Interpenetrated polymer networks of Poly(β-cyclodextrin) and Polyvinylpyrrolidone with synergistic and selective sorption capacities

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ABSTRACT

Interpenetrating polymer network (IPN) hydrogels were synthesised using β-cyclodextrin (β-CD) and N-vynil-2-pyrrolidone (NVP) crosslinked with epichlorohydrin and divinylbenzene, respectively, and prepared by four different procedures: simultaneous, sequential, hybrid and a novel one named hybrid-sequential.

The IPNs prepared have been characterised by infrared spectroscopy and thermal analysis. The equilibrium swelling in water and the sorption of model substances into the IPNs have also been studied. The model sorbates (1-naphthol, 2-acetylnaphthalene and tannic acid) were selected according to the affinities towards each one of the two constituent polymers.

Our studies reveal that these IPNs can be applied for the sorption of substances that can interact with the network by two mechanisms, i.e. inclusion within cyclodextrin cavities and/or via specific interactions with the functional groups present. Besides, due to the complementary character of their constituent polymers, these networks could also serve to retain two substances of different nature such as cetirizine and pseudoephedrine.

Keywords: cyclodextrin polymers; Poly(N-vinylpyrrolidone); IPN; sorption; hydrogels

1. Introduction

An interpenetrating polymer network (IPN) consists of a combination of two or more polymer networks, at least one of which is polymerised and/or crosslinked in the immediate presence of the other (Sperling, 1996). An IPN is a polymer comprising two or more networks that are at least partially entangled on a molecular scale but not covalently bonded to each other and cannot be separated unless chemical bonds are broken. In addition, a semi-IPN is formed when a linear polymer is embedded within a first network but not crosslinked; therefore, the resulting polymer blend can be separated without breaking chemical bonds.

There are several strategies in the synthesis of IPNs (Sperling, 1996) which lead to a classification of the materials produced. A sequential IPN is obtained by the swelling of a single network into a solution of the monomer, initiator, activator and crosslinker of the second polymer. On the other hand, a simultaneous IPN is formed by mixing the precursors of both networks and synthesising the two polymers at the same time, provided that the chemical routes of polymerization are independent and non-interfering (Dragan, 2014). Finally, in gradient IPNs, the composition of the polymer blend varies gradually through the material (Sperling, 1996).

Single-network hydrogels often exhibit poor mechanical and swelling/deswelling properties, which can be improved by the preparation of multicomponent IPNs (Dragan, 2014). The formation of IPN structures is an effective way to improve the properties of hydrogels due to an additive effect of the different polymers. In this sense, it is possible to tailor the characteristics of the IPN to achieve specific properties by combining different materials (Matricardi, Di Meo, Coviello, Hennink, & Alhaique, 2013; Sahiner, Sagbas, & Bitlisli, 2015).

IPN hydrogels have been successfully applied in drug delivery (Bacaita, Ciobanu, Popa, Agop, & Desbrieres, 2014; Kim, Lee, & Park, 2018; Soni et al., 2018) and tissue engineering (Dobreikina, Shklyar, Safronov, & Blyakhman, 2018; Fan, Zhang, Fang, Xu, & Li, 2015; Gsib et al., 2017; Jimenez-Rosales & Flores-Merino, 2018; Xiao et al., 2011). IPN systems with stimuli responsive behaviour have been also prepared (Xing et al., 2011). Furthermore, in the field of separations, these systems exhibit good sorption characteristics for metals and

dyes together with a high level of reusability (Dragan, 2014), (Bai, Li, Zhang, Wang, & Dong, 2018). Recent studies have developed IPN gels for food formulations (Niu, Xia, Li, Wang, & Yu, 2019).

The present study involves the formation of different IPNs containing a β-cyclodextrin polymer (β-CDP) and a poly(N-vinylpyrrolidone) polymer (PVP). Cyclodextrins (CDs) are torus-shaped cyclic oligosaccharides composed of several glucopyranose units linked by α-1,4-glycosidic bonds (González-Gaitano, Isasi, Vélaz, & Zornoza, 2017) These molecules are capable of forming inclusion complexes with a variety of guest molecules, which get hosted in the CD cavity. Cyclodextrin polymers can be obtained by crosslinking with appropriate agents. These materials have been also applied in the environmental field (Morin-Crini & Crini, 2013). In addition, CD polymers have found pharmaceutical applications; soluble polymers have been used to increase drug solubility (Gidwani & Vyas, 2014), whereas insoluble polymers have been proposed as drug delivery systems (Machín, Isasi, & Vélaz, 2013).

Poly(N-vinylpyrrolidone) (PVP) is a water-soluble polymer with interesting electrical and optical properties, and a good biocompatibility. Its uses include electrical devices, medicines and environmental applications (Halake et al., 2014). The insoluble polyvinylpyrrolidone polymer (PVPP), which can be produced using a crosslinking agent, behaves as a gel and it has been employed in controlled drug release and also as an adsorbent of phenolic compounds in food processes (Folch-Cano, Olea-Azar, & Speisky, 2013), and different pollutants.

The aim of this investigation was to prepare and characterise novel interpenetrating networks formed by β-CD crosslinked with epichlorohydrin (EP) and a second polymer formed by N-vinylpyrrolidone (NVP) crosslinked with divinylbenzene (DVB). We intend to evaluate the influence of the synthetic procedures on the properties of the final product, especially regarding the sorption capability towards solutes of different chemical nature.

Depending on the chemical moieties of a given solute and the IPN structure, it is hypothesised that either synergistic or additive sorption can be achieved as long as the solute can favourably interact with both parent polymers. If the affinity of the molecule for both constituent polymers depends only on their composition, an additive sorption would be observed, irrespective of their network topology. In other words, a physical mixture of both

parent polymers would sorb as much as the corresponding IPN structure. On the other hand, due to the inclusional nature of the CDP interactions, we postulate that a synergistic sorption could be produced in some instances if a certain sorbate molecule can be linked by two simultaneous mechanisms, such as inclusion of its nonpolar moiety in the CD cavity and specific interactions of its polar residue with the PVPP structure.

