Drug transport in stimuli responsive acrylic and methacrylic interpenetrating polymer networks

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ABSTRACT

The interpenetrating polymer networks (IPNs) are recently gaining attention as sustained drug delivery systems because they could ensure a proper combination of functionality and network density to control the drug release profiles. The present study aims to reveal how the functionality of two IPNs based on polyacrylamide and respectively poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA) influences their smart behavior as well as their properties as delivery systems of the cationic drug verapamil hydrochloride (VPM). The “extra” α -methyl group of PMAA results into a loss of the temperature sensitivity in the studied region and changes the pH responsivity of the PMAA/PAAM IPNs as compared to the PAA/PAAM IPNs. Moreover, the VPM diffusion in both IPNs depends on their composition due to the change in their functionality as well as of their network density. The “extra” α -methyl group of PMAA defines its enhanced hydrophobicity and hence influences the VPM diffusion mechanism.

INTRODUCTION

In the recent years polymer based vehicles for modified drug release are an object of intensive work because of their many advantages as smart drug delivery systems. The drug delivery potential of a polymeric material depends on the drug release rate as well as on the extent of drug release/unloading. These two parameters are controlled by the drug solubility in the release media as well as by the drug diffusion in the polymer matrix. They could be additionally tuned via change in temperature and pH of the media when stimuli responsive drug delivery systems are used. Thus, smart polymer materials are increasingly gaining attention and their potential in the area of modified drug delivery is gradually being revealed although it is still not fully exploited at the moment.

It is well known from the literature that polymeric systems based on poly(acrylic acid) (PAA) and polyacrylamide (PAAM) are simultaneously pH¹ and temperature responsive (exhibiting upper critical solution temperature, UCST, type behaviour^{2,3}). The presence of pendant COOH groups in PAA defines their pH-sensitivity: at pH > pK_a^{PAA}~4.5⁴ these groups are deprotonated, which results into their mutual electrostatic repulsion and increased swelling ability of the polymeric material. Hence, such materials could ensure an enhanced drug diffusion towards the release media as the pH changes from acidic, e.g. stomach-like conditions, to neutral, i.e. intestine like conditions. For example, this effect was utilized when developing a controlled release system for the antihypertensive drug losartan potassium⁴. With time, more and more carboxylic groups from PAA became deprotonated which resulted into a gradual increase in the polymer network swelling and thus to a prolonged drug release up to 34 hours.⁴

The temperature sensitivity of PAA/PAAM based materials is due to the hydrogen bonding between their side chain pendant groups: –COOH and –NH₂. At temperatures below UCST, the hydrogen bonds formed between these groups result into the collapse of the polymeric material. With increasing temperature, >UCST, the hydrogen bonds start to disrupt which increases the swelling of the material. Katono et al.^{5, 6} have studied in details the interpenetrating polymer networks (IPNs) of poly(acrylamide-co-butyl methacrylate) and PAA and revealed their potential as delivery systems for ketoprofen. At temperature above their UCST, these IPNs are in the so called „on” state (increased swelling ability) and thus start to release the loaded ketoprofen⁵. With decreasing temperature below UCST, a transition to almost completely “off” state is observed⁶. Similar “on-off” behaviour is also reported by Wang et al.⁷, who have utilized sequential IPNs from poly(acrylic acid)-*graft*-β-cyclodextrin (PAAc-*g*-β-CD) and polyacrylamide (PAAM) for the controlled release of ibuprofen. The cyclic change of temperature from 25°C to 37°C, at constant pH, resulted into a pulsatile (modulated) drug release, following non-Fickian release mechanism of the ibuprofen. Thus, the polymer vehicle’s smart behavior and its ability to change its structure and properties according to external stimuli, such as pH, temperature, ionic strength, etc., are lying behind the change of the mode of the drug transport into the polymer matrix and thus the drug release profile is controlled.

