European Polymer Journal 133 (2020) 109773

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

# Polyanionic self-healing hydrogels for the controlled release of cisplatin

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ARTICLE INFO

*Keywords:*
Self-healing hydrogel
Kabachnik-Fields reaction
Cisplatin
Controlled-release

ABSTRACT

The development of multifunctional self-healing hydrogels is limited by the lack of simple methods to prepare multifunctional polymers. In this work, a multifunctional polymer containing phenylboronic acid (PBA) and phosphonic acid (PA) groups was prepared via a one-step Kabachnik-Fields (KF) reaction and free radical polymerization followed by an effective hydrolysis reaction. The negatively-charged polymer can react with poly (vinyl alcohol) to generate a polyanionic self-healing hydrogel under mild conditions (25 °C, pH = 7.4) via dynamic borate ester bonds. The hydrogel has a low cytotoxicity and can be used for 3D cell culture. The negative charged PA groups in this hydrogel efficiently bind positively-charged cisplatin, resulting in a significant improvement of its safety. The polyanionic self-healing hydrogel demonstrates a new application of the KF reaction in interdisciplinary areas that will prompt broader studies on multicomponent reactions in polymer chemistry and material science.

## 1. Introduction

Self-healing hydrogels are new type of hydrogels [1–5]. They are different from traditional hydrogels that are cross-linked by covalent bonds. Self-healing hydrogels mainly use dynamic bonds or physical crosslinks to construct the hydrogel networks. The dynamic bonds are balanced between deconstruction and reconstruction to give the hydrogels unique self-healing properties, such as the ability to spontaneously repair surface and internal damages without external assistance. Meanwhile, making good use of physical crosslinks also create many elegant self-healing hydrogels including protein/peptide-based, alginate-based, and cyclodextrin-based self-healing hydrogels [6–9]. Self-healing hydrogels represent a new generation of smart soft matter and have a great potential as biomaterials. For example, self-healing hydrogels have been successfully used as media for 3D cell culture and injectable carriers to deliver drugs, while having a much better performance for tumour therapy and wound-healing than traditional treatments [10–15]. Nowadays, self-healing hydrogels are at the frontier of soft matter research. The development of new functional biofriendly self-healing hydrogels is important for fundamental research and has practical applications. However, exploring self-healing hydrogels with new functions typically needs laborious multi-step reactions to introduce new functional groups into the structure. This limits the in-depth studies and future applications.

Recently, Meier et al. reported the preparation of poly-condensates through a tri-component Passerini reaction [16]. This triggered more efforts in polymer chemistry to prepare new polymers by using multicomponent reactions (MCRs). Different MCRs have been used by polymer chemists to prepare many elegant polymers. They include the Passerini, Biginelli, Ugi, Hantzsch, Kabachnik-Fields (KF), and Mannich reactions, as well as metal-catalysed and thiolactone-based multicomponent reactions [16–38]. The new polymers have unique properties and functions due to the multicomponent moieties in the main chains or the side chains. This expands the scope of applications of MCRs outside organic chemistry. Meanwhile, MCRs efficiently introduce two or more new functional groups in one step when used as coupling tools. Therefore, MCRs are excellent tools to prepare multifunctional polymers and polymeric materials. Here, we report a multifunctional polymer containing phenylboronic acid (PBA) and phosphonic acid (PA) groups. This polymer was mixed with poly(vinyl alcohol) (PVA) to prepare a polyanionic self-healing hydrogel (Scheme 1).

The KF reaction was developed by Martin Izrailevich Kabachnik and Ellis K. Fields in 1952 [39,40]. The reaction uses an aldehyde, an

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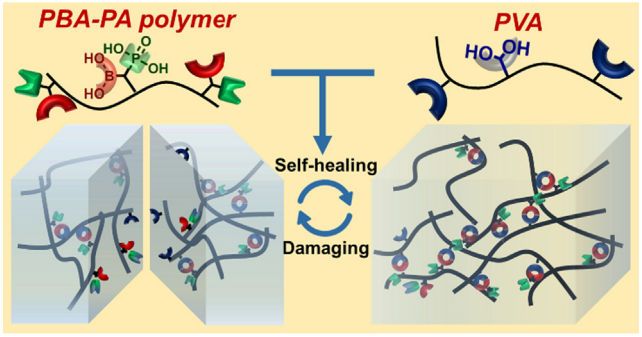
https://doi.org/10.1016/j.eurpolymj.2020.109773
Received 25 March 2020; Received in revised form 7 May 2020; Accepted 12 May 2020
Available online 18 May 2020