Two naphthalene derivatives with different polarities (1-naphthol and 2-acetylnaphthalene) and a polyphenol (tannic acid) have been selected as model molecules to study the new IPNs. On the one hand, naphthalene derivatives are known to establish inclusional interactions with β-CD cavities. On the other hand, tannic acid, which is present in plant extracts, can be separated with the aid of PVPP. Thus, the potential applications in the environmental field of the new IPN materials can be tested using these phenolic and naphthalene model molecules. In relation to prospective pharmaceutical uses, besides those three model molecules, two active ingredients have been selected, namely cetirizine dihydrochloride (antihistamine) and pseudoephedrine hydrochloride (descongestant), two drugs used for the treatment of the effects of allergy that are already administered together in a single tablet on a commercial scale (Reactine®, Johnson & Johnson Inc.).

2. Experimental section

2.1. Materials

β-cyclodextrin (β-CD) was manufactured by Roquette (Laisa España S.A.). Epichlorohydrin (EP), N-vinylpyrrolidone (NVP), divinylbenzene (DVB) and azobisisobutyronitrile (AIBN) were from Aldrich. NaOH and acetone were from Panreac Química S.A., Spain. Sodium borohydride ($NaBH_4$) was from Probus S.A. All the reagents were used without further purification. Tannic acid and 2-acetylnaphthalene (99%) were purchased from Sigma-Aldrich (USA) and 1-naphthol (99+%) from Merck (Germany). Cetirizine dihydrochloride and pseudoephedrine hydrochloride were a gift from Laboratorios Cinfa S.A., Spain. The structures of the sorbates can be found in the Supporting Information section (Figure S1). Poly(vinylpolypyrrolidone), an insoluble crosslinked poly(N-vinylpyrrolidone) (PVPP) also known as crospovidone was purchased from ISP (USA) (Polyplasdone^{TM} XL).

2.2. Methods

2.2.1. Preparation of polymers

The crosslinking of β-CD with EP occurs in basic aqueous media (in the presence of a small amount of $NaBH_4$, to avoid oxidation). Self-polymerization of EP is favoured at high temperatures. The mole ratio CD:EP selected was 1:13.4 and the temperatures chosen were 25 ºC and 55 ºC. The toxicity of EP can be a concern when preparing these materials; in a previous work (Machín, et al., 2013), we reported that, after the purification step, the presence of free residual EP is improbable, as shown by toxicity essays. On the other hand, NVP polymerizes by an addition mechanism in the presence of AIBN. DVB, a bifunctional reagent, is used to obtain a crosslinked polymer with a 1:6.7 DVB/NVP mole ratio (1:5 v/v). Four types of interpenetrating polymer networks based on CD/EP and NVP/DVB were prepared (see scheme 1). The selected mass feed ratio of both monomers CD/NVP in all batches was 1:2.5. The complete synthesis data are summarized in the Supporting Information section.

Sequential (SE) IPNs were prepared using a three-step procedure: firstly, a β-CDP network was prepared following standard procedures (García-Zubiri, González-Gaitano, & Isasi, 2007) under constant stirring in a temperature controlled bath (25 ºC or 55 ºC) until the gel point was reached. After purification, dried β-CDP resins were embedded in acetone with the appropriate amounts of DVB and AIBN at room temperature. After solvent evaporation, the polymer was soaked into NVP, whose polymerization was carried out at 55 ºC.

Simultaneous (SI) IPNs were prepared using a single step mechanism: all the reagents were mixed in the same vessel and both polymerisation reactions occurred simultaneously at 55 ºC.

Hybrid (HY) IPNs were obtained in two steps. As in the previous case, all the reagents were added together. Then, the mixture was stirred at 25 ºC (below 45 ºC, to assure AIBN is stable) to crosslink the CD moieties with EP. Then, the temperature was increased up to 55 ºC to activate AIBN, in order to start the addition polymerisation process for NVP and DVB.

Finally, a new procedure was proposed in this work, named *hybrid-sequential (HS)* (see scheme 1). β-CD, EP and $NaBH_4$ were mixed with DVB and AIBN in a basic aqueous solution. The crosslinking of CD was carried out using constant stirring at 25 ºC, to avoid the decomposition of AIBN. Once the reaction was finished, the resins were dried, and soaked into NVP. Finally, the polymerisation of the latter was achieved at 55 ºC. Some additional batches were prepared using different volume ratios for DVB/NVP (1:10 and 1:20 besides

1:5).

The obtained polymers have been named according to the method of synthesis (sequential, SE; simultaneous, SI; hybrid, HY; hybrid-sequential, HS) and the temperature employed to polymerize β-CD. Accordingly, the five IPNs synthesized are labelled as SE25, SE55, SI55, HY25 and HS25. In addition, a single β-CD polymer (CDP25, synthesised at 25 ºC) and a commercial crosspovidone (PVPP) (Polyplasdone^{TM} XL, ISP, USA) have been also used for this study for comparison purposes.

2.2.2. Characterization of IPNs

Fourier-transform infrared (FTIR) spectroscopy. Infrared spectra were collected (an average of 32 scans) between 600 and 4000 cm^{-1} with a Nicolet-FTIR Avatar 360 (Thermo Fisher) or an IR Affinity-15 (Shimazdu) spectrometer, using a MKII Golden Gate attenuated total reflectance (ATR) device with a resolution of 4 cm^{-1}, and they were analyzed using OMNIC E.S.P. software.

Swelling in water. The swelling capacities of the synthesised IPNs have been studied by the determination of apparent volumes (Romo, Peñas, Sevillano, & Isasi, 2006). A weighed amount of dry polymer is placed into a graduated tube (± 0.1 mL) with an excess of water (10 mL) and the evolution of the swelling gel volume is registered. Swelling is measured as the ratio between the apparent total volume of the swollen gel and dry resin mass.

$$\frac{V_{Total}}{dry\ polymer\ mass}\ (mL/g) \qquad \text{(eq. 1)}$$

Thermogravimetric analysis. The thermal behavior of HS25 has been studied by simultaneous thermal/thermogravimetric analysis under nitrogen atmosphere at 2 ºC/min, using a Mettler Toledo TGA/SDTA 851. The parent polymers (β-CDP and PVPP) as well as a physical mixture of both (60.7% β-CDP) were also analysed for comparison purposes.

