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Cyclodextrin polymers as efficient adsorbents for removing toxic non-biodegradable pimavanserin from pharmaceutical wastewaters

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ABSTRACT

Presence of even small amount of active pharmaceutical ingredients in the environment carries risks to human and animal health, presenting an important issue. The paper presents issues related to the new drug - pimavanserin (PMV). Biological treatment efficiency of pimavanserin (PMV) was evaluated using lab-scale Sequencing Batch Reactor (SBR). It has been shown to have a negative effect on aquatic organisms by classifying it as a toxic compound (EC_{50} = 8 mgL^{-1}). The level of biological degradation of PMV was insufficient (37%) and intensively foam formation caused operational problems. For this reason, in this study polymers based on cyclodextrins (CDs) were synthesized and used as adsorbents alternative to active carbons to effectively separate PMV from real industrial waste streams. Crosslinked β- and γ-CD polymers (β- and γ-NS), obtained in reaction with carbonyldiimidazol (CDI), were fully characterized by physicochemical methods. The adsorption equilibrium data were interpreted using Freundlich and Langmuir models. The sorption process was fast (60 s) and the efficiency of PMV separation from model waste waters was 93% and 81% for β- and γ-NS, respectively. Maximum polymer capacity was found at 52.08 mg g^{-1} for β-NS and 23.26 mg g^{-1} for γ-NS. The interactions of PMV with CDs have been studied and indicate that major mechanism of the sorption is based on supramolecular interaction and capture to polymer network. Described biodegradable and reusable

materials are perfect example of correctly selected adsorbent for separation of target substance from postproduction aqueous media.

Keywords: cyclodextrin, polymer, pimavanserin, pharmaceutical wastewaters

1. Introduction

Wastewater from industrial and municipal streams contain undesirable organic pollutants (Morin-Crini et al., 2018). Conventional wastewater treatment technologies are not sufficient for certain pollutants removal to the desired levels (Mamba et al., 2007). The residuals of active pharmaceutical ingredients (APIs) threat the environment, human and animal health (Walter and Mitkidis, 2018). Biological (Zupanc et al., 2013), membrane processes (Shojaee Nasirabadi et al., 2016), electrochemical and chemical techniques (Ensano et al., 2017; Menapace et al., 2008), with particular emphasis on advanced oxidation (Kanakaraju et al., 2018) and adsorption processes (Al-Asheh et al., 2003; Bo et al., 2016) are the best-known industrial methods of wastewater treatment. Due to the fact that industrial effluents are very complex and time-dependent mixtures of organic and inorganic pollutants, the treatment is based on the combination of various processes that allow obtaining the required water quality in the most economical way (Morin-Crini and Crini, 2013). Of all the proposed treatments, the adsorption process is one of the most popular methods due to its simplicity, cost-effectiveness and wide range of pollutants removal from aqueous solutions.(Putra et al., 2009). Active carbons are the most common sorbents used to lower the concentration of many organic compounds in water, but the significant problem is adsorbents regeneration (Kovalova et al., 2013; San Miguel et al., 2001). Recently, much effort has been assigned to the development of cheaper and more effective adsorbents including natural polymers (Corsi et al., 2018). Oligosaccharides, such as cyclodextrins (CDs) (Arora and Dhingra, 2018; Fourmentin et al., 2018) are well known,

biodegradable and renewable resources (Janarthanan et al., 2016; Orprecio and Evans, 2003). Converting CDs into crosslinked polymers (nanosponges (NSs)) by condensation with bi- or multifunctional electrophilic reagents (Karoyo and Wilson, 2016; Pratt et al., 2010; Szejtli et al., 1978) allows to obtain water insoluble natural adsorbents used in separation and purification processes (Morin-Crini and Crini, 2013). The adsorption mechanism of NSs is related to inclusion complexation, physical sorption in network and hydrogen bonding (Crini et al., 1998; Yilmaz et al., 2010).

Many modern drugs have complex chemical structure. Pimavanserin (PMV) belongs to this category. PMV is an atypical antipsychotic drug, recommended for the treatment of hallucinations and delusions associated with Parkinson's psychosis (Chendo and Ferreira, 2016). The Food and Drug Administration agency approved PMV as the first drug to treat Parkinson's disease in 2016 and it is also being developed to treat other psychotic disorders, including schizophrenia (Combs and Cox, 2017). With the increasing role in pharmaceutical treatment, the amount of PMV discharged to the environment may increase accordingly, therefore toxicity and biodegradability tests are necessary. To the best of the authors' knowledge, no such studies have been carried out.

Additionally, it should be emphasized that so far attention has been given to make PMV synthesis environmentally friendly. The biggest achievement is the exclusion of isocyanates and replacing them with raw materials obtained by reaction with urea and carbonic acid derivatives (Fig. 1). What important is that, the acids derivatives could be used directly in the main reaction without the need for isolation and the intermediate purification. The obtained PMV solution in an organic solvent (usually ethyl acetate) is purified by repeated extraction with water or aqueous solutions of HCl (NH_4Cl) and NaCl. At this stage post-production raffinates containing different amount of PMV are produced.

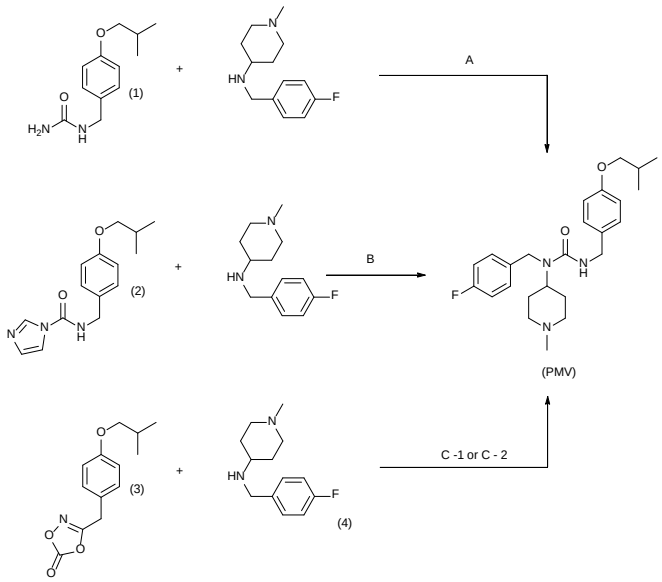

Fig. 1. Raw materials used in the synthesis of PMV, excluding isocyanates. Waste streams generated during the synthesis of PMV in method: A and B - aqueous raffinates, C-1 aqueous raffinates contain NH_4Cl and NaCl; C-2 acidic raffinates contain HCl and NaCl (Chen-Wei and Chin-Wei, 2018; Rapolu et al., 2019)