**Scheme 1.** Schematic illustration of the principle of a polyanionic self-healing hydrogel.

amine, and a phosphite to effectively create an α-aminophosphonate. The KF reaction has been widely studied in organic chemistry and in pharmaceutical chemistry because many α-aminophosphonate derivatives are peptide mimetic molecules and have a significant bioactivity as antibacterial or antioxidant agents [41–44]. Recently, the KF reaction has been introduced into polymer chemistry to prepare new functional polymers [27–31]. It is a distinctive MCR to prepare phosphorus products and offers a facile approach to prepare polymers containing PA groups.

In this study, a bi-functional polymer containing PBA and PA groups has been easily synthesized by a one-step KF reaction and a free radical polymerization (FRP) followed by an efficient hydrolysis reaction. The resulting water-soluble and biocompatible multi-functional polymer quickly cross-links poly(vinyl alcohol) (PVA) via dynamic borate bonds between PBA and the diol groups in PVA to achieve a self-healing hydrogel. The PA groups in the polymer structure confer the hydrogel with unique polyanionic properties that allow binding positively-charged drugs. The polyanionic self-healing hydrogel prepared has a low toxicity for cells. When used as a 3D matrix for cell culture in the presence of cis-dichlorodiammineplatinum (II) (CDDP), the hydrogel clearly improves the cyto-safety of CDDP via electrostatic interactions between the PA group in the polymer chain and the positively-charged CDDP. This result suggests that the polyanionic self-healing hydrogel is a potential candidate for CDDP delivery. Our approach might pave a new way for the development of multifunctional polymer materials for many practical applications.

## 2. Results and discussion

### 2.1. Synthesis of the precursor polymer (P1) and the PBA-PA polymer (P2)

The precursor polymer (P1) has been easily obtained via a one-step KF and an FRP (Fig. 1a). Briefly, N-(3-aminopropyl) methylacrylamide (APMA), 4-formylphenylboronic acid (4-FPBA), diethyl phosphite (DEPP), and poly(ethylene glycol) methyl ether methacrylate (PEGMA, $M_n$ ~ 950 g/mol) were mixed in ethanol/acetonitrile (1:1, v/v) with a molar ratio of APMA and PEGMA of 2:1. 2,2-Azobis(2,4-dimethylvaleronitrile) (ABVN, 1% to monomers) was used as an initiator. After purging with nitrogen for 30 min, the mixture was kept in a 60 °C oil bath for 12 h. The final polymer was then purified by dialysis against methanol for 48 h and named P1.

The $^1$H NMR spectrum of P1 (Fig. 1b) clearly shows the distinctive peaks of the phenyl group (7.43 and 7.83 ppm), the methylene group by the amine (2.49 ppm), and the methyl group in α-aminophosphonate (1.14 and 1.25 ppm). The integral ratio between the phenyl group and the methoxyl group at the PEG chain end (3.37 ppm) ($I_{7.43}/I_{3.37}$) is 3.74/3, which is consistent with the theoretical value of 4/3. Meanwhile, the $^{11}$B (18 ppm) and $^{31}$P NMR (25 ppm) spectra of P1 showed prominent peaks suggesting the successful synthesis of P1.

Then, P1 was hydrolysed to obtain the target PBA-PA polymer (P2).

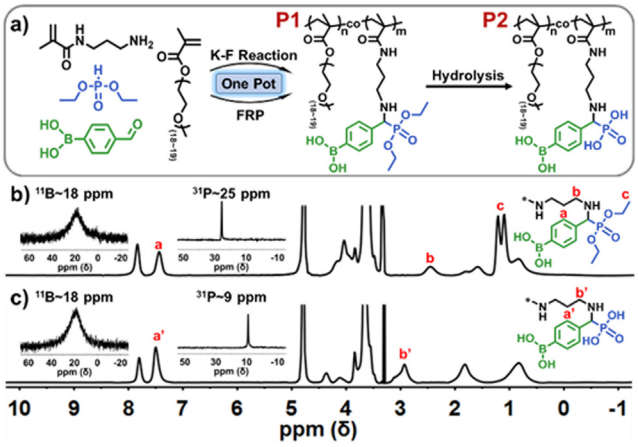



**Fig. 1.** a) Preparation of P1 ([APMA]/[PEGMA]/[4-FPBA]/[DEPP]/[ABVN] = 100/50/110/140/1.5, 60 °C, 12 h) and P2 ([α-aminophosphonate]/[TMS-Br] = 1:10, 65 °C, 12 h); b) $^1$H, $^{11}$B and $^{31}$P NMR spectra ($D_2O$, 400 MHz) of purified P1; c) $^1$H, $^{11}$B and $^{31}$P NMR spectra ($D_2O$, 400 MHz) of purified P2.

