride, and/or nano-sized rubber particles.

[0085] In some embodiments, the particles of the active pharmaceutical ingredient have an average size of less than 1 μm. The encapsulated particles of the API can have an average size of less than 0.9 μm, less than 0.8 μm, less than 0.6 μm, less than 0.4 μm, less than 0.2 μm, less than 0.1 μm, less than 0.05 μm, less than 0.01 μm, less than 0.005 μm, or less than 0.001 μm.

[0086] In a non-limiting example, the pharmaceutical composition can have about 1% to about 50% by weight the API. The pharmaceutical composition can have at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 8%, at least 10%, at least 20%, at least 30%, or at least 40% by weight the API. The amount of the API in the present pharmaceutical composition can be, for example, about 1% to about 40%, about 1% to about 30%, about 1% to about 20%, about 2% to about 40%, about 2% to about 30%, about 2% to about 20%, about 2% to about 15%, about 2% to about 10%, about 5% to about 40%, about 5% to about 30%, about 5% to about 20%, or about 5% to about 10% by weight. In some embodiments, the pharmaceutical composition comprises about 2% to about 20% by weight the API, such as about 4%, about 6%, about 8%, about 10%, about 12%, about 14%, about 16%, or about 18% by weight.

[0087] As a non-limiting example, the present disclosure provides a pharmaceutical composition, in which the encapsulating medium includes the polymeric material UHMWPE, the API comprises

gentamicin sulfate (GS), and the particles of the API have an average size of less than 1 μm, and which comprises about 1% to about 20% (such as about 2% to about 20% or about 2% to about 10%) by weight the API.

[0088] In a non-limiting example, the pharmaceutical composition may be a solid composition. The solid composition may be formed by known techniques, such as compression, molding, extrusion, or other suitable methods. For example, the pharmaceutical composition may be a molded solid.

[0089] As will be described in further detail in the example below, the present pharmaceutical composition may have improved mechanical properties as compared to conventional compositions. As a non-limiting example, the present pharmaceutical composition may have an ultimate tensile strength (UTS) of at least 30 MPa, and elongation break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa.

[0090] The present pharamaceutical composition may have improved release profile of the encapsulated API as compared to conventional compositions. The release rate can be adjusted, for example, by controlling the API load, the porosity of the encapsulating medium, and the inclusion of other components in the formulation. For example, the release rate can be measured at a pre-determined API load (wt %) over a period of time under relevant conditions (such as release in water at 37°C). In some embodiments, the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C. Release rate is synonymous with elution rate and they both refer to rate at which the API is released from the encapsulating medium. In some embodiments the unit for the release rate is defined as the mass of API per day per surface area of the encapsulating medium. In some embodiments the encapsulating medium is a tibial implant used in total knee arthroplasty surgery – typically the articular surface area together with the surface area of the side wall of the implant is approximately 100 cm^2. Therefore, the release rate can be measured as mass of API released per day per 100cm^2, for example, to represent the release rate from a tibial implant fabricated from an encapsulating medium comprising API. Other implant shapes will have different API release rates and those can be calculated by proper normalization of the surface area of the implant that has the encapsulating medium that comprises API. The release rate can be, for example, at least 0.2 mg/day, at least 0.5 mg/day, at least 1 mg/day, at least 2 mg/day, at least 5 mg/day, or at least 10 mg/day, per 100 cm^2 for 28 days. The cumulative release can be, for example, at least 5%, at least 10%, at least 15%, or at least 20% in 5 days. As a non-limiting example, the pharmaceutical composition comprises

at least 6% by weight gentamicin sulfate and has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

[0091] Method of Preparation

[0092] In another aspect, the present disclosure provides a method of preparing a pharmaceutical composition. The method comprises: generating a dispersion of an active pharmaceutical ingredient in a liquid phase comprising a solvent; and contacting the dispersion of the active pharmaceutical ingredient with a porous encapsulating medium, thereby producing the pharmaceutical composition, wherein particles of the active pharmaceutical ingredient are encapsulated in the pores of the porous encapsulating medium.

[0093] The method may be used to prepare a pharmaceutical composition as described herein. In some embodiments, the particles of the active pharmaceutical ingredient have an average size of less than 1 μm. In some embodiments, the encapsulating medium comprises a polymeric material. For example, the polymeric material can comprise ultra-high molecular weight polyethylene (UHMWPE). In some embodiments, the active pharmaceutical ingredient comprises an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof. In some embodiments, the active pharmaceutical ingredient comprises an antibiotic. For example, the antibiotic can comprise gentamicin sulfate. In some embodiments, the antibiotic is gentamicin sulfate. In some embodiments, the pharmaceutical composition produced by the present method comprises about 1% to about 50% (such as about 2% to about 20% or about 2% to about 10%) by weight the active pharmaceutical ingredient.

[0094] The solvent used herein can include any medium in which the active pharmaceutical ingredient can be dissolved. Suitable solvents include polar, nonpolar, aqueous, and organic solvents, and mixtures thereof. Example solvents include, for example, water, ethanol, isopropanol, acetone, or a combination thereof. In some embodiments, the solvent comprise water.

[0095] The active pharmaceutical ingredient can form a solution in the solvent, from which a dispersion of the active pharmaceutical ingredient in a liquid phase can be generated. The dispersion can include particles of the active pharmaceutical ingredient and can be formed, for example, by adding other agents to a solution of the active pharmaceutical ingredient.

[0096] The current disclosure describes the use of inactive ingredients in some embodiments. Inactive ingredients are added to solvents or mixtures of solvents. In some embodiments the inactive ingredients increase the dispersion of API particles or alter solubility of APIs to create said API particles. Inactive ingredients are substances that have no known therapeutic effects but augment the API by providing better control over the loading capacity of the active ingredient and/or the release kinetics of the

ingredients. These include but not limited to viscosity modifiers, salts, pH modifiers, surfactants, solvents, and/or gases or mixtures thereof. In some embodiments, the liquid phase further comprises an inactive ingredient, a precipitating agent, a viscosity modifier, a surfactant, a pH modifier, an emulsifying agent, or a combination thereof.

[0097] In a non-limiting example, the liquid phase further comprises a precipitating agent. A precipitating agent as used herein can include any chemical agent that facilitates precipitation or separation of the active pharmaceutical ingredient from a solution of the active pharmaceutical ingredient in a solvent. Precipitation agent can include any solvents, gases, solutions, and/or pH modifiers that change the solubility of a compound in a solvent and result in the precipitation of that compound. Compounds, such as an API, have different solubility in different solvents. The solubility in that solvent can be a function of temperature, pH, and/or other attributes of that solvent. Typically, solvents with high solubility for a compound are also called good solvents for that compound, and ones with low solubility are called bad solvents (or non-solvents) for that compound. A bad solvent or a non-solvent for a compound also can be a precipitating agent for that compound when that compound is in solution in a solvent. With the addition of the precipitating agent, the active pharmaceutical ingredient may form particles, thereby a dispersion of the active pharmaceutical ingredient may be produced. Suitable precipitating agent may include, for example, non-solvents, salts, or mixtures thereof. A non-solvent can include any substance (e.g., aqueous or organic liquids) in which the API is not soluble or has low solubility, as compared to the solvents as used herein. In some embodiments, the liquid phase of the dispersion further comprises a precipitating agent, which comprises a non-solvent.

[0098] The present method includes encapsulating API particles in an encapsulating medium. The API particles are particles which may or may not be spherical in morphology. Particle size range may vary; for instance, about a 0.001 to 100 micrometer or 0.001 to 10 micrometer. In some embodiments, the API particles have an average size of less than 1 μm. Particles are produced either in liquids or using other techniques, including but not limited to microfluidic fabrication, freeze drying, spray drying, and/or nanoprecipitation. The API particles comprise an API, water, and/or other solvents. For example, when GS is precipitated out of a water solution by adding ethanol to that solution the particles formed comprise GS and water and/or some trace amount of ethanol.

[0099] The API particles are preferably in a size range that enables the said particles to penetrate the porosity (comprising pores, holes, and/or channels) in the encapsulating media. Regardless of the polarity (hydrophilic or hydrophobic) or surface charges of the encapsulating media any API particle is able to penetrate the porosity in a liquid carrier phase (for example water/alcohol mixture). This

liquid carrier keeps the API in particle form while creating a favorable environment between the surface/porosity of encapsulating media and API particles. In one embodiment liquid carrier is the mixture that is used for API particle formation. In one embodiment, the encapsulating media is subjected to compression (channel-die compression, uniaxial compression, or hydrostatic compression) after the API particles are placed in the porosity of the said encapsulating media.

[00100] In some embodiments, the API comprises gentamicin sulfate, the solvent is an aqueous solvent (such as water), and the liquid phase comprises a non-solvent to facilitate formation of a dispersion of the API. The non-solvent can be, for example, ethanol. For example, gentamicin sulfate particles are formed with nanoprecipitation by dissolving GS in water and adding ethanol to GS/water solution to cause GS to precipitate and form particles that comprise GS. For example, the method may comprise generating a dispersion of GS in a liquid phase comprising about 30% (v/v) water and about 70% (v/v) ethanol. In one embodiment the API particles are fabricated by dissolving API in water and adding an alcohol to precipitate API particles in the solution. For instance, adding 140 proof ethanol to an aqueous solution of gentamicin sulfate would precipitate gentamicin sulfate particles: these particles will settle under gravity or by centrifugation. These particles can also be forced into suspension by violent shaking, such as by vortexing. These particles primarily comprise GS and some water and/or some ethanol. The suspended particles of gentamicin sulfate can be mixed with UHMWPE powder. This powder mixture is then dried and dehydrated, and then compression molded to encapsulate the gentamicin sulfate in UHMWPE. Machining the said UHMWPE into an implant shape would result in an implant that is capable of eluting gentamicin sulfate. In another embodiment, vancomycin hydrochloride particles are formed by adding ethanol to vancomycin hydrochloride aqueous solution. In yet another embodiment, gentamicin sulfate and vancomycin hydrochloride particles are formed by adding ethanol to an aqueous solution of both of these APIs.

[00101] The API particles formed in an aqueous solution are mixed with encapsulating media either as a suspension or as individual particles. The individual particles are isolated from the aqueous solution in which they are formed. The particles can be isolated through centrifugation or settling the particles by gravity and removing the supernatant. In most embodiments, the API particles are mixed with the encapsulating media while they are in suspension in the aqueous solution. In some embodiments, the API is hydrophobic; therefore organic solvents are used to dissolve the API and a non-solvent is added to precipitate the particles.

[00102] In some embodiments a dispersion agent is added to the solution containing API particles to form a suspension of the API particles in the said solution. Dispersion agent comprises viscosity modifier(s), surfactant(s), buffer(s), salt(s), pH modifier(s), precipitation agent(s), gases, and/or solvent(s) or mixtures thereof. The dispersion agent is added to the solution comprising particles

of one or more APIs. Preferably the API particles are formed in situ in the solution comprising dispersion agent, preferably by precipitating API particles from an API solution with the addition of a precipitation agent. The API particles are added to encapsulating medium.

[00103] In some embodiments viscosity modifiers are added to the solution containing API particles. Viscosity modifiers comprise polyvinylpyrrolidones (PVP) (preferably having a molecular weight of about 10,000 or less to about 360,000 or more, as well as mixtures containing one or more grades of PVP with different molecular weight), cellulose derivatives (including, but not limited to, hydroxyethyl cellulose, carboxymethyl cellulose or its salts, hydroxypropyl methylcellulose or hypromellose, and the like), glycosaminoglycans including but not limited to heparin, chondroitin sulfate, keratan sulfate, heparan sulfate or their salts, carrageenan, guar gum, chitosan, alginates, carbomers, polyethylene glycols, lipids, oils, sugars, polyvinyl alcohol, xanthan gum, and/or their derivates or mixtures thereof.

[00104] In some embodiments, surfactants are added to the solution containing API particles, either after forming the particles or before forming the particles. Surfactants comprise nonionic, anionic, cationic, zwitter ionic, and/or amphoteric compound. Typically surfactants are used to reduce interfacial tension. For example, surfactant is used the reduce the interfacial tension between the API particles and the surrounding solution. Examples of nonionic surfactants are poly(vinyl alcohol) (PVA), poloxamer 188, polyoxyethylene sorbitan fatty acid esters (Polysorbate, Tween®), polyoxyethylene 15 hydroxy stearate (Macrogol 15 hydroxy stearate, Solutol HS15®), polyoxyethylene castor oil derivatives (Cremophor® EL, ELP, RH 40), polyoxyethylene stearates (Myrj®), sorbitan fatty acid esters (Span®), polyoxyethylene alkyl ethers (Brij®), and/or polyoxyethylene nonylphenol ether (Nonoxynol®) and lecithin) or mixtures thereof. Examples of anionic surfactants are ammonium lauryl sulfate, sodium laureth sulfate, sodium lauryl sarcosinate, sodium myreth sulfate, sodium pareth sulfate, sodium stearate, sodium lauryl sulfate, α olefin sulfonate, and/or ammonium laureth sulfate or mixtures thereof. Examples of cationic surfactants are benzalkonium chloride, and/or cetylpyridinium chloride or mixtures thereof. Examples of amphoteric surfactants are betaines or sulfobetaine and natural substances such as amino acids and/or phospholipids or mixtures thereof. One of the preferred surfactants used herein is poly (vinyl alcohol). Another preferred surfactant is vitamin E.

[00105] In some embodiments, the encapsulating medium comprises an antioxidant. In one embodiment, vitamin-E is blended with UHMWPE flake then API particles are encapsulated in the flakes followed by molding. Examples of antioxidants are alpha- and delta-tocopherol; propyl, octyl, or dedocyl gallates; lactic, citric, and tartaric acids and their salts; orthophosphates, tocopherol acetate, and Irgonox 1010 (see, for example, WO 01/80778, U.S. Pat. No. 6,448,315). Vitamin E, a common

antioxidant, comprise a group of eight fat-soluble compounds that include four (alpha, beta, gamma, delta) tocopherols and four (alpha, beta, gamma, delta) tocotrienols. Tocopheryl acetate is also known as vitamin E.

[00106] In some embodiments, the encapsulating medium comprises a crosslinking agent. Examples of crosslinking agents are peroxides such as inorganic peroxides, organic peroxides, diacyl peroxides, peroxyesters, peoxydicarbonates, dialkyl peroxides, ketone peroxides, peroxyketals cyclic peroxides, peroxymonocarbonates and hydroperoxides benzoyl peroxide, dicumyl peroxide, methyl ethyl peroxide ketone peroxide, acetone peroxide, 2,5 - Di (tert - butylperoxy) -2,5 - dimethyl - 3 - hexyne (Luperox® 130), 3,3,5,7,7 pentamethyl - 1,2,4 trioxepane (Trigonox®311), etc. or mixtures thereof. Other examples of peroxides are dilauryl peroxide, methyl ether ketone peroxide, t - amyl peroxyacetate, t - butyl hydroperoxide, t - amyl peroxybenzoate, D - t amyl peroxide, 2,5 - Dimethyl 2,5 – Di(t - butylperoxy) hexane, t - butylperoxy isopropyl carbonate, succinic acid peroxide, cumene hydroperoxide, 2,4 - pentanedione peroxide, t - butyl perbenzoate, diethyl ether peroxide, acetone peroxide, arachidonic acid 5 - hydroperoxide, carbamide peroxide, tert butyl hydroperoxide, t - butyl peroctoate, t - butyl cumyl peroxide, Di - sec - butyl - peroxydicarbonate, D - 2 - ethyl hexylperoxydicarbonate, 1,1 – Di(t - butylperoxy) cyclohexane. Other examples of peroxides are members of the Luperox® family supplied by Arkema. Other examples of peroxides are 1,1 Di(tert - butylperoxy)-3,3,5 - trimethylcyclohexane, 2,5 - Dimethyl - 2,5 - di (tert - butylperoxylhexane , 3,3,5,7,7 - Pentam ethyl - 1,2,4 - trioxepane, Butyl 4,4 - di (tert - butylperoxy) valerate , Di (2,4 - dichlorobenzoyl)peroxide, Di (4 methylbenzoyl)peroxide , Di(tert - butylperoxyisopropyl benzene, tert - Butyl cumyl peroxide, tert - Butyl peroxy - 3,5, 5 - trimethylhexanoate , tert - Butyl peroxy 2 - ethylhexyl carbonate. Other examples of peroxides are members of the Trigonox™ or Perkadox™ family supplied by Akzo Nobel.

[00107] In some embodiments, salts are added to API solution (from which the API dispersion is formed) to cause pH buffering, this pH buffering/alterations can be used to form the API particles or change the particle size or change the interaction between API and encapsulating media. Salts include but are not limited to sodium chloride, calcium chloride, citrates, acetates, potassium dihydrogen phosphates, disodium hydrogen phosphates, or mixtures thereof.

[00108] In certain embodiments pH modifiers are added to the API solution to initiate or complete the API particle formation. The pH modifiers either increase or decrease the pH of the solution they are added to. Examples include but are not limited to soda ash, sodium hydroxide, sodium silicate, sodium phosphates, lime, sulfuric acid, hydrofluoric acid, tri-potassium citrate monohydrate, sodium hydrogen carbonate, tartaric acid, and/or adipic acid or mixtures thereof.

[00109] In some embodiments, solvents are used to dissolve APIs and/or other additives such as salts, pH modifiers, and other solid substance(s). In some embodiments non-solvents are added to these solutions to precipitate particles, such as nanoparticles, for encapsulation. Solvents can be either an organic or aqueous solvent. Examples are aqueous solvents such as sterile water, phosphate buffer, saline solution, and organic solvents such as DMSO ethyl acetate, chloroform, dichloromethane. Solvents also include alcohols, such as ethanol, iso-propanol, and ketones, such as acetone. Preferably the API is dissolved in a solvent and then a precipitation agent, such as a non-solvent, is used to precipitate API particles.

[00110] In some of the embodiments, dispersion or emulsifying agents are used to facilitate and control the formation of particles. The dispersion or emulsifying agents act like a surfactant and help in particle formation, for instance in the form of emulsion droplets or dispersions, and stabilize the emulsion or dispersion. Dispersion agent(s) aid in inhibiting the aggregation of particles formed in the dispersion fluid. Dispersion agent(s) comprise at least one chemically hydrophobic group and at least one hydrophilic group. These chemical groups can be amines, carboxylic acid, hydroxyls, and any potential side group that can interact with API(s) and encapsulating media. Dispersion agents may include but not limited to vitamins such as vitamin E, vitamin K, amino acids such as L-Lysine, L-Valine, L-Tryptophan, L-Phenylalanine, L-Methionine, L-Leucine, L-Threonine, L-Isoleucine, L-Arginine, L-Histidine, L-Tyrosine, L-Carnitine, L-Serine, L-Glutamine, Aspartic Acid, L-Proline, L-Glycine, Taurine, L-Cysteine, Gamma-aminobutyric acid (GABA), L-Alanine, and L-Glutamic acid and their other conformations thereof.

[00111] In some embodiments, aqueous solutions are used in many embodiments to form API particles. An aqueous solution is a solution in which solutes such as dispersion agent(s), for example PVA, emulsifying agent(s), compound(s), and/or API(s) are solubilized in water, ionized water or PBS or other aqueous solvents. The aqueous solution also comprises salts such as sodium chloride.

[00112] Some of the APIs or compounds used in the current disclosure are hygroscopic. For instance, gentamicin sulfate or vancomycin hydrochloride are hygroscopic APIs. In some embodiments the APIs are encapsulated in a polymeric material and subsequently heated and pressurized to consolidate shapes that would allow fabrication of medical devices. Direct compression molding into a finished or semi-finished medical device shape are used. Extrusion or compression molding are also used, typically followed by machining to fabricate a medical device that contains API and can elute API. Thermal degradation rate of hygroscopic APIs is higher when the said APIs are hydrated. In some embodiments the blend of API and encapsulation agent are dehydrated to reduce the water content to minimize the degradation during the subsequent molding stage. In some embodiments, dehydration can be performed in air, in vacuum, or in inert gasses such as argon gas.

[00113] Particles of API and/or compounds are formed in a solvent or a mixture of solvents. For instance, gentamicin sulfate is dissolved in water; ethanol is added to this aqueous solution of gentamicin sulfate. The addition of ethanol causes gentamicin sulfate to form particles in the water/ethanol mixture. These particles are easily encapsulated in the pores found in UHMWPE flakes. Subsequently, the mixture of gentamicin sulfate/water/ethanol/UHMPWE is dried to partially or fully evaporate the solvents, for example by heating in air, in inert gas, or in vacuum. In a non-limiting example, the pharmaceutical composition may be dried and/or dehydrated to produce a dried pharmaceutical composition. For example, the drying step can follow dehydration to minimize the bound water in the hygroscopic API. In some embodiments, the dried and/or dehydrated mixture of gentamicin sulfate particles in UHMWPE flake is compression molded and, optionally machined, to form a medical device.

[00114] In a non-limiting example, the method comprises molding the dried pharmaceutical composition by a heat molding process. Suitable heat molding processes may include, for example, ram extrusion, extrusion, direct compression molding, compression molding, calendaring, thermoforming, welding, lamination, pultrusion, forging, and other techniques. The appropriate conditions for the heat molding process can depend on the chemical nature of the active pharmaceutical ingredient, the components of the encapsulating medium, and intended application of the pharmaceutical composition.

[00115] A representative process of preparing a pharmaceutical composition (e.g., containing GS particles encapsulated in UHMWPE) according to the present preparation method is illustrated in FIGS. 1A and 1B. As a non-limiting example, the composition produced by the method can be incorporated in a medical device (such as an implant) by known technique (such as heating molding) and shaped (e.g., by machining) into desired size and shape.

