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Removal of Erythromycin from Water by Ibuprofen Driven Pre-Organized Divinyl Sulfone Cross-Linked Dextrin

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Abstract: Water recycling and reuse are corner stones in the water management that may be compromised by the presence of pollutants. Among them, pharmaceuticals can overcome the standard water treatments and require sophisticated approaches to remove them. Sorption is an economically affordable alternative limited by the need of sorbents that exhibit sorption coefficient (Kd) higher than 500 L/kg to be useful in wastewater treatment plants (WWTPs). We report that th cross-linking of dextrin (Dx) with divinyl sulfone (DVS) in presence of 1 mmol or 5 mmol of ibuprofen (IBU) yields the insoluble polymers **pDx1** and **pDx5** with improved affinity for IBU, Kd higher than 600 L/kg for ciprofloxacin (CIP) and ofloxacin and an outstanding Kd higher than 4000 L/kg for erythromycin (ERY), when assayed against a cocktail of 6 drugs. The characterization of the polymers by XRPD, TGA and SEM reveals that both **pDx1** and **pDx5** share similar features, with an ERY Kd of 13 x 10^3 for **pDx1** and 6.4 x 10^3 for **pDx5**. The facts that new affinities and improvements in Kd can be achieved by cross-linking Dx in presence of other molecules that promote a pre-organization, broaden the applications of DVS cross-linked polysaccharide as sustainable and eco-friendly sorbents.

Keywords: cross-linking; dextrin; divinyl sulfone; erythromycin; emerging pollutant; biodegradable polymers; sorbent material; water management

1. Introduction

Water management is a current challenge and water-stressed regions are distributed across every continent. According to the UN World Water Development Report 2020, water and climate change are linked, and this connection represents a risk for the water resources [1]. Additionally, over the last century the water needs have grown more than twice the rate of population increase, compromising the delivery of reliable water services [2]. Water recycling and re-use is becoming a critical issue to address the water scarcity (i.e. excess of water demand over available supply), in particular in agriculture, that accounts for 70% of global freshwater withdrawals and more than 90% of its consumptive use [2].

The presence of pollutants may compromise water re-use and increase the cost of water treatment. Among the different emerging pollutants, pharmaceuticals represent a challenge since wastewater treatment plants (WWTPs) are not designed to remove them [3]. Antibiotics are a major concern because besides those used in farms, in 2015 the worldwide consumption was 34.8 billion daily doses [4]. Antibiotic consumption plays a central role in the dissemination of antibiotic resistance genes (ARGs) that promotes antibiotic resistant bacteria (ARBs). Although due to their low

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toxicity antibiotics may not represent a direct human health risk, the occurrence of ARGs and ARBs is an evolutionary pressure that contributes to the development of antibiotic resistance (AR) in humans and this is a serious health threat. Thus, the US Centers for Disease Control and Prevention (CDC) estimates that in USA, more than 2.8 million antibiotic-resistant infections occur each year, causing the death of more than 35000 people [5]. Additionally, AR induces poverty and has a direct impact on the health system estimated in a global increase in healthcare cost ranging from US$300 billion to more than US$1 trillion per year by 2050 [6].

A recent study on AR within U.S. streams affected by WWT discharges under varying instream flow conditions found that under low instream flow conditions, 26% of the streams did not meet the antibiotic resistance safety threshold for ciprofloxacin (CIP) and erythromycin (ERY) [7]. It is important to highlight that 5% of the dose of ERYis excreted in the active form through urine and that ERY is recalcitrant to different treatments in WWTPs, being the effluents from WWTPs, pharmaceutical facilities and hospitals the main contributors to the spread of ERY [8]. As a result, different concentrations of ERY have been reported in inland waters, groundwaters, marine systems, biosolids and sewage sludge from WWTPs and sediments, and the presence in finished tap/drinking water and the bioaccumulation in aquatic biota is a matter of special concern [8].

