Exploiting Inherent Instability of 2D Black Phosphorus for Controlled Phosphate Release from Blow-Spun Poly (lactide-co-glycolide) Nanofibers

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**ABSTRACT:** Efforts have been made to stabilize black phosphorus (BP) to utilize its tunable band gap and anisotropic mechanical properties. Here, the intrinsic instability of BP is exploited for controlled therapeutic ion release, namely phosphate. BP was incorporated into degradable poly (lactide-co-glycolide) fibers via solution blow spinning. Raman spectroscopy confirmed the incorporation of 2D-BP into the nanocomposite along with ICP-AES. It was also demonstrated that modifying the initial loading of 2D-BP in the PLGA fibers permitted tunable release rates of phosphate ions over an 8 weeks in vitro study.

**INTRODUCTION**

Phosphorene, or monolayer black phosphorus is a novel two-dimensional (2-D) material which is composed of single layer of phosphorus atoms 1-3. 2D-BP is derived from bulk BP which is thermodynamic allotrope of phosphorus synthesized at high pressures and temperatures 1. Recently, 2D-BP has attracted attention for electronics 4, sensors 5, biochemical sensing 1, and biomedical applications 6-8 primarily due to its unique characteristics including semiconductivity 9, thickness dependent direct band gap 10-13, and anisotropic mechanical properties 14. 2D-BP nanosheets are generally synthesized by mechanical exfoliation 15 or liquid phase exfoliation of bulk BP 10-12. 2D-BP has been used for bioimaging 9, 16, photothermal cancer therapy 17-19, drug delivery 20, 21, neurodegenerative disorder therapy 22.

Upon exposure to water and oxygen, 2-D BP is degraded via oxidation into non-toxic phosphorus species (phosphate and phosphonate) 6, 23. As the material is a useful 2D semiconductor, significant efforts have been made to suppress the chemical degradation of 2D BP, with strategies including encapsulation in oxides 24, encapsulation with other inert 2D materials such as (hexagonal boron nitride) hBN 25, as well as using sterically hindered solvents for liquid phase exfoliation (LPE) 4. However the inherent instability properties of BP may actually be an advantage for biomedical engineering.17 To the best of our knowledge the only example currently of an application using the breakdown of BP to phosphate species for bone therapeutic applications is in osteosarcoma treatment and subsequent material-guided bone regeneration 17. However, the BP material was only dip-coated on the surface of 3D printed bioglass. Bioglass is a fragile material, and thus load-bearing implants e.g. in joints and limbs are prohibitive. Additionally the control of phosphate release was not explored. Our system presented here circumvents both of these problems; the phosphate release can be tuned potentially by matching breakdown rate of BP with the PLGA polymer, and the system we use is soft and flexible for potential implantation into high-stress areas of the body.

Previously silicate 26, phosphate 27, and borate 28 glasses have been exploited for bone regeneration due to their tunable degradation and therapeutic ion release to stimulate osteogenesis. Such glasses are often brittle, and efforts have been made to produce hybrid materials with the desired mechanical properties 29, 30. In this study, we explore the use of 2-D BP as a source of phosphate ions by exploiting its inherent instability for controlled phosphate ion release from 3-D nanocomposite for potential bone tissue engineering. We demonstrate the first example of degradable biocompatible soft organic three-dimensional (3-D) scaffolds with tunable long term therapeutic phosphate ion release from embedded 2-D BP in poly (lactide-co-glycolide) (PLGA) nanofibers. These polymeric PLGA composites are both biocompatible and biodegradable 31 and could be useful in biomedical applications including wound healing 32, nerve regeneration 33, bone regeneration 34 and drug delivery 35. BP/PLGA nanosphere composites are currently being explored for photothermal therapy and have been fabricated using an oil-in-water emulsion solvent evaporation method.36 However, that report only studied weight loss of PLGA from the system. Our study presents the quantitative measurement of phosphorus release from fibers. Our results show that P is released steadily over time and we have developed spectroscopic methodology for assessing this that will be useful to a range of researchers. In our study BP was exfoliated in propan-2-ol (IPA) and then it is combined with solutions of PLGA and spun into the fibers via solution blow spinning 37, 38 (SBS) to produce 3-D nanocomposite scaffolds (Scheme 1). Our blow spinning methods are advantageous in that we can produce fibrous materials that are macroscopic and can be manipulated without resort to manual handling techniques such as centrifugation or wet chemistry techniques such as precipitation. We can directly produce the materials in bulk – and extremely rapidly, providing a significant step in processing methodology. The materials are flexible solids that could, for example be formed into implants that could be exploited for future bone tissue engineering applications.