Sorption equilibrium data. The sorption equilibrium measurements were carried out at 25 ºC, using 0.150 g of the resin. The polymer was mixed with 50 mL of a stirred aqueous solution of 1-naphthol, 2-acetylnaphthalene or tannic acid in a capped amber bottle. UV measurements of the supernatant were performed using a Hewlett Packard 8452A spectrophotometer. According to our previous kinetics experiments, the mixtures were stirred for different time lengths (always above 1 hour), and the supernatant solution was measured after one hour of

equilibration. The experimental conditions of initial concentration, wavelength and contact time were, respectively, as follows: phenol (50 mg/L, 272 nm, >1 h), 1-naphthol (76.5 mg/L, 293-322 nm, 2.5 h), 2-acetylnaphthalene (9.9 mg/L, 284 nm, >1 h), tannic acid (86 mg/L, 256-296 nm, 3 h).

2.2.3. Additional sorption studies with HS25

As the hybrid-sequential IPN sample (HS25) seemed to be the most promising resin (see below), it was selected to carry out further studies with pharmaceutical sorbates. The sorption behaviours of cetirizine dihydrochloride and pseudoephedrine hydrochloride in HS25 were studied by analysing their sorption isotherms at 15, 25, 35 and 45 ºC. In addition, the sorbates retention in the parent polymers (pure β-CDP and PVPP) was analysed for comparison purposes.

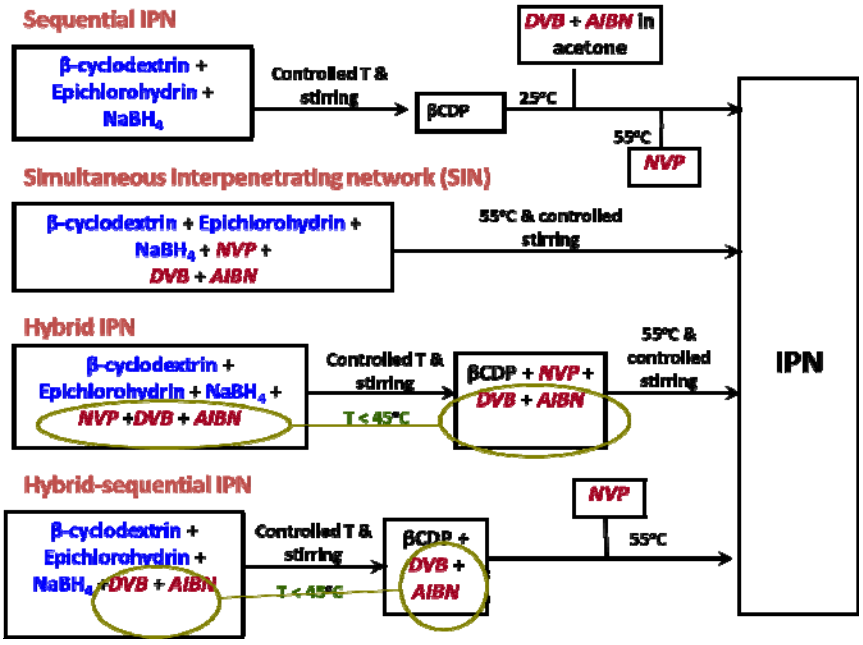
Firstly, 200 mg of polymer were added to ten capped amber bottles. Then 50 mL of sorbate (cetirizine or pseudoephedrine) aqueous solutions of concentrations ranging from 300 to 3000 mg/mL were added to each bottle. The bottles were placed in a thermostatic bath with magnetic stirring until equilibrium was reached (three hours). 1 mL samples of the supernatant were taken, centrifuged, diluted and quantified spectrophotometrically. The results of such sorption experiments have been fitted to the Freundlich equation.

3. Results and discussion

IPNs have been classified, according to the synthesis procedures of their networks, mainly in two families, namely sequential and simultaneous. Sequential IPNs are prepared by synthesising polymer I network in the first place; later on, monomer II, crosslinker II, and their activator are introduced into network I and polymerized in situ. On the other hand, simultaneous IPNs are formed when both monomers, I and II, are mixed with their respective crosslinkers and activators, and are polymerised simultaneously. A hybrid class between these two main types has been also reported, in which two sets of monomers, crosslinkers and activators are mixed at first, but the polymerisation is performed in two subsequent steps. In our case, besides these three types already reported in the literature, we have carried out an additional method that we have named "hybrid-sequential" IPN (see experimental section and scheme 1).

β-CD can be easily crosslinked with epichlorohydrin, a bifunctional reagent (which can also

be self-polymerized) in a basic medium using $NaBH_4$ as an antioxidant at a temperature between room temperature (ca. 25 ºC) and 55 °C. The second network will be constituted by N-vinylpyrrolidone (NVP) crosslinked with divinylbenzene (DVB), which can be polymerized using azobisisobutyronitrile (AIBN) as an initiator of the polymerization reaction at a temperature above 55-60 °C. The polymerization mechanisms are different in both cases (condensation and addition, respectively), so the interlocking networks could be obtained either simultaneously or successively (scheme 1).



Scheme 1. *Methods of preparation of CDP/PVP interpenetrating networks.*

Obviously, the level of crosslinking (the average distance between two crosslinking chains) is a key factor that determines the mesh size of the IPN structures. Our previous results indicated that the feed molar ratio β-CD:EP does not affect significantly the amount of CD moieties in the polymer (I. X. García-Zubiri, González-Gaitano, & Isasi, 2009; Renard, Deratani, Volet, & Sebille, 1997). Nevertheless, temperature does have a major effect in the resulting mesh size (ξ). In the case of the β-CDP polymers, it was found that the self-polymerization of EP is favoured at high temperatures (Renard et al., 1997). Therefore, a similar ratio β-CD:EP in two polymers obtained at different temperatures would correspond to a remarkable difference in their corresponding mesh sizes. Because of their hydrophilic character, swelling studies in water will be valuable to their characterization (see below).

The yields obtained for all the products prepared using these different procedures can be found in the Supporting Information section (Table S1) It can be observed that the hybrid and simultaneous (both at high and low temperatures) methods give the lowest yields. The highest yields correspond to the hybrid-sequential method (ca. 50%) and the sequential (30%).