The impact of ERY resistance on healthcare is significant. ERY is a macrolide antibiotic prescribed for the treatment of different gram-positive and gram-negative bacterial infections and as an alternative to penicillin in patients allergic to that antibiotic, as well as used in veterinary applications. ERY resistance has been reported in *Streptococcus pneumoniae* and *Streptococcus agalactiae* [5] and, among others, in *Neisseria gonorrheae* [9],*Bordetella pertussis* [10] and in meat associated bacteria [11]. A recent study on the ERY resistance in blood of *Staphylococcus aureus*, an indicator organism of the European Antimicrobial Resistance Surveillance Network, revels a correlation between ERY resistance in blood methicillin-susceptible *Staphylococcus aureus* and the consumption of macrolide, lincosamide and streptogramin B antibiotics [12].

The removal of ERY from water has been addressed by the implementation of different methods including coagulation-flocculation, powered activated carbon, granular activated carbon, reverse osmosis, membrane bioreactors or biological activated filters that yield different degree of success [13]. However, from a practical standpoint cost is an important parameter to consider for their application, especially in less developed countries. We have previously demonstrated the hypothesis that the cross-linking of carbohydrates with divinyl sulfone (DVS) is a feasible approach to obtain biodegradable sorbent polymers from economically affordable and sustainable starting materials [14,15]. In the context of antibiotic removal, we have reported that the cross-linking of starch with DVS yields a low cost and eco-friendly sorbent polymer that traps CIP from water with Kd of 1469 L/Kg and removal rates higher than 92% [16]. In this work we further explore our hypothesis and describe a novel sorbent polymer with high affinity for ERY.

2. Materials and Methods

2.1. Reagents

Dextrin from potato starch (Dx, Fluka, Saint Louis, MO, USA), divinyl sulfone (DVS, 99.5%, TCI, Zwijndrecht, Belgium), ibuprofen[(RS)-2-(4-Isobutylphenyl)propanoic acid] (IBU, 98%, BDLpharm, Kaiserslautern, Germany), erythromycin [(3R,4S,5S,6R,7R,9R,11R,12R,13S,14R)-6-{[(2S,3R,4S,6R)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-14-ethyl-7,12,13-trihydroxy-4-{[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione] (ERY, >98%, TCI, Zwijndrecht, Belgium), atenolol [(RS)-2-[4-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]ethanamide](98%, TCI, Zwijndrecht, Belgium), hydrochlorothiazide [6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide] (> 97%, TCI, Zwijndrecht, Belgium) ciprofloxacin [1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid] (CIP, 98%, TCI, Zwijndrecht, Belgium), ofloxacin [(RS)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid] (98%, BDLpharm, Kaiserslautern, Germany), carbamazepine

 doi:10.20944/preprints202403.0165.v1

[5H-Dibenzo[b,f]azepine-5-carboxamide] (98%, BDLpharm, Kaiserslautern, Germany), were used as received. Anhydrous sodium carbonate (99.5%) and anhydrous sodium acetate (99%) were purchased from Sigma-Aldrich.

2.2. Synthesis of DVS cross-linked polymers

The pH of either 1 mmol (0.206 g) or 5 mmol (1.03 g) of IBU in 200 mL of water was adjusted to 9.5 by adding 13 mL of 0.83 M sodium carbonate pH 12 and then, an amount of 10 g of Dx was added and sonicated to promote the dissolution. After 5.5 h of gently stirring, 100 mL of water and 5 mL of DVS (5.7 g, 48.4 mmol) were added and the gently stirring was extended 30 min prior to adding 187 ml of 0.83 M sodium carbonate to reach pH 12. The reaction proceeded for 16 hours with gently stirring and the obtained solid was isolated by filtration, thoroughly rinsed first with water until neural pH, then acidulated with 5% HCl to protonate the IBU that might remain trapped and then with methanol and finally with diethyl ether. After drying under vacuum for 18 h at 40 °C the obtained amounts of polymer synthesized in presence of 1 mmol (**pDx1**) and 5 mmol (**pDx5**) of IBU were 7.86 g and 5.43 g respectively. A control polymer (**pDx0**) synthesized under the same conditions but in absence of IBU yielded 8.41 g.