**EXPERIMENTAL SECTION**

**Materials.** PLGA (85:15 (lactide:glycolide), inherent viscosity 3.1 dL g-1) was purchased from Corbion Purac Corp (Netherlands). BP crystals (purity 99.998 %) were purchased from Smart Elements of Austria. Chloroform (HPLC grade, ≥ 99.1 %) was obtained from Sigma Aldrich Corp. Acetone (purity ≥ 99.98 %) and propan-2-ol (IPA, AR, purity 95 %) were obtained from Fisher Scientific Corp.

**Liquid Phase Exfoliation.** BP (100 mg, 3.2 mmol) was suspended in degassed IPA (15 mL) in a sealed, N2 filled glass vial. The suspension was placed in an Elmasonic P 70 H bench-top ultrasonic bath (820 W across four horns) and sonicated at 37 kHz at 30 % power for 12 hrs with a constant temperature of 25 °C using a cooling coil. After sonication, the sample contained 0.66 % w/v BP. To obtain 1 and 2 % w/v BP solutions, without evaporating the solvent, 1 and 1.2 mL of the bulk exfoliated BP solution was transferred into the separate glass vials (2 mL) and centrifuged at 8000 rpm for 30 min. Then, 340 and 804 μL of the IPA was removed from each vial and resuspended, respectively.

**Solution Blow Spinning.** The SBS apparatus consisted of a compressor (Bambi VT150D oil-free and water-free air compressor), concentric nozzle, AL-1000 model injection pump (World Precision Instruments, Inc.), plastic syringe and collector. Blends of PLGA in different BP solvents including IPA, NMP and DMF were prepared. PLGA at 4 % w/v was dissolved in the three different solvent mixtures at 3 mL with solvents ratio (v/v/v) of 80 % chloroform, 10 % acetone and 10% IPA/DMF/NMP. PLGA (control sample) 4 % w/v was dissolved in 80:20 (v/v) chloroform/acetone. 2-D BP containing samples with different concentrations of BP in IPA (0.66, 1 and 2 % w/v) we prepared by first dissolving PLGA at 4 % w/v in a 3 mL solution of chloroform/acetone/suspended BP in IPA at a ratio of 80:10:10 (v/v/v). Then, the samples were stirred with a magnetic stirred bar at 100 rpm at room temperature. PLGA-1 was used as a control with no BP. Solutions to produce PLGA-2, PLGA-3 and PLGA-4 contained 1.6, 2.5, and 5 wt.% BP, respectively. Each sample was transferred into the 5 mL Luer-lok plastic syringe and placed in the injection pump with controllable feed rate of 80 μL min-1 and were injected through the 1.6 mm inner nozzle at pressure of 80 psi (~551 kPa). The fibers were deposited on the collector with a of working distance of 20 cm. The yield of BP incorporation in all cases was measured by ICP-AES and found to be around 10% yield.

**Scanning Electron Microscopy.** Fibers were collected on carbon tabs mounted on aluminum stubs. All samples were coated with 3 nm Au/Pd at 40 mA (Quorom Q150R-S) for 120 s and imaged with SEM (Phenom-World, BV, Eindhoven, The Netherlands) using backscattered electrons (BSE) at 5 eV. Fiber diameters were determined using ImageJ and at least 100 diameters were measured (version 1.50i, NIH, USA).

**Nano-Tomography (Nano-CT).** The fibers (one sample from each group) were placed inside commercially available polyimide tube (inside diameter: 1.0 mm; wall thickness: 0.025 mm) and scanned using the imaging system 2211 Nano-CT (Bruker microCT, Kontich, Belgium). The images were acquired with an isotropic resolution of 330 nm per voxel, 42 kV accelerating voltage, 320 μA current, without using any physical filters. The samples were rotated by 180° about the vertical axis at a step size of 0.20°, with exposure time of 1000 ms, averaging frames of 3. The total scan time per sample was approximately 1.5 hours. Images were reconstructed with NRecon software (v.1.7.1.0, Bruker microCT) using a filtered back-projection algorithm with the following parameters: no ring artifact correction, beam hardening correction of 20 % and smoothing of 3 (Gaussian).