In a previous study, we have revealed the potential of IPNs of PAA and PAAM for the sustained release of verapamil hydrochloride (VPM)⁸. The tuning of the IPNs composition through varying the PAA/PAAM ratio allowed for modifying the VPM release profile. The best sustained release profile was observed for the IPN with the highest PAAM content: no initial burst effect occurred and ~ 90% of the drug VPM was released for over 25 hours. We have widened up our study by the synthesis of similar IPNs comprising the same side groups but replacing the poly(acrylic acid) (PAA) with

poly(methacrylic acid) (PMAA) and applied these new systems for the VPM sustained release⁹. The replacement of PAA with PMAA has changed the swelling ability of the IPNs due to the enhanced hydrophobicity of the latter, which has influenced the VPM release profile^{8,9}.

In this study we aim to directly compare both IPNs – PAA/PAAM and PMAA/PAAM and to reveal how the “small” change in the structure of one of the monomers would change their smart behavior. To this purpose the pH and the temperature responsiveness of both IPNs was studied. Moreover, as the “extra” α -CH₃ group was expected to influence also the transport of the loaded cationic drug, the transport characteristics of the cationic drug VPM within both IPNs was compared.

Thus, the aim of the study is to reveal how the “extra” α -CH₃ group in PMAA changed the smart behavior of and the drug (VPM) transport in PMAA/PAAM IPNs as compared to PAA/PAAM IPNs.

EXPERIMENTAL

Materials

Acrylamide (AAM, purum, 98.0%) was purchased from Fluka AG, Germany. Acrylic acid (AA, anhydrous, 99%) and methacrylic acid (MAA, extra pure, 99.5%) were purchased by Across Organics, Belgium. Potassium peroxodisulfate (PPS) and N,N-methylenebisacrylamide (MBAA) were purchased from Sigma-Aldrich. Verapamil hydrochloride (VPM) was provided by Knoll AG, Germany. All reagents were used as received without further purification.

IPNs' synthesis

The procedure to obtain IPNs of PAA/PAAM and PMAA/PAAM is described elsewhere^{8,9}. Briefly, a two stage sequential method was applied. At the first stage, a single network (SN) of the polyacid was obtained via free crosslinking radical polymerization of the acidic monomer (AA or MAA), MBAA (4 mol.%) and PPS (0.1 mol.%). Each of thus prepared SN hydrogels was purified in distilled water to completely remove traces from the nonreacted chemicals (the residuals were checked by UV). Then, the 2nd (PAAM) network was *in situ* synthesized into the 1st SN. To this purpose, dry SNs were transferred into aqueous solutions with different AAM concentrations (from 1M to 5M), containing also MBAA (0.1 mol.%) and PPS (0.1 mol.%). Each of the synthesized IPN's was washed out with distilled water to completely remove traces from the non-reacted chemicals (the residuals were checked by UV). Following this procedure, IPNs with different composition, i.e. weight fraction of the polyacid, were obtained using respectively PAA (Table 1) and PMAA (Table 2).

The exact IPNs' composition was determined by: (i) titration of the residual acidic monomer (respectively AA or MAA) in the waste waters obtained after the 1st stage (polyacid SN purification) and (ii) determination of the non-reacted AAM in the waste waters obtained after purification of the

IPNs by using UV method for AAM determination. More details for the synthetic procedure and the determination of the IPNs' composition are provided in the Supplementary info.

Temperature responsiveness

Measurements of the equilibrium swelling ratio (ESR) for both types IPNs were performed at different temperatures in the range 20-65°C. To this purpose, dry disk-shaped samples with diameter 4.5 mm were left to swell at certain temperature in distilled water. After reaching an equilibrium (typically for 7 hours, as detected by the lack of change in their weight after this period), their weight in the swollen state was measured. ESR at a defined temperature was calculated by using the equation:

$$ESR^{T^0C} = (m_{swollen}^{T^0C} - m_{dry}) / m_{dry} \quad (1)$$

Here, $m_{swollen}^{T^0C}$ and m_{dry} are respectively the weights of the swollen at certain temperature sample and in dry state. The data were averaged for at least three pieces.