2.3. Characterization

Polymers were characterized by elemental analysis with a Thermo Scientific Flash 2000 elemental analyzer (Thermo Scientific) to determine the presence of S from the sulfone group of the DVS cross-linker. Structural characterization of the polymers was addressed by X-ray powder diffraction (XRPD) and Fourier transform spectroscopy (FTIR). X-ray diffractograms were collected with a D8 discover equipped with a Pilatus3R 100K-A detector (Bruker), operation voltage and current of 50 kV and 1 mA respectively and Cu Kα sealed tube (λ = 1.54 Å). Data were collected from 2θ 5° to 85° with a 0.02° step and 40 s of integration. IR spectra from 400 to 4000 cm^{-1} were measured with a Spectrum Two FT-IR spectrometer (PerkinElmer) in ATR mode by accumulating 30 scans.

Polymers were further characterized by electron microscopy to observe the morphology and by thermogravimetric analysis (TGA) to study the thermal stability and identify the products of decomposition. TGA was performed in nitrogen atmosphere at 950 °C and heating rate of 20 °C/min using a Shimadzu TGA-50H instrument (Shimadzu) coupled to a Nicolet 550 IR-FT spectrometer (Thermo Scientific). For the electron microscopy analysis the samples were covered with carbon and analyzed with a Zeiss SUPRA40VP field emission scanning microscope (Zeiss).

2.4. Sorption studies

Sorption experiments were conducted at room temperature in batch mode. For the study of the sorption of IBU, 0.1 g of polymer and 10 mL of IBU water solutions (concentration ranging from 0.5 to 2 mg/L) were mixed in Falcon tubes and shaken in a tube rotator (VWR) for 3 h. Then the IBU solution was separated by centrifugation at 4000 rpm and its concentration was quantified with an F2000 fluorescence spectrophotometer (Hitachi) by interpolating the emission at 290 nm (λex 260 nm) in a calibration curve [17].

For the evaluation of the polymer as sorbents of a cocktail of drugs, 0.1 g of polymer and 10 mL of a water solutions containing a mixture of carbamazepine, atenolol, hydrochlorothiazide, ofloxacin, CIP and ERY ranging for 2 to 50 µg/L of each drug was assayed as described above and analyzed by mass spectrometry. With the help of an Acquity FTN AutoSampler (Waters Corporation), a volume of 10 µL of sample was injected in an ultrapultraperformance liquid chromatograpy (UPLC) system consisting of a Quaternary Solvent Manager Acquity (Waters Corporation) equipped with a column C18 BEH 1.7 mm 100 mm and coupled with a triple quadrupole mass spectrometer XEVO-TQS (Waters Corporation). The mobile phase of the UPLC system consisted of 0.1% (v/v) formic acid in water (Solvent A) and 0.1% (v/v) formic acid v/v in acetonitrile (Solvent B). The flow rate was 0.3 mL/min and the gradient was from 80% solvent A: 20% solvent B to 80% solvent A: 20% solvent B within 8 min and then back to 80% solvent A: 20% solvent B within 2 min. Electrospray ionization

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mass spectra (ESI-MS) were acquired in the positive (ESI +) except for hydrochlorothiazide, that was acquired in the negative (ESI -). LC-MS/MS acquisition parameters for the target molecules were as follows: Carbamazepine237.00 > 178.99 and 237.00 > 194.07; Atenolol 267.13 > 145.01 and 267.13 > 190.05; CIP 332.23 > 288.16 and 332.23 > 314.10; Ofloxacin 362.24 > 261.11 and 362.24 > 318.17; ERY 734.81 > 158.10 and 734.81 > 576.35; Hydrochlorothiazide 295.93 > 205.00 and 295.93 > 268.96.

The performance of the polymers as sorbents was evaluated by the sorption coefficient, Kd, which is defined as the ratio between the concentration of drug in solution (Ce) and in the polymer (qe) and is estimated as the slope of the plot qe (mg/kg) versus Ce (mg/L) at equilibrium.