In this work, preliminary PMV toxicity and biodegradability studies were evaluated. We have proposed the use of water-insoluble NS based on β- and γ-CD as adsorbents for the separation of this drug from industrial raffinates. NSs were obtained by condensation polymerization reactions with a carbonyl cross-linked 1,1'-carbonyldiimidazole (CDI) (Trotta and Tumiatti, 2005). The obtained NSs were characterized in detail. Studies were focused to achieve the best conditions of adsorption. After each sorption stage, the NSs were regenerated. Finally, the adsorption efficiency of NSs were compared with the adsorption efficiency obtained with the use of commercially available activated carbons. The adsorption mechanisms of PMV by NSs were investigated, based on the interaction between drug and natural cyclodextrin. In addition to only one the patent available in the literature, which mentions that cyclodextrins can be used in pimavanserin preparations as complexing agents (Gant and Sarshar, 2008), detailed study on interaction of PMV with CDs has not been published so far. This work offers a new way to effectively separate pollutants from wastewater by using selective, biodegradable and fully regenerable materials based on cyclic oligosaccharides.The

presented research concerns the area of environmentally friendly technologies and can be easily accessible to large-scale fabrication.

2. Materials and methods

2.1. Chemicals and materials

Pimavanserin tartrate (PMV, ≥99.9%) and free base (PMV-b) was synthesized, based on procedures described in patent US2018/0208556 A1(Chen-Wei and Chin-Wei, 2018). Pimavanserin tartrate standard was obtained from LGM Pharma (USA). 1,1'-carbonyldiimidazol (CDI, ≥98%), methanesulfonic acid (CH_3SO_3H, ≥99%), β-cyclodextrin (β-CD, ≥97%) and γ-cyclodextrin (γ-CD, ≥98%) were purchased from Sigma-Aldrich. Acetonitrile (HPLC-grade) was supplied by Chempur (Poland). Methanol (CH_3OH, ≥99.8%), ethanol (C_2H_5OH, anhydrous, ≥99.8%,), and dimethyl sulfoxide $(CH_3)_2SO$, ≥99.9) were purchased from POCH. Potassium bromide (KBr, spectroscopy grade) were purchased from Fisher Scientific and dried before use. All chemical were used without further purification. Water used in all experiments was purified by Hydrolab-system (HLP- SPRING, temp. 22 °C, κ= 2.70 μS). Activated carbons Norit SX1 (S_{BET}= 900 m^2/g) (N-SX1) was obtained from Brenntag and Organosorb 200-C303 (S_{BET}= 1200 m^2/g) (O-C303) was obtained from Lenntech.

2.2. Synthesis procedures

β- and γ-NS were synthesized following the procedure previously reported (Trotta and Tumiatti, 2005) with some minor modifications. Detailed information on the synthesis of NSs, their analysis, as well model post-production raffinates preparation are presented in SI (Text S3 and S4, Fig. S1-S8, Table S1-S5).

2.3. Methods

Biological experiments were performed using the activated sludge donated from municipal wastewater treatment plant (Swarzewo, Poland). The biological unit of this treatment plant was sequencing batch reactor (SBR). The total suspended solids of the sludge samples were determined according to standard methods reported by American Public Health Association (American Public Health Association (APHA), 2005).

The progress of PMV biological degradation was determined using high-performance liquid chromatography (HPLC). Toxicity test of PMV was performed by the Microtox bioassay according to the Strategic Diagnostic (USA) company's standard procedure requirements (details in SI, Text S1, S2).

Adsorption experiments of PMV were studied at 25°C using digital vortex mixer (OHAUS VXHDDG) at 1,000 rpm. Aqueous suspension used for PMV removal experiments were centrifuged at 11,000 rpm for 10 min (MPW-250) and filtered through glass microfiber filters (Whatman, grade GF/F).

Ultraviolet-visible (UV-vis) spectra were recorded over the range 190-400 nm (HACH LANGE UV-VIS DR 6000), corrected against appropriate background spectrum.

Infrared spectroscopy (FT-IR) was performed on a Thermo Nicolet iS10 using the KBr pellet method. The spectral resolution was 4 cm^{-1} and the scanning range was from 400 to 4000 cm^{-1}.

The Nuclear Magnetic Resonance (NMR) spectra were recorded in D_2O on a Bruker Avance III HD 400 MHz spectrometer at 25 ºC.

Nitrogen (N_2) adsorption-desorption isotherms were conducted at 77 K using ASAP 2420 V2.09A apparatus. The specific surface area was measured by the Brunauer-Emmett-Teller (BET) (Brunauer et al., 1938) method and pore size distribution (PSD) was measured

using the classical Barrett-Joyner-Halenda (BJH) model (Barrett et al., 1951) and the Harkins and Jura t-Plot method.

Scanning electron micrograph (SEM) observation was performed on a Quanta FEG 250 scanning electron microscope.