pH responsiveness

Measurements were performed in a similar to the above described way but using different pH values in the range from 2 to 10 at temperature 24±1°C. Briefly, dry disk shaped samples with diameter 4.5 mm were swollen in buffer media with defined pH. After reaching equilibrium (typically for 24 hours) the mass of each piece in its swollen state was measured. ESR was calculated for each pH value using the equation:

$$ESR^{pH} = (m_{swollen}^{pH} - m_{dry}) / m_{dry} \quad (2)$$

Here, $m_{swollen}^{pH}$ and m_{dry} are respectively the weights of the swollen piece at certain pH and when dry. Buffer solutions, used throughout the experiment, were prepared following the procedure described by Pourjavadi et al¹⁰.

Drug loading and release

The VPM loading and release were described elsewhere^{8,9}. Briefly, dry disk shaped samples with diameter of 8 mm were immersed in water solution of VPM with concentration 100 mg/ml, at temperature 24°C±1°C. After swelling for 24 h, the drug loaded samples were drawn from the loading media, their surface was gently washed out with distilled water and the samples were left at room temperature to dry.

The drug release was performed by using a dissolution test apparatus (Erweka DT 600, Germany). The USP paddle method was applied. The test was carried out at a paddle rotation speed of 50 rpm, in

500 mL dissolution medium maintained at $37\pm0.5^{\circ}\text{C}$ with changing pH throughout the release experiments. To this purpose, the VPM loaded IPNs were first immersed in 0.1 mol L^{-1} HCl solution (pH 1.2) for 2 h and then transferred into phosphate buffer solution (pH 6.8) for up to 24 h. 5 mL aliquots of dissolution media were withdrawn at selected intervals up to 24 h. Each sample was filtered through a 0.45- μm membrane filter (Sartorius cellulose acetate filter, Germany). The quantity of the drug in the sample solution was determined by UV spectroscopy at $278\pm2\text{ nm}$ using a Hewlett-Packard 8452 A Diode Array spectrophotometer, USA. The cumulative percentage of the drug release was calculated and the average of six determinations was used in the data analysis.

VPM transport in IPNs

The drug transport in both types of IPNs was studied by applying the Korsmeyer-Peppas model. The Korsmeyer-Peppas Model was developed especially for modeling the release of a drug molecule from a polymeric matrix, such as a hydrogel. This semi-empirical model assumes an exponential relation of the drug release and the elapsed time¹¹. Thus, the type of the drug transport could be evaluated by applying the equation:

$$\frac{M_t}{M_{\infty}} = k_{KP} t^n \quad (3)$$

where M_t stays for the amount of the drug released at time t ; M_{∞} is the amount of the drug that should be released at infinite time, $t=\infty$; k_{KP} , is the rate constant, and n is the diffusion exponent, which value depends on the sample geometry and reveals the mode of the drug diffusion. This equation is valid when the release is one-dimensional and the sample width-to-thickness ratio is at least 10^{12} . The relation between n values and the drug diffusion mode is presented in Table 3¹³.

From the diffusion exponent values, taking into account the *cylindrical* geometry of our IPNs samples, one could obtain the diffusion coefficient of the drug (VPM), using the equation:

$$D = \sqrt[n]{\frac{K_{KP}}{4}} \pi l^2 \quad (4)$$

where K_{KP} is the same from equation (3), π is the Ludolphine number ($\pi=3.14$), l is the sample height (in meters) and n is the diffusion exponent from equation (3).

RESULTS AND DISCUSSION

Temperature responsiveness of acrylic and methacrylic IPNs

The dependence of ESR^{T^0C} on temperature for IPN PAA/PAAM is presented in Figure 1. All studied IPNs PAA/PAAM are temperature sensitive and exhibit UCST as demonstrated by their ESR increase with temperature.