Kd=dqe/dCe

2.5. Modeling of the sorption experiments

Data fitting was carried out with ISOT-Calc, a macro for MS-Excel that performs a non-linear regression to distinct isotherms, being the minimization of the mass balance (i.e the difference between the estimated and the experimental Ce values) the objective function (U) [18]. U is defined as the sum of squared residual errors (e_i) obtained from the difference between the experimental and the corresponding values estimated by the guessed model, with w_i being statistical weights:

$$U = \sum_{i=1}^{n} w_i \cdot e_i^2$$

Data were fitted to the four parameters isotherm of 2-sites Langmuir, the three parameters isotherms of Vieth-Sladek and Redlich-Peterson and, the two parameters isotherms of Temkin, Freundlich and Langmuir as defined by ISOT-Calc and depicted in Table S2. The goodness of the fitting was judged by evaluating the standard deviation of the parameters defining the isotherm and the mean weighted square error (MWSE) defined as:

$$MWSE = \frac{U}{(n-p)}$$

where n indicates the number of experimental points and p is the number of parameters refined.

3. Results

Sorption is an economically affordable procedure for the treatment of wastewater. The search for sorbent materials is driven not only by the affinity towards the pollutants, but also by the sustainable ways of producing them. We have previouly reported that it is feasible to obtain sorbent polymers by cross-linking biodegradable carbohydrates with
DVS and, in particular, that the eco-friendly material resulting from the cross-linking of starch shows a high affinity for CIP and makes it suitable for inland water and seawater remediation[14–16]. Nevertheless, this approach failed to obtain sorbent materials with the ability to trap IBU despite both CIP and IBU show some degree of structural similarity (Figure S1). It was concluded that the cavities formed during the cross-linking were not suitable to host the IBU molecule. On this basis we hypothesized that the pre-incubation of the carbohydrate with IBU prior to the addition of the cross-linker DVS may pre-organize the systems in a manner that resembles the molecular imprinting technology. Being aware that it is unlikely that the cross-linking of polysaccharides generates cavities complementary in size and charge to small molecules such as IBU, we were encouraged by the fact that the cross-linking of cyclodextrin in the presence or absence of toluene yields different polymers, being mainly linear in the former case and globular in the latter [19].

3.1. Synthesis and characterization

Natural polymers such as chitosan, cyclodextrin, sodium alginate, starch, cellulose, lignin and their derivatives have been used to prepare molecular imprinted polymers(MIPs) [20]. In addition, along our previous research we have generated a library of polymers using starch, Dx and/or β-cyclodextrin as building blocks [14–16]. However, for the purposes of this work we focus

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on Dx because, unlike starch, it shows an excellent water solubility and, as a linear molecule, it is more flexible than cyclodextrins because the cavities are not preformed. Prior to conducting the cross-linking reaction, the solution of Dx in carbonate was pre-incubated with either 0 mM, 1 mM or 5 mM of IBU for 5.5 hours. Then, DVS was added and the reaction was allowed to proceed overnight with slow agitation, resulting in the insoluble polymer **pDx0**, **pDx1** and **pDx5** with yields (i.e., percentage of the mass of reactants recovered as an insoluble polymer) of 52.3%, 49.4% and 33.6% respectively. The elemental analysis detected a content of sulfur ranging from 5.85% to 6.31% (Table S1), being 2.2 and 2.1 the ratio Glc/DVS estimated for **pDx0** and **pDx1**, and 2.4 for **pDx5**, and indicating that the degree of cross-linking is lower at higher concentration of IBU.

These insoluble polymers were characterized by XRPD, FTIR and SEM. The XRPD analysis (Figure S2) of the starting material Dx reveals dispersive broad peaks centered at 2θ 17° and 22° anticipating the amorphous structure of the materials resulting from its cross-linking with DVS, regardless of the pre-incubation with IBU. FTIR spectra (Figure S3) show the broad signal of the O-H stretching at 3500 cm^{-1} and the expected double signal at 1282 and 1313 cm^{-1} distinctive of the sulfone group and of the DVS cross-linked carbohydrates [16,21]. The spectra of **pDx1** and **pDx5** obtained in presence of IBU do not show the signature of the C=O stretching, supporting that IBU does not remain entrapped after the cross-linking but that it is released during washes in the isolation, process resulting in the synthesis of IBU-free polymers. SEM characterization shows that polymers share a lobular appearance (Figure 1, column A), a smooth outer surface and a homogeneous interior (Figure 1, column B). The typical diameter of the lobules is in the range of 3 μm, regardless the concentration of IBU during their synthesis (Figure 1, C1 and C2). A higher magnification reveals the cauliflower-like surface of the lobules and the filamentous structure that connects them (Figure 1, C3).