P1 was treated with bromotrimethylsilane (TMS-Br) in acetonitrile at 65 °C for 12 h (Fig. 1a). The target polymer was obtained after dialysis against methanol. In the $^1$H NMR spectrum of P2 (Fig. 1c), the methyl peaks of α-aminophosphonate completely disappeared and the methylene group by the amine moved from 2.49 ppm to 2.93 ppm. The integral ratio between the phenyl group and the methoxyl group at the PEG chain end ($I_{7.49}/I_{3.31}$ = 3.80/3) remained almost unchanged. Meanwhile, P2 has nearly the same $^{11}$B NMR spectrum as P1, whereas the $^{31}$P NMR spectrum of P2 significantly shifted to 9 ppm (Fig. 1c, inset). This suggests the successful preparation of P2 from the complete hydrolysis of P1.

### 2.2. Preparation of the self-healing hydrogels

P2 quickly cross-links PVA to generate a hydrogel via dynamic PBA-diol bonds. Typically, equal volumes of a P2 solution (8 wt%, pH = 7.4) and a PVA solution (8 wt%, pH = 7.4) were mixed and a hydrogel (named Gel-8) quickly formed in several seconds (Fig. 2a). Different hydrogels with different solid contents of 4 wt% and 6 wt% have been similarly prepared and were named Gel-4 and Gel-6, respectively. These hydrogels were kept at 25 °C for 2 h to homogenize the internal structure prior to analysis. The storage moduli (G′s) of Gel-4, Gel-6, and Gel-8 gradually increased with the solid contents (Fig. 2b). Meanwhile, the scanning electron microscope (SEM) images of the hydrogels indicated that a higher solid content led to a denser microstructure (Fig. 2c-e). This suggests that the strength of the hydrogel is tuneable by changing the solid content.

PBA-diol bonds are well-known dynamic covalent bonds to prepare many self-healing materials [45–53]. The hydrogels prepared herein are constructed using dynamic PBA-diol bonds and their self-healing properties are subsequently studied.

Typically, we tested the hydrogel with the highest G′ (Gel-8). The hydrogel was placed in a syringe and pushed through a 22-gauge needle (Fig. 3a, blue). The fragments of Gel-8 hydrogel regenerated into an integral hydrogel within 1 h. As a control, a hydrogel made from gelatin (Fig. 3a, red, 8%) went through the same injection process but remained in broken pieces throughout the observation. This preliminarily demonstrates the self-healing properties of the Gel-8 hydrogel.

Next, the self-healing properties of Gel-8 were quantitatively tested. The G′ values of Gel-8 were ~2300 Pa at a low strain < 10% (Fig. 3b). When the strain increased, the G′ value for Gel-8 decreased and was finally lower than G″ at ~170%, suggesting shear-thinning properties. Then, alternate strains (1% and 400%) were applied to Gel-8 (Fig. 3c). At a high strain of 400%, the value of G′ decreased to ~500 Pa, which is