2.4. Biological treatment

The PMV biological treatment was performed in a special model reactor with a working volume of 5 L. The reactor was equipped with an aeration system O_2, stirrer, pH and temperature sensors. The activated sludge was aerobically conditioned for 24 hours to minimize pollutants level. Then, activated sludge was mixed with PMV wastewater in concentration of 10^{-3} M. After 30 minutes the mixture was withdrawn, filtered using paper filter (00A102.180, Chemland) and the chemical oxygen demand (COD) (Vial Test, Hach), and ammonia nitrogen (Nitrogen-Ammonia reagent set, Nessler, Hach) were measured. The whole experimental process lasted 24 hours, per analogy to real purification cycle in municipal water resource recovery facility in Swarzewo. Reactors were operated under anoxic/aerobic conditions, in which the first three hours were anoxic (dissolved oxygen DO $\leq$ 0.1 mgO_2 L^{-1}) followed by aeration (DO 2.5-5 mg O_2 L^{-1}). After 24 hours a sample was taken again, treated as above and analyzed. To determine the total PMV removal after 24 hours of biological wastewater treatment, the possible residual drug was also analyzed on the activated sludge. For this purpose, the precipitate was filtered, frozen at -20 °C, and then lyophilized in a freeze-dryer (Novalyphe-NL 500) for 24 h at -50 °C. The resulting brown powder was homogenized by grinding, then extracted with methanol and the drug content determined using HPLC.

The percentage removed of PMV during biological wastewater treatment process was calculated according to the equation:

$$Removal\ efficiency\ (\%) = \frac{D_{0(\min)} - (D_{24(hours)} + D_{AS})}{D_{0(\min)}} \cdot 100$$

where $D_{0(min)}$ (g) is the initial content of PMV, $D_{24(hours)}$ (g) and D_{AS} (g) are the PMV content in filtrate and active sludge after 24 hours of biological wastewater treatment process, respectively.

2.5. Adsorption experiments

All experiments were carried out at ambient temperature using PMV aqueous solution (85.5 mg L^{-1}). In each study, accurately weighed amount of adsorbent was transferred to 5 mL of PMV solution in plastic vials (7 mL) and sealed. The mixture was then shaken on a digital vortex mixer at 1,000 rpm. Experiments were performed for various time intervals to determine the adsorption equilibrium and maximum amount of PMV adsorbed. The solid phase was separated by centrifugation and filtration. The PMV concentrations in solutions were measured spectrometrically at λ_{max} = 271 nm. The efficiency of removal of PMV (%) by β-NS or γ-NS was calculated based on the following equation:

$$Adsorption\ efficiency\ (\%) = \frac{C_0 - C_e}{C_0} \times 100 \quad (1)$$

where C_0 (mg L^{-1}) and C_e (mg L^{-1}) are the initial and equilibrium concentration of PMV in the stock solution and filtrate, respectively.

The amount of PMV adsorbed was determined by the following equation:

$$q_e = \frac{(C_0 - C_e)V}{m} \quad (2)$$

where q_e (mg g^{-1}) is the amount of PMV bound to the sorbent per g of sorbent, m (g) the mass of sorbent used in the experiment, V (L) the volume of PMV solution used.

The influence of the pH was determined at a pH ranging from 1.0 to 8.0 and adjusted with NaOH (0.01M) or HCl (0.01M)2.6. Adsorption isotherms

30 mg of β-NS or 120 mg of γ-NS was accurately weighed and transferred to a 7 mL plastic vials, and 5 mL of PMV stock solutions ranging from 42.8 to 428 mg L^{-1} was added. Then, the mixtures were shaken on digital vortex mixer at 1,000 rpm for 30 min to reach equilibrium. Then, the suspensions were separated by centrifugation and filtration. The absorbance of the filtrates was measured at wavelength at λ_{max}= 271 nm.

2.6.1. Freundlich isotherm

This type of isotherm is an empirical equation employed to describe an adsorption on heterogeneous surfaces and is calculated using the following equation (Rao et al., 2012):

$$q_e = K_F C_e^{1/n_F} \quad (3)$$

where, q_e (mg g^{-1}) is the equilibrium PMV concentration on adsorbent, C_e (mg L^{-1}) is the concentration of PMV at equilibrium in solution, K_F (L g^{-1}) is the Freundlich constant and $1/n_F$ is the heterogeneity factor.

A linear form of the Freundlich adsorption isotherm was obtained by plotting $\ln q_e$ versus $\ln C_e$ in the following equation:

$$\ln q_e = \frac{1}{n_F} \ln C_e + \ln K_F \quad (4)$$

2.6.2. Langmuir isotherm

The non-linear expression of Langmuir isotherm model is represented as follows (Ho et al., 2002):

$$q_e = \frac{x}{m} = \frac{K_L C_e}{1 + a_L C_e} \quad (5)$$

where, q_e (mg g^{-1}) is the equilibrium PMV concentration on adsorbent, *x* (mg) is the amount of PMV adsorbed, m (g) the amount of adsorbent used, C_e (mg L^{-1}) is the concentration of PMV at equilibrium in solution, a_L (L mg^{-1}) and K_L (L g^{-1}) are the Langmuir isotherm constants.

Langmuir adsorption isotherm in a linear form was generated by plotting $C_e q_e^{-1}$ against C_e in the following equation:

$$\frac{C_e}{q_e} = \frac{a_L}{K_L} C_e + \frac{1}{K_L} \quad (6)$$

The maximum adsorption capacity, q_{max} of the adsorbent described the theoretical monolayer capacity was calculated as follows:

$$q_{max} = \frac{K_L}{a_L} \quad (7)$$

The equilibrium parameter, R_L, also called the separation factor, is calculated using the equation (Hall et al., 1966; McKay, 2007):

$$R_L = \frac{1}{1 + a_L C_0} \quad (8)$$

where, C_0 is the initial concentration (mg L^{-1}).

The R_L value assumes feasibility and the nature of adsorption process is specified in the following: irreversible (R_L=0), favorable (0<R_L<1), linear (R_L=1), unfavorable (R_L>1).2.7. Regeneration experiments

0.03 g of β-NS or 0.12 g of γ-NS was accurately weighed and transferred to a 7 mL plastic vial, and 5 mL PMV stock solution (0.2 mmol L^{-1}) was added. Then, the suspension was shaken on digital vortex mixer at room temperature for 30 minutes. After this time, the mixture

was centrifuged and filtered through Whatman glass microfiber filters (grade GF/F). The PMV content in the filtrate was determined spectrophotometrically. Material regeneration was carried out according to the developed methodology based on five times rinsing with methanol (5x 10 mL), spectrophotometric checking of the presence of PMV in the last filtrate, in the case of content below the detection limit, the material was further washed five times with water (5x10 mL) to remove polar substances and salts. Otherwise the procedure was repeated and the next step was to rinse with water. Finally, the adsorbents were again washed with 10 mL MeOH to remove water from the NS. Then the NS was dried to constant weight on a moisture analyzer and reused in the PMV adsorption process. This adsorption-desorption cycle was carried out three times.