Polymers were further characterized by TGA. Polymers **pDx1** and **pDx5** are very similar and slightly different to **pDx0**, the latter losing weight to a some degree at lower temperatures (Figure S4). When they are heated to 950 °C in a nitrogen atmosphere at a heating rate of 20 °C/min, a first mass loss ranging from 2.7% to 3.9% with a maximum speed of decomposition between 108 ºC and 120 °C (Tp1) takes place, that is within the expected values for DVS cross-linked carbohydrate polymers and it is associated to the vaporization of bound water [16]. A second mass loss related to depolymerization and decomposition of both the polymers and the structure of Dx starts within the range 306 °C and 313 °C (T_{onset}), reaching the maximum speed of decomposition (Tp2) at 344 °C for **pDx0** (Figure S5) and 354 °C for **pDx1** and **pDx5** (Figures S6 and S7). Beyond 500 °C the degradation of organic matter occurs, leaving a residue as ash that accounts for 0.87% to 2.65% of the initial mass. The IR spectra collected during the analysis allow the detection of signals assigned to CO2 (3734, 3626, 2357, 2321and 666 cm^{-1}), CO (2176, 2116 cm^{-1}), and SO2 (1375, 1340 1166, and 1131 cm^{-1}), as well as weak signals that may indicate the formation of formaldehyde (2899, 2743, 1749 and 1163 cm^{-1}), acetaldehyde (1749 cm^{-1}), ethene (3126, 3015 and 948 cm^{-1}) and methane (3015 cm^{-1}) (Figures S8 to S10).

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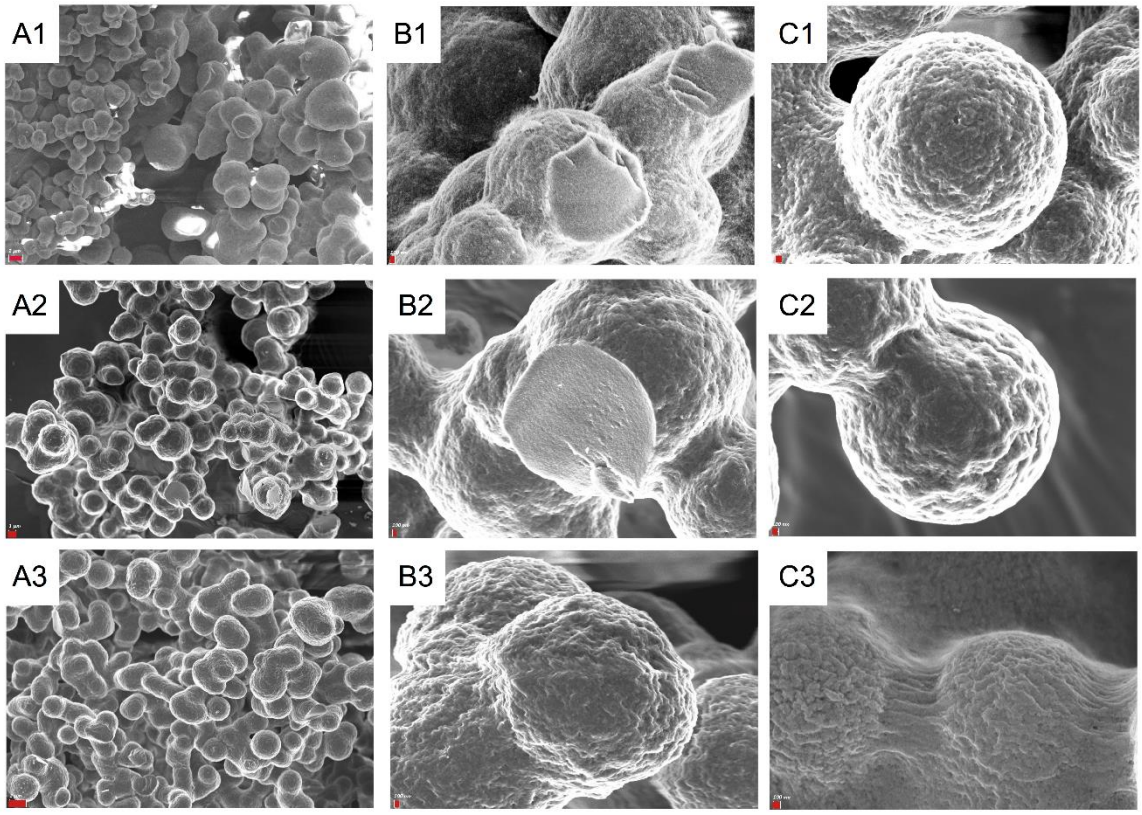