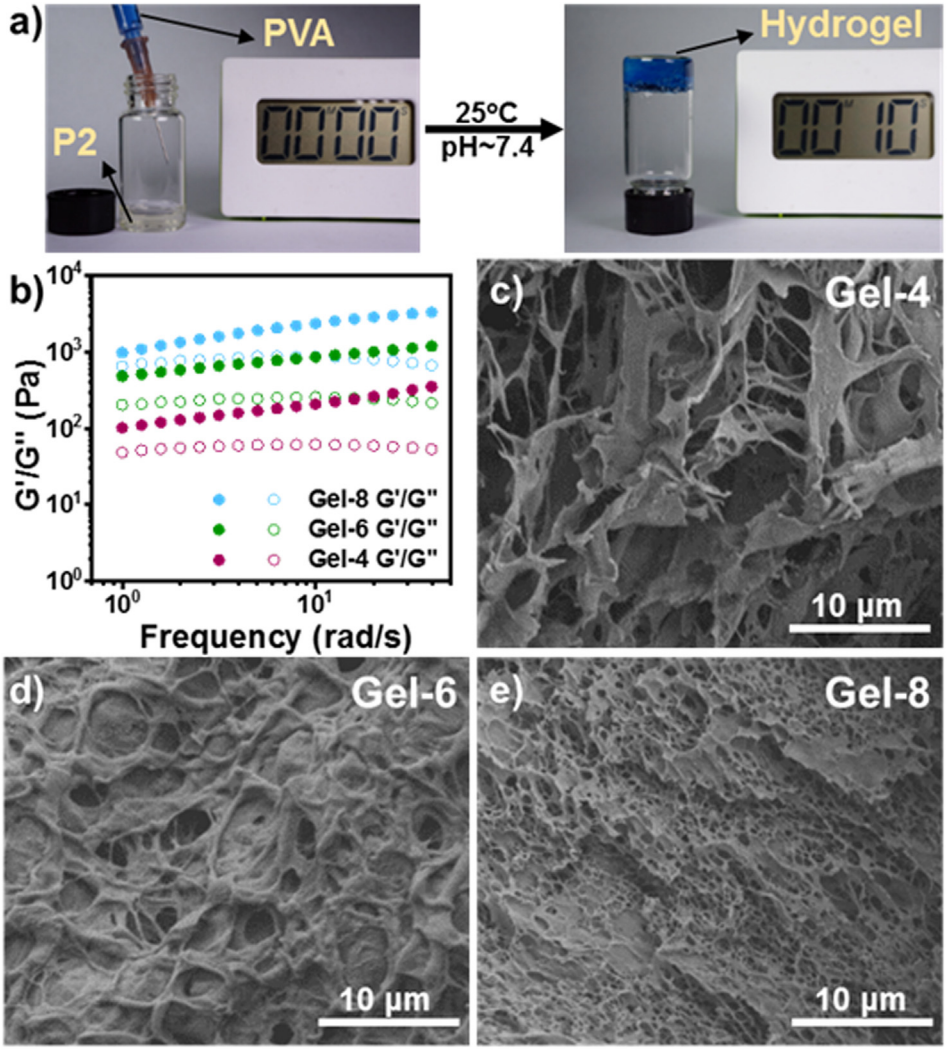



**Fig. 2.** a) Preparation of Gel-8 (the PVA was stained blue for better observation); b) storage moduli (G′s) and loss moduli (G″s) of the hydrogels with different solid contents; c-e) SEM images of the microstructures of the lyophilized hydrogels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lower than G″, indicating the fragmentation of the network in Gel-8. Under a low strain of 1%, G′ and G" were quickly restored to their original values, suggesting the reconstruction of the inner structure. This process was repeatable, suggesting excellent self-healing properties for Gel-8. Gel-4 and Gel-6 were tested similarly and showed similar results (Fig. S1), suggesting the shear-thinning and self-healing properties of the hydrogels constructed by PBA-diol bonds can be generalized.

Moreover, a series of P1-PVA hydrogels was similarly prepared and tested. These hydrogels had a similar strength and self-healing properties as P2-PVA hydrogels (Figs. S2 and S3). This suggests that the hydrogel properties are mainly determined by the PBA-diol bonds and that the phosphonic acid groups negligibly affect the hydrogel properties under the tested conditions.

### 2.3. Binding of CDDP with α-aminophosphonic acid (PA)

P2 is a polyanionic polymer because of the PA moieties and should efficiently bind small positively-charged molecules. To verify this hypothesis, we used a positive charged small molecule, namely CDDP, and studied the interaction between CDDP and the PA groups.

We prepared a small molecular α-aminophosphonic acid and used it as a model (Fig. 4a, A). An α-aminophosphonate was used as the control (Fig. 4a, B).

CDDP reacted with *o*-phenylenediamine (OPDA) to generate a blue complex in N,N-dimethylformamide/water (1:1, v/v).[54] This complex was mixed with compound A and the pale blue colour faded in 30 min (Fig. 4a). On the contrary, the colour did not significantly change in the presence of compound B (Fig. 4a). The visual observations agreed well with the quantitative analysis made by monitoring the absorption at 720 nm using N,N-dimethylformamide/water (1:1, v/v) as the reference (Fig. 4b). A PBA-containing α-aminophosphonic acid (Fig. S4a, C) and a PBA-containing α-aminophosphonate (Fig. S4a, D) were also tested and produced similar results (Fig. S4b). Our results indicate a strong interaction between the PA group in α-aminophosphonic acids and CDDP.