2.8. Purification of model post-reaction raffinates.

From each sample, 5 mL of the solution was withdrawn and quantitatively transferred to falcon tube containing 75 mg β-NS or 25 mg of activated carbon O-C303. The content of falcon tubes was shaken, this time for 30 min due to the higher concentration of PMV and the presence of additional substances in the samples.

All adsorption experiments were performed in triplicate.

3. Results and discussion

3.1. Biological treatment

To study the biological treatment efficiency of PMV, the chemical oxygen demand (COD), ammonium ($N\text{-}NH_4^+$) and drug content (DC) before and after degradation were determined. To assess the possibility of precipitation of the compound during the degradation process, the content of the drug after 30 min of aeration and its residue on the activated sludge after 24 hours were also determined. The results presented in Table 1 show, that degree of

253 removal of PMV is only 37%. An almost three-fold increase in the concentration of ammonium
254 nitrogen is observed and a slight increase of the COD parameter indicating the adverse effect
255 of PMV on the active sludge organisms. In this situation, the bacteriostatic effect of the drug
256 cannot be ruled out, which inhibits the nitrification and denitrification processes, consequently
257 the initial ammonification process proceeds with low efficiency. During the biological
258 treatment of PMV wastewater, significant foaming of the activated sludge is observed, which
259 undoubtedly causes serious problems in its operation. In addition, the standard Microtox test
260 showed a very low EC_{50} level for PMV (EC_{50} = 8 mgL^{-1}) and according to the Waste Framework
261 Directive (WFD, 2008/98 / EC) the drug can be classified as hazardous to the environment
262 (Weltens et al., 2014).

263 **Table 1.**
264 Composition of treated wastewater of PMV.

Parameters	Before treatment	After treatment (24 hours)
COD [mgO_2 L^{-1}]	362	392
$N\text{-}NH_4^+$ [$mgN\text{-}NH_4^+L^{-1}$]	0.76	2.05
DC [g]	0.151 (0 min) 0.075 (30 min)	0.066 0.029 (AS)

265 COD- chemical oxygen demand; $N\text{-}NH_4^+$ ammonium; DC- content of PMV; AS- active sludge.

266

267 3.2. Adsorption experiments

268 3.2.1. Effect of adsorbent mass

269 The adsorption of PMV on NSs (β-NS or γ-NS) was studied by maintaining constant
270 volume of stock solution of PMV (85.5 mg L^{-1}), temperature (25 °C) rotation speed (1,000
271 rpm), contact time (30 min) and pH (pH = 7) whilst changing the amounts of sorbent in the
272 solution. The results presented in Fig. 2 show that the percentage of PMV removal increased
273 with the adsorbent dosage. The gradual increase in sorption due to the increased mass of the
274 adsorbent is typical and is the result of incomplete filling of the NS surface. After saturation of

the material, stabilization occurs, and consequently the amount of adsorbed drug is constant. For this reason, 0.03 g (β-NS) and 0.12 g (γ-NS) mass of adsorbent were chosen for the next experiments.

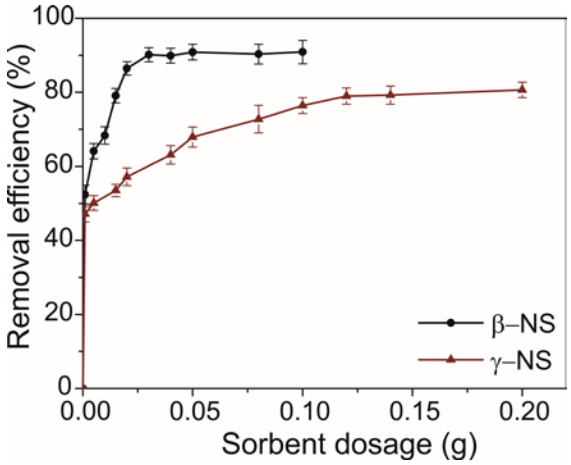

Fig. 2. Effect of adsorbent mass on the removal efficiency of PMV by β-NS (black) and γ-NS (red); PMV concentration = 85.5 mg L^{-1} and solution volume 5 mL; contact time = 30 min, temperature = 25 °C, , pH = 7, rotational speed (1,000 rpm).

3.2.2. Effect of contact time

A series of experimental data for the adsorption of PMV versus contact time is presented in Fig. 3. All the experiments were performed at pH = 7 with initial concentration of PMV (85.5 mg L^{-1}), amount of adsorbent (0.03 g for β- and 0.12 g for γ-NS) and agitation speed (1,000 rpm). It was observed that both cyclodextrin adsorbents required less than 1 min to reach equilibrium and the maximum amounts of PMV adsorbed were 12.8 and 2.9 mg g^{-1} for β- and γ-NS, respectively.

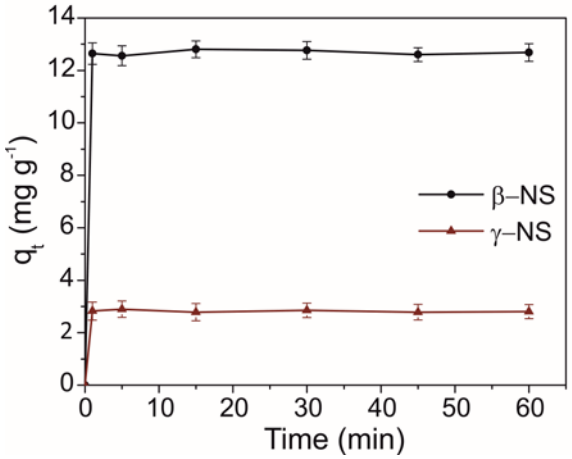

Fig. 3. Effect of time on the adsorption of PMV by β-NS (black) and γ-NS (red); PMV concentration = 85.5 mg L^{-1} and solution volume 5 mL; room temperature, pH = 7, temperature = 25 °C, rotational speed (1,000 rpm).