[00116] In one embodiment, an API solution is prepared by dissolving the API in a solvent; then, the said API solution is mixed with another solvent that is not a good solvent (or a non-solvent) for the said API, resulting in the formation of API particles. Thus, the API particles form a dispersion in the two solvent mixture, where one solvent is a good solvent, and the other is a bad solvent or a non-solvent for the said API. The API dispersion in the solvent mixture is then mixed with an encapsulation agent and the mixture is dried to substantially evaporate the solvents. It is beneficial to reduce the solvent content in the mixture as much as possible before molding. In some embodiments the API is dissolved in one or solvents. Some of these individual solvents may not dissolve the API by themselves but mixing with other solvents may increase the solubility. Solubility can also be increased by increasing temperature.

[00117] In other embodiments, the API is dissolved in a mixture of solvents. In some solvents and mixtures of solvents the API is dissolved at elevated temperatures.

[00118] In some embodiments, it is preferential to have the encapsulating media in powder form to achieve better mixing with the API particles or the dispersion particles. In some cases, it is beneficial to have the encapsulation agent be porous to better encapsulate the API particles.

[00119] In some embodiments, encapsulating media has flakes, such as UHMWPE; the flakes consist of antioxidants, such as vitamin E, and crosslinking agents, such as peroxides.

[00120] In one embodiment, an aqueous solution of gentamicin sulfate (GS) is prepared by dissolving GS in water; then the said aqueous solution of GS is mixed with ethanol. Mixing with ethanol results in GS particle formation; if left undisturbed the GS in water/ethanol mixture phase separates into an amber-colored viscous solution (also called a plug) that settles to the bottom of the container and a clear supernatant liquid lying above the said plug. The same phase separation is obtained if the GS in water/ethanol mixture is centrifuged. The GS in water/ethanol mixture is then shaken to mix the two phases, that is the viscous, amber-colored plug and the clear supernatant, to form a liquid dispersion, where the GS particles are dispersed in the water/ethanol mixture. The liquid dispersion is then mixed with UHMWPE powder and the mixture is dried to substantially evaporate water and ethanol. The dried mixture is then dehydrated to further remove residual water and ethanol and then molded. It is beneficial to reduce the water and ethanol content in the mixture as much as possible before molding.

[00121] In another aspect, the present disclosure provides a pharmaceutical composition produced by the preparation method as descried herein. The produced pharmaceutical composition may have improved mechanical properties and/or improved API elution profile. By elution profile is meant the profile of the curve of elution as a function of time. In some embodiments, the pharmaceutical composition produced by the present method has an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa. In some embodiments, the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C. In some embodiments, the API in the pharmaceutical composition produced by the present method comprises gentamicin sulfate.

[00122] Medical Devices

[00123] In another aspect, the present disclosure provides a medical device comprising a pharmaceutical composition as described herein or a pharmaceutical composition produced by the preparation method as described herein. For example, the medical device may be an implant.

Examples of medical devices that comprise API encapsulated in an encapsulating media are tibial inserts, acetabular liners, joint spacers, total knee femoral component, femoral head, acetabular shell, tibial trat, glenoid, trauma plate, fracture fixation devices, cochlear devices, visual prostheses, brain computer interfaces contact lenses, intraocular lenses, urinary and peripheral vascular catheters, endotracheal tubes, cardiac valves, embolic coils, vascular grafts, pacemakers, coronary stents, hernia meshes, total heart replacements and their cables, left ventricular assist devices and their cables, dental implants, penal implants, mammary implants and plastic surgery augmentation devices. In some embodiments, the implant is a joint replacement implant. In some embodiments, the implant is a joint replacement spacer implant to treat and/or prevent infection.

[00124] In another aspect, the present disclosure provides a joint replacement implant, which comprises a heat molded polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE) and gentamicin sulfate (GS), wherein particles of GS are encapsulated in pores of the heat molded polymeric material. In some embodiments, the particles of gentamicin sulfate have an average size of less than 1 μm. In some embodiments, the joint replacement implant comprises about 2% to about 20% (including, for example, about 2% to about 10% and about 5% to about 10%) by weight gentamicin sulfate.

[00125] In another aspect, the present disclosure provides a method of preparing an implant, which comprises generating a dispersion of a gentamicin sulfate (GS) in a liquid phase comprising a solvent and a non-solvent. The method further comprises contacting the dispersion of GS with a porous polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE), thereby producing an implant composition, wherein particles of GS are encapsulated in the pores of the porous polymeric material. The method further comprises heat molding the implant composition to produce the implant. The solvent and non-solvent may be any of the previously described solvents and non-solvents. The heat molding process can be carried out by the techniques as described herein.

[00126] In a non-limiting example, the method further comprises removing the solvent and the non-solvent from the implant to produce a dried implant composition and heat molding the dried implant composition to produce the implant.

[00127] In a non-limiting example, the method further comprises machining the implant produced by heat molding to form a shaped implant.

[00128] In some embodiments, the particles of gentamicin sulfate in the implant preparation method have an average size of less than 1 μm.

[00129] In some embodiments, the implant comprises about 2% to about 20% (including, for example, about 2% to about 10% and about 5% to about 10%) by weight gentamicin sulfate.

[00130] In some embodiments, the implant preparation method further comprises machining the implant produced by heat molding to form a shaped implant.

[00131] In another aspect, the present disclosure provides ab implant produced by the implant preparation method as described herein. For example, the produced implant can be shaped to be used as a joint replacement implant or a joint replacement spacer implant to treat and/or prevent infection .

[00132] The examples provided below illustrate the method, compositions, and device detailed herein, and are not intended to be limiting.

[00133] Examples

[00134] Example 1. Gentamicin sulfate particle formation with 140 proof ethanol and mixing with UHMWPE.

[00135] GS (1,770 mg) was added to 17.70 ml of 140-proof ethanol (70% v/v ethanol in water mixture). GS rapidly formed an agglomeration with a gummy appearance. The mixture was then vortexed to break down the agglomeration. After several minutes of vortexing, the mixture turned into a liquid dispersion. Under gravity or following centrifugation, the dispersion phase separated: (i) first phase was a clear supernatant and (ii) the second phase was a translucent, amber-colored, highly viscous fluid that settled at the bottom of the container. A sample of the amber-colored fluid on a glass slide revealed the presence of particles, likely GS particles, under optical microscopy. The phase-separated mixture was reversibly converted to the liquid dispersion form by shaking, for instance by vortexing. The mixture in its liquid dispersion form was mixed with 13,500 mg of GUR 1020 UHMWPE powder using a plastic spatula to generate a wet powder mixture. The wet powder was either used as-is (wet powder) or after it was dried in a fume hood at room temperature for about 16 hours through evaporation of the liquid water/ethanol phase (dry powder).

[00136] Example 2. Wet tablet molding using blend from Example 1.

[00137] The wet powder mixture of Example 1 was used to make tablets. The powder was placed inside cavity of a 13-mm diameter die and a plunger was used to apply 5 metric tons of force. The pressed tablets were left in a fume hood at room temperature for about 16 hours to dry through evaporation of the liquid phase (water/ethanol mixture). The tablets were subsequently dehydrated by heating in an oven at 110°C for 2 hours. The dehydrated tablets were then consolidated at 170°C and 20MPa in an aluminum/bronze mold. The mold and the plunger were heated first and then the tablets were placed in the mold cavity. The tablets were molded by applying a 20MPa pressure with the plunger.

[00138] Example 3. Dry powder molding using blend from Example 1.

[00139] The dry powder mixture of Example 1 was dehydrated in an oven at 110°C for 2 hours. The dehydrated powder mixture was then consolidated at 170°C and 20MPa in an aluminum/bronze mold in a manner similar to the one described in Example 2. The molded sample was cut with a razor blade and imaged using an optical microscope, revealing a "cobblestone" morphology with embedded domains comprising GS. The domains were located on either side of the typical resin flake boundaries of molded UHMWPE (FIG. 2).

[00140] Example 4. Dry tablet molding using blend from Example 1.

[00141] The dry powder mixture of Example 1 was used to make tablets. The powder was placed inside cavity of a 13-mm diameter die and a plunger was used to apply 5 metric tons of force. Tablets were dehydrated in an oven at 110°C for 2 hours. The dehydrated tablets were then consolidated at 170°C and 20MPa in an aluminum/bronze mold in a manner similar to the one described in Example 2.

[00142] Example 5. Gentamicin sulfate particle formation with ethanol or acetone addition to aqueous GS solution and mixing with UHMWPE.

[00143] Multiple aqueous GS solutions (aqGS) were prepared, each by adding 1,770 mg of GS to 5.31 ml of water. Non-solvents were added to these solutions as shown in Table 1 to obtain formulations F5.1, F5.2, F5.3, F5.4, and F5.5. The addition of non-solvents to aqGS solutions caused GS to precipitate. Subsequent shaking, for instance by vortexing, formed liquid dispersions. The liquid dispersion comprised API particles and carrier media. Under gravity or following centrifugation, the liquid dispersions of F5.1, F5.2, and F5.3 phase separated: (i) the first phase was a clear supernatant and (ii) the second phase was a translucent, amber-colored, highly viscous fluid that settled at the bottom of the container. Samples of the amber-colored fluid on a glass slide revealed the presence of particles, likely GS particles, under optical microscopy.

[00144] Under gravity or following centrifugation, the liquid dispersion of F5.4 separated into 4 phases: (i) a clear supernatant, (ii) a white supernatant, (iii) a dark amber color layer, and (iv) a translucent, amber-colored, highly viscous fluid that settled at the bottom of the container. Optical microscopy revealed the presence of particles, likely GS particles, in fluid layers (ii), (iii), and (iv) on a glass slide.

[00145] The phase-separated forms of all four of these mixtures were reversibly converted to their liquid dispersion forms by shaking, for instance, by vortexing. The mixtures, in their liquid dispersion form, were individually mixed (manual mixing) with 13,500 mg of GUR 1020 UHMWPE powder using a plastic spatula. The manual mixing can be replaced or augmented by using a hand cranked or motorized mixer, such as a bone cement mixer. The resulting wet powder blends were either

used as-is (wet powder) or after they were dried in a fume hood at room temperature for about 16 hours through evaporation of the liquid water/ethanol phase (dry powder).

Table 1

Formulation IDs	Non-Solvent	Amount of Non-Solvent (ml)
F5.1	Ethanol	12.39
F5.2	Acetone	12.39
F5.3	Ethanol	1.77
	Propanol	10.62
F5.4	Vitamin-E in Ethanol Solution [a]	12.39
F5.5	Methanol	12.39
[a] Ethanol solution with a concentration of 12mg/mL Vitamin-E		

[00146] Example 6. Dry powder molding using blends from Example 5.

[00147] The dry powders of Example 5 (F5.1, F5.2, F5.3, and F5.4) were individually dehydrated in an oven at 110°C for 2 hours. The dehydrated powder mixtures were then individually consolidated at 170°C and 20MPa in an aluminum/bronze mold in a manner similar to the one described in Example 2.

[00148] The wet powder of F5.4 from Example 5 was dried in an oven at 45°C for about 16 hours. The dried powder was dehydrated in an oven at 110°C for 2 hours. The dehydrated powder mixture was then consolidated at 170°C and 20MPa in an aluminum/bronze mold in a manner similar to the one described in Example 2.

[00149] Example 7. Dry tablet molding using blend from Example 5.

[00150] The dry powder of Example 5 (F5.1) was used to make tablets. The powder was placed inside cavity of a 13-mm diameter die and a plunger was used to apply 5 metric tons of force. Tablets were dehydrated in an oven at 110°C for 2 hours. The dehydrated tablets were then consolidated at 170°C and 20MPa in an aluminum/bronze mold in a manner similar to the one described in Example 2.

[00151] Example 8. Dry powder molding with different drying/dehydration conditions using blend from Example 1.

[00152] The wet powder of Example 1 was dried in an oven at different temperatures and durations followed by consolidation in a mold. The dried and then dehydrated powder blends were consolidated at 170°C and 20MPa in an aluminum/bronze mold as described in Example 2. Most of

the drying and dehydration was carried out in air as indicated in Table 2, indicating that the oven was filled with air at ambient pressure. Partial vacuum drying/dehydration conditions were achieved by partially evacuating the air from the oven chamber using a vacuum pump. When the oven is under partial vacuum the pressure in the oven chamber is below ambient pressure. In some embodiments the oven chamber is filled with an inert gas before evacuating to achieve partial vacuum. Below in Table 2 are the various sequences used in drying and dehydrating the wet powder blend (GS and UHMWPE) of Example 1.

Table 2

Treatment IDs	Oven Drying Conditions	Oven Dehydration Conditions
T8.1	45°C for 1 hour in air	110°C for 2 hours in air
T8.2	45°C for 16 hours in partial vacuum	110°C for 2 hours in air
T8.3	70°C for 1 hour in air	110°C for 2 hours in air
T8.4	90°C for 1 hour in air	110°C for 2 hours in air
T8.5	45°C for 16 hours in air	90°C for 3 hours followed by 60°C for 30 min in air
T8.6	45°C for 4 hours in partial vacuum	90°C for 3 hours followed by 60°C for 30 min in air
T8.7	22°C for 16 hours in air	110°C for 2 hours in air

[00153] Example 9. Vancomycin Hydrochloride (VH) particle formation with ethanol or acetone addition to aqueous VH solution and mixing with UHMWPE.

[00154] Multiple aqueous VH solutions (aqVH) were prepared, each by adding 708 mg of GS to 5.31 ml of water. Non-solvents were added to these solutions, as shown in Table 3 to obtain the formulations F9.1, F9.2, F9.3, and F9.4. The addition of non-solvents to aqVH solutions caused VH to precipitate. The dispersion was milky and slightly pink-colored. The VH particles were suspended in the liquid phase.

[00155] The liquid dispersions of Table 1 were individually mixed with 14,400 mg of GUR 1020 UHMWPE powder to prepare wet blends. The wet blends were used as dry powder blends after evaporating the liquid phase as described in Example 12 below.

Table 3

Formulation IDs	Non-Solvent	Amount of Non-Solvent (ml)
F9.1	Ethanol	12.39
F9.2	Acetone	12.39
F9.3	Ethanol	1.77
	Propanol	10.62
F9.4	Methanol	12.39

[00156] Example 10. Vancomycin Hydrochloride (VH) particle formation with ethanol or acetone addition to aqueous VH solution and mixing with UHMWPE.

[00157] Multiple VH solutions were prepared, each by adding 354 mg of VH to 17.70 ml of ethanol-water mixtures, including 80, 90,100,120, and 140 proof ethanol. The solutions were individually mixed with 14,700 mg of GUR 1020 UHMWPE powder to prepare wet blends. VH particle formation occurred in situ in and/or around the PE flakes after blending as a result of changes that occurred in the ethanol to water ratio in the mixture during drying as described in Example 12 below.

[00158] Example 11. VH and GS particle formation with ethanol addition to aqueous VH/GS solution and mixing with UHMWPE.

[00159] VH and GS solutions were prepared by dissolving 354 mg VH and 1,062 mg GS in 5.31 ml water. Following the recipe for F5.1 of Table 1, ethanol was added to the VH/GS aqueous solution to form VH and GS particles. There was a phase separation in the aqueous VH/GS dispersion similar to what was observed in Example 5. Following shaking and/or mixing, 13,800 mg of GUR 1020 UHMWPE powder was added to the liquid dispersion to form a wet blend. This wet blend was used as dry a powder blend after evaporating the liquid phase as described in Example 12 below.

[00160] Example 12. Dry powder molding with different drying/dehydration conditions using blends from Examples 9, 10 and 11.

[00161] The wet blends from Examples 9, 10, and 11 were dried in an oven at different temperatures and durations (T12.1, T12.2, T12.3, T12.4, T12.6, T12.7), then consolidated in a mold. The dried and then dehydrated powder blends were consolidated at 170 °C and 20MPa in an aluminum/bronze mold as described in Example 2. Most of the drying and dehydration were carried out in the air, as indicated in Table 4. In some embodiments, T12.5 drying conditions can be used.

Table 4

Treatment IDs	Oven Drying Conditions	Oven Dehydration Conditions
T12.1	22°C for overnight in air	110°C for 2 hours in air
T12.2	45°C for 6 hours in partial vacuum	110°C for 2 hours in air
T12.3	45 ° C for 6 hours ramped to 90 overnight	110°C for 2 hours in air
T12.5	45°C for 16 hours in partial vacuum	90°C for 3 hours followed by 60C for 30 min in air
T12.6	45°C for 4 hours in partial vacuum	90°C for overnight in air
T12.7	45°C for 4 hours in partial vacuum	90°C for overnight followed by 110C for 2 hours in air

[00162] Example 13. Blending, drying, and dehydration with Dual Asymmetric Centrifuge and powder molding.

[00163] An aqueous GS solution was prepared by adding 18.80 g of GS to 70.8 ml of water. 165.2 ml ethanol was added to this solution, which caused a phase separation, resulting in a liquid dispersion. 184 g of GUR 1020 UHMWPE was added to the liquid dispersion to make a mixture, which was placed into a Dual Asymmetric Centrifuge device (Speedmixer, Flacktek). The SpeedMixer was operated at 800rpm for 1 minute to blend the mixture. This is also known as homogenization of the mixture to increase the uniformity of the GS particles blended in with the UHMWPE flakes. The rotational speed of the SpeedMixer was then increased to 1400 RPM under vacuum to evaporate the solvents, that is ethanol and water. The rotational mixing achieved in the mixture caused an increased in temperature, which together with vacuum helped dry and dehydrate the mixture in about 20 minutes. Several such blends were made and stored either in sealed jars with minimal headspace or in vacuumed and heat-sealed pouches until they were consolidated. Dehydrated powder blends were consolidated at 170 °C and 20MPa in an aluminum/bronze mold, as described in Example 2.

[00164] Example 14. Blending, drying, and dehydration with industrial scale blender and powder molding.

[00165] An aqueous GS solution was prepared by adding 18.80 g of GS to 70.8 ml of water and placed in Littleford M-5 industrial mixer. 165.2 ml ethanol was then added to the mixer and the mixer was operated at 3Hz for 10 minutes to make a liquid dispersion of GS particles in water/ethanol mixture. The mixer was brought to a stop and 184 g of GUR 1020 UHMWPE was added to the

dispersion in the mixer. The mixer was operated at 3Hz under vacuum and heated to 45 °C to dry the blend. Drying removes both ethanol and water. The blending was continued for 16 hrs. under vacuum at 45 °C as which point the temperature of the mixer was increased to 90 °C and mixing continued for three additional hours under vacuum to dehydrate the samples. In some embodiments, the dehydration temperature can be 110°C. In some embodiments, following dehydration, the temperature of the mixer was reduced to 60°C. Dehydrated blends were stored in sealed jars with minimal headspace or vacuumed pouches until consolidated. Dehydrated powder blends were consolidated at 170 °C and 20MPa in an aluminum/bronze mold, as described in Example 2.

[00166] Example 15. Gentamicin sulfate particle mixtures and mixing with UHMWPE under high pressure.

[00167] The ethanol/aqGS/UHMWPE mixture from sample 5 is poured into a high-pressure chamber. The pressure is set at a minimum of 1 bar, and the mixture is left under pressure for at least 1 minute. After pressure release, the pressurized wet powder mixture is left at room temperature for at least 16 hrs. to evaporate the liquid (water/ethanol mixture) or placed in an oven at a temperature above room temperature, for instance at any of the oven drying conditions listed in Table 2. The powder mixture is then further heated in an oven at 110 °C for 2 hrs. to further remove the bound water in GS or any dehydration conditions listed in Table 2. The dehydrated powder mixture is then consolidated at 170 °C and 20MPa in an aluminum/bronze mold.

[00168] Example 16. GS Particle Encapsulation in Peroxide Crosslinked UHMWPE

[00169] The API particles and the carrier media (water and ethanol) from Example 5 were added to UHMWPE GUR 1050 blended with di-cumyl peroxide and vitamin E (see US17/222,398 High Temperature Melting, US14/389,852 Peroxide Cross-Linking of Polymeric Materials in the Presence of Antioxidants (Abandoned), US16/291,283 Peroxide cross-linking and high temperature melting, US17/703,288 Di-Cumyl Peroxide Crosslinking of UHMWPE, US 2004/0156879; U.S. application Ser. No. 11/465,544, filed Aug. 18, 2006; PCT/US2006/032329 Published as WO 2007/024689). Methods to prepare UHMWPE Blended with di-cumyl peroxide and vitamin E are described in various patents referred to above, all of which are incorporated in full by reference herein. The wet powder mixture was left at 45 °C for at least 16 hrs. to evaporate the carrier liquid in an oven. The powder mixture was then further heated in an oven at 110 °C for 2 hrs. to further remove the bound water in the GS. Then, the dehydrated powder mixture was consolidated at 170 °C and 20MPa in an aluminum/bronze mold under ventilation.

[00170] Example 17. GS Particle Encapsulation in UV Crosslinked UHMWPE

[00171] The API particles and the liquid carrier media (water and ethanol) from Example 5 are added to UHMWPE blended with a UV initiator, for instance 4h-benzophenone or other initiators mentioned in US16/635,105 UV-Initiated Reactions In Polymeric Materials. The wet powder mixture is dried and heated to further remove the bound water in the GS. Then, the dehydrated powder mixture is consolidated. The consolidated blocks are machined into implant shape and crosslinked by shining UV light on surfaces, preferably on articular surfaces.

[00172] Example 18. GS Particle Encapsulation in Radiation Crosslinked UHMWPE

[00173] The molded blocks from Examples 6, 7, and 8 are radiation crosslinked either before or after the molded blocks are machined into the shape of an article such as an implant. Crosslinking is achieved by ionizing radiation, such as electron beam, gamma radiation, x-ray radiation, or radiation methods described in US8,933,145 High Temperature Melting, US7,205,339 Selective controlled manipulation of polymers, US14/400375 Antioxidant-stabilized joint implants the details of which incorporated in full.