### 2.4. Release of CDDP from the hydrogel

Subsequently, we investigated the release mechanism of CDDP in the presence of P1 and P2 according to previously published methods [54–56] (Fig. S5). CDDP was released more slowly in the presence of P2 than in the presence of P1, suggesting that the negatively-charged P2 triggered a slow release of positively-charged CDDP. Then, CDDP was loaded in a P2-PVA hydrogel (8 wt%, pH = 7.4). The hydrogel was placed in a dialysis bag and immersed in a saline solution (0.9% NaCl,

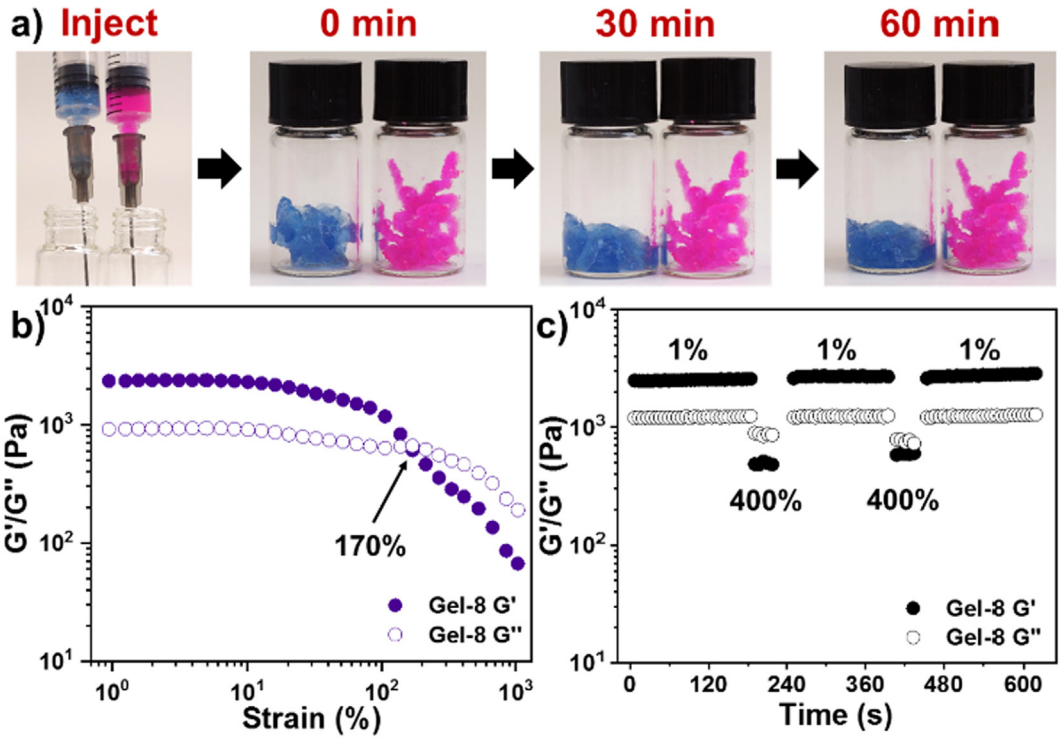



**Fig. 3.** a) Self-healing process of Gel-8 (blue) after injection with a 22-gauge needle. A hydrogel made from gelatin (8%, red) was used as the control; b) evolution of the G′ and G″ moduli of Gel-8 with different strains; c) G′ and G″ moduli of Gel-8 with alternate strains of 1% and 400%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