3.2.3. Effect of pH

It is well known that pH of the solution plays an important role during the process of pollutants adsorption. The acidity and basicity of the solution can easily change the ionization degree of the adsorbate. The adsorption of PMV on NSs (0.03 g for β- and 0.12 g for γ-NS) was studied by maintaining constant volume of stock solution of PMV (85.5 mg L^{-1}), temperature (25°C), rotation speed (1,000 rpm), contact time (30 min), whilst changing the value of pH of solution. Fig. 4 exhibits that the PMV uptake by β- and γ-NS are slightly influenced by pH in the range of 1-2 and 5-8. Conducting tests in the pH> 8 range is not possible due to the two-phase system. It is well known that pimavanserin in the form of the free base shows limited solubility in water and even less in the case of an alkaline environment. The polymer material itself is not sensitive to pH due to the lack of groups capable of ionizing in such mild conditions.

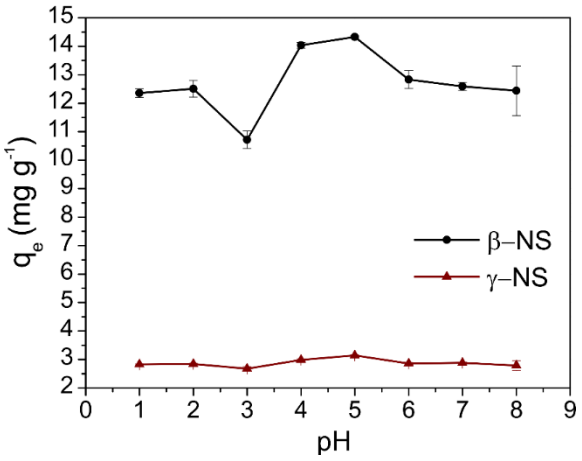

Fig. 4. Effect of pH on PMV adsorption capacities of β- and γ-NS.

3.2.4. Effect of adsorbent type

The adsorption experiments were performed for the uptake of PMV through various type of adsorbents (β-NS, γ-NS, O-C303 and N-SX1) with a constant initial drug concentration of 85.5 mgL^{-1}. On the first stage of experiment, we decided to select carbon adsorbents mass for adsorption equilibrium, as it was done for β- and γ-NS (Fig. S9). Finally, the studies were performed for the mass of 0.03 g, 0.12 g, 0.01 g and 0.02 g for β-NS, γ-NS, O-C203 and N-SX1, respectively, and the time of 1 min. According to the results, we can conclude that all types of adsorbents enabled PMV removal from aqueous solution with high efficiency: 92.95, 92.67, 91.82 and 80.50% for O-C303, β-NS, N-SX1, and γ-NS, respectively within impressively short time.

3.2.5. Regeneration experiments

An undoubted advantage of the presented NSs is the possibility of their simple regeneration and reuse. The important thing is that the effectiveness of PMV adsorption with the use of regenerated materials remain at a similar level, as evidenced by the results presented in the form of UV-vis spectra in Fig.5. The difference is small and amounts to 5.4% (87.6-

93.0%) and 2% (78.5-80.5), for β-NS and for γ-NS, respectively. During regeneration, multiple rinsing with water can be applied. The advantage of the method is the use of an environmentally friendly solvent. The disadvantage is the considerable volume of the waste aqueous drug solution. A much better method is the use of methanol, a very selective PMV extractant. From the resulting solution, the solvent can be easily regenerated by distillation, affording the PMV, and reused. Rinsing with methanol do not affect the structure of the material as evidenced by the FTIR spectra after each stage of the regeneration process (Fig. S8).

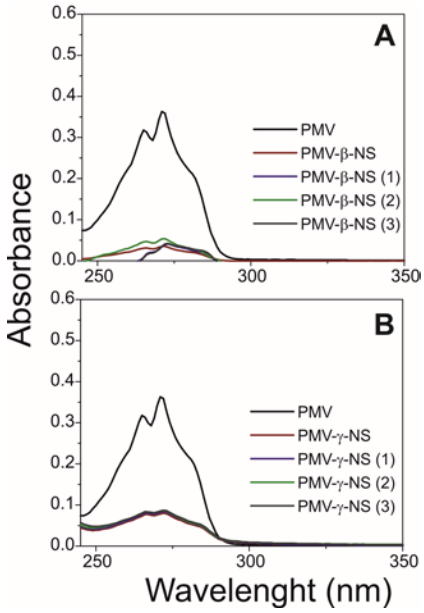

Fig. 5. UV-vis spectra recorded before and after regeneration process (one to three times) for β-NS (A) and γ-NS (B).

3.2.6. Adsorption equilibrium

The Langmuir and the Freundlich isotherms were used to express the distribution of PMV between the adsorbent and the solution at equilibrium. Adsorption experiments were performed for different initial PMV concentrations (42-421 mg L^{-1}), maintaining a constant pH = 7, temperature (25 °C), contact time (30 min) and agitation speed (1,000 rpm).

Data obtained from adsorption experiments were expressed using the Langmuir and Freundlich isotherms (Fig. 6).

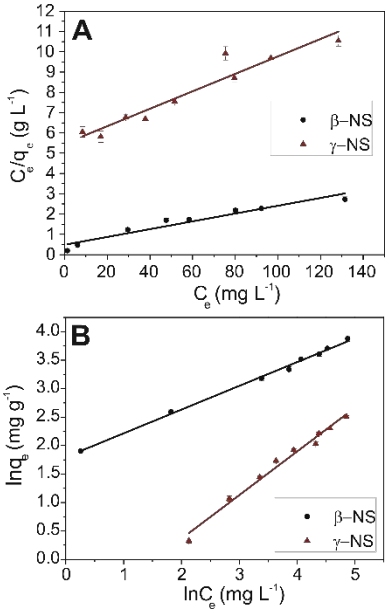

Fig. 6. Langmuir (A) and Freundlich (B) isotherm of PMV adsorption by β-NS (black) and γ-NS (red).