3.1. Infrared spectroscopy

Infrared spectroscopy is a useful tool in the characterization of organic materials such as macromolecular networks. However, for single CD polymers crosslinked with EP, the changes observed are difficult to analyse because of the similarity between the chemical groups of both the CD moieties and the crosslinking network. Therefore, the spectroscopic characterization of CD/EP polymers provides little information regarding their composition differences. The infrared spectral wavenumbers of saccharide polymers crosslinked with EP can be found in the literature (Delval et al., 2004; Dumoulin, Alex, Szabo, Cartilier, & Mateescu, 1998). The infrared spectrum of β-CD has also been reported (Bratu et al., 1998), but only a few studies analyse the infrared spectra of CD polymers crosslinked with EP (Yu, Jiang, Liu, Yu, & Zhang, 2003). It has been pointed out that some differences between the IR spectrum of CD and its polymers suggest the crosslinking reaction (Yu et al., 2003). Thus, stretching (2890-2880 cm^{-1}) and bending (1480-1070 cm^{-1}) peaks of C-H bonds confirm the polymerization.

PVPP and β-CDP infrared spectra correspond to those reported in the literature (Isasi, Cesteros, & Katime, 1993; Machín, Isasi, & Vélaz, 2012). As can be seen in Figure 1, PVPP shows a double band ca. 1650 cm^{-1} attributable to the presence of the cyclic amide carbonyl group. For β-CDPs, the spectra show the deformation band of the OH bond at 1083 cm^{-1}, the CO stretching band at 1017 cm^{-1}, and the characteristic bands of the hydroxyl bond deformation in the range 1350-1320 cm^{-1}. Both polymers possess bands around 2900 cm^{-1}, due to the stretching of methylenes, and also in the range 1445-1485 cm^{-1}, attributed to the corresponding deformation modes.

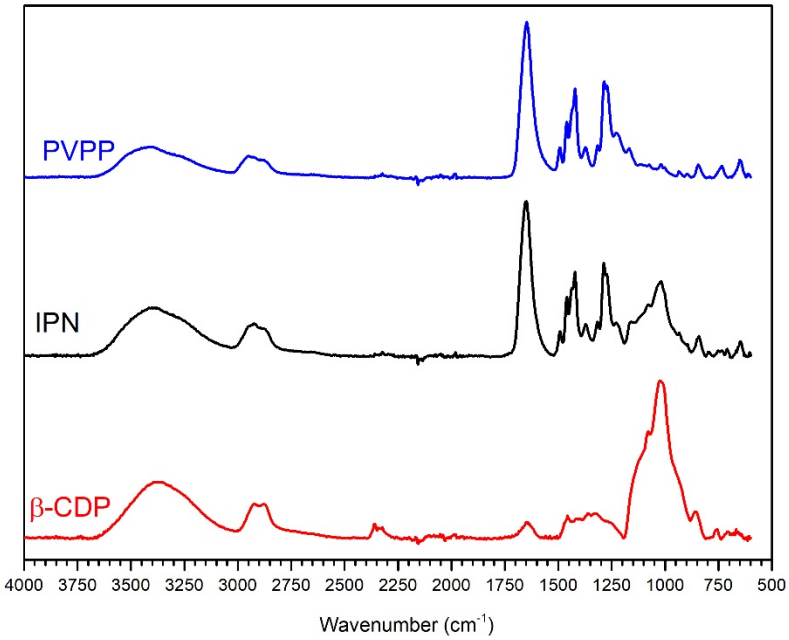


Figure 1. *FTIR spectra (from top to bottom) of PVP, a sequential IPN (SE25) and a cyclodextrin polymer (CDP25).*

In order to determine the ratio between both parent polymers, βCDP and crosslinked poly(N-vinylpyrrolidone) (PVPP), in the different IPNs, the analysis can be performed by comparison of the peak intensities corresponding to the PVP amide carbonyl bands at 1647 cm^{-1} with the stretching CO band of β-CD, located at 1020 cm^{-1}. Thus, a calibration curve was obtained by calculating this intensities ratio from physical mixtures of PVPP and β-CDP (Supporting Information, Figure S2). To a first approximation, the IPN spectra are the sum of the two contributing polymers, as occurs for the physical macroscopic mixtures. Although specific interactions between both IPN components could be responsible for some minor changes in the spectra, we have found no significant modifications. Additionally, the PVP bands located at 1420 cm^{-1} and 1286 cm^{-1} were also compared to the CO stretching band of β-CDP. These results can be averaged to give the compositions shown in Table 1 (complete information of all batches can be found in the SI section, Table S2).

As can be seen in Table 1, both the simultaneous and the hybrid method yield a high percentage of β-CDP. In other words, PVPP was not efficiently incorporated into the network. With regard to the sequential method, it was found that the ratio favours β-CDP at 25 °C

while at 55 °C the proportion is more balanced (ca. 50/50). This result confirms our previous studies (García-Zubiri et al., 2007): the CD network, which in these two procedures is synthesised first, possesses a considerable larger mesh size when the reaction temperature is higher. The penetration of the reactants corresponding to the second network is easier, so we can prepare IPNs with a larger PVPP ratio.

Table 1. IPN compositions obtained from FTIR calibration curves (average values of two batches; n=3 for HS25 1/5, n=1 for HS25 1/20).

	%β-CDP (1647/1020)	%β-CDP (1420/1020)	%β-CDP (1286/1020)	%β-CDP Average	% PVPP	Swelling (mL/g)
SE25	72	74	69	72	28	4.2
SE55	47	50	51	49	51	5.4
SI55	86	95	90	91	9	12.3
HY55	100	94	88	94	6	15.1
HS25 1/5	49	58	53	53	47	6.7
HS25 1/10	73	79	75	74	26	6.9
HS25 1/20	78	81	76	78	22	7.9

In the case of the hybrid-sequential method, we have tested three different crosslinker (DVB)/monomer (NVP) ratios. We found that, when using a 1:5 DVB/NVP ratio, a more balanced composition (i.e. closer to 50/50) between β-CDP and PVPP is obtained. In contrast, using lower crosslinker amounts (ratios 1:10 and 1:20) the PVPP ratio in the IPN decreases. It can be concluded that an excess of DVB is necessary to achieve a better incorporation of PVPP in the final IPN structures. In order to prepare IPNs with a higher amount of PVPP and also better yields (see above), the NVP monomer must be added after the β-CDP polymer has been formed (as in the sequential and hybrid-sequential methods). In addition, the non-polar character of its crosslinker (i.e. DVB) is compatible with the relatively hydrophobic β-CD cavities, which could have a protective effect of these molecules by inclusion complexation phenomena.