**Atomic Force Microscopy.** A 20 µL aliquot of BP was suspended in IPA was placed onto a freshly cleaved mica substrate mounted on an SPM specimen stub (Agar Scientific, UK). The precipitated BP was imaged in air (humidity of < 50 %) with ScanAsystTM mode using a Bruker Multimode AFM (tapping mode) with a Nanoscope V controller and a "J" scanner. Imaging was carried out using ScanAsyst-Air probes with nominal spring constant of 0.4 N m-1 (Bruker AXS S.A.S, France) and the system was controlled via the Bruker Nanoscope software (v8.15). Thickness, Peak-Force Error and in-phase images with scan sizes of 2 µm2 were captured and analyzed using Nanoscope Analysis software (v1.5).

**Raman Spectroscopy.** The Raman spectroscopy of the PLGA-BP composites were carried out using the Renishaw System 1000 instrument with 514 nm excitation laser operating at 1.17 mV.

**Measurement of phosphate ion concentration.** The solution blow spun BP-PLGA fibers were prepared with 0, 1.6, 2.5, and 5 wt.% BP. Each sample was loaded at 0.5 mg mL-1 in 10 mL deionized water and placed in incubator at 37 °C at 60 rpm. After 4 hrs, 1, 3, 7, 14, 21, 28, 35, 42, 49, and 56 days, 1 mL of each sample was removed and stored in an Eppendorf tube at –85 °C until further use. Finally, the concentration of the phosphate ion (P) of each solution was measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES; Perkin-Elmer, 5300) 39.

**RESULTS AND DISCUSSIONS**

2-D BP was obtained by liquid phase exfoliation (LPE) of bulk BP crystals in IPA via sonication for 24 hours. IPA was selected as a solvent for exfoliation due to its low boiling point that facilitates the fiber spinning process. The use of IPA during the fiber spinning process reduced the average PLGA fiber diameter from 469 to 283 nm (Figure S1). Then, a solution of PLGA in chloroform and acetone was mixed with the BP suspension. After LPE, the 2-D BP layers were characterized using atomic force microscopy (AFM) to investigate the morphology and thickness. Previous studies have reported that monolayers and bilayers of 2-D BP have thicknesses around 0.53 - 0.9 nm and 1.6 nm, respectively 12, 40, 41. AFM revealed that the flakes had thicknesses in the monolayer range of 0.3 – 1.2 nm and lateral dimensions between ca. 55 – 559 nm (N=7, Figure 1a-d) confirming the synthesis of 2-D BP (Figure S2 a,b). For applications in electronics and photonics, variation in the number of layers significantly influences the electronic structure of BP 42. However, the electronic structure is not critical for the controlled release of phosphate species in our application.



**Scheme 1.** Schematic representation of liquid phase exfoliation of bulk BP crystal to BP nanosheets, formation of precursor solution, solution blow spinning with PLGA, and potential application for phosphate release.

2-D BP was incorporated at different weight ratios into degradable and cytocompatible PLGA 43-45 fibers by solution blow spinning (Scheme 1) . The PLA/PGA ratio can be tuned to obtain desired degradation rates 43, 46. Conventional biomaterials for controlled release, such as those produced by freeze casting 47, porogen leaching 48, and foaming 49 have high tortuosity leading to poor mass transport and permeability. Such issues can be resolved via the use of fiber networks; hence, 2-D BP was dispersed in PLGA and spun using SBS into a 3-D fiber network. SBS is a novel technique for fabricating 3-D micro-/nanofiber networks, providing adequate interfiber spacing enhancing mass transport, without the use of electric fields 37, 50, 51. The SBS process can also generate fibrous structures at much higher rates than other techniques such as electrospinning 37.To fabricate the 2-D BP nanocomposites, a solution of PLGA (4% w/v) in chloroform and acetone was mixed with the 2-D BP suspension to obtain a precursor solution with different weight ratios of 2-D BP (PLGA-1 PLGA-2, PLGA-3 and PLGA-4 corresponding to 0, 1.6, 2.5 and 5 wt.% BP). The PLGA-BP precursor solutions were spun into fibers via SBS toward a stainless-steel mesh collector at a working distance of 20 cm. The deposited fibers formed a 3-D mat on the collector.