Figure 1. SEM study of **pDx0** (A1 and B1), **pDx5** (A2, B2 and C2) and **PDx5** (A3, B3, C1 and C3). The scale bar (in red) and the magnification are 1 μm and x2000 for A1 and A2, 2 μm and x2500 and for A3, 100 nm and x14000 for B1, x13000 for B2, x16000 for B3, x19000 for C1 and C2, and x22000 for C3.

3.2. Evaluation of the polymers as sorbents of IBU

Providing that a solution of IBU emits fluorescence at 290 nm when it is excited to 260 nm [17], the ability of the polymers to remove IBU from an aqueous solution was evaluated by incubating 0.1 g of the polymer with 10 mL of 10 solutions with concentrations ranging from 0.5 to 8mg/L (Figure S11). As expected, **pDx0** does not trap IBU from the solution. The pre-incubation and synthesis in the presence of IBU to yield polymers **pDx1** and **pDx5** improves Kd up to 192 L/kg. However, for the purpose of removal of pollutant by sorption in WWTPs, sorbents with Kd lower than 500 L/kg are useless [22]. These results led us to conclude that although **pDx1** and **pDx5** are different to **pDx0,** none of them is suitable as scavenger of IBU and we hypothesized that **pDx0**, **pDx1** and **pDx5** may act as sorbent of other drugs.

3.3. Evaluation of polymers as sorbents of a cocktail of drugs

The NORMAN network has identified more than 700 substances in the European aquatic environment, among them the antihypertensives atenolol and hydrochlorothiazide, the antibiotics CIP, ofloxacin and ERY and the anticonvulsant carbamazepine [23]. To put to test our hypothesis we evaluated by mass spectrometry the polymers as scavengers against a cocktail of these six drugs at concentrations ranging from 50 to 2 μg/L, that is in the range of concentration of the emerging pollutants. As depicted in **Table 1** none of the three polymers is suitable for the removal of carbamazepine or hydrochlorothiazide in WWTPs, **pDx0** is close to the 500 L/Kg threshold for atenolol and **pDx1** and **pDx5** are slightly above for ofloxacin. The use of IBU yields a 14-fold and 10-fold improvement of Kd for the sorption of CIP in **pDx1** and **pDx5** respectively, the former being suitable for WWTPs, although to a lesser extent than the reported polymer resulting from the cross-linked starch (Kd 1469 L/kg) [16]. This enhanced affinity for CIP was not unexpected providing that CIP and IBU share some degree of structural similarity (Figure S1). However, the outstanding

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performance of **pDx1** and **pDx5** towards ERY to yield a 26- and 29-fold improvement in Kd and to reach values of 4285 and 4658 L/kg respectively was not anticipated since, compared to IBU, ERY presents larger molecular weight (733.9 g/mol vs 206.3 g/mol), octanol-water partition coefficient (4.52 *vs* 2.17) [24] and topological polar surface area (193.91 *vs* 32.30 Å^2) [25].

Table 1. Sorption coefficients (Kd) of six drugs analyzed as a cocktail on the sorbents **pDx0**, **pDx1** and **pDx5**. The coefficients of determination are shown in brackets and italics.