Furthermore, subtractions of β-CDP spectra to those of IPNs were performed as an additional method for proving the presence of PVP in the network. The subtraction of spectra is frequently employed to verify the presence of a component in a mixture when it is masked by the other components. In our case, a subtraction of spectra was carried out to confirm the absence of significant modifications in the PVP spectrum (see Supporting Information, Figure S3).

3.2. Apparent swelling behaviour

The degree of swelling of a hydrogel can be defined as the mass or volume of the swollen hydrogel in relation to that of the dry polymer. Resins with values greater than 5 are usually considered highly swellable hydrogels, while values below 1.5 correspond to low swelling degrees. In the case of single β-CDP gels, higher degrees of swelling are observed for those synthesized at higher temperatures (see above). In the sequential method, the broader mesh sizes obtained in the first step at 55 ºC (i.e. the CD reticulation process) explain the higher swelling degree in the final IPN produced after the NVP polymerization step (Table 1).

It is also observed that the swelling degree is much higher for the simultaneous and hybrid methods. For both methods, the amount of PVPP in the final IPN is comparatively quite low. In this case, the linking of NVP chains by DVB has not been efficient enough to prevent the resin from swelling more. In the hybrid-sequential samples it is observed that the swelling degree varies from 5.5 to 8 mL/g, which is explained by the higher PVPP ratios. Besides, in these materials, the higher the DVB/NVP ratio, the lower the swelling degree, as expected.

3.3. Thermogravimetric analysis

The results obtained in the characterization of the different IPN led us to choose HS25 as the most promising product obtained. For this reason, it was further studied by thermal analysis. After the quantification of the amount of each polymer present in the IPNs by infrared spectroscopy, thermal analysis was used to investigate if the possible interactions in the IPNs at a molecular level have an influence on the degradation patterns. From the comparison of the TG and DTG curves (Figure 2), three regions are considered: weight loss below 100 °C, which corresponds to the evaporation of water molecules trapped in the polymer cavities; loss around 350 °C, which corresponds mainly to the degradation of the CD polymer; and finally,

the loss around 420 °C, corresponding to the degradation of the polymer of NVP crosslinked by DVB.

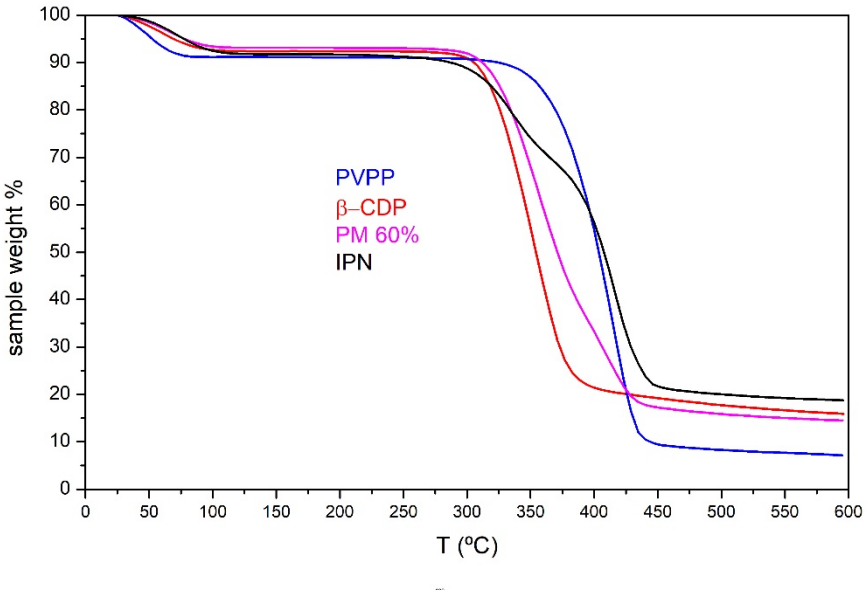
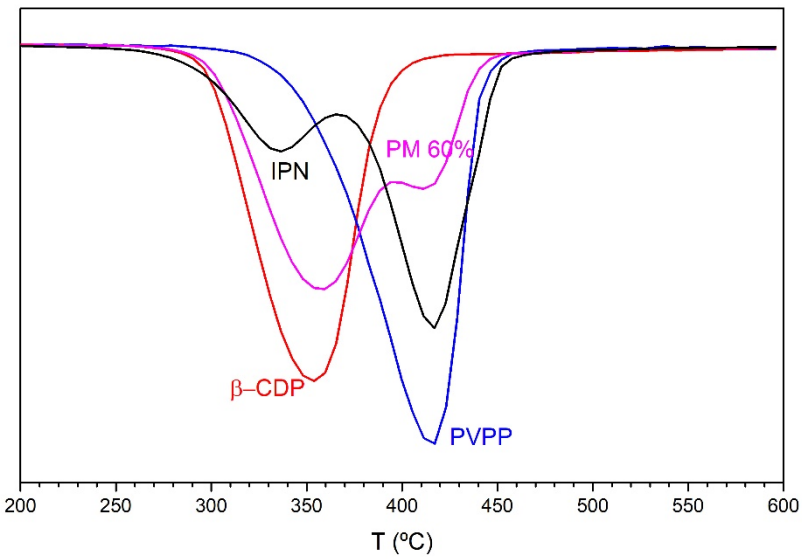


Figure 2. *TG (top) and DTG (bottom) curves of PVPP, a cyclodextrin polymer (CDP25), a*



hybrid-sequential IPN (HS25) and a physical mixture (PM) of CDP and PVPP (60% of CDP)

For the IPN prepared by the hybrid-sequential method (HS25) and the corresponding physical mixture, significant weight losses are observed in the three zones described, which indicate the presence of both polymers, besides water molecules, in the structure. In order to distinguish the two thermal events attributed to the degradation of β-CDP and that of PVPP, decomposition of the DTG curves by means of the Multiple Peak Fit tool of the Origin 8.5 software has been performed. It becomes clear that the patterns found in the DTG curves of

the IPN and the corresponding physical mixture are totally different, which confirm a high level of interpenetration at a molecular level. As can be seen in Figure 2, the presence of the PVPP component delays the degradation of the β-CD moieties in the IPN.