[00174] Example 19. GS particle formation with ethanol addition to aqueous GS solution and mixing with Polymethylmethacrylate

[00175] An aqueous GS solution with ethanol was prepared by dissolving 1000 mg of GS in 14.16 ml of water and by adding 33.04 ml of ethanol. Another aqueous GS solution with ethanol was prepared by dissolving 1000 mg of GS in 4.248 ml of water and by adding 9.912 ml of ethanol. The liquid dispersions formed contained particles of GS. After shaking and/or mixing, the liquid dispersions were individually mixed with Simplex-P bone cement by blending the liquid dispersions with 40 g of premix PMMA powder, including 6 g PMMA, 30 g of methyl methacrylate-styrene-copolymer (containing 1.7% Benzoyl peroxide), and 4 g of Barium sulfate. The mixtures were further mixed with a bone cement mixer (MixeVac III, Stryker). The resulting blends were wet and needed to be dried by evaporating the water and ethanol. The dried blends were individually sieved with a 300-micrometer sieve. Following sieving, a solution of 19.5 ml methyl methacrylate 0.5ml N,N dimethyl-para-toluidine and 75 ppm hydroquinone was added to the dry blend and mixed to cure the materials. The curing boFne cement is used as a bone void filler, as a fixation device to fix implants in place, and/or as a spacer to treat periprosthetic joint infection patients.

[00176] Example 20. Enhanced Antibiotic Release and Mechanical Strength in UHMWPE Antibiotic Blends: The Role of Sub-Micron Getnamicin Sulfate Particles

[00177] Materials

[00178] Ethanol and isopropyl alcohol were sourced from Sigma Aldrich (St. Louis, MO), GUR 1020 UHMWPE flakes from Ticona (Florence, KY), and gentamicin sulfate (GS) from Fujian Fukang Pharmaceutical Co. (China).

[00179] Methods

[00180] Preparation of GS Particles and Blending with UHMWPE: The sub-micron particles were produced by adding ethanol into a water-based GS solution, resulting in GS particle dispersions in the ethanol-water mixture. These dispersions with GS precipitates were then blended with UHMWPE flakes using a dual asymmetric centrifugal (DAC) mixer, specifically the SpeedMixer DAC 1200-1000 Twin Vacuum model (Flacktek, South Carolina) operated at 1200 RPM under 25 mbar vacuum to help remove ethanol and water from the mixture. The sub-micron GS particles were blended with UHMWPE flakes at concentrations of 6%, 8%, and 10% by weight and molded to produce the sub-micron GS UHMWPE blends.

[00181] As-received particles were sieved with a 75 μm sieve. Particles under 75 μm in size were then blended with UHMWPE flakes at a concentration of 10% by weight using the DAC, operated at 1200 RPM under 25 mbar vacuum and molded to produce the as-received GS UHMWPE blends.

[00182] Resolidified particles were produced by freezing a GS aqueous solution for 16 hours at -20°C and subsequently lyophilizing it for 48 hours. A mortar and pestle were used to break down the lyophilized residue, which was sieved first through a 150-μm and then a 75-μm sieve. Particles between 75 and 150 μm in size were blended with UHMWPE flakes at a concentration of 10% by weight using the DAC, operated at 1200 RPM under 25 mbar vacuum and molded to produce the resolidified GS UHMWPE blends.

[00183] Consolidation of GS UHMWPE Blends: GS UHMWPE blends were compression molded in an aluminum-bronze rectangular mold (50×85 mm^2) at 170°C for 20 minutes under 5MPa for 5 minutes, 10MPa for 5 minutes, and 20 MPa for 10 minutes and allowed to cool under 20MPa of pressure for 50 minutes. The thickness of the molded test samples was 1cm.

[00184] Imaging: Digital light microscopy, SEM, and FIB-SEM were performed to investigate the morphology of the consolidated GS UHMWPE blends.

[00185] The morphology of sub-micron, as-received, and resolidified GS UHMWPE blends were visualized using digital light microscopy. Samples were prepared by cutting thin films off the molded articles using a microtome. The thin films were then imaged using a light microscope (SZX12 Optical Microscope / DP11 Digital Camera from Olympus Life Sciences, USA) and a digital light microscope (Keyence VHX-6000) and VH-ZST (ZS-200) lens under ring light imaging technique to visualize domains of GS in UHMWPE.

[00186] The morphology of the 10% sub-micron GS UHMWPE blend was visualized using freeze-fractured SEM samples that were coated with 5 nm of 80:20 Pt:Pd using a Q150T sputter coater

(Quorum Technologies, East Sussex, UK). Imaging was performed with a JEOL JSM-7900F field emission gun scanning electron microscope (Peabody, MA) at 5 kV. Elemental analysis was also performed at 10 kV using an Ultim Max EDS detector (Oxford Instruments, Concord, MA).

[00187] The morphology of the 10% sub-micron GS UHMWPE blend was visualized using FIB-SEM (Zeiss Crossbeam 550 Focused Ion Beam with Gemini 2, Germany) with samples coated with 1 μm Pt precursor in the chamber. A window was machined with FIB (3-15 nA) to visualize the subsurface particles.

[00188] Mechanical testing: Type V tensile specimens were prepared by machining 3.2-mm thick sections (Shopbot Tools, Inc., Durham, NC) and templating the sections with a die sample cutter using Dewes-Gumbs Manual Expulsion Press, Model 1.5T DGD (Dewes-Gumbs Die Company, Long Island City, NY), and Expulsion die for press Model ASTM D638-V (Dewes-Gumbs Die Company, Long Island City, NY). Specimens were tested on an MTS Insight 2 electromechanical load frame (Eden Prairie, MN) at a crosshead speed of 10 mm/min. An MTS LX300 laser extensometer was used to measure true strain. ASTM D638 standards were followed to calculate the % elongation-at-break (EAB), yield strength (YS) in MPa, and the ultimate tensile strength (UTS) in MPa.

[00189] IZOD specimens were made by machining the molded blocks to the desired dimensions (63.5×12.7×3.2 mm). The resulting bars were notched using a Panpress 502 with posi-stop (PanaVise, Reno, NV) and validated geometry using an STM6 Measuring Microscope (Olympus, Waltham, MA). The toughness was determined using a CEAST 9050 pendulum impact testing machine (Instron, Norwood, MA) following ASTM F648.

[00190] Pin on disk (POD) wear testing: A multidirectional Ortho-POD™ wear tester (AMTI, Watertown, MA) was used to determine the wear rate of the GS UHMWPE blends as outlined in ASTM F732-17 Annex A2 (ASTM. Vol. 13.01 ASTM Standard F732-17 (2017)). Flat-ended cylindrical pins, 9 mm in diameter and 13 mm in height, were articulated against flat polished CoCr discs with Ra < 0.06 μm in a 10 mm x 5 mm rectangular path at 2 Hz. A Paul-type variable load curve with a peak contact stress of 5.1 MPa was applied axially during articulation. Testing was done in room temperature bovine calf serum (Sigma-Aldrich, St. Louis MO) preserved with ethylenediaminetetraacetic acid (EDTA, Acros Organics, Waltham MA) and a penicillin-streptomycin solution (Sigma-Aldrich). It was interrupted after an initial 0.5 million-cycles (MC) and then daily after every 0.157 MC for assessment until a full week of testing was completed with 1.128 MC total.

[00191] At each assessment interval, the pins were cleaned, dried, and weighed. A wear rate was calculated via linear regression omitting the initial 0.5 MC of testing and expressed in milligrams per million cycles.

[00192] The POD pins were pre-conditioned to ensure accurate POD wear testing results and eliminate the influence of weight changes due to the release of GS (gentamicin sulfate) from the UHMWPE blends. The UHMWPE pins, infused with sub-micron GS, underwent a thorough soaking phase. This involved immersing the pins in a specially prepared 50ml solution containing bovine calf serum, EDTA, and a penicillin-streptomycin mix. The purpose of this pre-soaking was to reach an equilibrium state where the pins absorbed fluid into the pores, left behind by eluting GS, thereby stabilizing their weight.

[00193] During this pre-conditioning phase, the pins were periodically removed from the solution, dried, and weighed. This process was repeated until a crucial stability criterion was met: the weight of the pins had to remain consistent, with two consecutive measurements showing a variation of less than 0.1%. Achieving this stability was crucial; it indicated that the release of GS from the pins had ceased, and any subsequent weight changes during POD wear testing would be attributed to wear and not to GS elution.

[00194] Elution: Prismatic elution strips ($3\times5\times20$ mm^3) were machined and washed according to an ultrasonic cleaning procedure for orthopaedic implants (Orchid, Detroit, MA). Specifically, two ultrasonic baths (Fisher, Waltham, MA) were prepared, the first containing 10g/l solution of concentrated, anionic detergent (Alconox, White Plains, NY) and the second containing DI water. The baths were heated to 49°C. Strips were then submerged in each bath for 15 minutes and sonicated. After washing, the strips were swirled in a beaker containing 100% isopropyl alcohol and left to dry overnight in a fume hood.

[00195] Six prismatic strips (n=6) of each GS UHMWPE blend were eluted in 2ml or 20ml syringes filled with DI water and in a shaking incubator at 37°C. Entire eluent was collected at predetermined time points and refreshed with DI water (0.25, 1, 2, 3, 4, 7, 10, 14, 21, and 28 days). The collected samples were derivatized using the fluorometric *o*-phthalaldehyde assay and measured with a spectrofluorometer plate reader (Biotek, Agilent, Santa Clara, CA). Cumulative and percent cumulative releases were calculated for normalized 100 cm^2 surface area as well as the daily release rate. MATLAB was used to analyze release data with a single-compartment pharmacokinetic model to predict in vivo concentrations of GS UHMWPE blends.

[00196] Antimicrobial testing:

[00197] GS function after elution from the molded 10% sub-micron GS UHMWPE blend was validated by antimicrobial susceptibility testing according to Clinical and Laboratory Standards (CLSI) protocol M07-A10. *Staphylococcus aureus* American Type Culture Collection (ATCC) 12600 strain were cultured overnight at 35°C on tryptic soy agar (TSA) plates. After 6 hours of elution at 37°C, the gentamicin concentration of eluents from six elution strips was determined. 50 µl eluents were serially

diluted using 50 µl cationic adjusted- Mueller Hinton Broth (CA-MHB) in a sterile 96-well plate to achieve a concentration range that included expected MIC for gentamicin. Further, 50µl of CA-MHB was added to all the wells. Subsequently, 4-5 well-isolated colonies from each plate were suspended in 3 ml of normal saline to achieve an initial turbidity of $1x10^8$ CFU/ml. The bacterial suspension was then diluted 100× in CA-SMHB. 100 µl of the diluted bacteria stock was added to all wells to achieve 10^4-10^5 CFU/ml, except for media control. The assay plate was incubated overnight for 16-20 hours (depending on CLSI guidelines for each strain) at 35°C.

[00198] MIC was defined as the lowest concentration of antibiotic that completely inhibited the growth of the microorganism as detected by the unaided eye. For a test to be considered valid, a ≥2mm button or definite turbidity needed to be observed in growth-control wells and no wells were skipped.

[00199] MBC was determined by drop plating three 5µl volumes of MIC, 2×MIC, and 4×MIC, withdrawn from their corresponding wells. These plates were incubated at 35°C overnight. The MBC was defined as the concentration that exhibited no growth across all three replicates.

[00200] Nuclear Magnetic Resonance (NMR): Three prismatic elution strips made from 10% sub-micron GS UHMWPE blend were placed in 5 ml of deuterated water for 24 hours of elution at 37°C. GS eluted in deuterated water from these samples and 2 mg/ml GS solution in deuterated water (control) were analyzed with ^1H NMR (500MHz Varian spectrometer (Palo Alto, CA) and MNova software (MestreLabs, Santiago de Compostela, Spain). NMR results of the eluted GS were compared to that from the control GS solution.

[00201] Statistics: The tensile test results of GS UHMWPE blends were analyzed using one-way Analysis of Variance (ANOVA) followed by Tukey's Honestly Significant Difference (HSD) test to assess the effect of loading. This method was applied separately for the investigation of GS particle types and sub-micron loading ratios. Additionally, the influence of the sub-micron particle loading ratio on the wear rate was examined using the same statistical approach. For elution experiments, a two-way ANOVA with least significant differences was employed, followed by Tukey HSD to explore the impact of time and loading on the outcomes. All statistical analyses were conducted using IBM SPSS Statistics, version 28.0.0.0 (190).

[00202] Results

[00203] Morphology: The morphological examination of UHMWPE loaded with resolidified, as-received, and sub-micron GS particles showed marked variations. The resolidified and as-received particles formed distinct GS domains within the UHMWPE matrix (FIGS. 10A-10B). In contrast, sub-micron particles were distributed along the contours of the UHMWPE flakes inside the fusion lines (see arrows in FIGS. 10C-10D), creating a distinctive "cobblestone" pattern. Scanning Electron Microscopy (SEM) confirmed the presence of sub-micron GS particles and the development of this

cobblestone structure; elemental analysis indicated a higher concentration of oxygen and sulfur along the fusion lines of the flakes, confirming the presence of small GS particles forming the cobblestone structure (FIGS. 10E-10H). Additionally, Focused Ion Beam (FIB) SEM imaging disclosed sub-micron-sized pores, likely the original locations of GS particles, which were presumably displaced during the FIB-SEM surface cut, leaving only the pores visible (FIGS. 10I-10L). As shown in the schematic of FIG. 10M, in the resolidified and as-received states, the presence of GS particles inhibits the effective fusion of UHMWPE flakes, interrupting the fusion lines and partially replacing them with an interface between the UHMWPE flakes and the GS inclusion with poor interfacial strength. These particles create a barrier between the flakes, preventing them from forming complete fusion. Conversely, in the GS UHMWPE blend, the distribution of sub-micron particles within the UHMWPE pores allows for complete fusion of UHMWPE flakes.

[00204] Mechanical Properties: As the GS particle size increased from sub-micron to as-received and then to resolidified, there was a noticeable decrease in ultimate tensile strength (UTS), elongation at break (EAB), and yield strength (YS) (FIGS. 11A-11C). Specifically, the YS was significantly higher for sub-micron particles compared to both as-received and resolidified GS UHMWPE blends ($p<0.01$). On the other hand, YS of sub-micron GS UHMWPE blends similar to each other ($p>0.05$) (2% to 10% sub-micron GS blending: 20.4±0.3, 20.4±0.2, 20.2±0.4, 20.3±0.2, and 21.1±1.2 MPa). The UTS of the sub-micron blend was significantly higher than that of the resolidified blend ($p<0.01$) and was not different from that of the as-received blend. The EAB of sub-micron blends was similar to those of resolidified and as-received GS UHMWPE blends. Within the sub-micron GS UHMWPE blends, increased GS content led to reductions in EAB, UTS, and IZOD impact strength (FIGS. 11D-11F). The IZOD impact strength of 6% GS UHMWPE blend was similar to that of virgin UHMWPE, whereas the impact strengths of 8% and 10% blends were lower (FIG. 11F).

[00205] Pin on Disc Wear Testing: The wear rates of sub-micron GS UHMWPE blends when articulating against polished Co-Cr discs remained unchanged compared to the virgin UHMWPE. The measurements for 10%, 8%, 6% sub-micron GS UHMWPE blends and virgin UHMWPE were -12.98 ± 1.56, -11.43 ± 1.39, -13.24 ± 1.31, and -12.14 ± 0.98 mg per million cycles, respectively ($p>0.05$ for all comparisons).

[00206] Antimicrobial Testing: Antimicrobial testing against *Staphylococcus aureus* confirmed the activity and the stability of eluted GS: Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) ranges of GS eluted from the GS UHMWPE blends regardless of GS particle size on the blends (0.5-2 μg/ml and >4 μg/ml, respectively) and control GS solutions were not different.

[00207] Elution: The release rate, percent cumulative release, and cumulative release as a function of elution time were highest for the 10% sub-micron GS UHMWPE blend in comparison with the resolidified and as-received GS UHMWPE blends with the same GS loading. In terms of the release rate, that of the 10% sub-micron GS UHMWPE blend was followed by that of the 10% resolidified and then that of the 10% as-received GS UHMWPE blend in descending order (FIG. 12A-12C). The elution rate of the 10% sub-micron GS UHMWPE blend on the 28th day was dramatically higher than those of the resolidified GS blend and as-received GS UHMWPE blend (11.28 vs. 0.11 and 0.26 mg/day, respectively). Among the sub-micron GS UHMWPE blends, the release rate decreased with decreasing GS content (FIG. 12D-12F). On the 28th day, the release rates of 6% and 8% sub-micron GS particles were 0.12 and 1.30 mg/day, respectively. The release rate of 6% was not statistically different between elution days 1-28. The 10% sub-micron GS UHMWPE blend had more cumulative release over the 28 days compared to all other groups ($p<0.01$). The release rate of the 10% sub-micron GS UHMWPE blend was similar between days 1-21, and on day 28, it was approximately 10 and 100 times more compared to those of the 8% and 6% sub-micron GS UHMWPE blends, respectively. Predicted in-vivo concentrations resulting from gentamicin release from the 8% and 10% sub-micron GS UHMWPE blends were higher than 100×MIC for 28 days while those of resolidified and as-received GS UHMWPE blends rapidly fell below this level (FIG. 12G-12H).

[00208] Pharmacokinetic model: a pharmacokinetic (PK) model was employed to predict the in vivo release of gentamicin sulfate (GS) from GS UHMWPE blends. This model computes clearance of GS using the half-life of GS and a first-order kinetics. Due to the absence of data on intra-articular half-life of GS, amikacin sulfate (AS) was utilized as a surrogate, given its similar serum half-life to GS (2-3 hours as per aminoglycoside guidelines). Hence, GS's intra-articular half-life was inferred from the known intra-articular half-life of AS (3.8-4.6 hr). The following equations describe the pharmacokinetics of GS:

$$t_{1/2} = \frac{0.693}{\lambda}, \qquad (Eq\ 1)$$

where $t_{1/2}$ is half-life of GS (in hours) and λ is the decay constant (in 1/hours) and;

$$dC = C_t - C_t \times e^{-\lambda dt} + k \times \frac{dt^n}{V}, \qquad (Eq\ 2)$$

where, C_t is the concentration of GS in the synovial fluid (mg/ml) at a given time, t, and dC is the concentration change in a time derivative (dt, in hours), and λ is the decay constant of GS within the synovial fluid. The coefficients k and n were derived through the application of the Korsmeyer-Peppas model to the cumulative elution profile of the GS blends (mg). During the concentration

calculation process, values obtained from the Korsmeyer-Peppas equation (k and n) were normalized by the corresponding effect volume, denoted as V. The typical volume of synovial fluid in healthy adults ranges from 0.5 to 4 mL, with increased volumes observed in cases of knee infection-induced swelling. For the calculations, a fixed volume of 4 mL was employed. The time derivative of cumulative release curves was computed using the Korsmeyer-Peppas equation, and a nonlinear regression model was applied in MATLAB (R2022b Update 1, MathWorks, US). The resulting model served as input for Eq 2, allowing the estimation of instantaneous concentration within the specified volume. Three different scenarios were simulated with varying half-life values of intraarticular GS: short, nominal, and long (3, 4.5, and 6 hours, respectively) (FIGS. 13A-13B). The predicted GS concentration in the knee stayed below the bolus injection levels (80 mg) for all scenarios, indicating that use of the GS UHMWPE blends in a clinical setting could be safe. Additionally, two different scenarios were simulated with varying half-life values of GS in joint spaces: 3 and 6 hours. (FIGS. 14A-14B). Predicted GS concentration profiles in joint spaces for different sizes of GS UHMWPE blends, including resolidified, as-received, and sub-micron GS and calculated drug concentrations over time for both 3-hour and 6-hour half-life scenarios, assessing the ability of each blend size to maintain therapeutic levels above 100× MIC. The findings indicate no significant differences in the GS concentration profiles between the 3-hour and 6-hour half-life scenarios across all blend sizes. However, a critical distinction was observed in the ability to maintain the 100× MIC threshold. While resolidified and as-received blends failed to sustain this threshold, sub-micron GS UHMWPE blends consistently maintained concentrations significantly above the 100× MIC limit.

[00209] NMR: The ^{1}H NMR analysis of the eluted GS revealed no significant shifts in the observed peaks compared to those of the control GS (FIG. 15). The comprehensive list of chemical peaks can be found in Table 5.

Table 5. Multiplets of GS eluted from sub-micron GS UHMWPE blend.

	Name	Shift	Range	H's	Integral	Class	Method
1	A (m)	5.86	5.91 - 5.80	1	0.27	m	Peaks
2	20 (d)	5.09	5.11 - 5.07	1	0.26	d	Peaks
3	10 (m)	4.17	4.21 - 4.09	2	0.29	m	Peaks
4	3,12,22' (m)	3.98	4.07 - 3.95	2	0.46	m	Peaks
5	18,22",29 (qd)	3.8	3.86 - 3.75	3	0.55	qd	Peaks
6	15" (m)	3.55	3.61 - 3.49	1	0.19	m	Peaks
7	5,13,16 (m)	3.45	3.49 - 3.39	3	0.57	m	Peaks
8	28 (s)	2.88	2.90 - 2.86	4	0.68	s	Peaks
9	26 (s)	2.71	2.73 - 2.69	1	0.23	s	Peaks
10	6" (m)	2.49	2.56 - 2.46	1	0.11	m	Peaks
11	31 (s)	2.49	2.51 - 2.47	1	0.18	s	Peaks
12	8,15' (m)	2.01	2.10 - 1.97	2	0.35	m	Peaks
13	7' (s)	1.88	1.89 - 1.86	1	0.21	s	Peaks
14	6' (m)	1.54	1.59 - 1.49	1	0.25	m	Peaks
15	4,7",24 (m)	1.27	1.32 - 1.22	7	1.37	m	Peaks

[00210] In analyzing the NMR spectra of GS eluted from a sub-micron GS UHMWPE blend, MestReNova software (version 14.2.0-26256) was employed. The spectra of both samples were compared using the superimpose mode, with an auto assignment tool assisting in identifying the peaks (as shown in FIG. 16). In this comparison, while the original GS showed 16 multiplets corresponding to 32 hydrogen atoms, it is noted that the GS eluted from the blend displayed 15 multiplets for 31 hydrogen atoms (details in Table 5).