Drug	pDx0	pDx1	pDx5
Atenolol	413.7 (*0.983*)	264.7 (*0.990*)	415.7 (*0.890*)
Hydrochlorothiazide	28.4 (*0.865*)	33.3 (*0.815*)	35.0 (*0.870*)
Ofloxacin	No linear fitting	677.9 (0,915)	631.8 (0.951)
Ciprofloxacin	65.6 (*0.589*)	926.9 (*0.832*)	654.0 (*0.940*)
Carbamazepine	18.0 (*0.989*)	20.1 (*0.968*)	22.5 (*0.990*)
Erythromycin	61.0 (*0.975*)	4285.0 (*0.988*)	4657.7 (*0.954*)

3.4. Evaluation of the polymers as sorbents of ERY

The structure of the aromatic ring of ERY makes it resistant to degradation. More than 5% of the dose of ERY is excreted in the active form through urine and ERY is recalcitrant to different treatments in WWTPs. In fact, ERY has been detected in inland waters, marine systems, ground waters and, what it is matter of concern, in finished drinking water, questioning the efficiency of the advanced treatment systems [8]. Therefore, new approaches for the removal and degradation of ERY residues from wastewater are important and sorption is an economically affordable approach.

The above result of the sorption of ERY from a complex matrix containing five additional drugs was pure serendipity and encouraged us to further characterize the sorption of ERY on the IBU driven pre-organized polymers. First, we evaluated the kinetics of the sorption by mass spectrometry. The analysis of the evolution of the concentration of 1.5 mL of a solution of ERY at 10 µg/L incubated with 15 mg of polymer **pDx1** showed that the equilibrium is reached within 20 min (Figure 2A). The sorption process is very fast and within 2 min of incubation a remarkable 82.7% of ERY is removed from the solution. In practical terms this value implies that the circulation of the wastewater through a filter or a column-like device for 2 min reduces the concentration of ERY in the outlet water to 1.7 ppb

Next, the ability of the polymers to remove ERY from an aqueous solution was studied by incubating 15 mg of polymer with 1.5 mL of twelve ERY solutions with concentrations ranging from 2 to 250 µg/L and quantifying by mass spectrometry the amount of

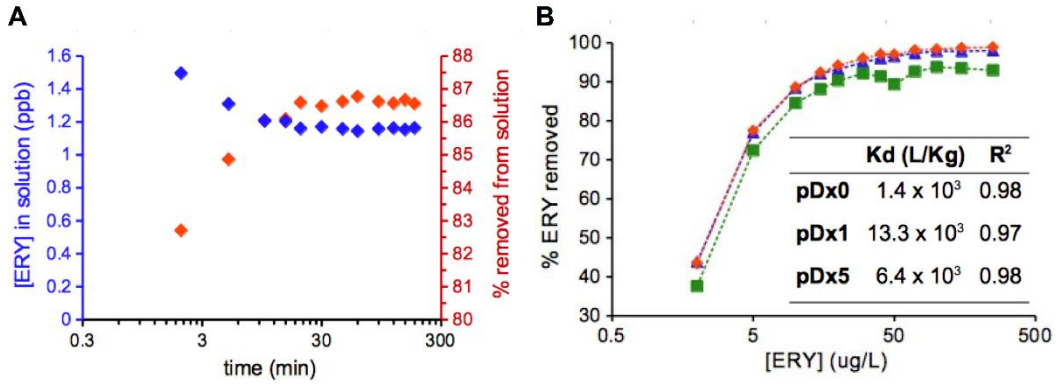

Figure 2. (A) Kinetics of the sorption of ERY on **pDx1**. The scale of the x-axis is logarithmic. (B) Isotherm of the sorption of ERY on **pDx0** (green), **pDx1** (red) and **pDx5** (green) expressed as percentage of ERY removed from the solution. Insert, sorption coefficient (Kd) and coefficient of determination (R^2). The x-axis is in logarithmic scale.