3.4. Sorption of model compounds

Three model molecules, 1-naphthol, 2-acetylnaphthalene and tannic acid have been used to test the sorption capabilities of the IPNs. They have been selected for their potential abilities to establish specific interactions through hydrogen bonding and/or inclusional complexation within β-CD moieties. Although 1-naphthol was successfully employed as a model molecule in previous studies dealing with CD polymers (García-Zubiri et al., 2007), accurate determinations of its concentration after the sorption experiments have been somewhat problematic in this case. Besides, the amount sorbed is very similar for both parent polymers. For these reasons, an additional model compound was required, which can be sorbed in β-CDP, but shows little affinity for PVP. 2-Acetylnaphthalene is an aromatic compound which can form inclusion complexes with β-CD moieties but lacks the hydroxyl groups which provide chemical affinity to 1-naphthol with the PVPP. Undoubtedly, tannic acid is an excellent choice as a model molecule, since it represents an entire family of chemicals which are frequently eliminated from different vegetables, and, more specifically, from wine and tea. In fact, PVPP is used industrially for this purpose. Figure 3 shows the average values of sorption obtained for the model compounds in the parent polymers; β-CDP has been synthesised in our laboratory whereas PVPP has been purchased (additional values for all batches can be found in Tables S3 and S4, SI section).

Considering the parent polymers first, we can find some differences in the sorption of the three model molecules. The amount of tannic acid sorbed by PVPP doubles that trapped by β-CDP. In the case of 2-acetylnaphthalene, the opposite is observed. These results confirm both substances as appropriate model molecules. In addition, 1-naphthol, which was also selected for its affinity to the CD moieties, does present a higher sorption in β-CDP compared to PVPP, but the difference is not as important as in the case of 2-acetylnaphthalene. Thus, the affinity of 1-naphthol for both networks is somewhat similar.

Finally, the sorption of the model molecules in the interpenetrated networks has also been analysed. It is observed that the adsorption of 1-naphthol is the highest in SE, SI and HY samples, and 2-acetylnaphthalene also presents similar adsorption results for HS samples. In

contrast, tannic acid presents more variable sorption values, which should be related to the PVPP content in the networks. Nevertheless, the most interesting result is that, for the two naphthalene derivatives, the adsorption is better in all IPN samples than in the parent polymers, pointing to a synergistic sorption behaviour. In the case of tannic acid, the sorption values are, in general, intermediate between those found for the parent polymers, which is an indication of an additive behaviour for this sorbate.

With regard to the differences between the IPNs, these preliminary results seem to indicate that those samples with moderate to high PVPP contents (such as HS25), show better sorption capabilities. In the next section, a better comparison between an IPN with similar contents of both components and the corresponding parent polymers is performed using two other model molecules.