[00211] The primary discrepancies in multiplet assignments were observed within the chemical shift ranges of 4.18-4.04, 3.61-3.38, 2.52-1.9, and 1.32-1.22 ppm, as detailed in FIG. 17. Closer examination revealed that these differences predominantly involve variations in peak heights and minor peak shifts. Such changes are consistent with concentration differences between the control GS sample and the eluted sample.

[00212] Importantly, these observed variations in the NMR spectra do not indicate alterations in the molecular structure or functional integrity of GS. The core molecular framework and pharmacological functionality of GS remain intact, as the differences in NMR spectra can be attributed to concentration effects rather than structural modifications. Thus, the essential characteristics of GS are preserved, even when eluted from a sub-micron GS UHMWPE blend.

[00213] Discussion

[00214] Our hypothesis regarding the effect of particle size in gentamicin sulfate particle encapsulation in UHMWPE tested positive; the morphological analysis of resolidified, as-received, and sub-micron GS particles and their integration within the UHMWPE matrix revealed distinct morphological features, which significantly influenced the resultant material properties.

[00215] UHMWPE is not melt-processable due to its high molecular weight (around 2-5 million g/mol), very highly entangled molecular structure, and high melt viscosity. Instead, UHMWPE flakes are sintered together by applying heat and pressure without substantial flow, commonly referred as consolidation21. Finished articles, such as implants, are machined after the sintering/consolidation step. Mechanical properties depend on the quality of the fusion of the resin flakes where any fusion defects adversely affect material strength. Diffusion of the UHMWPE chains across the flake boundaries is necessary for the efficient fusion of the material and improved mechanical properties. In gentamicin-loaded UHMWPE, the flakes consolidated around the GS particles, creating discontinuity and fusion defects in the case of as-received and resolidified particles, adversely affecting mechanical properties. In contrast, the sub-micron GS particles did not interfere with fusion as these particles were situated on either side of the fusion lines, not resulting in fusion discontinuities (FIG. 10M). These effects were reflected in the improved mechanical properties in the sub-micron GS UHMWPE blends in comparison with the other blends (FIGS. 11A-11C).

[00216] The UHMWPE incorporated with sub-micron GS particles demonstrated a unique 'cobblestone or honeycomb' morphology (FIGS. 10C-10D). The fusion lines were clearly visible after consolidation, with the sub-micron particles concentrated on both sides of these lines. This particular arrangement, as observed through SEM, FIB-SEM, and digital microscopy (FIGS. 10C-10M), implies better fusion of the polymer chains across grain boundaries and a more cohesive and potentially stronger fusion. In other words, the polymer diffusion across the grain boundaries is minimally hindered by the sub-micron GS particles during consolidation. This distinct cobblestone structure was only apparent with sub-micron GS particles, which were small enough to penetrate into the porosity of UHMWPE flakes during blending, thus not interrupting the fusion of flakes during consolidation.

[00217] The POD wear rates of UHMWPE were not affected with the addition of sub-micron GS particles, mirroring the results reported with as-received particles. The wear rate of UHMWPE has been largely linked to the plastic deformation of the network, where orientation in the principal direction of motion would weaken the material in the transverse directions. Since the EAB of the GS UHMWPE blends are not affected largely, it is likely that the large-scale deformation ability of the network is not significantly affected by therapeutic drug domains, thus also resulting in similar wear rates. In addition, the voids in the polymer resulting from the elution of GS may induce better lubrication by acting as reservoirs of bovine serum used as lubricant during wear testing. The

maintenance of wear rates at a similar level to virgin UHMWPE is particularly significant, as it suggests that sub-micron GS UHMWPE blends could have short- and mid-term performance similar to conventional primary implants fabricated with virgin UHMWPE.

[00218] The incorporation of sub-micron particles boosted elution rates (higher elution rates at each time point and overall higher elution as evidenced by the release rate curve) in addition to enhancing mechanical properties, which can be attributed to the unique distribution of sub-micron particles along the fusion lines within the UHMWPE matrix. The sub-micron GS particles created a uniform spatial arrangement which can be described by a 2D Archimedean honeycomb percolation model. Increased percolation of this structure would allow for more efficient permeation and release of the antibiotic, leading to the observed substantial increase in the elution rate, which is a critical factor in preventing infections in conjunction with orthopedic implants. For instance, Whiteside et al. ("Intra-articular infusion". *The Bone & Joint Journal* 98-B, 31-36 (2016)) reported that maintaining high local concentrations (3956 to 32150 μg/ml) with direct intraarticular infusion of antibiotics led to infection free results in 95% of the patients, while intra-articular concentrations close to the MIC of the antibiotics (2 to 3× MIC) failed.

[00219] NMR analysis of the GS released in deuterated water from the 10% sub-micron GS UHMWPE blend demonstrated the heat stability of GS after exposure to 170°C for 20 minutes during consolidation, as evidenced by the absence of significant shifts in the observed peaks (FIGS. 16 and 17). In addition, MIC/MBC studies confirmed the stability and functionality of eluted GS from consolidated samples. Together, these findings affirm that the ng process used to create sub-micron GS UHMWPE blend blocks did not compromise the stability or functionality of the GS, thereby confirming the potential of this method for preparing these materials for medical use.

[00220] As described herein, the novel method of incorporating drug particles into ultra-high molecular weight polyethylene (UHMWPE) flakes could enable the sustained and consistent delivery of a diverse array of drugs. The tortuosity of UHMWPE flakes enables the penetration of sub-micron-sized particles into the UHMWPE, and due to very low melt flow rate, particles stay inside the pores, creating a confined structure during molding. The findings confirmed that the new morphology created by the incorporation of the drugs with reduced particle size significantly enhanced the mechanical properties of the material and, more importantly, led to a prolonged and intensified drug release. Mechanical properties of GS UHMWPE blends prepared with sub-micron GS particles were comparable to those of clinically available implant materials, highlighting the potential of using GS-loaded UHMWPE in other joint arthroplasty applications. This potential paradigm shift could enable the incorporation of therapeutics into UHMWPE with minimal loss of strength and controlled sustained therapeutic release, making the technology suitable not only for antibiotic spacers to treat

infected total joint patients but also in various surgical scenarios, including high-risk revision cases, other revision surgeries, and even as a prophylactic measure in primary surgeries to prevent infections. This development could have a substantial clinical impact, potentially saving the US healthcare system approximately a billion dollars annually. Moreover, adopting this honeycomb percolation model for encapsulating other drugs could pave the way for UHMWPE becoming a new drug delivery material potentially addressing a range of medical conditions.

[00221] Each reference identified in the present application is herein incorporated by reference in its entirety.

[00222] While present inventive concepts have been described with reference to particular embodiments, those of ordinary skill in the art will appreciate that various substitutions and/or other alterations may be made to the embodiments without departing from the spirit of present inventive concepts. Accordingly, the descriptions provided herein are meant to be exemplary and does not limit the scope of present inventive concepts.

[00223] A number of examples are provided herein. Nevertheless, it should be understood that various modifications may be made. For example, suitable results may be achieved if the described techniques are performed in a different order and/or if components in a described system, architecture, device, or circuit are combined in a different manner and/or replaced or supplemented by other components or their equivalents. Accordingly, other implementations are within the scope of the present inventive concepts.

[00224] It will be appreciated by those skilled in the art that while the disclosed subject matter is described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. Each reference cited herein is incorporated by reference in its entirety.

[00225] Various features and advantages are set forth in the following claims.

[00226] For reasons of completeness, various aspects of the invention are set out in the following numbered clauses:

[00227] Clause 1. A pharmaceutical composition comprising:

a porous encapsulating medium; and

particles of an active pharmaceutical ingredient encapsulated in the pores of the porous encapsulating medium.

[00228] Clause 2. The pharmaceutical composition of clause 1, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm.

[00229] Clause 3. The pharmaceutical composition of any one of clauses 1-2, wherein the encapsulating medium comprises a polymeric material.

[00230] Clause 4. The pharmaceutical composition of clause 3, wherein the polymeric material comprises ultra-high molecular weight polyethylene (UHMWPE).

[00231] Clause 5. The pharmaceutical composition of any one of clauses 1-4, wherein the active pharmaceutical ingredient comprises an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof.

[00232] Clause 6. The pharmaceutical composition of clause 5, wherein the active pharmaceutical ingredient comprises an antibiotic.

[00233] Clause 7. The pharmaceutical composition of clause 6, wherein the antibiotic comprises gentamicin sulfate.

[00234] Clause 8. The pharmaceutical composition of any one of clauses 1-7, comprising about 1% to about 50% by weight the active pharmaceutical ingredient.

[00235] Clause 9. The pharmaceutical composition of clause 1, wherein the encapsulating medium comprises ultra-high molecular weight polyethylene (UHMWPE), wherein the active pharmaceutical ingredient comprises gentamicin sulfate, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm, and wherein the pharmaceutical composition comprises about 1% to about 20% by weight the active pharmaceutical ingredient.

[00236] Clause 10. The pharmaceutical composition of any one of clauses 1-9, which is a molded solid.

[00237] Clause 11. The pharmaceutical composition of any one of clauses 1-10, having an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa.

[00238] Clause 12. The pharmaceutical composition of any one of clauses 1-11, wherein the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and wherein the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

[00239] Clause 13. The pharmaceutical composition of clause 12, wherein the active pharmaceutical ingredient comprises gentamicin sulfate.

[00240] Clause 14. A method of preparing a pharmaceutical composition, the method comprising:

generating a dispersion of an active pharmaceutical ingredient in a liquid phase comprising a solvent; and

contacting the dispersion of the active pharmaceutical ingredient with a porous encapsulating medium, thereby producing the pharmaceutical composition, wherein particles of the active pharmaceutical ingredient are encapsulated in the pores of the porous encapsulating medium.

[00241] Clause 15. The method of clause 14, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm.

[00242] Clause 16. The method of any one of clauses 14-15, wherein the encapsulating medium comprises a polymeric material.

[00243] Clause 17. The method of clause 16, wherein the polymeric material comprises ultra-high molecular weight polyethylene (UHMWPE).

[00244] Clause 18. The method of any one of clauses 14-17, wherein the active pharmaceutical ingredient comprises an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof.

[00245] Clause 19. The method of clause 18, wherein the active pharmaceutical ingredient comprises an antibiotic.

[00246] Clause 20. The method of clause 19, wherein the antibiotic comprises gentamicin sulfate.

[00247] Clause 21. The method of any one of clauses 14-20, where the produced pharmaceutical composition comprises about 1% to about 50% by weight the active pharmaceutical ingredient.

[00248] Clause 22. The method of any one of clauses 14-21, wherein the liquid phase further comprises an inactive ingredient, a precipitating agent, a viscosity modifier, a surfactant, a pH modifier, an emulsifying agent, or a combination thereof.

[00249] Clause 23. The method of clause 22, wherein the liquid phase further comprises a precipitating agent, which comprises a non-solvent.

[00250] Clause 24. The method of any one of clauses 14-23, comprising generating a dispersion of gentamicin sulfate in a liquid phase comprising about 30% (v/v) water and about 70% (v/v) ethanol.

[00251] Clause 25. The method of any one of clauses 14-24, wherein the porous encapsulating medium comprises an antioxidant.

[00252] Clause 26. The method of any one of clauses 14-25, wherein the porous encapsulating medium comprises a crosslinking agent.

[00253] Clause 27. The method of any one of clauses 14-26, further comprising drying and/or dehydrating the pharmaceutical composition to produce a dried pharmaceutical composition.

[00254] Clause 28. The method of clause 27, further comprising molding the dried pharmaceutical composition by a heat molding process.

[00255] Clause 29. A pharmaceutical composition produced by the method of any one of clauses 14-28.

[00256] Clause 30. The pharmaceutical composition of clause 29, having an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa.

[00257] Clause 31. The pharmaceutical composition of any one of clauses 29-30, wherein the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and wherein the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

[00258] Clause 32. The pharmaceutical composition of any one of clauses 29-31, wherein the active pharmaceutical ingredient comprises gentamicin sulfate.

[00259] Clause 33. A medical device comprising the pharmaceutical composition of any one of clauses 1-13 and 29-32.

[00260] Clause 34. The medical device of clause 33, which is an implant.

[00261] Clause 35. The medical device of clause 34, which is a joint replacement implant.

[00262] Clause 36. The medical device of clause 34, which is a joint replacement spacer implant to treat and/or prevent infection.

[00263] Clause 37. A joint replacement implant comprising a heat molded polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE) and gentamicin sulfate, wherein particles of gentamicin sulfate are encapsulated in pores of the heat molded polymeric material.

[00264] Clause 38. The joint replacement implant of clause 37, wherein the particles of gentamicin sulfate have an average size of less than 1 μm.

[00265] Clause 39. The joint replacement implant of any one of clauses 37-38, comprising about 2% to about 20% by weight gentamicin sulfate.

[00266] Clause 40. A method of preparing an implant, the method comprising:

generating a dispersion of a gentamicin sulfate in a liquid phase comprising a solvent and a non-solvent;

contacting the dispersion of gentamicin sulfate with a porous polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE), thereby producing an implant composition,

wherein particles of gentamicin sulfate are encapsulated in the pores of the porous polymeric material; and

heat molding the implant composition to produce the implant.

[00267] Clause 41. The method of clause 40, comprising:

removing the solvent and the non-solvent from the implant composition to produce a dried implant composition; and

heat molding the dried implant composition to produce the implant.

[00268] Clause 42. The method of any one of clauses 40-41, wherein the particles of gentamicin sulfate have an average size of less than 1 μm.

[00269] Clause 43. The method of any one of clauses 40-42, wherein the implant comprises about 2% to about 20% by weight gentamicin sulfate.

[00270] Clause 44. The method of any one of clauses 40-43, further comprising machining the implant produced by heat molding to form a shaped implant.

[00271] Clause 45. An implant produced by the method of any one of clauses 40-44.

CLAIMS

1. A pharmaceutical composition comprising:

a porous encapsulating medium; and

particles of an active pharmaceutical ingredient encapsulated in the pores of the porous encapsulating medium.

2. The pharmaceutical composition of claim 1, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm.

3. The pharmaceutical composition of claim 1, wherein the encapsulating medium comprises a polymeric material.

4. The pharmaceutical composition of claim 3, wherein the polymeric material comprises ultra-high molecular weight polyethylene (UHMWPE).

5. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient comprises an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof.

6. The pharmaceutical composition of claim 5, wherein the active pharmaceutical ingredient comprises an antibiotic.

7. The pharmaceutical composition of claim 6, wherein the antibiotic comprises gentamicin sulfate.

8. The pharmaceutical composition of claim 1, comprising about 1% to about 50% by weight the active pharmaceutical ingredient.

9. The pharmaceutical composition of claim 1, wherein the encapsulating medium comprises ultra-high molecular weight polyethylene (UHMWPE), wherein the active pharmaceutical ingredient comprises gentamicin sulfate, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm, and wherein the pharmaceutical composition comprises about 1% to about 20% by weight the active pharmaceutical ingredient.

10. The pharmaceutical composition of claim 1, which is a molded solid.

11. The pharmaceutical composition of claim 1, having an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa.

12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and wherein the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

13. The pharmaceutical composition of claim 12, wherein the active pharmaceutical ingredient comprises gentamicin sulfate.

14. A method of preparing a pharmaceutical composition, the method comprising:

generating a dispersion of an active pharmaceutical ingredient in a liquid phase comprising a solvent; and

contacting the dispersion of the active pharmaceutical ingredient with a porous encapsulating medium, thereby producing the pharmaceutical composition, wherein particles of the active pharmaceutical ingredient are encapsulated in the pores of the porous encapsulating medium.

15. The method of claim 14, wherein the particles of the active pharmaceutical ingredient have an average size of less than 1 μm.

16. The method of claim 14, wherein the encapsulating medium comprises a polymeric material.

17. The method of claim 16, wherein the polymeric material comprises ultra-high molecular weight polyethylene (UHMWPE).

18. The method of claim 14, wherein the active pharmaceutical ingredient comprises an antibiotic, a non-steroid anti-inflammatory drug, an analgesic, a local anesthetic, a therapeutic biomolecule, or a combination thereof.

19. The method of claim 18, wherein the active pharmaceutical ingredient comprises an antibiotic.

20. The method of claim 19, wherein the antibiotic comprises gentamicin sulfate.

21. The method of claim 14, where the produced pharmaceutical composition comprises about 1% to about 50% by weight the active pharmaceutical ingredient.

22. The method of claim 14, wherein the liquid phase further comprises an inactive ingredient, a precipitating agent, a viscosity modifier, a surfactant, a pH modifier, an emulsifying agent, or a combination thereof.

23. The method of claim 22, wherein the liquid phase further comprises a precipitating agent, which comprises a non-solvent.

24. The method of claim 14, comprising generating a dispersion of gentamicin sulfate in a liquid phase comprising about 30% (v/v) water and about 70% (v/v) ethanol.

25. The method of claim 14, wherein the porous encapsulating medium comprises an antioxidant.

26. The method of claim 14, wherein the porous encapsulating medium comprises a crosslinking agent.

27. The method of claim 14, further comprising drying and/or dehydrating the pharmaceutical composition to produce a dried pharmaceutical composition.

28. The method of claim 27, further comprising molding the dried pharmaceutical composition by a heat molding process.

29. A pharmaceutical composition produced by the method of claim 14.

30. The pharmaceutical composition of claim 29, having an ultimate tensile strength (UTS) of at least 30 MPa, an elongation at break (EAB) of at least 300%, and/or a yield strength of at least 15 MPa.

31. The pharmaceutical composition of claim 29, wherein the pharmaceutical composition comprises at least 6% by weight the active pharmaceutical ingredient, and wherein the active pharmaceutical ingredient has a release rate of at least 0.1 mg/day per 100 cm^2 for 28 days and/or a cumulative release of at least 3% in 5 days, as measured in water at 37°C.

32. The pharmaceutical composition of claim 29, wherein the active pharmaceutical ingredient comprises gentamicin sulfate.

33. A medical device comprising the pharmaceutical composition of claim 1.

34. The medical device of claim 33, which is an implant.

35. The medical device of claim 34, which is a joint replacement implant.

36. The medical device of claim 34, which is a joint replacement spacer implant to treat and/or prevent infection.

37. A joint replacement implant comprising a heat molded polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE) and gentamicin sulfate, wherein particles of gentamicin sulfate are encapsulated in pores of the heat molded polymeric material.

38. The joint replacement implant of claim 37, wherein the particles of gentamicin sulfate have an average size of less than 1 μm.

39. The joint replacement implant of claim 37, comprising about 2% to about 20% by weight gentamicin sulfate.

40. A method of preparing an implant, the method comprising:

generating a dispersion of a gentamicin sulfate in a liquid phase comprising a solvent and a non-solvent;

contacting the dispersion of gentamicin sulfate with a porous polymeric material comprising ultra-high molecular weight polyethylene (UHMWPE), thereby producing an implant composition,

wherein particles of gentamicin sulfate are encapsulated in the pores of the porous polymeric material; and

heat molding the implant composition to produce the implant.

41. The method of claim 40, comprising:

removing the solvent and the non-solvent from the implant composition to produce a dried implant composition; and

heat molding the dried implant composition to produce the implant.