A close up of text on a black background

Description generated with very high confidence

**Figure 1:** Atomic force microscopy images of 2-D BP produced by liquid phase exfoliation of bulk BP in IPA on mica substrates. (a), (b), (c), and (d) show the line profiles of several flaks along the dotted white lines marked in the AFM image. Inset: shows a large 2-D BP flake with a height in the order of 1 nm (a) corresponding to a bilayered structure, which is also the case for flakes b and c. The line profile for (d) covers multiple flakes with heights of ~ 0.3 nm corresponding to monolayered 2-D BP. The AFM images highlight the presence of monolayered and bilayered 2-D BP.

Scanning electron microscopy images (SEM) illustrate the typical fiber morphology for PLGA-1, PLGA-2, PLGA-3, and PLGA-4 (Figure 2). Nano-CT confirmed the continuous open-fiber structure, relatively free from defects such as beads (Figure 2e and Figure S3). Furthermore, Energy-dispersive X-ray (EDX) spectroscopy imaging confirmed the successful incorporation of BP nanosheets within the PLGA fibers (Figure S2 c-f). The subsequent fibers had a smooth surface topography, an open structure, and a mean fiber diameter ranging from 469 to 671 nm (distribution insets, Figure 2). The presence of BP in the PLGA solution increased the average fiber diameter around 43%, which was likely due to changes in the precursor solution properties (for example viscosity and surface tension). In addition, IPA has a relatively higher boiling point (82.6 °C) than chloroform (61.2 °C) and acetone (56 °C), which could have suppressed solvent evaporation during the SBS process leading to an increased fiber diameter. For the first time, the BP-PLGA composite provided the 3-D structure with the ability to encapsulate the BP for controlled release compared with other recent BP-based composites including BP/PLGA nanospheres 36, BP/polycarbonate 52, BP/Carbon Nanotube (CN) 53 and **­**BP/ Graphene oxide (GO) 54 composites.

A close up of some grass

Description generated with high confidence

**Figure 2** Showing representative SEM images of fibers produced via SBS for (a) PLGA-1, (b) PLGA-2, (c) PLGA-3, (d) PLGA-4. Left insets: Showing the fiber diameter distributions along with the mean fiber diameter and standard deviation. Right insets: Showing higher magnification images of fibers. All samples have an open fiber network with random orientations. (e) exhibits the Nano-CT image of PLGA-4 structure.

Raman spectroscopy was used to demonstrate the successful incorporation of 2-D BP into the nanocomposite at different concentration (1.6, 2.5 and 5 wt. % BP). The PLGA-2 nanocomposite exhibited three major peaks at 360.2, 436.4, and 464.2 cm-1 corresponding to the vibrational modes (out-of-plane), (in-plane) and (in-plane), respectively (Figure 3a and S4). The Raman shifts for the PLGA-3 and PLGA-4 samples occurred at 358.8, 436.4, and 462.7 cm-1 for , and , respectively (Figure 3a). According to previous reports, at monolayer thicknesses, the Raman shift increases to higher wavelengths (361.7, 437.4 and 464.7 cm-1 corresponding to , and , respectively) 55, 56. Both the PLGA-3 and PLGA-4 samples exhibited a decreased peak shift in the and vibrational modes.

A close up of a map

Description generated with high confidence Raman spectroscopy confirms the presence of 2-D BP in the PLGA fibers and gives insight into the relative concentration of 2-D BP with respect to PLGA. Figure 3b shows that as the concentration of BP is increased the relative intensity of the BP bands (, , ) is concomitantly increased compared to the most intense band of PLGA (stretching mode of :2950 cm-1, indicating higher 2-D BP loadings in the nanocomposites at higher 2-D BP concentrations (Figure 3b).

**Figure 3**Raman spectroscopy of PLGA-BP composites. (a) Raman spectra of control sample and PLGA-BP composites. The Raman intensity of all samples was normalized to the most intense peak in the spectrum associated with PLGA. The main peaks are the stretching mode of CH3 of PLGA at 2950 cm-1 and 2D-BPshifts at vibrational modes (out-of-plane, 360.2 cm-1), (in-plane, 436.4 cm-1) and (in-plane, 464.2 cm-1). (b) The relative intensity of the PLGA stretching mode at 2950 cm-1 (IPLGA:2950) and 2-D BP vibrational modes , , and (IBP) were compared for each sample. As the loading of 2-D BP increased the relative intensity of the IBP peak increased, confirming higher loadings. Inset showing the relationship of initial amount of BP inside each of the PLGA samples with the Raman intensity of PLGA and BP peaks.