It is known from the literature, that for any system (copolymers, blends, IPNs, etc.), consisting of PAA and PAAM, an UCST is observed due to the hydrogen bond formation between PAA's carboxylic groups and PAAM's amide groups² (Scheme 1A). At temperature below the UCST, PAA preferentially forms interpolymer hydrogen bonds with PAAM, and the IPN PAA/PAAM hydrogels shrink due to the chain-chain zipper effect¹⁴. When the temperature becomes higher than UCST, the interpolymer hydrogen bonds between PAA and PAAM are disrupted and the IPN hydrogels swell through the relaxation of both polymer networks' chains. Therefore, the IPNs swell to higher ESR at temperatures above the UCST due to the disruption of the PAA/PAAM hydrogen bonds (Scheme 1B).

The IPNs with comparable content of PAA and PAAM, e.g. PA41 and PA28, show an abrupt change in their ESR when temperature increases (Figure 1). This could be explained by the higher number of hydrogen bonds between PAA and PAAM upon which disruption the ESR increases stronger. On the contrary, when PAAM prevails (e.g. in IPN 19 and IPN22), the number of interpolymer hydrogen bonds decreases and the ESR increases *continuously* with temperature (Figure 1). Similar behaviour we have observed also for the microgels of PAA/PAAM IPN¹⁵ and were also reported by Katono et al.^{5,6}. Thus, the number of the hydrogen bonds between PAA and PAAM below UCST defines the "strength" of the temperature response of the IPNs PAA/PAAM.

From Figure 1, it could be also concluded that the higher PAA content results into higher ESR of the IPNs PAA/PAAM. This trend is expected as PAA is charged at neutral pH (polyanion) and the repulsive forces between its COO⁻ anions keep the IPN network expanded when the PAA content is higher. When the number of COO⁻-containing monomeric units decreases, i.e. PAA content decreases, the swelling ratio of the IPNs is also expected to decrease.

The UCST values for the studied IPNs PAA/PAAM were determined as the inflection point of the respective experimental curve (Figure 1) and the obtained values are presented as a function of the IPNs' composition in Figure 2. There, it could be seen that UCST decreases as the PAA content in the IPN PAA/PAAM increases. This is related, as discussed above, to the increased swelling ability of the IPNs PAA/PAAM in water as the PAA content increases. The PAA interaction with water is enhanced either through an increased number of hydrogen bonds between the PAA and water molecules or by the enhanced COO⁻ solvation by water molecules, which together with the repulsive forces between adjacent COO⁻ results into higher swelling ability of the IPNs.

In summary, the temperature responsiveness of the IPNs PAA/PAAM is defined by the balance between *polymer-polymer* vs. *polymer-solvent* (water) interactions. As the IPNs' composition varies, this balance changes and the UCST increases from 38 to 47°C (Figure 2). The IPNs' composition defines the number of the hydrogen bonds formed between PAA and PAAM in the IPN. That is why, as the ratio between both components declines from ~1:1, the ESR dependence on temperature changes from discontinuous to continuous.

In Figure 3, the temperature dependence of ESR for IPN PMAA/PAAM is presented. No clear trend for the ESR could be seen as temperature rises, i.e. IPNs of PMAA/PAAM do not show temperature responsiveness in the studied range from 25 to 65°C. It was expected, that as the IPNs PMAA/PAAM have the same side groups (-COOH and -NH₂) as the IPN PAA/PAAM, they would also exhibit UCST. On the other hand, the increased hydrophobicity of PMAA as compared to PAA, could be expected to define a lower critical solution temperature (LCST) due to the PMAA's ability to form hydrophobic clusters, i.e. the hydrophilic-hydrophobic balance is expected to change with temperature. The lack of any trend in Figure 3 allows to conclude that both effects: (i) the increased hydrophobicity and (ii) the hydrogen bonding between PMAA and PAAM act against each other, thus resulting into a temperature insensitive IPNs PMAA/PAAM in the studied temperature range. As far as we are aware, PMAA based materials are not reported to be temperature sensitive unless the other component is not temperature sensitive itself, e.g. PNIPAM^{16,17}.