42. The method of claim 40, wherein the particles of gentamicin sulfate have an average size of less than 1 μm.

43. The method of claim 40, wherein the implant comprises about 2% to about 20% by weight gentamicin sulfate.

44. The method of claim 40, further comprising machining the implant produced by heat molding to form a shaped implant.

45. An implant produced by the method of claim 40.

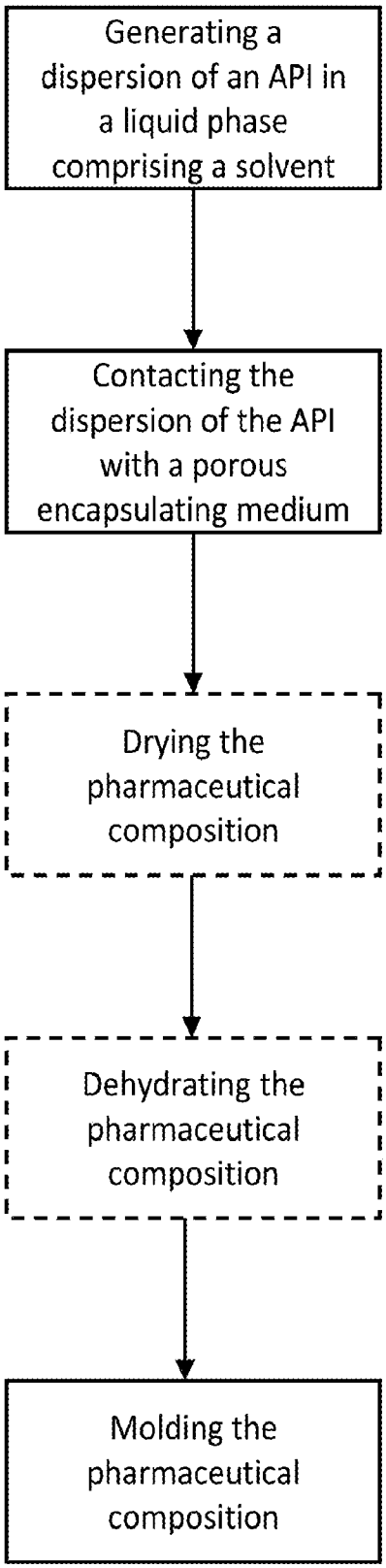

Generating a dispersion of an API in a liquid phase comprising a solvent
Contacting the dispersion of the API with a porous encapsulating medium
Drying the pharmaceutical composition
Dehydrating the pharmaceutical composition
Molding the pharmaceutical composition

FIG. 1A

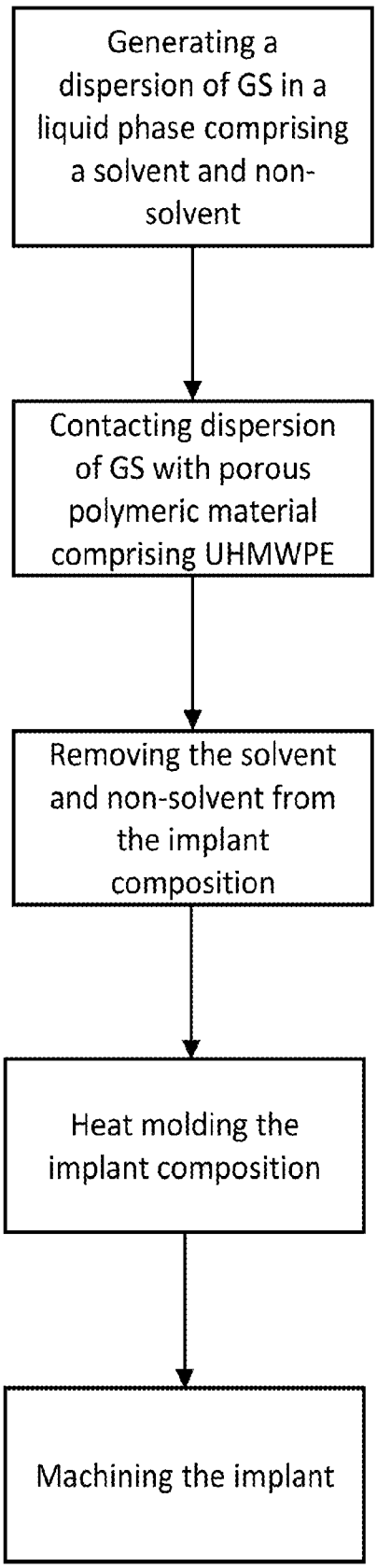

Generating a dispersion of GS in a liquid phase comprising a solvent and non-solvent
Contacting dispersion of GS with porous polymeric material comprising UHMWPE
Removing the solvent and non-solvent from the implant composition
Heat molding the implant composition
Machining the implant

FIG. 1B

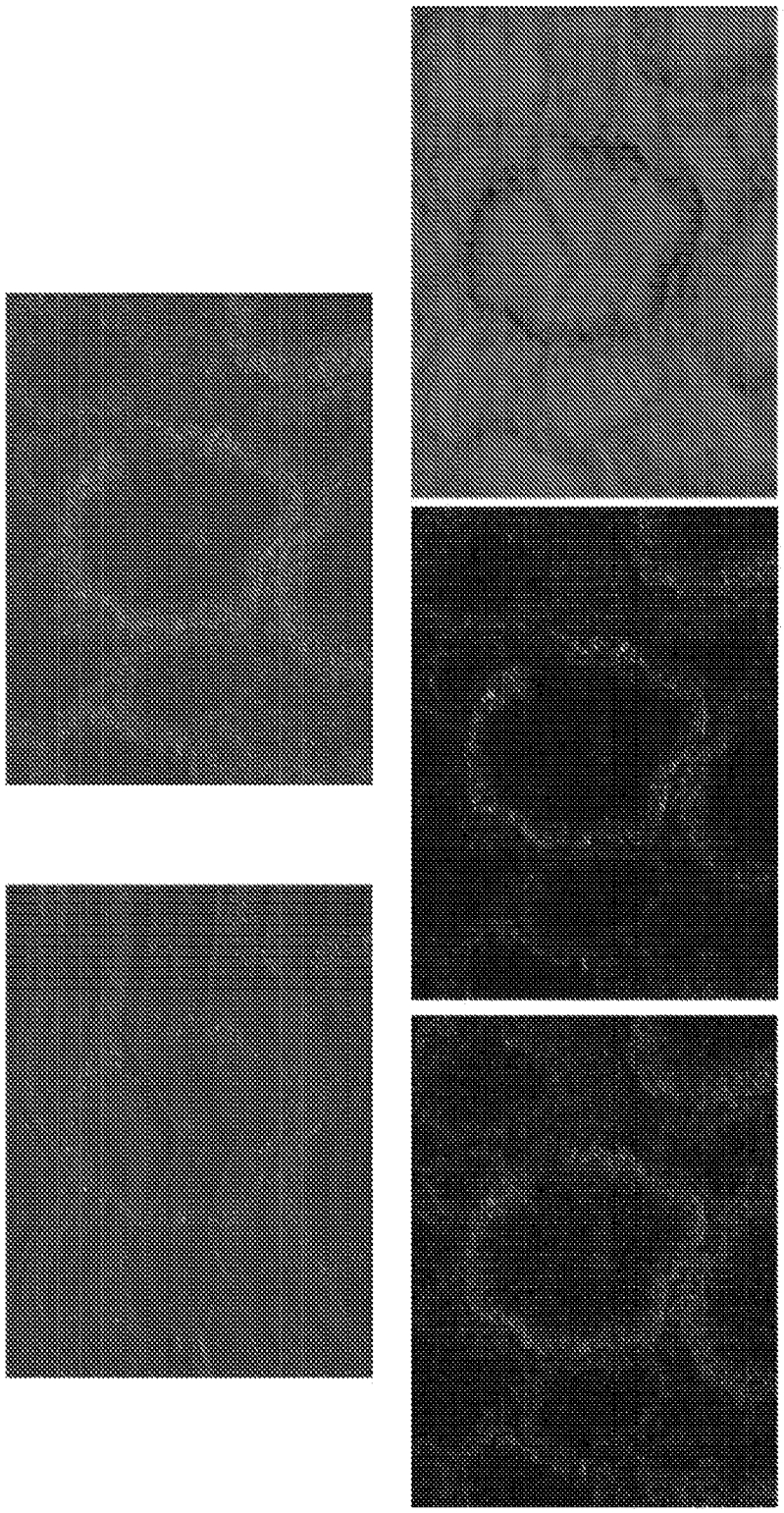


FIG. 2

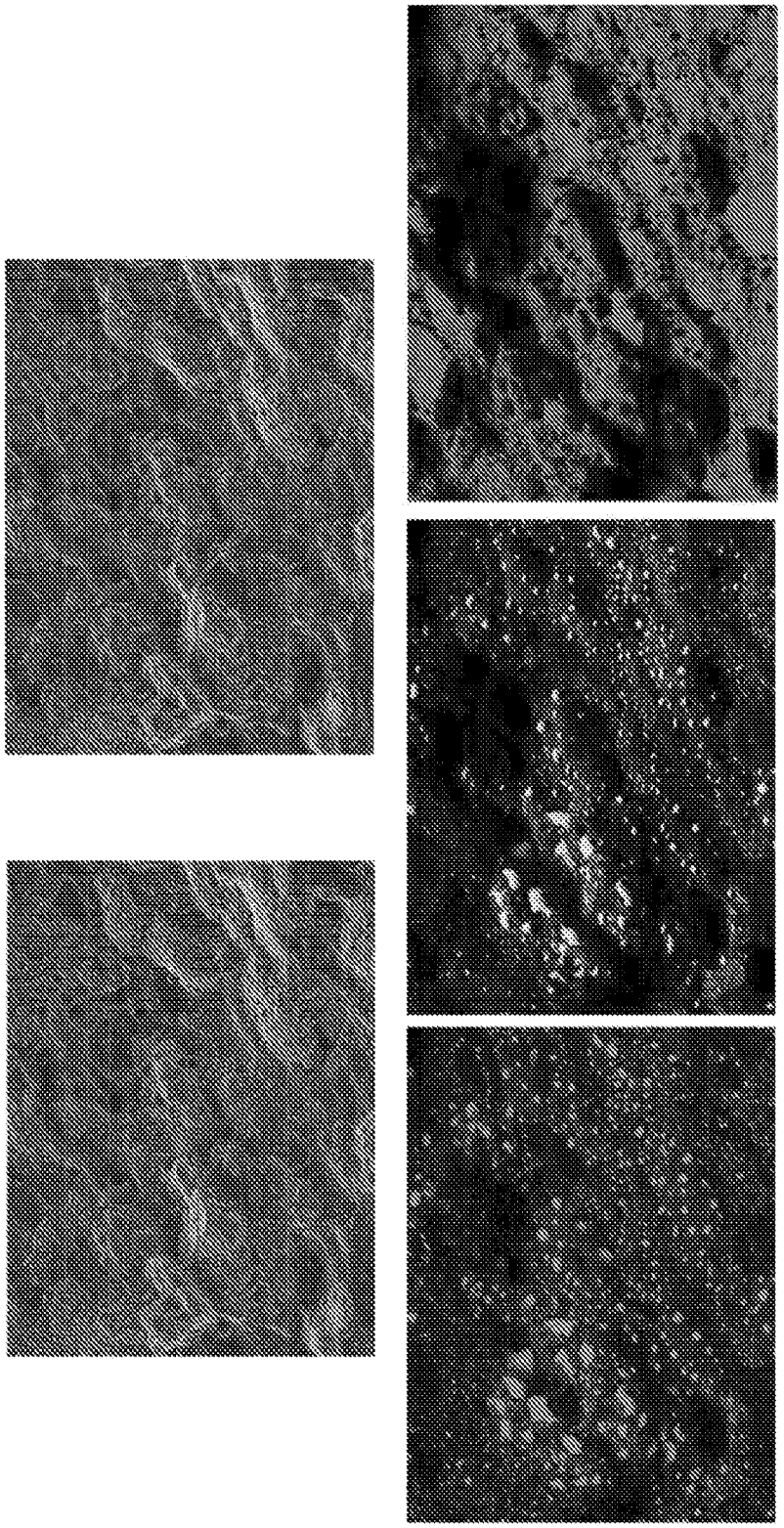


FIG. 3

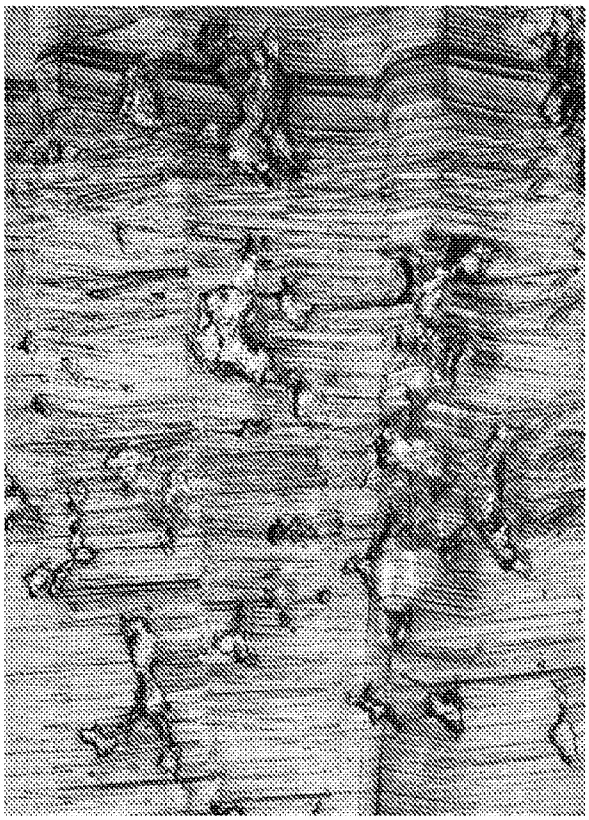


FIG. 4B

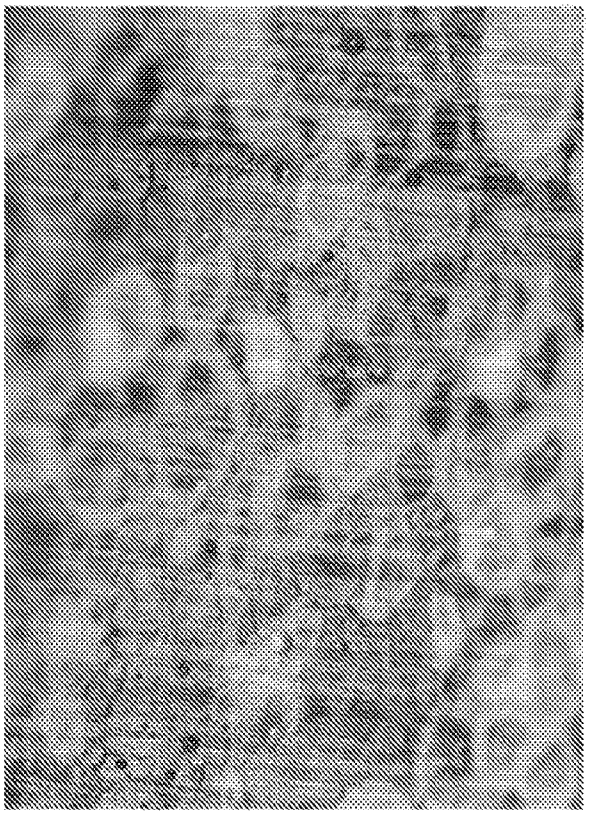


FIG. 4A

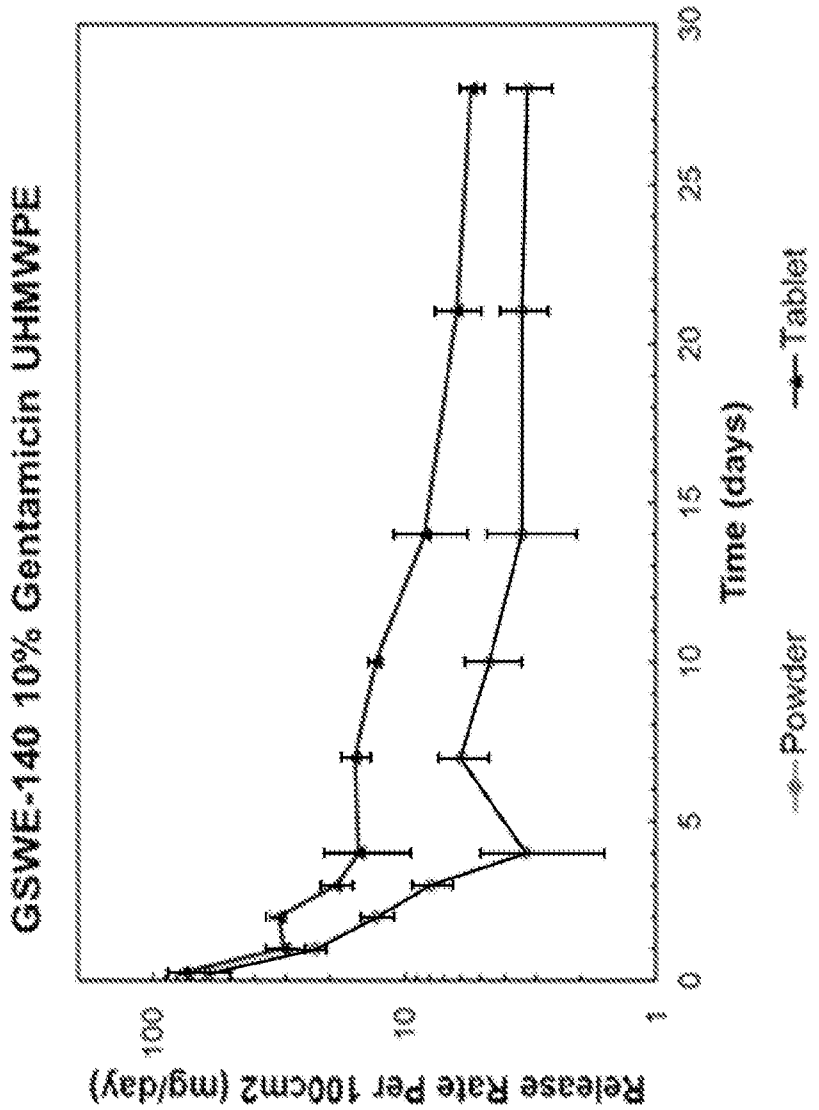

GSWE-140 10% Gentamicin UHMWPE
Release Rate Per 100cm2 (mg/day)
100
10
1
0
5
10
15
20
25
30
Time (days)
Powder
Tablet

FIG. 5A

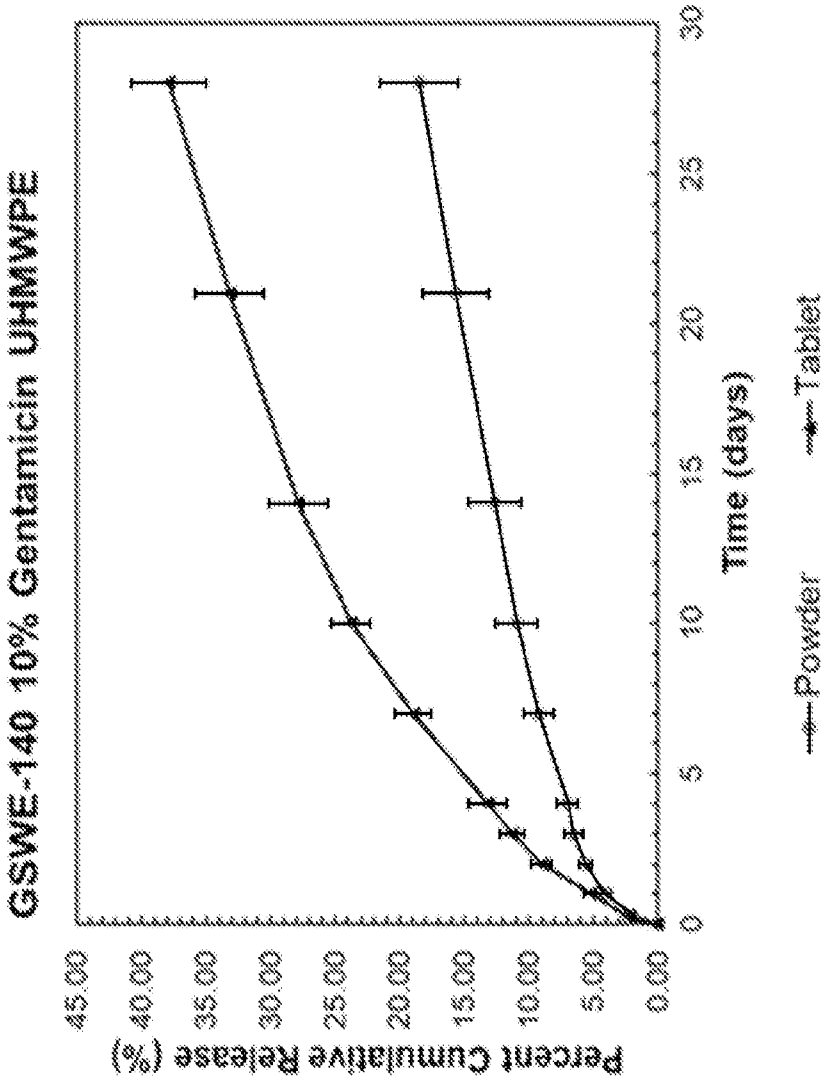

GSWE-140 10% Gentamicin UHMWPE
Percent Cumulative Release (%)
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
0
5
10
15
20
25
30
Time (days)
Powder
Tablet

FIG. 5B

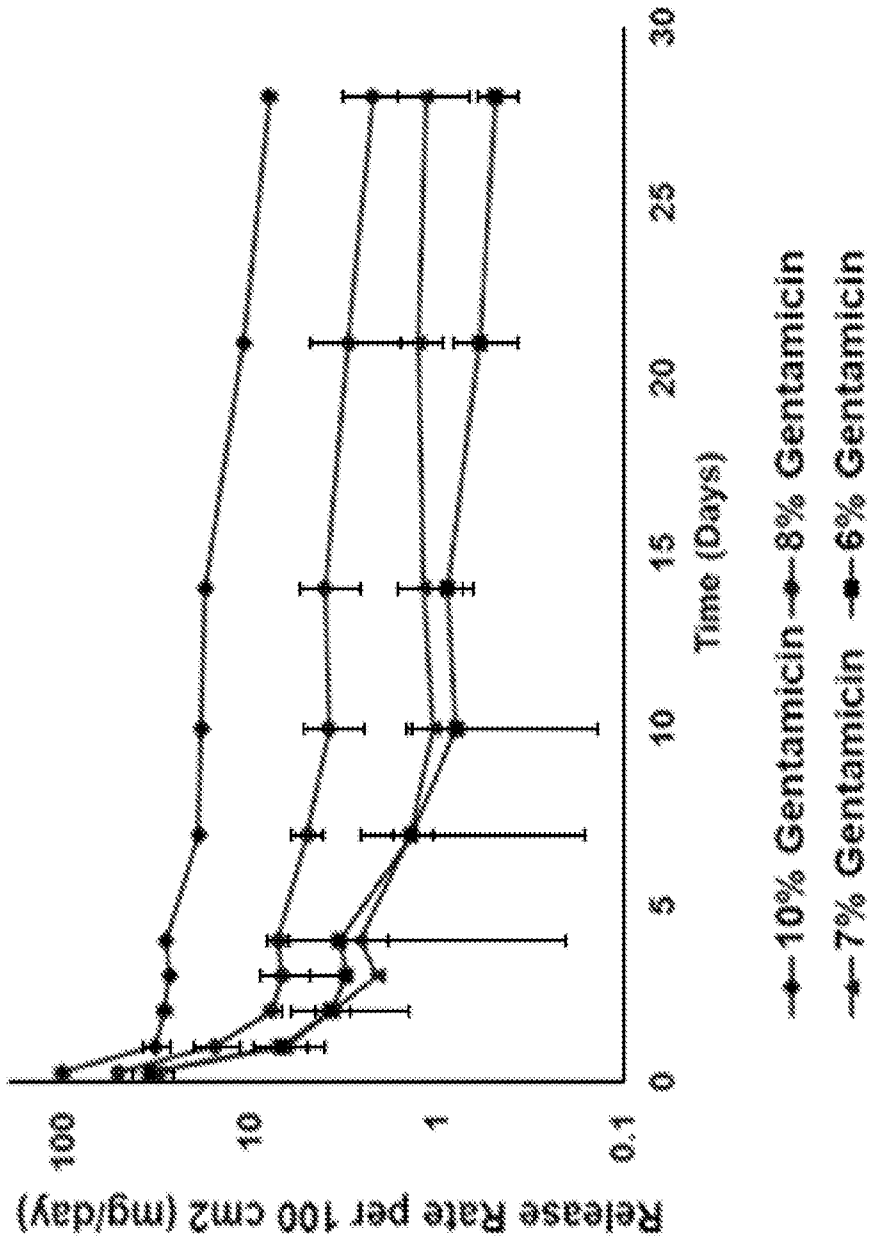

Gentamicin Release Profiles
Release Rate per 100 cm2 (mg/day)
100
10
1
0.1
0
5
10
15
20
25
30
Time (Days)
10% Gentamicin
8% Gentamicin
7% Gentamicin
6% Gentamicin