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ERY that remained in solution after 30 min. The isotherms are very similar, reaching a removal efficiency close to 93% for **pDx0** and 99% for of **pDx1** and **pDx5**. A closer analysis of the isotherm allowed to estimate the Kd as 1.4 x 10^3, 13.3 x 10^3 and 6.4 x 10^3 L/kg for **pDx0**, **pDx1** and **pDx5** respectively, which represents 2.8, 26.6 and 12.0 times the 500 L/kg threshold for their use as sorbents in WWTPs (Figure 2B). It is important to highlight that the one order of magnitude improvement of Kd for **pDx0** when assayed against a solution of ERY has no practical application since with the cocktail of the six drugs the Kd decreases to 161.0 L/kg, showing higher affinity for Atenolol, whereas the improvement for **pDx1** and **pDx5** is not affected by the presence of other pollutant as these do not change the magnitude of their Kd. These data support the high affinity of **pDx1** and **pDx5** for ERY whereas **pDx0** is less selective.

With the help of the tool ISOT_Calc [18] data were fitted to the two parameters isotherms of Temkin, Freundlich and Langmuir, the three parameters isotherms of Vieth–Sladek and Redlich–Peterson and the four parameters isotherm of 2-sites Langmuir as defined in Table S2. Our efforts were focused on non-linear fitting because linearization implies bias, despite the fact that the linearized forms of the isotherms have been extensively referenced in the literature. Most fittings converged in a solution for the different isotherms, but when the goodness of the fitting was evaluated on the basis of the standard deviation (% r.s.d.) of the parameters defining the isotherm and the mean weighted squared error (MWSE), data only fit to the Temkin isotherm that assumes that sorption is a multilayer process (Table 2). The values of the constants K_1 and K_2 correlate with the Kd estimated for the three polymers. However, they do not provide any additional insight into the sorption mechanism because the Temkin isotherm is an empirical model without an effective theoretical support [26].

Table 2. Values of the parameters and the mean weighted squared error (MWSE) resulting from the fitting to the sorption of ERY to the Temkin isotherm by ISOT_calc. In brackets the percentage of the root mean square deviation (rmsd).

	K_1	K_2	MWSE
pDx0	5.951 (1.828)	39.34 (1.944)	0.05
pDx1	18.690 (0.908)	128.80 (0.874)	0.01
pDx5	13.040 (0.906)	89.180 (0.820)	0.03

4. Conclusions

Water scarcity is one of the consequences of climate change and emerging pollutants that overcome the standard water treatments compromise water recycling and reuse, especially in less developed countries where sophisticated approaches are not affordable. Sorption is an attractive approach, and the search for sorbent materials is driven no only by the requirement of Kd higher than 500 L/kg, but also by the sustainable ways of producing them. In this context, polymeric materials obtained by cross-linking of polysaccharides represent an appealing option that combines both the use of renewable and non-toxic building blocks with their biodegradability. New affinities and improvements in Kd can be achieved by cross-linking in the presence of other molecules that promotes a pre-organization. This is a versatile and economically affordable strategy that can be scaled up and expands the potential application of these sustainable sorbents. In particular, the results reported here make **pDx1** and **pDx5** outstanding materials for the removal of ERY from contaminated water, with Kd values of 13.3 x 103 and 6.4 x 103 L/kg, respectively, fast sorption kinetics and good selectivity in the presence of other pollutants

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: Superimposition of two conformers of IBU on CIP; Figure S2: XRPD of the starting material Dx, **pDx0**, **pDx1** and **pDx5**; Figure S3: FTIR of **pDx0**, **pDx1** and **pDx5**; Figure S4: TGA curves of **pDx0**, **pDx1** and **pDx5**; Figure S5: Derivative TGA of **pDx0**; Figure S6: Derivative TGA of **pDx1**; Figure S7: Derivative TGA of **pDx5**; Figure S8: IR-TGA of **pDx0**; Figure S9: IR-TGA of **pDx1**; Figure S10: IR-TGA **of pDx5**; Figure S11: Sorption of IBU by **pDx0**, **pDx1** and **pDx5** and estimation of the sorption coefficient; Table S1:

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Elemental analysis of the ibuprofen pre-incubated cross-linked polymers; Table S2: Equations of the isotherm model assayed for the fitting of the experimental sorption data as defined by ISOT_calc.

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