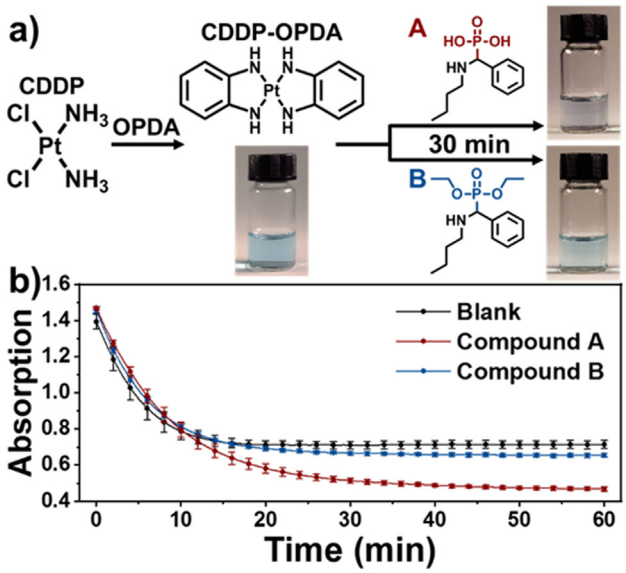



**Fig. 4.** a) Schematic illustration and photographs of the binding study; b) absorbance of the CDDP-OPDA complex over time at 720 nm. The data are represented as mean ± SD, n = 4.

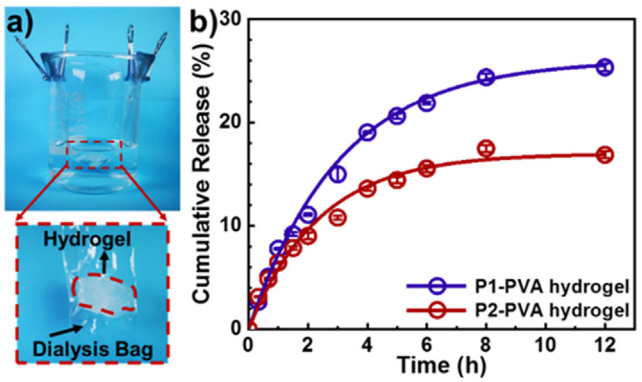



**Fig. 5.** a) Experimental setup used to study the release of CDDP release; b) cumulative release profiles of CDDP from the P1-PVA hydrogel (blue) and the P2-PVA hydrogel (red). The data are represented as mean ± SD, n = 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

37 °C) to study the release of CDDP (Fig. 5a). A CDDP loaded P1-PVA hydrogel (8% solid content, pH = 7.4) served as the control.

After 12 h, around 17% and 26% CDDP were released from the P2-PVA hydrogel and the P1-PVA hydrogel, respectively (Fig. 5b). This indicates that the hydrogels avoid the burst release of the small molecules and the polyanionic network further slows down the release of positively-charged small drugs. Therefore, the polyanionic P2-PVA hydrogel appears to be a better carrier than the non-charged P1-PVA hydrogel to deliver CDDP for a long-term release.

### 2.5. Evaluation of the P2-PVA hydrogel as a CDDP carrier

A drug carrier should be biocompatible. We therefore evaluated the cytotoxicity of the P2-PVA hydrogel. First, the cytotoxicity of P2 was tested using a cell-counting kit-8 (CCK-8) assay. L929 murine fibroblast cells and human cervical cancer HeLa cells were used as models (Fig. 6a).

Both cells had a high viability (L929: 91%, HeLa: 88%) for a high concentration of P2 of 16 mg/mL, which indicated a low cytotoxicity for P2. Similar results were obtained for P1 and PVA (Fig. S6), suggesting that all for the components of the P1-PVA and P2-PVA hydrogels were safe for the cells.

Next, the L929 cells were encapsulated in a P2-PVA hydrogel and cultured for 24 h. A fluorescein diacetate/propidium iodide (FDA/PI) double staining assay was used to simultaneously observe the living and

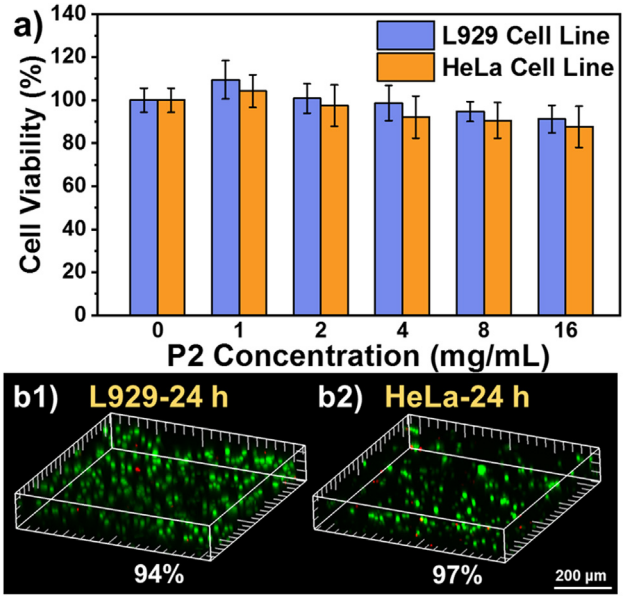



**Fig. 6.** a) Cytotoxicity of P2 for L929 and HeLa cells. The results are represented as the mean ± SD, n = 6; b1, b2) confocal images of L929 and HeLa cells cultured in P2-PVA hydrogel for 24 h. The cells were stained by FDA and PI.