FIG. 6A

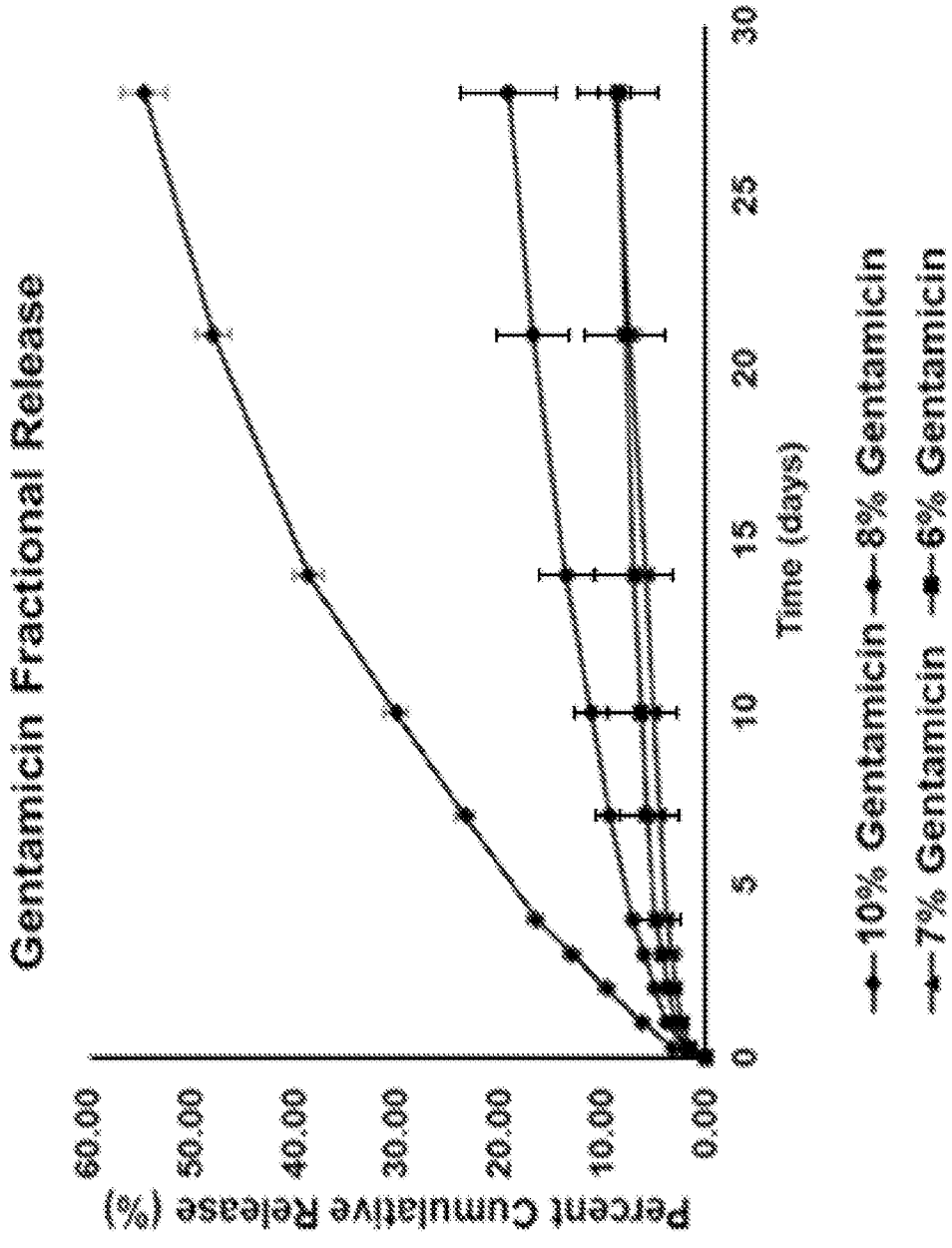

Gentamicin Fractional Release
Percent Cumulative Release (%)
60,00
50,00
40,00
30,00
20,00
10,00
0,00
0
5
10
15
20
25
30
Time (days)
10% Gentamicin
8% Gentamicin
7% Gentamicin
6% Gentamicin

FIG. 6B

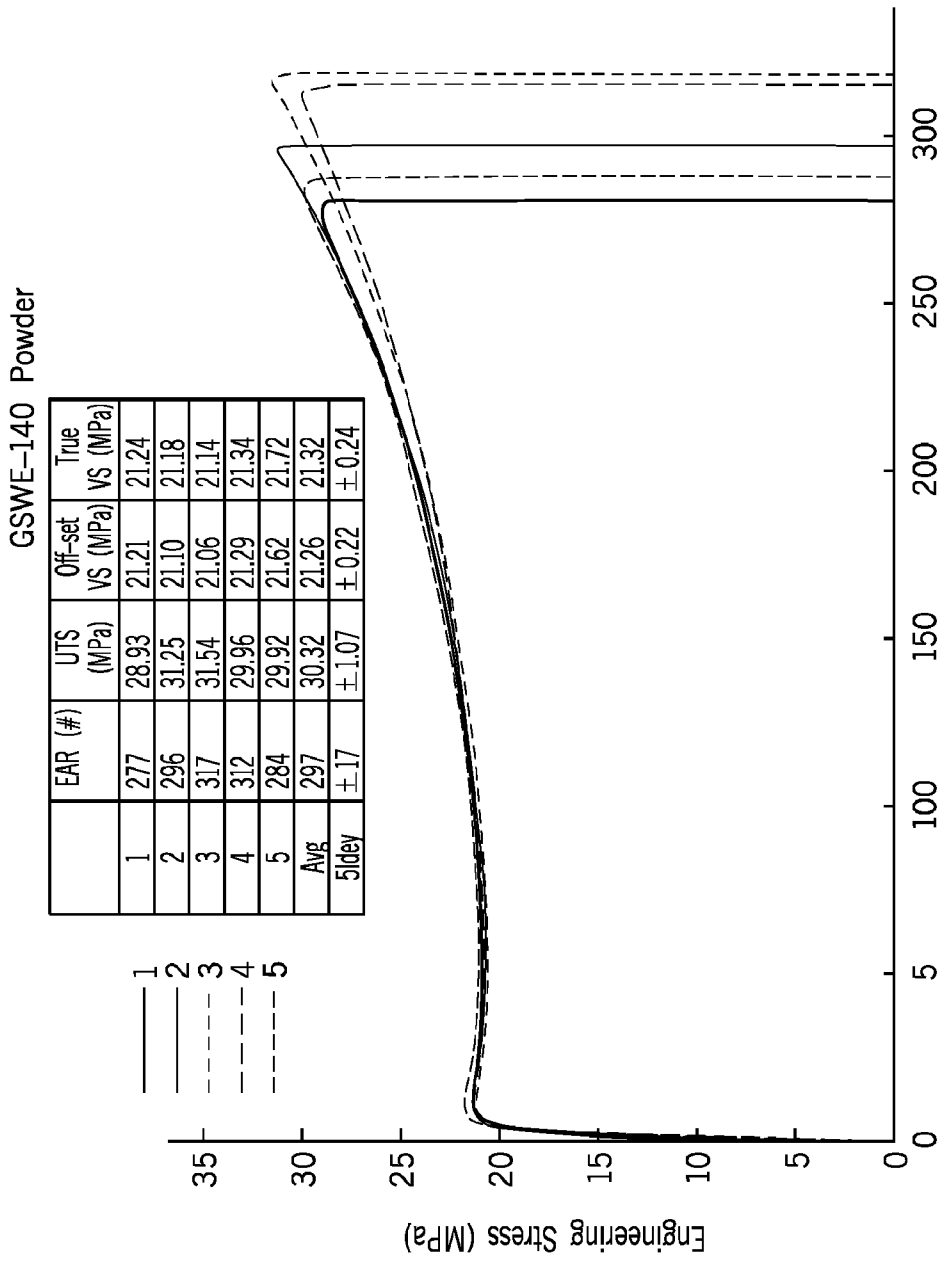
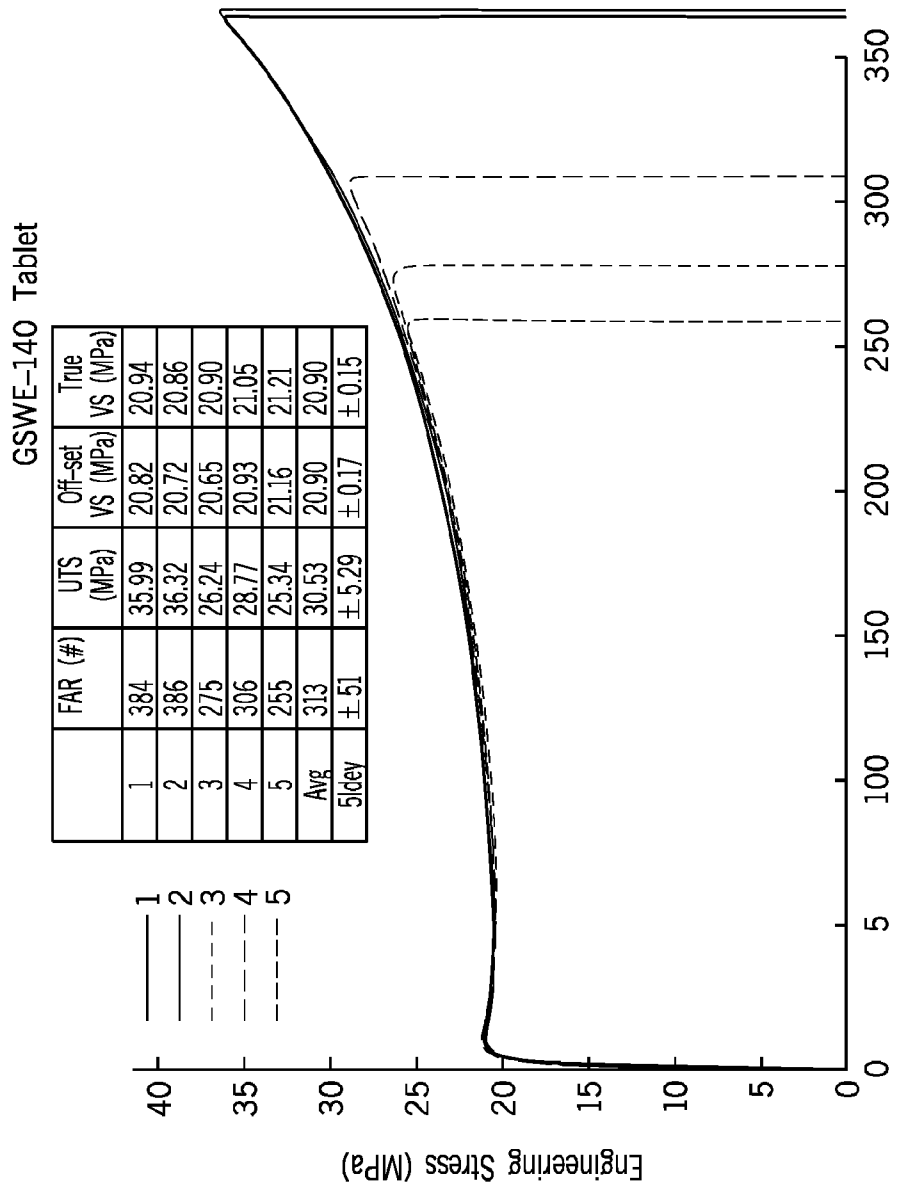

GSWE-140 Powder
EAR (#) UTS (MPa) Off-set VS (MPa) True VS (MPa)
1 277 28.93 21.21 21.24
2 296 31.25 21.10 21.18
3 317 31.54 21.06 21.14
4 312 29.96 21.29 21.34
5 284 29.92 21.62 21.72
Avg 297 30.32 21.26 21.32
5Idev ±17 ±1.07 ±0.22 ±0.24
1
2
3
4
5
Engineering Stress (MPa)
0
5
10
15
20
25
30
35
0
5
100
150
200
250
300
Strain (%)

FIG. 7A



	FAR (#)	UTS (MPa)	Off-set VS (MPa)	True VS (MPa)
1	384	35.99	20.82	20.94
2	386	36.32	20.72	20.86
3	275	26.24	20.65	20.90
4	306	28.77	20.93	21.05
5	255	25.34	21.16	21.21
Avg	313	30.53	20.90	20.90
5Idev	± 51	± 5.29	± 0.17	± 0.15

FIG. 7B

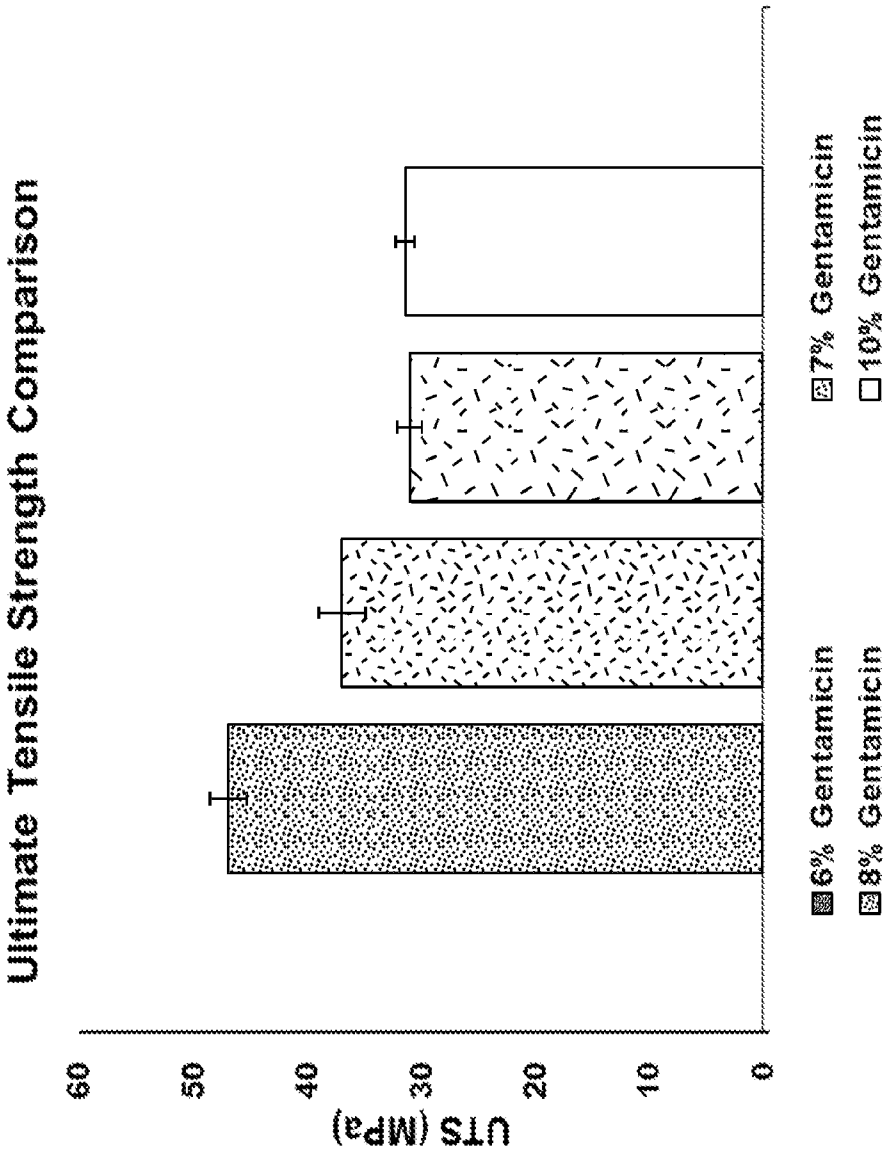

Ultimate Tensile Strength Comparison
UTS (MPa)
0
10
20
30
40
50
60
6% Gentamicin
8% Gentamicin
7% Gentamicin
10% Gentamicin

FIG. 8A

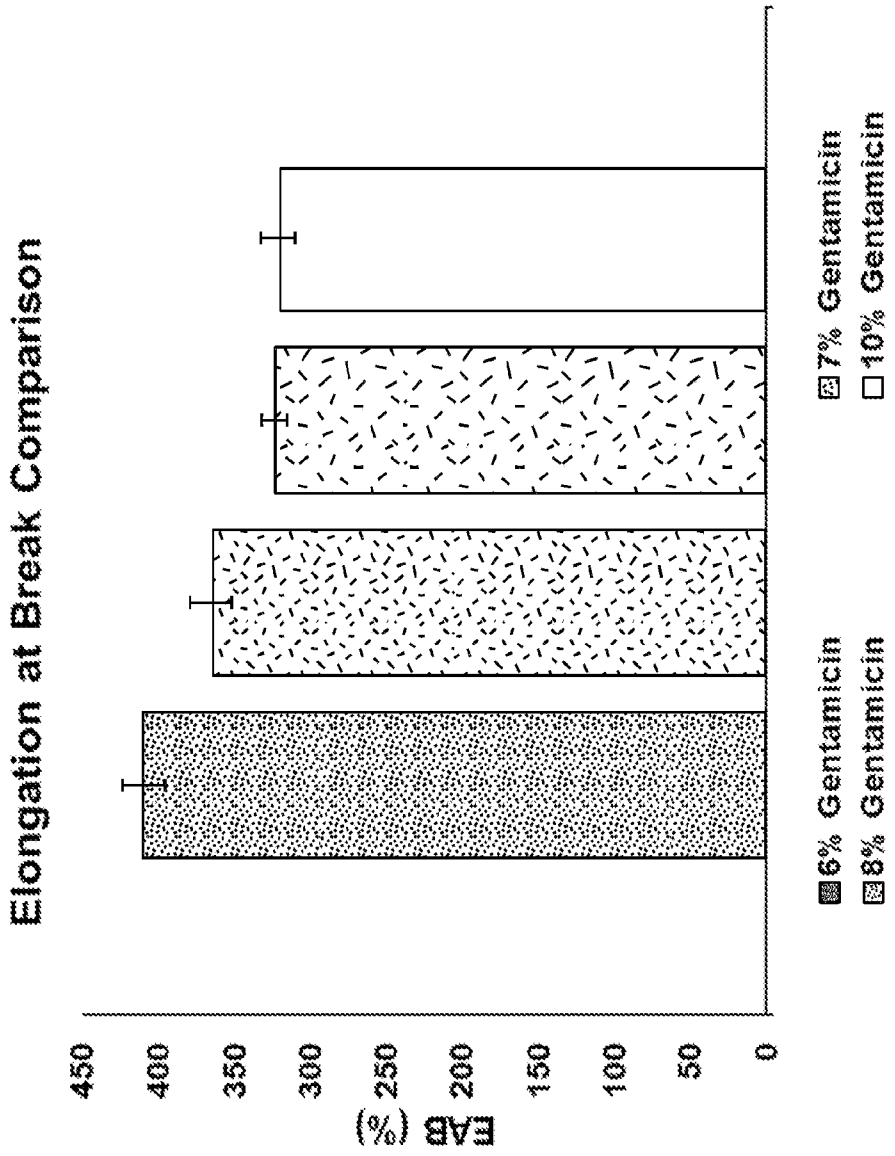

Elongation at Break Comparison
EAB (%)
450
400
350
300
250
200
150
100
50
0
6% Gentamicin
8% Gentamicin
7% Gentamicin
10% Gentamicin