The results obtained show that both isotherms are linear within all established initial concentrations. The determined values including correlation coefficients (R^2) indicate a worse adjustment to the Langmuir model (R^2 = 0.93 for β-NS and R^2 = 0.92 for γ-NS; Fig. 5A) than the Freundlich model (R^2 = 0.99 for β-NS and R^2 = 0.98 for γ-NS, Fig. 5B). Freundlich's isotherm describes sorption on heterogeneous surfaces or surfaces with different affinities. The model assumes that the stronger binding sites are first occupied and the binding force decreases with the degree of occupancy. The adsorption parameters of Freundlich and Langmuir are given in Table 2. The values of the Freundlich exponent n=2.40 (β-NS) and n=1.30 (γ-NS) in the range of 1-10 described favorable adsorption. For the Langmuir-model adsorption the dimensionless constant separation factor (R_L) was calculated according to Eq. 8 to classify isotherm shape. The R_L value lying in the range of 0-1 confirms the favorable uptake of the PMV. According to the obtained results, the Freudlich isotherm is reliable model describing the PMV removal from water by NSs. This is related to heterogeneous surfaces of NSs (data are

presented in SI, Fig. S2-S4 and Table S3-S5). The presence of heterogeneous absorption sites on the CD-NS surfaces is also visually confirmed based on the SEM analysis (Fig. S8).

Table 2
Parameters of the equilibrium sorption models and of linear (R^2) regression coefficient.

Equilibrium model	Parameter	Value	
		β-NS	γ-NS
Langmuir isotherm	q_{max} (mg g^{-1})	52.08 ± 2.59	23.26 ±1.01
	K_L (L g^{-1})	2.05 ± 0.21	0.18 ± 0.01
	a_L (L mg^{-1})	0.04 ± 0.002	0.01 ± 0.0003
	R_L	0.06-0.38	0.25-0.77
	R^2	0.93	0.92
Freundlich isotherm	K_F (L g^{-1})	6.03 ± 0.17	0.31 ± 0.02
	n_F	2.40 ± 0.03	1.30 ± 0.03
	R^2	0.99	0.98

For comparison of the sorption capacity of different cyclodextrin based adsorbents, the q_{max} parameter obtained with the Langmuir isotherm was evaluate. In the literature, the wide variety of cross linking agents and CDs, make difficult the comparison obtained results of adsorption. Furthermore, to the best of the authors' knowledge, no adsorption studies of PMV from aqueous media have been carried out so far. For this reason, we decided to present a table were compare the results of polymers based on cyclodextrins, take into account that different organic compounds, mainly pharmaceuticals, were employed in the related studies (Table 3).

Table 3
Comparison of the adsorption properties of different polymers based on cyclodextrins.

Pharmaceutical	Polymer	Adsorption capacity, q_{max} (mg g^{-1})	References
Phenolphthalein	β-CDs-GNS	468	(Tan and Hu, 2017)
Ciprofloxacin	β-CD-EDTA	448	(Yu et al., 2018)
Ibuprofen	β-CD-CH	240.7	(Bany-Aiesh et al., 2015)
Chloroxylenol	β-CD-TFP	144.1	(Zhou et al., 2019)
Carbamazepine	β-CD-TFP	136.4	(Zhou et al., 2019)
Bisphenol A	β-CD-TFP	88.00	(Alsbaiee et al., 2016)

17β-estradiol	β-CD-PLGA	85.80	(Jiang et al., 2017)
Aspirin	β-CD-N-CNT	71.94	(Mphahlele et al., 2015)
Rhodamine B	β-CD-DPC	56.88	(Lee et al., 2019)
Pimavanserin	β-CD-CDI	52.08	This work
Procaine	CS-ED-CD	47.03	(Zhao et al., 2017)
Imipramine	CS-ED-CD	44.30	(Zhao et al., 2017)
Paracetamol	β-CD-N-CNT	41.00	(Mphahlele et al., 2015)
Congo red	β-CD-HMDI	36.2	(Ozmen and Yilmaz, 2007)
Direct Red 83:1	HP-α-CDs-EPI	23.4	(Pellicer et al., 2018)
Pimavanserin	β-CD-CDI	23.26	This work
Direct Blue 78	γ-CD-EPI	14.16	(Semeraro et al., 2018)
Phenol	β-CD-CA	13.80	(Zhao et al., 2009)
Methyltestosterone	β-CD-Si	13.09	(Carvalho et al., 2019)
Methylene Blue	β-CD-M	11.43	(Yadav et al., 2019)
Direct Blue 78	β-CD-EPI	4.99	(Semeraro et al., 2018)
p-Nitrophenol	β-CD-HMDI	1.00	(Salgın et al., 2017)

GNS- graphene, EDTA- ethylenediaminetetraacetic acid, TFP -Tetrafluoroterephthalonitrile, N-CNT- nitrogen doped carbon nanotubes, DPC- diphenyl carbonate, CDI- diimidazole carbonate, HMDI- hexamethylene diisocyanate, EPI- epichlorohydrin, CA- citric acid, M- Maleic acid

3.3. Adsorption mechanism studies

Because the adsorption process by NS mainly consists in the inclusion, we decided to take a closer look on this phenomenon. We chose ^{1}H NMR spectroscopy allowing obtaining the information about the stoichiometry and the structure of PMV supramolecular complexes formed with CDs.

377 3.3.1. Inclusion phenomena

378 A characteristic feature of the signals present in the ^{1}H NMR spectrum of PMV is the
379 widening resulting from the presence of chiral centers. As a consequence, a mixture of
380 enantiomers is analyzed instead of one. The PMV spectrum is significantly simplified when
381 forming a complex with β-CD, which may indicate that only one of the isomers is included.
382 The PMV molecule is too large to fit into the host cavity. At the same time, it consists of three
383 important moieties: 4-fluorobenzylamine (**A**), 4-isobutylbenzylamine (**B**) and *N*-
384 methylpiperidine (**C**), each of which can form inclusion complexes. Analyzing further the
385 recorded spectra, typical changes in the chemical shifts of internal CD protons (H-3 and H-5)
386 were observed, resulting from the involvement in inclusion complex formation. The spectra of
387 β-CD and γ-CD complexes are presented in Fig. 6A. Discussed CDs internal protons are down
388 fielded. The chemical shifts (Δδ) of β-CD is -0.150 for H-3 and -0.127 for H-5. In the case of
389 γ-CD, Δδ for the same protons are -0.168 and -0.179, respectively (Table S6).