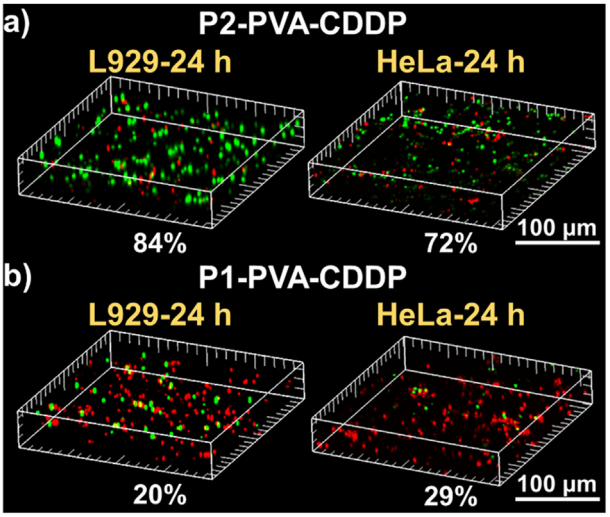



**Fig. 7.** a, b) Confocal images of cells cultured in hydrogels with 100 μg/mL CDDP, 24-h culture. Cells were stained by FDA and PI.

dead cells. The L929 cells remained highly-viable in the P2-PVA hydrogel (~94% viability) (Fig. 6b1). Similar results were obtained when the HeLa cells were cultured in the same hydrogel (~97% viability) (Fig. 6b2). Our results suggest an excellent cyto-safety for the P2-PVA hydrogel.

Afterwards, CDDP (100 μg/mL) was inserted in the P2-PVA hydrogel. We evaluated the viability of different cells in this P2-PVA-CDDP hydrogel using the same method (Fig. 7). The P1-PVA hydrogel was also biocompatible for 3D cell culture (Fig. S7) and was used as the control.

Both L929 and HeLa cells were highly-viable in the P2-PVA-CDDP hydrogel (L929: 84%, HeLa: 72%) (Fig. 7a). On the contrary, only a few cells survived in the P1-PVA-CDDP hydrogels (L929: 20%, HeLa: 29%) (Fig. 7b). This suggests that the polyanionic P2-PVA hydrogel reduces the cytotoxicity of CDDP and constitutes a promising carrier to deliver CDDP in medical and biological applications.

## 3. Conclusions

In summary, a multifunctional polymer with both phenylboronic acid (PBA) and negatively-charged α-aminophosphonic acid (PA) groups was simply prepared via a one-step KF and FRP reaction followed by an effective hydrolysis reaction. The multifunctional polymer quickly cross-linked PVA under mild conditions (25 °C, pH = 7.4) to generate a self-healing hydrogel via dynamic PBA-diol bonds. The negatively-charged PA groups in the multifunctional polymer gives polyanionic properties to the hydrogel. The polyanionic self-healing hydrogel is biocompatible. It efficiently binds CDDP via electrostatic interactions and improved the cyto-safety of CDDP by reducing its release rate. Our results suggest that this polyanionic self-healing hydrogel has potential biological and medical applications as a 3D cell culture matrix and an injectable carrier to deliver positively-charged small drugs for chronic diseases.

## CRediT authorship contribution statement

**Ye Tian:** Data curation, Investigation, Methodology, Writing - original draft. **Yuan Zeng:** Methodology, Software. **Yongsan Li:** Methodology, Software. **Xianzhe He:** Methodology, Software. **Haibo Wu:** Methodology, Software. **Yen Wei:** Funding acquisition, Writing - review & editing. **Yuwei Wu:** Funding acquisition, Writing - review & editing. **Xing Wang:** Funding acquisition, Writing - review & editing. **Lei Tao:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

This research was supported by the National Nature Science Foundation of China (Nos. 21971141, 21574008).

## Data Availability

The raw/processed data required to reproduce these findings cannot be shared at this time due to technical or time limitations.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eurpolymj.2020.109773.

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