FIG. 8B

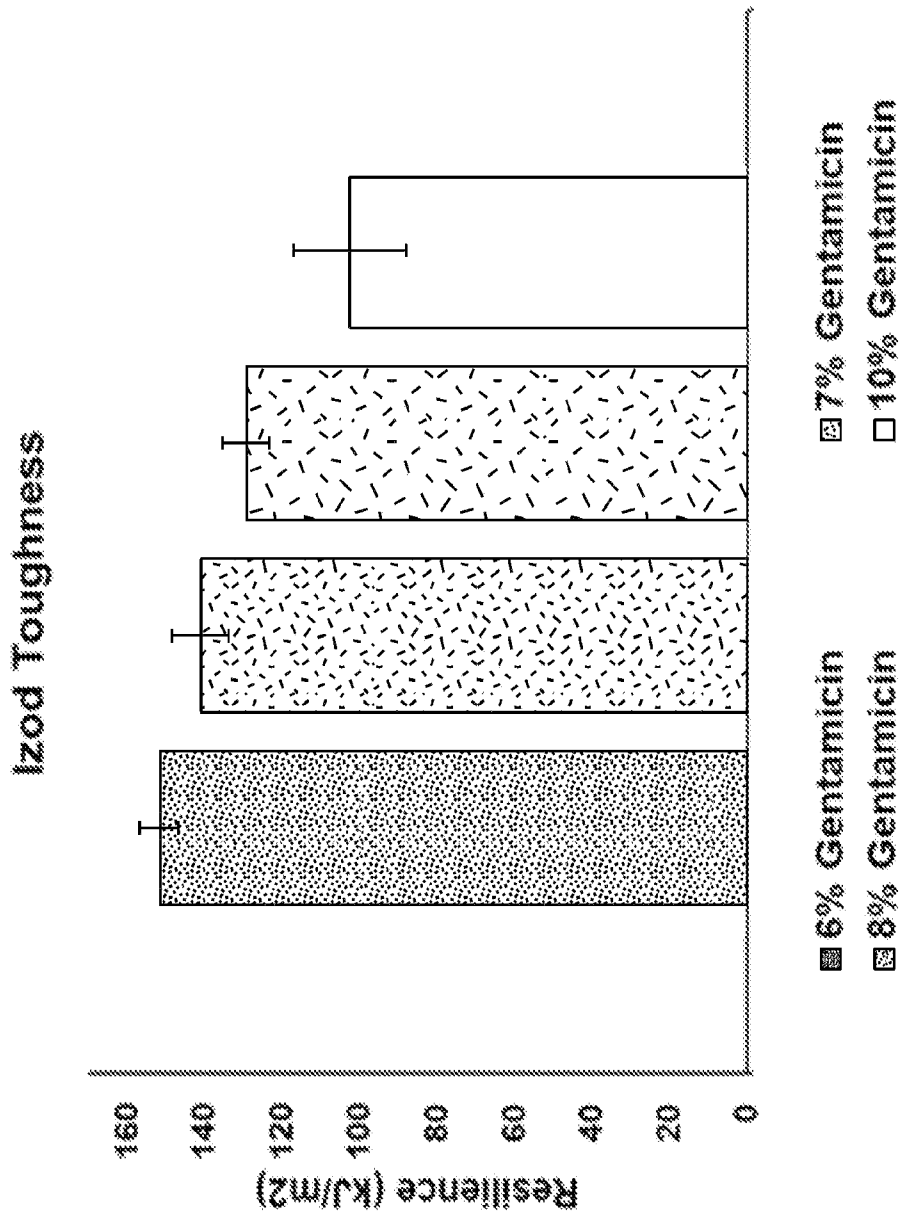

Izod Toughness
Resilience (kJ/m2)
160
140
120
100
80
60
40
20
0
6% Gentamicin
8% Gentamicin
7% Gentamicin
10% Gentamicin