390 In comparison to the free drug spectrum, the spectra of inclusion complexes with CDs
391 show the most change in aromatic field. The **B** moiety protons do not overlap with aromatic
392 protons of **A** moiety, but separate/particular peaks are observed. The **B** moiety of PMV probably
393 is included in the CD cavity. Analyzed protons have a larger chemical shifts in PMV-β-CD
394 complex than protons of **A** moiety. In the case of the PMV-γ-CD complex, separate/particular
395 peaks broadened may indicate fast exchange, or be a result of the larger size of the γ-CD cavity,
396 enabling the formation of complexes with various PMV stereoisomers.

397 The stoichiometry of PMV with β- and γ-CD inclusion complexes were determined by
398 Jobs method. The plots of Fig. S11 show that for the both binary systems the maximum of the
399 curves is obtained for r = 0.5, that indicates 1:1 host-guest stoichiometry.

400 Unfortunately, ^{1}H NMR spectra give not an unambiguous response which of the two
401 aromatic rings of PMV is involved in the complexation, the geometry of the complexes was

analyzed considering intermolecular NOEs obtained from ROESY spectra (Fig. 6B and 6C). The obtained results show that PMV insert to β- and γ-CD cavity from the side of **B** moiety. As visualized in Fig. 6B and 6C, PMV is inserted deeper in γ-CD hydrophobic cavity than in β-CD, since the cross peaks between IV protons of **B** moiety of guest with internal H-3 protons (from the side of wider rim) are not visible, but occur between H-5 protons (from the side of narrow rim).

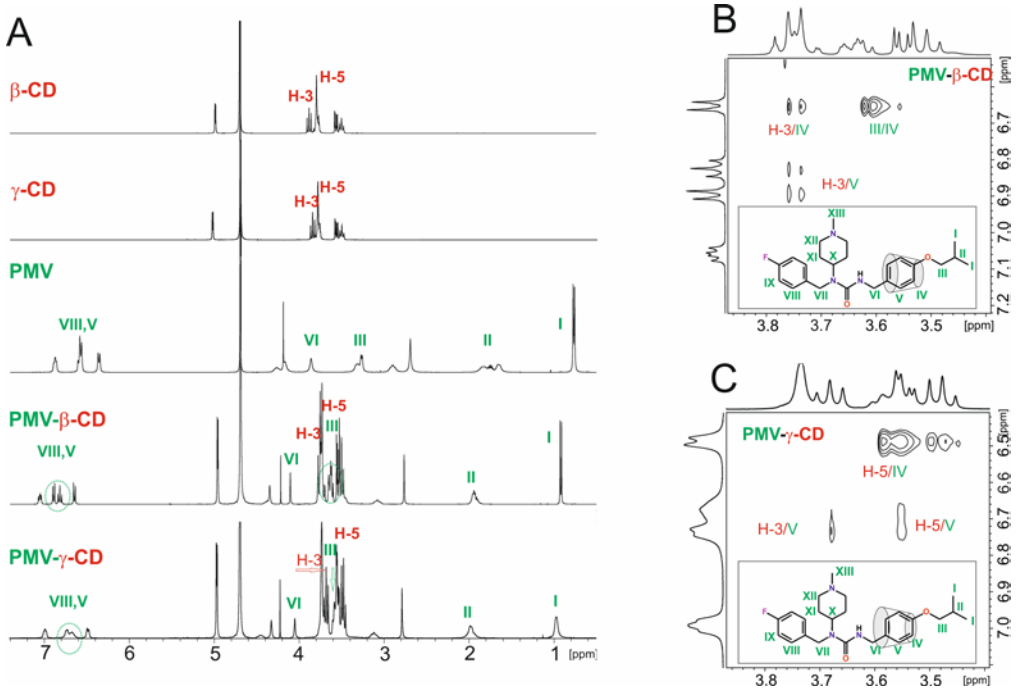

Fig. 6. ^{1}H NMR (A), and ROESY spectra for PMV with β- (B) and γ-CD (C).

3.3.2. Pore texture

The obtained materials consist of particles with a dimension of 172 nm and 431 nm for β-NS and γ-NS, respectively (SI, Fig. S5). The main structural elements of obtained sponges are mesopores (Barrett-Joyner-Halenda method, Fig. S4, Table S5). The **B** moiety, which is suspected for complex formation, is small in size, so it can be adsorbed in micropores. The analysis of the NS surface showed that the micropores have only β-NS, they constitute 13% of the total BET surface area (Harkins and Jura t-Plot, Fig. S3, Table S4).

Considering the obtained results, we believe that the mechanism of CD-NS sorption involves inclusion complexation, hydrogen bonding and physical sorption in the network (**Fig. 7.**).

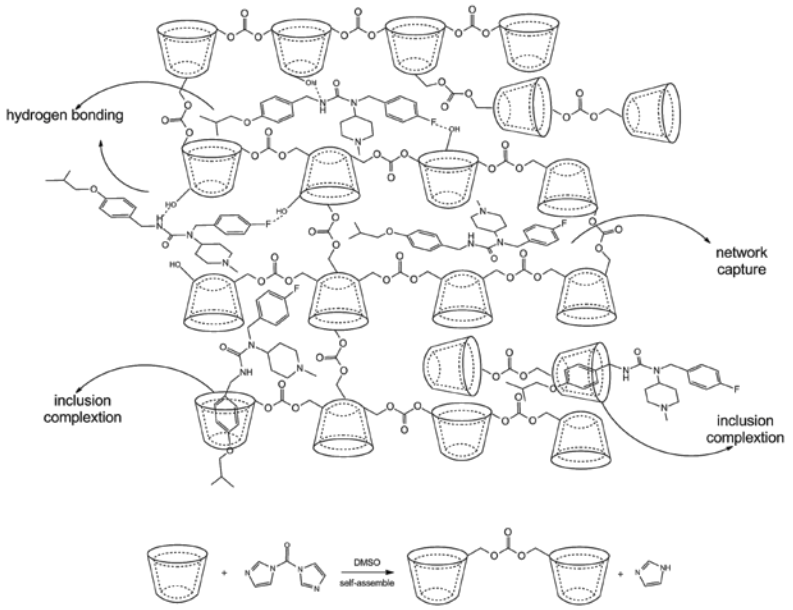

Fig. 7. Cross-linked structure of β-CD-NS and related sorption mechanism of PMV.