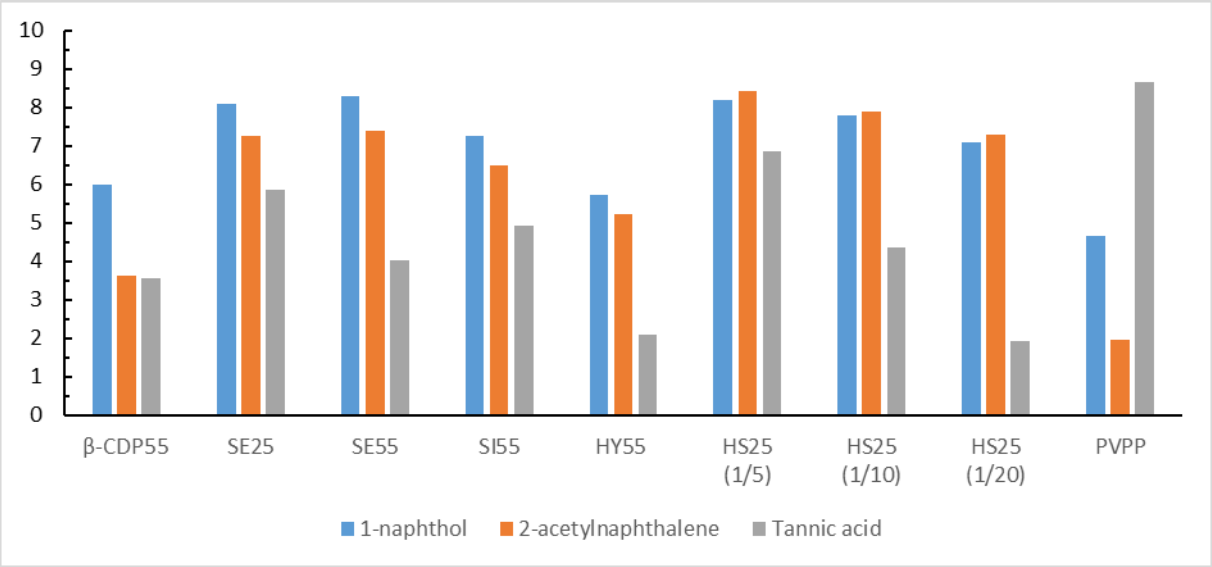


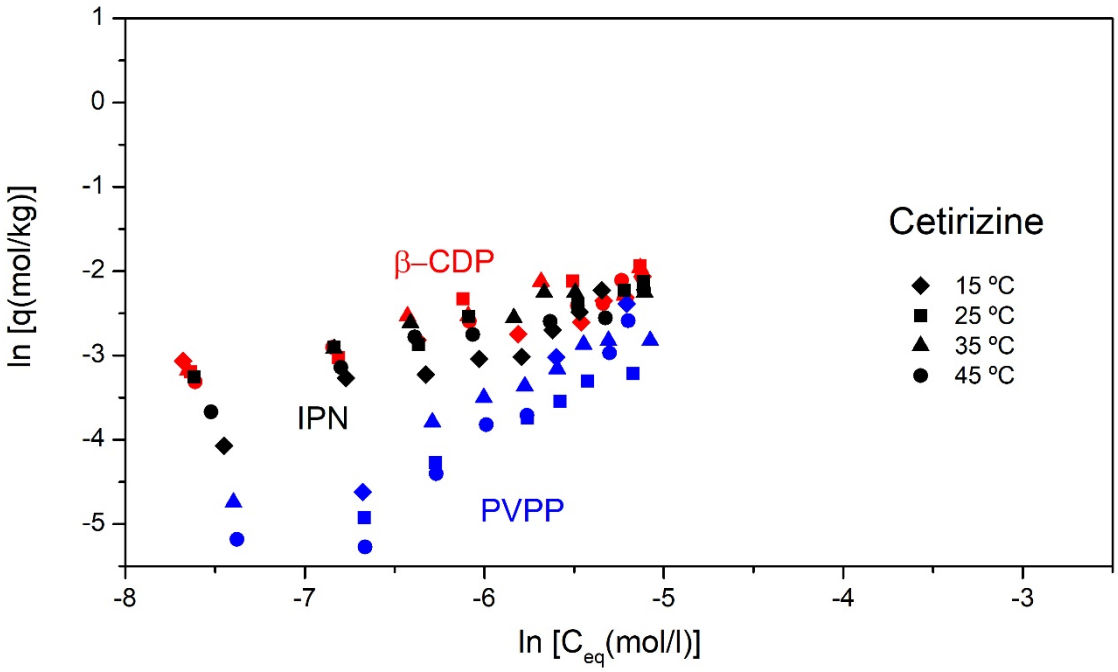
Figure 3. *Sorption (mg/g) of model compounds in IPNs and both parent polymers*

3.5. Additional sorption studies: cetirizine and pseudoephedrine

The interaction of cetirizine and pseudoephedrine with the IPN HS25 and the parent polymers, PVPP and β-CDP has been characterised by analysing their corresponding sorption isotherms in water at temperatures ranging between 15 and 45 ºC. In a previous work (García-Zubiri et al., 2009) we showed that, for CD polymers, the Freundlich isotherm is the appropriate simple model to compare the sorption capabilities of these heterogeneous materials. As can be seen in Figure 4, the difference between the amounts of cetirizine

absorbed by the parent polymers β-CDP and PVPP decreases as the concentration of sorbate in the medium increases. In other words, the lower the sorbate concentration, the higher the differences of loading efficiency between two given sorbents. In addition, the Freundlich fitting parameters corresponding to cetirizine (Table 2) show that for β-CDP the *n* exponent is clearly lower than 1, whereas for PVPP *n* is very close to unity. As already reported, *n* values lower than 1 are indicative of more heterogeneous sorbents. It seems, therefore, that cetirizine is absorbed in more than one type of site for β-CDP, while PVPP shows a more homogeneous behaviour.

With the knowledge we have acquired with regard to the structure of these sorbents, we hypothesize that β-CDP cyclodextrin cavities interact with the nonpolar aromatic rings of cetirizine while its hydrophilic edge is stabilized with the hydrophilic groups of the network. Thus, at low concentrations, the sorption is indeed significantly higher for β-CDP than for PVPP (whose network is mostly polar), but this difference is mitigated as the CD sites are filled and the polar interactions start to play a more significant role.



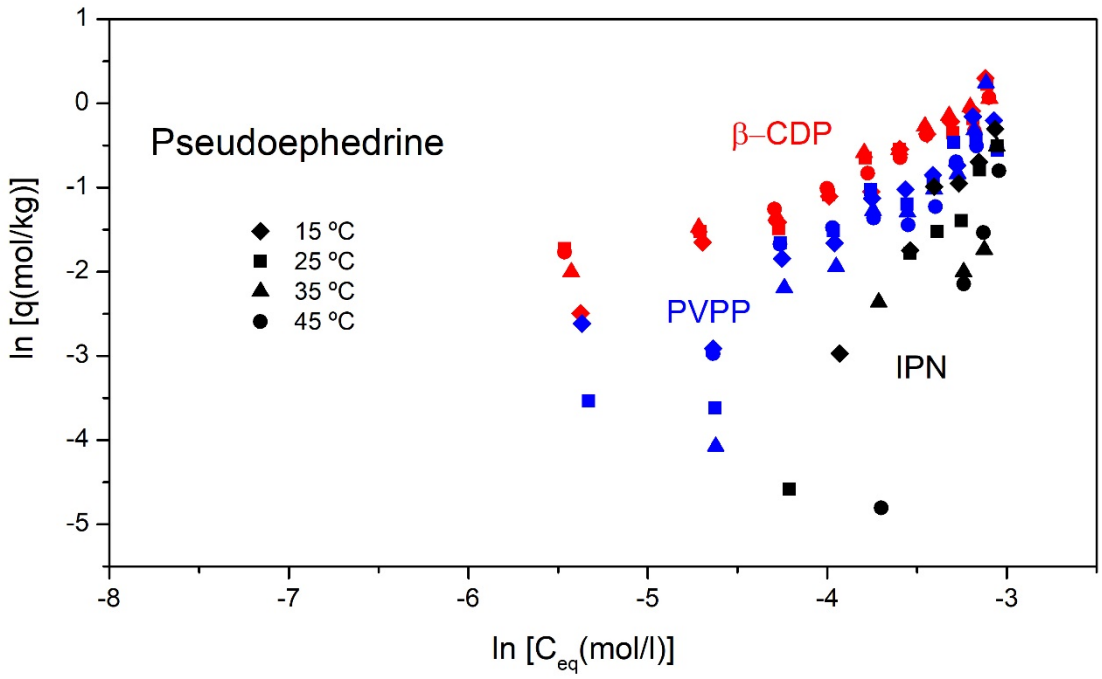


Figure 4. Sorption isotherms of cetirizine and pseudoephedrine in the IPN HS25 and the parent polymers, PVPP and β-CDP at different temperatures