FIG. 9

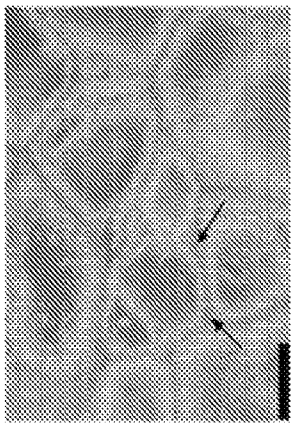


FIG. 10D

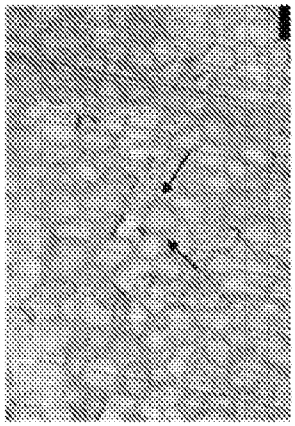


FIG. 10C

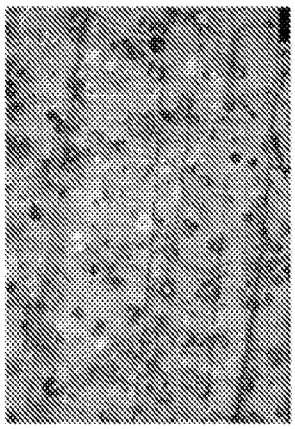


FIG. 10B

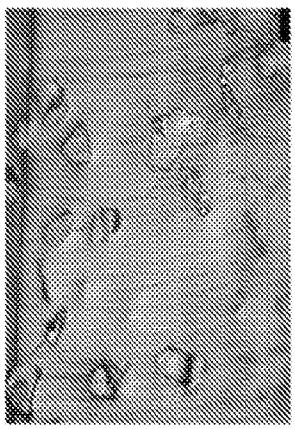


FIG. 10A

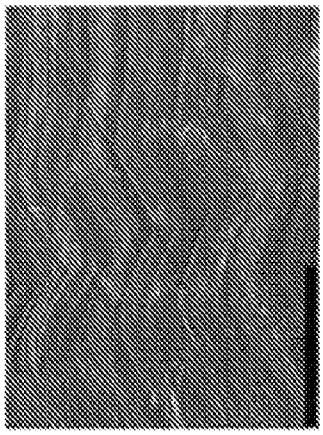


FIG. 10H

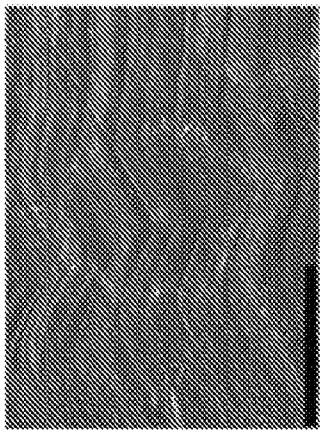


FIG. 10G

FIG. 10F

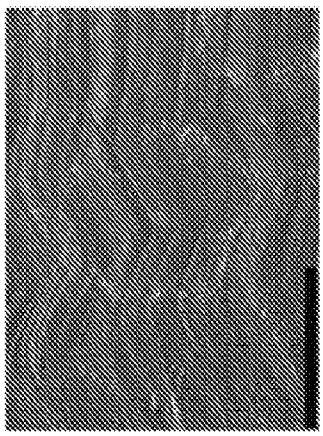


FIG. 10E

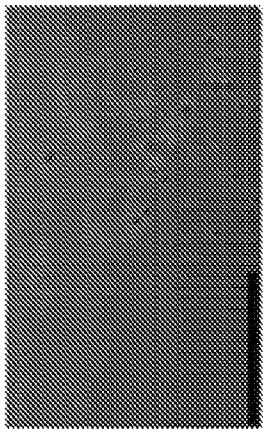


FIG. 10L

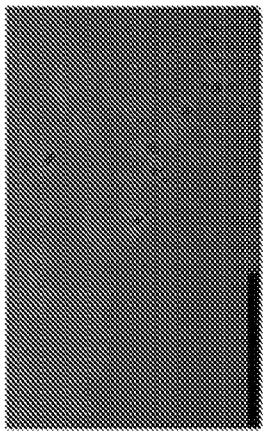


FIG. 10K

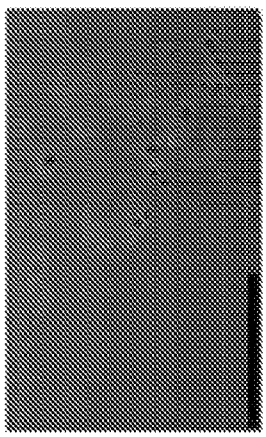


FIG. 10J

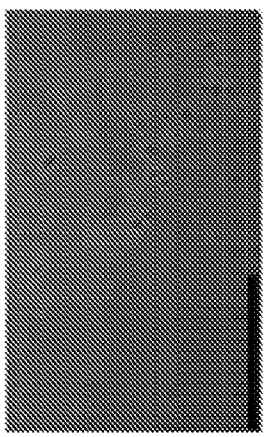


FIG. 10I

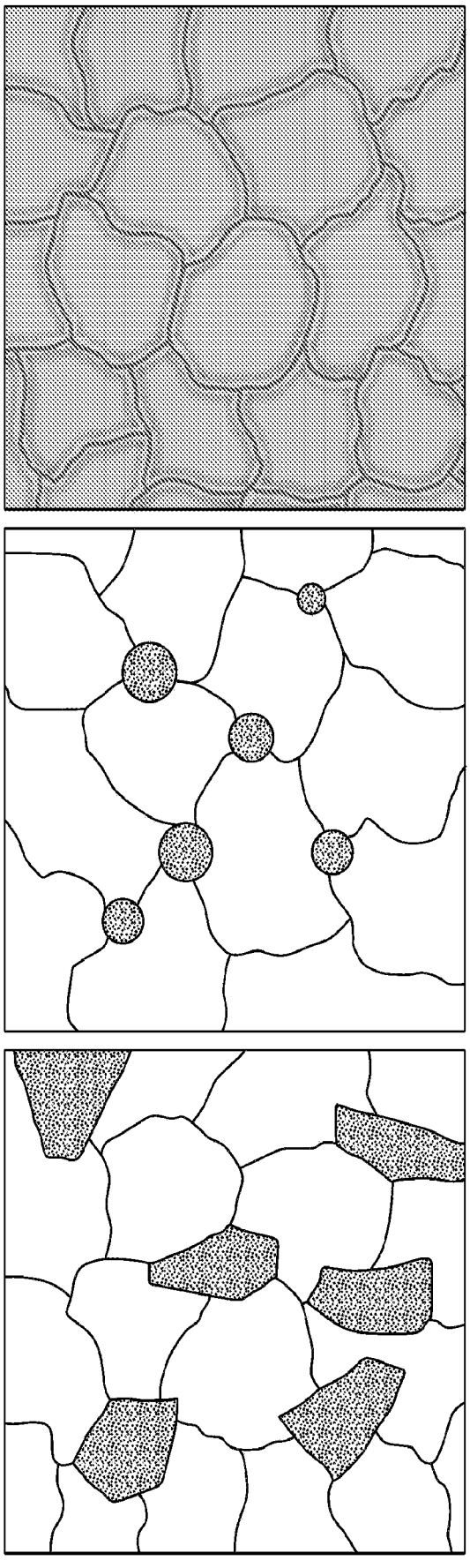


FIG. 10M

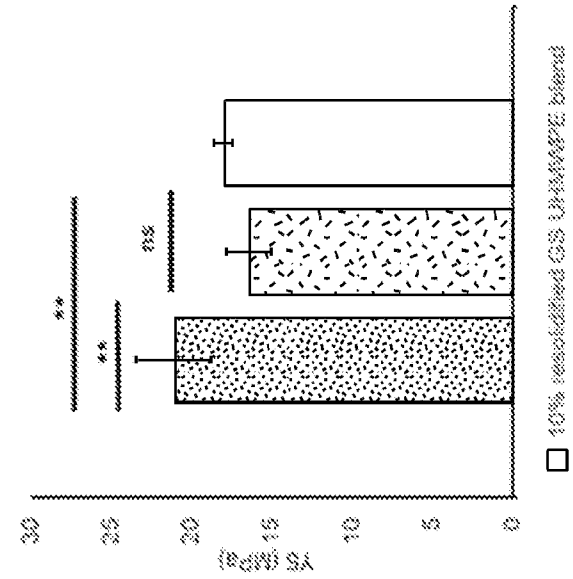


FIG. 11C

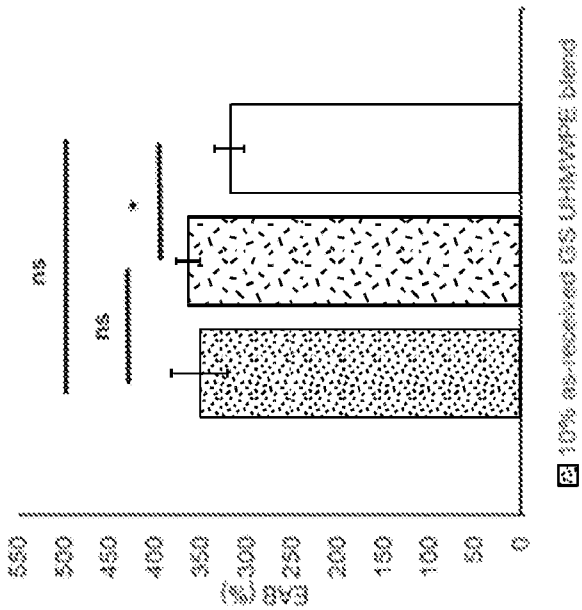


FIG. 11B

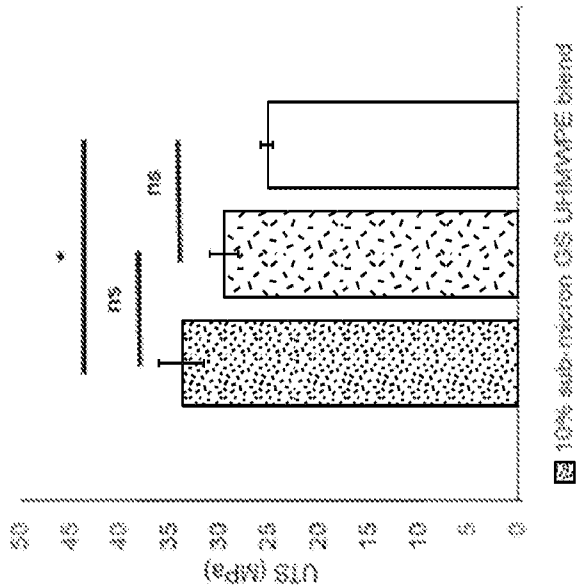


FIG. 11A

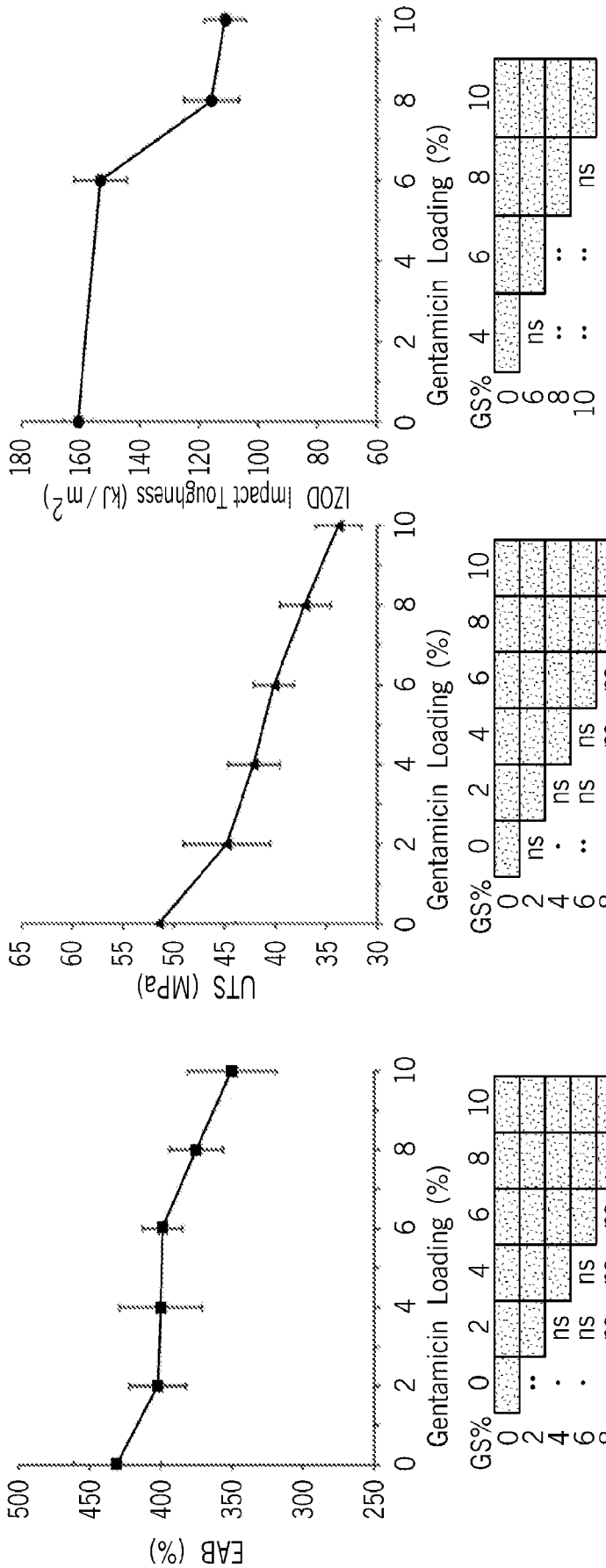


FIG. 11D

FIG. 11E

FIG. 11F

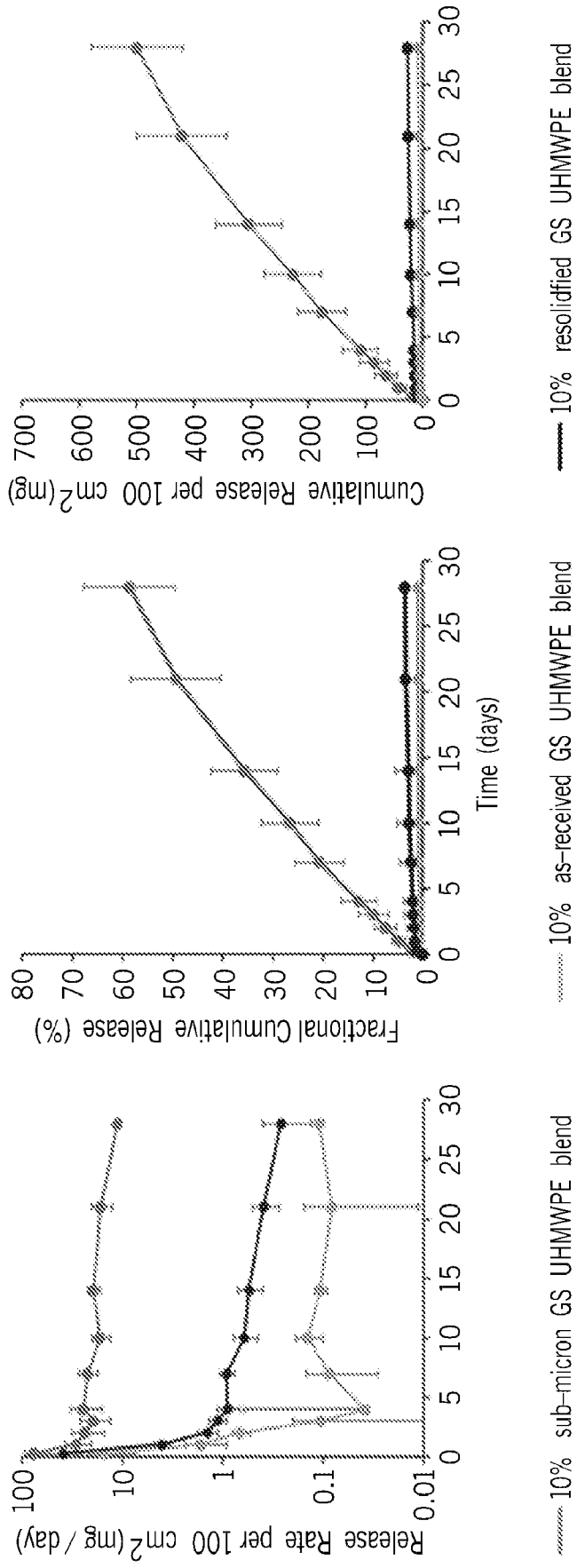


FIG. 12A

FIG. 12B

FIG. 12C

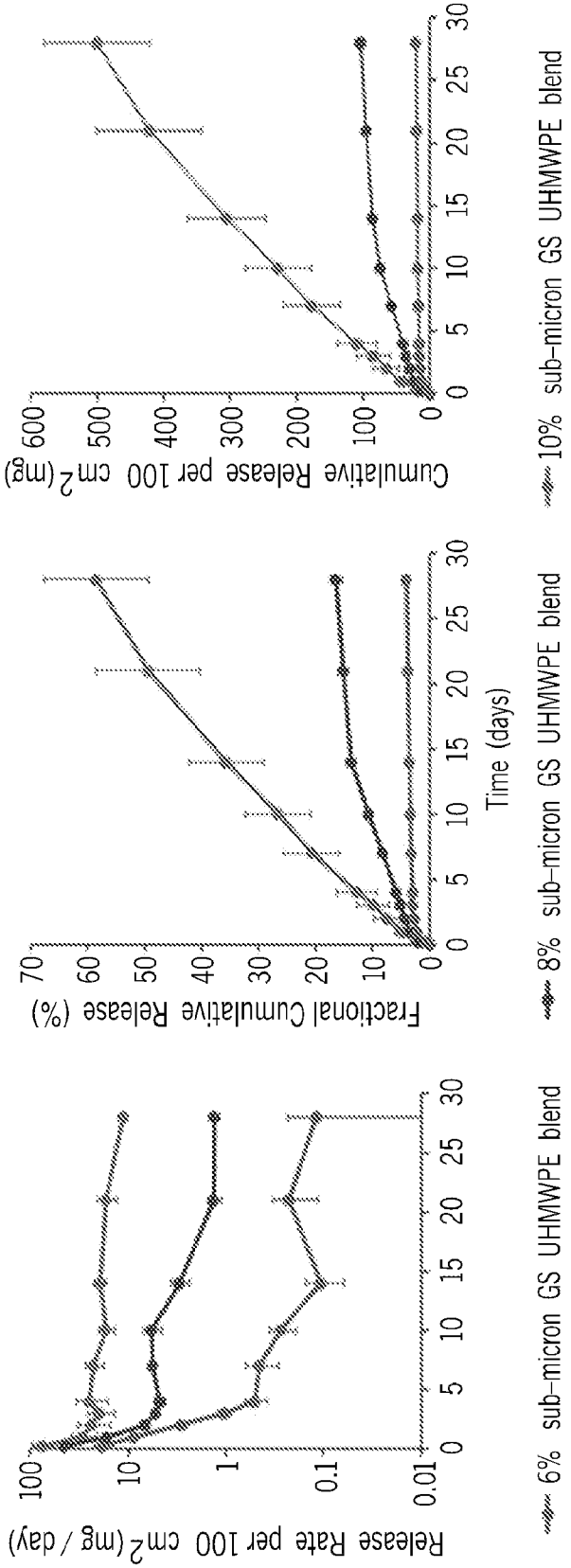


FIG. 12D

FIG. 12E

FIG. 12F

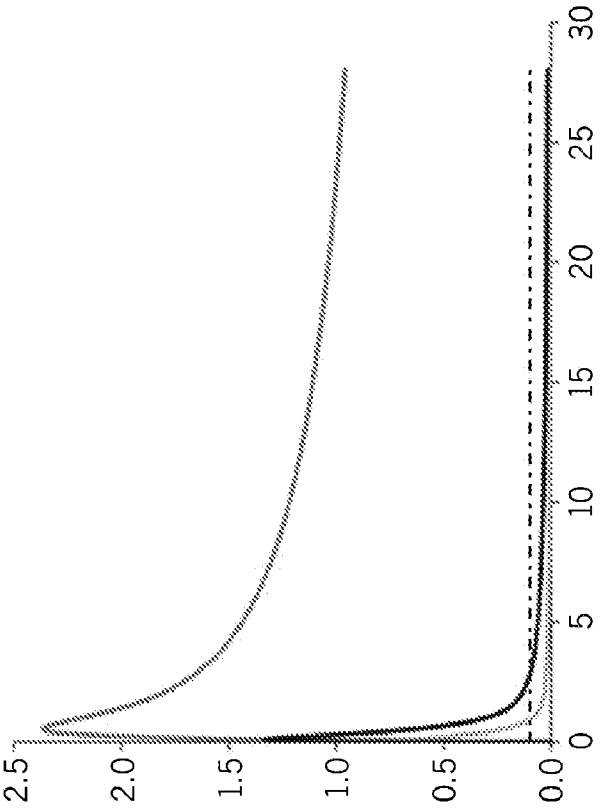


FIG. 12H

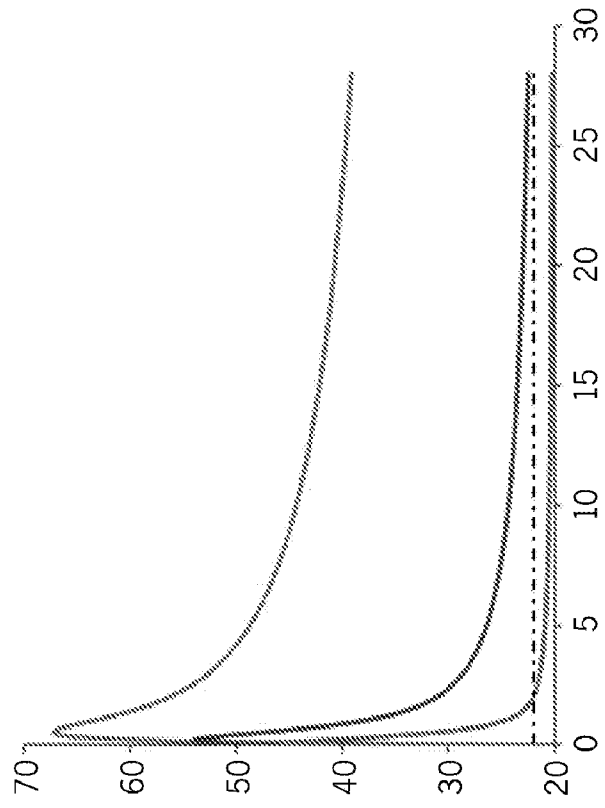


FIG. 12G

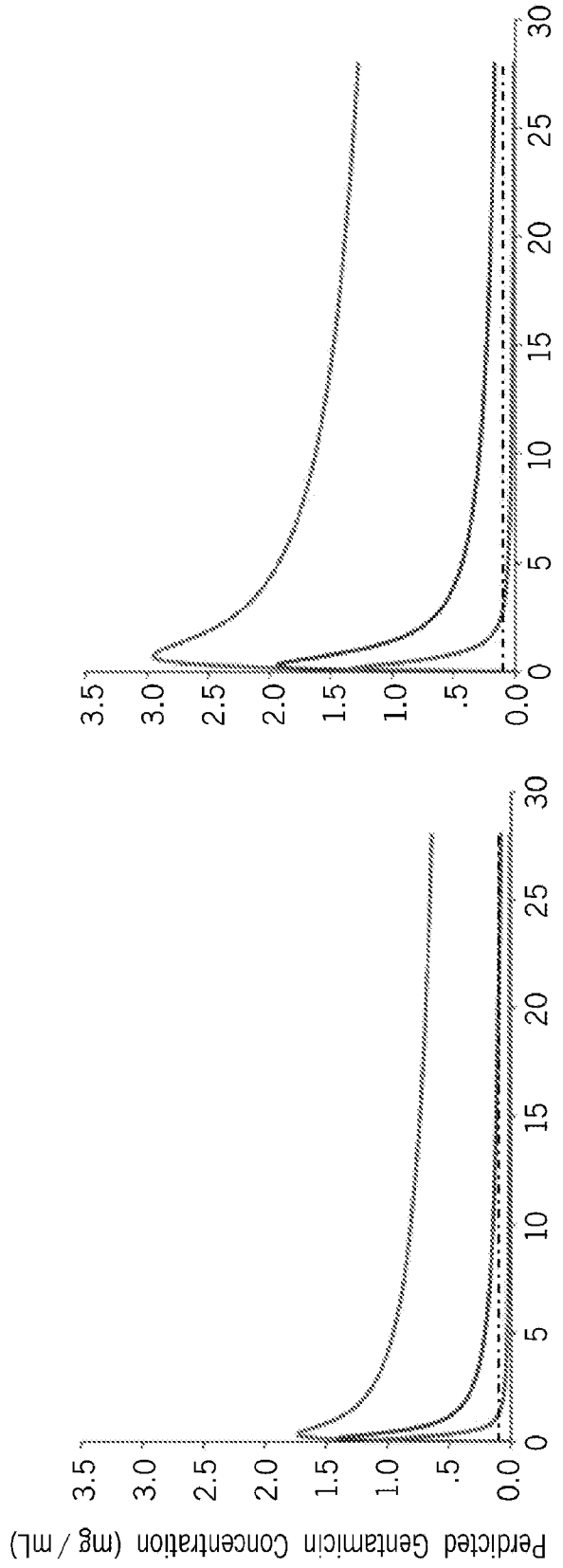


FIG. 13A

FIG. 13B

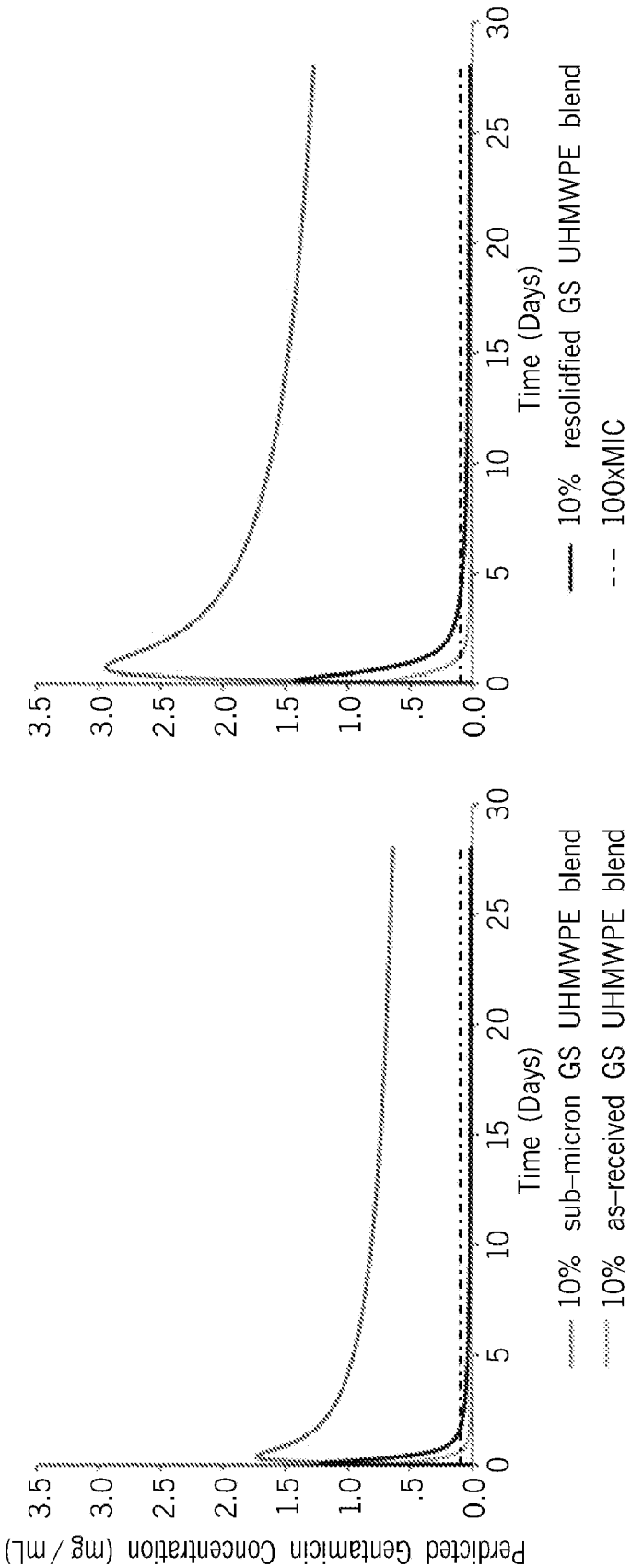


FIG. 14A

FIG. 14B

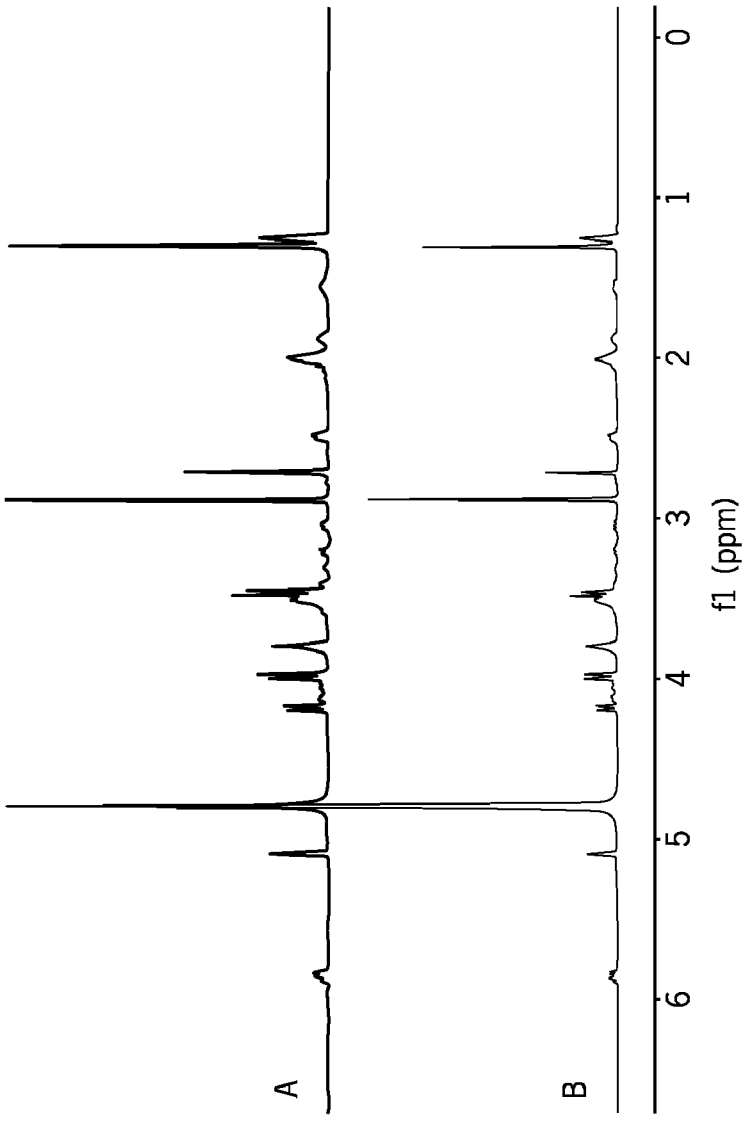


FIG. 15

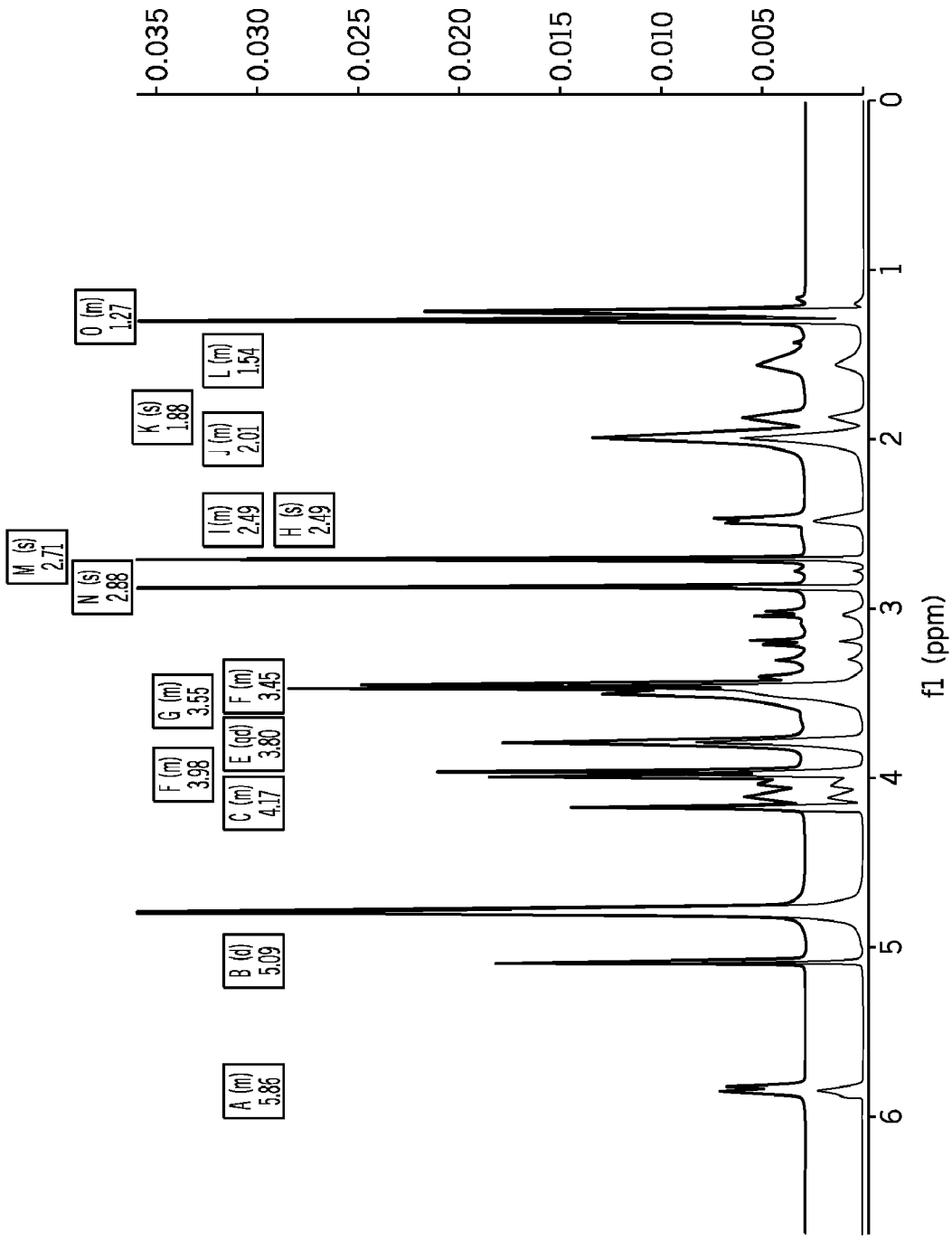

0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
1
2
3
4
5
6
f1 (ppm)
O (m) 1.27
L (m) 1.54
K (s) 1.88
J (m) 2.01
I (m) 2.49
H (s) 2.49
M (s) 2.71
N (s) 2.88
G (m) 3.55
F (m) 3.45
F (m) 3.98
E (qd) 3.80
C (m) 4.17
B (d) 5.09
A (m) 5.86

FIG. 16

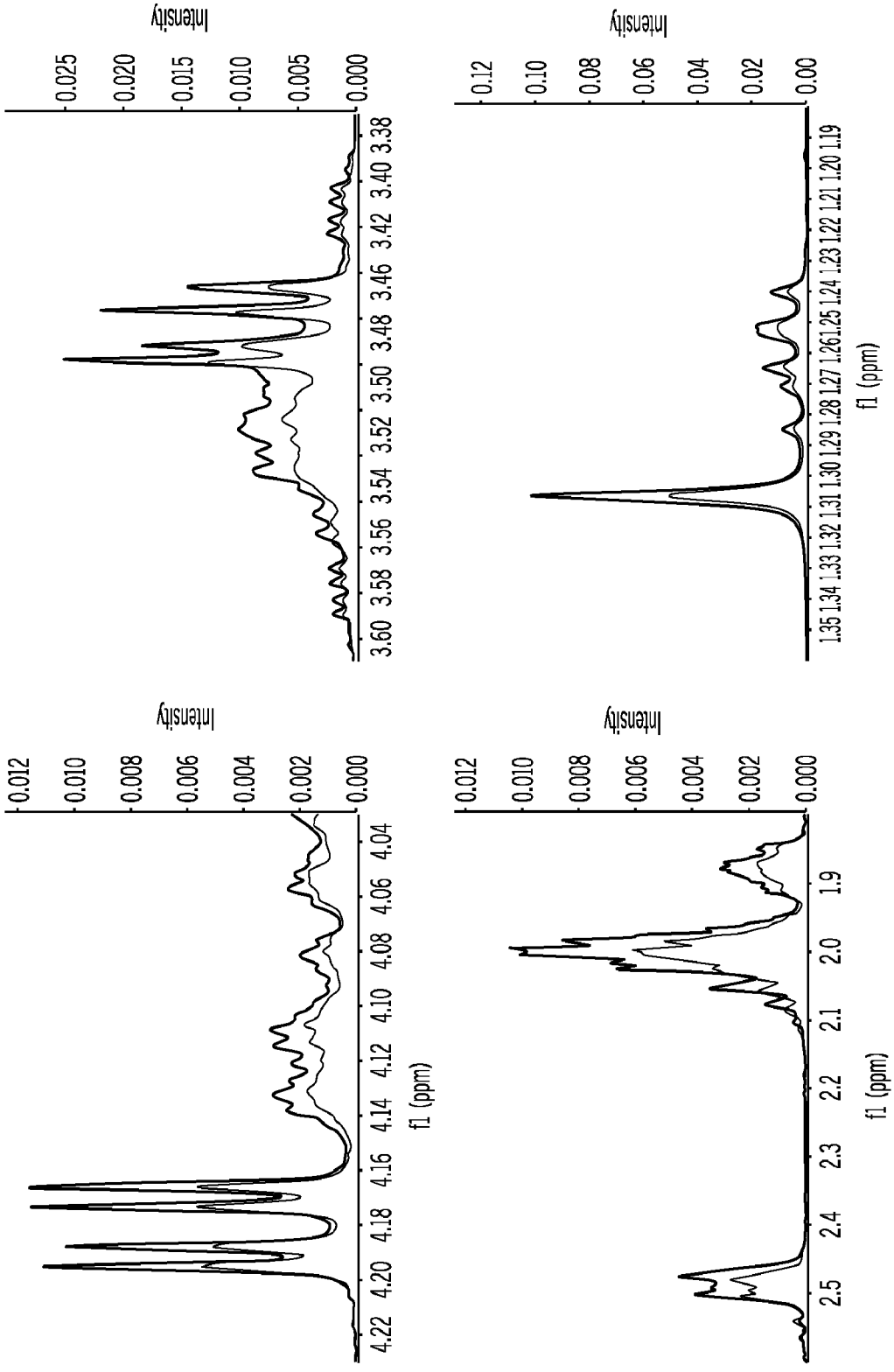

Intensity
0.025
0.020
0.015
0.010
0.005
0.000
3.60 3.58 3.56 3.54 3.52 3.50 3.48 3.46 3.42 3.40 3.38
Intensity
0.12
0.10
0.08
0.06
0.04
0.02
0.00
1.35 1.34 1.33 1.32 1.31 1.30 1.29 1.28 1.27 1.26 1.25 1.24 1.23 1.22 1.21 1.20 1.19
f1 (ppm)
Intensity
0.012
0.010
0.008
0.006
0.004
0.002
0.000
4.22 4.20 4.18 4.16 4.14 4.12 4.10 4.08 4.06 4.04
f1 (ppm)
Intensity
0.012
0.010
0.008
0.006
0.004
0.002
0.000
2.5 2.4 2.3 2.2 2.1 2.0 1.9
f1 (ppm)

FIG. 17