Comparing the created structures with the use of two cyclodextrins, the basic differences are the size of the cavity and the packing of toruses in the network. It is well known that the presence of internal hydrogen bonds in β-CD is responsible for additional stiffening of the molecule. Perhaps, in this particular case, it is also the reason for creating additional appropriately dimensioned spaces between torus able to trap PMV. The situation is different with γ-CDs. The large rim allows easy guest entry and exit. The flexible structure does not allow the creation of neat spaces between the toruses. As a result, the material is seemingly the same and in fact quite different.

3.4. Adsorption study of PMV in real post-reaction raffinates

PMV is on the market only since 2016, which explains the lack of literature data on the presence of the drug in the environment. Our preliminary studies have clearly shown that PMV does not degrade during biological treatment and is toxic to aquatic organisms. According to

one of the principles of green chemistry, it is always better to prevent than eliminate undesirable effects, PMV synthesis requires total drug recovery from all produced streams. For this purpose, three drug syntheses were performed using the patent description US 2018/0208556 A1 (Chen-Wei and Chin-Wei, 2018), which seems to be the most ecofriendly among those described in the literature. It is one pot synthesis provided in biodegradable organic solvent – ethyl acetate. Waste streams are formed only during purification time, when postreaction mixture is washed with water. Of course, part of the drug dissolves in the aqueous phases, consequently contaminating the raffinates. Small scale synthesis produces approximately 24 mL of raffinate for each gram of crude PMV. One gram of PMV is also the amount that a single patient takes in just one month of treatment. Thus, in the final phase, three streams of raffinate samples containing from 190 to 210 mg L^{-1} PMV were obtained (Table S1).

Literature data shows that during other PMV synthesis, not only aqueous, but also acidic and briny raffinates are also produced. Therefore, two mixtures containing comparable amounts of hydrochloric acid, sodium chloride and ammonium chloride to those used in additional patents have been prepared (Table S2). All raffinates were used in sorption tests by means of the best adsorbents, i.e. β-NS and activated carbon O-C303 (Table 4).

Comparing the results of sorption of PMV from aqueous raffinates, it can be stated that both adsorbents ensure the quantitative removal of the drug from salt-free aqueous solutions. In the case of low pH and presence of salt, the PMV uptake efficiency by activated carbon is reduced by 5%. Even more troublesome is to remove the drug from concentrated mixtures of sodium and ammonium chlorides. In this case, as much as 15% of the drug remains in the waste stream. Our material, regardless of the raffinate composition, selectively and quantitatively binds PMV. This is due to the specifics of the impacts. NS centers responsible for PMV inclusion are hydrophobic and remain indifferent to relatively small charged individuals molecules. It is also possible to recover adsorbed PMV during the regeneration of with methanol. The resulting

solutions contain only the drug and can be directed after concentration to the next stage of production, in which the pimavanserin base is converted into the corresponding salt. At the same time, the methanol separated during distillation can be reused for desorption of PMV from NS. Desorption of API from activated carbon, carried out in an analogous manner, is impossible, which means that each portion of activated carbon after the process becomes a hazardous waste.

Table 4 Percentage removal efficiency of PMV adsorption on β-NS (75 mg) and AC-O-C303 (25 mg); contact time = 30 min; room temperature, rotational speed (1,000 rpm).

Raffinate*	C_0 (mg L^{-1})	O-C303 removal efficiency of PMV (%)	β-NS removal efficiency of PMV (%)	Recovery of adsorbed PMV from β-NS (%)	Purity of desorbed PMV (HPLC method)
B-1	0.190	100	100	95	98
B-2	0.195			96	99
B-3	0.201			95	99
A	0.200	100	100	95	98
C-1		85	100	94	97
C-2		95	100	93	

*Each result is an average of three PMV tests carried out in parallel. Raffinate descriptions are available in table 1 and 2 in ESI.

4. Conclusions

The preliminary toxicity results of this work show that PMV can be classified as hazardous (EC_{50} = 8 mgL^{-1}). In biological wastewater treatment plant, the degree of PMV degradation is only 37% and can pose a serious environmental problem in the future. The obtained NSs are suitable for quantitative removal of PMV from model waste waters as well as from real post-reaction raffinates, even those characterized by the very low pH and high salt

concentration. Data obtained during adsorption experiments were expressed using the Langmuir and Freundlich isotherms. The β- and γ-NS presented a maximum adsorption capacity of 52.08 mg g^{-1} and 23.26 mg g^{-1} towards the PMV, respectively.Although, the results show that both isotherms are linear within all established initial concentrations, the adsorption process was better represented by Freundlich isotherm (R^2=0.99 for β-NS and R^2=0.98 for γ-NS). Despite of small specific surface area of obtained NSs, the effectiveness of adsorption of PMV from aqueous media were similar to active carbons and adsorption process took place in impressively short time (60 s). The obtained NSs materials are fully and easily regenerable without affecting their structure. The inclusion phenomena are extremely specific and allow for a much better use of the adsorbent's specific surface area. The mechanism of sorption is complex, dominated by chemisorptions via the formation of an inclusion complex with cyclodextrin present in the NSs structure, and to a lesser extent by surface adsorption and diffusion into the polymer network. However, diffusion into the polymer network is also important. The 4-isobutyl-benzylamine group is responsible for complex formation and this group is small in size, so it can be also adsorbed in micropores. Such pore size is presented only in β-NS material, and is also responsible for somewhat better results of PMV adsorption efficiency compared to γ-NS.

The experimental results clearly show that NS in the area of adsorbents are promising and can be successfully used to separate organic pollutants from industrial raffinates and wastewater.

Conflicts of interest

There are no conflicts to declare.

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