To confirm the initial 2-D BP loading in the nanocomposites 5 mg of fibers were dispersed into 10 mL of (5 %) nitric acid to permit accelerated degradation. Once the nanocomposite had degraded the concentration of phosphate species were analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES). The yield of BP incorporation in the PLGA fibers during the SBS process was found to be around 10 %. The amount of phosphate was calculated to be 0, 9.97, 11.55, and 22.9 µg corresponding to 0, 0.19, 0.23, and 0.45 wt.% loading of BP within the PLGA fibers (Figure 4b).

To assess the long term in vitro phosphate ion release fibers were dispersed in deionized water (DIW) at 0.5 mg mL-1. The phosphate ion release for each sample was measured using ICP-AES over 8 weeks as shown in Figure 4a. The release of BP from PLGA fibers in DIW is shown in Figure 4b and has a sigmoidal profile. At initial time points the BP was retained in the fibers for PLGA-2, PLGA-3 and PLGA-4. With increasing time, water permeated into the fibers, leading to the degradation of PLGA and hence increased the release of phosphate ions 57-59. After 37 days, the phosphate release reached saturation and plateaued. Figure 4a shows that both PLGA-2 and PLGA-3 exhibited the fastest phosphate release profiles reaching 95 % after 3 weeks. Whereas, PLGA-4 displayed a gradual sigmoidal phosphate release reaching > 95 % after 7 weeks. The release profiles exhibited similar behavior to reported PLGA microsphere-based drug delivery carriers, showing gradual and sigmoidal drug release over time 58, 59. Therefore, the ICP-AES illustrates that using PLGA-BP nanocomposite fibers, the release rate of phosphate ions can be controlled over time by compositional tuning. At the end of 8 weeks, the pH changed from 5.5 (initial pH of DIW) to 4.55, 4.29, 4.01 and 3.67 for PLGA-1, PLGA-2, PLGA-3, and PLGA-4, respectively. The reduced pH can be attributed to the synergistic release of phosphate species, lactic acid, and glycolic acid. With increasing BP concentration, the pH value decreased by 14.54% due to oxidation of BP in water and formation of phosphate (PxOy) species. By comparing the Raman and ICP results it can be observed that the intensity of the BP vibrational mode for each PLGA sample corresponds to the initial loading of BP. Hence, by increasing the initial amount of BP, the intensity of , and increased, confirming higher BP loadings (Figure 3b, inset).

Previous studies have demonstrated that the degradation rate of PLGA in aqueous media strongly depends on the PLA/PGA ratio 60, 61. Here, a high ratio of PLA monomers (85 wt. %) were used in the copolymer. The nanocomposites exhibited slow degradation compared to PLGA copolymers with a low ratio of PLA and hence gradual release of BP into the aqueous media 58. Thus, in future studies the ratio of PLA/PGA could be controlled to obtain desired degradation rates to match the application.



**Figure 4** Release dynamics of BP-PLGA composites. (a) Phosphate [P] release percentage measured by ICP-AES after incubation of PLGA-1, PLGA-2, PLGA-3, PLGA-4 samples in deionized water (DIW) for 8 weeks at 37 °C. PLGA-1 (control) shows no release. PLGA-2 and PLGA-3 show a faster release profile in comparison to PLGA-4. (b) release rate of BP from fibers as a function of time for PLGA-1, PLGA-2, PLGA-3, and PLGA-4. The results indicated that by increasing the soaking time, the initial amount of BP decreased in each sample at each time point. The black line in (b) corresponds to a sigmoidal fit.

**CONCLUSIONS**

In conclusion, we have developed fibrous PLGA-BP nanocomposites that exhibit gradual release of phosphate species over time. It was also demonstrated that the initial loading of 2-D BP could be changed to control the concentration of phosphate species released. Much emphasis has previously been directed at stabilizing 2-D BP for electronic and photonic applications, here, it was demonstrated that its inherent instability can be exploited for potential biological applications. Such nanocomposites are also advantageous over conventional bioglasses as they do not exhibit brittle behavior due to the soft organic phase. Future work will investigate the physiological and cellular relevance of the phosphate release from such nanocomposites. The preliminary results here are for few-layer BP: we are currently investigating the effects of different flake thicknesses and sizes as another way to tune P release. The 2D-BP composites produced here may find applications as novel biomedical materials for bone tissue engineering (e.g. osteogenesis), nerve regeneration, anti-bacterial implants and photothermal therapies.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Characterization, SEM images, EDX spectrum mapping, Nano-CT images, Raman spectra, ICP results.

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Notes

There are no conflicts to declare.

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