Table 2. Freundlich fitting parameters for β-CDP, PVPP and IPN (HS25) isotherms with cetirizine

Sorbent	*T* (°C)	*n*	r^2
β-CDP	15	0.4 ± 0.1	0.705
	25	0.6 ± 0.2	0.550
	35	0.5 ± 0.2	0.545
	45	0.5 ± 0.1	0.806
PVPP	15	1.0 ± 1.3	0.102
	25	1.0 ± 0.2	0.898
	35	0.9 ± 0.1	0.934
	45	2.1 ± 0.4	0.894
IPN	15	1.4 ± 0.2	0.900
	25	0.4 ± 0.1	0.853
	35	0.4 ± 0.1	0.792
	45	0.6 ± 0.1	0.748

As for the interpenetrated network sorption, the *n* values are also below one (Table 2), which also reflects its heterogeneity. More importantly, a synergistic effect of the two IPN components is shown, since the amount of drug absorbed in the IPN does not lie between the β-CDP and the PVPP (i.e. the additive behaviour expected for a physical mixture), but is closer to the values of the first.

For pseudoephedrine, in contrast, the sorption isotherms for both β-CDP and PVPP are much closer to each other in the concentration range tested (Figure 4b). The Freundlich fitting parameters (Table 5), show values of *n* around one, or higher, for both polymers. A clear conclusion cannot be drawn due to some scattering of the points obtained at the lowest sorbate concentrations. Besides, the concentration range tested for pseudoephedrine is different from that of cetirizine in accord with the fact that it is more soluble in water and the therapeutical dose is also markedly higher. As an example, some commercially available tablets contain 5 mg cetirizine and 120 mg pseudoephedrine (Reactine®, Johnson & Johnson Inc.). At lower concentrations of pseudoephedrine, the differences between these two sorbents, β-CDP and PVPP should be more evident. Pseudoephedrine also possesses an aromatic moiety capable of interacting with the CD cavities, plus two polar groups very close to it, which in turn could establish hydrogen bonds with both parent polymer networks.

Table 3. Freundlich fitting parameters for β-CDP, PVPP and IPN (HS25) isotherms with pseudoephedrine

Sorbent	*T* (ºC)	n	r^2
β-CDP	15	1.6 ± 0.2	0.940
	25	1.2 ± 0.2	0.891
	35	1.2 ± 0.1	0.949
	45	1.0 ± 0.2	0.873
PVPP	15	1.6 ± 0.2	0.919
	25	1.2 ± 0.2	0.887
	35	2.0 ± 0.4	0.908
	45	1.3 ± 0.2	0.878
IPN	15	1.6 ± 0.2	0.919
	25	1.2 ± 0.2	0.887
	35	2.0 ± 0.4	0.908
	45	1.3 ± 0.2	0.878

Nevertheless, the sorption behaviour of pseudoephedrine with respect to the IPN is surprising (Figure 4b); a negative synergy takes place in this case. Interpenetration reduces the sorption of this drug to values below those presented for PVPP.

In order to explain such a different behaviour for both drugs, we have also to consider that specific interactions will also occur between the two interpenetrated polymers. It is reasonable to think that hydrogen bonds will be established between the carbonyl groups of pyrrolidone and the hydroxyl groups of either the CD moieties or the crosslinking chains (Isasi et al., 1993). The sorbate molecules will compete for the most favourable interactions within the resulting associated interpenetrated network. In the cases studied here, it seems that the IPN-cetirizine interaction is greater than the interaction within the network itself, unlike what occurs with pseudoephedrine. Thus, cetirizine stabilization in the IPN matrix could be most favourable since its hydrophobic moieties would fit in the CD cavities and, at the same time, its carboxyl group would interact with the rest of the network. Its large size would allow cetirizine molecules to perform this role of "bridge" between the different active sites. Pseudoephedrine, on the other hand, would interact well with the polar groups of the network (thanks to its hydroxyl and amino groups), but not significantly better than the groups in the network with each other. On the other hand, its lower affinity for the CD cavities, would hinder the sorption, and, in the case of inclusion of the aromatic ring within a cavity, its small size would hinder the additional stabilization of its polar region with other IPN groups outside the cavity.

Unfortunately, the influence of temperature in the sorption process of these two model molecules is not clear. In Figure 4 it seems that the isotherms obtained at 15 ºC are somewhat higher, the data obtained are not sufficient to draw a firm conclusion. The sorption process would be exothermic, as found in most cases although not in all (García-Zubiri et al., 2007). In any case, the isosteric heat of sorption must be very small, considering the differences of coverage at the studied temperatures for a given equilibrium sorbate concentration.

4. Conclusions

The characterization of the IPNs synthesized by different procedures leads to interesting conclusions in relation with the synthetic approaches performed. It seems clear that the best synthetic methods are the sequential, despite its three step procedure, and the hybrid-sequential, because their yields and efficient incorporation of both polymers in the IPN. The advantage of the sequential mode over the hybrid sequential is the possibility of increasing

temperature in the β-CDP synthesis step. Nevertheless, the hybrid sequential method presents a better yield and higher swelling ratios. Both methods exhibit synergistic sorption of the naphthalene derivatives and additive sorption for tannic acid. Therefore, there would be no practical interest in using these IPNs to recover tannic acid, as they behave just as physical mixtures of both parent polymers. Moreover, we have found that a negative synergy is also a possibility due to the competing interactions within the interpenetrated network. The different sorption behaviours found for the five model molecules tested point out that both chemical and steric factors play a role in the sorbent-sorbate interactions. This study opens the possibility of preparing a tailored IPN for a specific purpose such as combined drug release or water treatment.

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Supporting Information. Structures of sorbates. Ratio of FTIR absorbances at 1647 and 1020 cm^{-1} as a function of CDP percentage obtained from physical mixtures of CDP and PVPP. Infrared spectra of (from top to bottom) a sequential IPN sample (SE25), the same after digital subtraction of CDP contribution (using β-CDP25 spectrum), and pure PVPP. Data for synthesis of IPN according to all experimental procedures. IPN compositions obtained from FTIR calibration curves and water swelling data. Sorption data of model compounds in the parent polymers and the IPNs.

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