Thus, the "extra" α -CH₃ group in PMAA resulted into loss of the temperature responsiveness of their IPNs with PAAM as compared to the IPNs of PAA/PAAM in the temperature range from 25 to 65°C.

pH responsiveness

The polyacid component in both IPNs, respectively PAA and PMAA, ensures their pH responsiveness. The dependences of ESR^{pH} on pH for IPNs PAA/PAAM and for IPNs PMAA/PAAM are presented in Figures 4 and 5, respectively.

The swelling ability of IPNs PAA/PAAM varies with pH depending on the IPNs' composition (Figure 4). The higher PAA content in the IPN, the stronger is its ESR change as pH increases from acidic to basic. For example, the ESR of the IPN28 increases ~ 5 times as pH changes from below to above pK_a of PAA (Figure 4). IPN22 and IPN19, which exhibited very similar temperature responsiveness (Figure 1), here also show very similar response to the pH change (Figure 4) – their ESR increase ~ 3 times as pH increases. Thus, it could be summarized, that the pH responsiveness of IPN PAA/PAAM depends of their composition in a similar way to their temperature responsiveness. The ESR increase is defined

by the increase in COO^- content and the related disruption of the hydrogen bonds between PAA and PAAM (Figure 1C).

If one compares the ESR increase under both temperature and pH increase, it could be concluded that the IPNs PAA/PAAM are more sensitive towards changes in pH rather than in temperature as their ESR changes stronger when pH increases. This strong pH dependence of the ESR of the studied IPNs PAA/PAAM means that these materials are good candidates for drug delivery applications. The IPNs PAA/PAAM could be appropriate for oral drug delivery as they will prevent the drug release in the stomach (low pH, low ESR, shrunk IPNs) and will preferably release the drug in intestine-like conditions (neutral pH, 3 to 5 times increase in ESR as compared to the acidic pH), i.e. they could define a targeted release of the loaded drug in the intestines.

It was expected that IPNs of PMAA/PAAM will show pH responsiveness similar to the IPNs of PAA/PAAM as they also possess COOH groups. Figure 5 presents the pH dependence of ESR^{pH} of IPN PMAA/PAAM. For all IPNs PMAA/PAAM' compositions, a *continuous increase in their ESR* is observed as pH rises. This behavior differs from the observed abrupt/discontinuous change in the ESR for the PAA/PAAM IPNs (Figure 4).

For the sample with the highest PMAA content, PMA71, a *continuous increase* of ESR with pH is observed which could be related to the gradual increase in the number of ionized COOH groups in PMAA as pH increases. Thus, the repulsive interactions between the formed COO^- result into a gradual increase in the IPNs' ESR. For all other IPNs PMAA/PAAM compositions, a plateau in their ESR dependence on pH is observed in the acidic pH range (from 3 to 5), which is followed by a linear increase (similar to PMA71) when pH rises to alkaline. The "acidic plateau" ends up at $\text{pH} \sim 5$, which corresponds to the pK_a value of PMAA (~ 5.5). Thus, the ESR plateau at $\text{pH} < 5$ could be explained by the formation of hydrogen bonds between PMAA (COOH) and PAAM (NH_2), which remain stable until the COOH ionization starts (at $\text{pH} \sim 5$). At $\text{pH} > 5$, as more and more COOH become ionized, the number of the hydrogen bonds decreases and the ESR increases due to the repulsive interactions between COO^- .

For PMA71, due to the significantly prevailing of PMAA in the IPN, the number of the hydrogen bonds between PMAA and PAAM is not as high as to keep the ESR constant in the acidic pH range. Thus, a gradual increase in ESR is observed.

For all IPNs PMAA/PAAM, the ESR increases ~ 3 times as pH changes from acidic to basic. Thus, the IPNs of PMAA/PAAM are also good candidates for oral drug delivery although their ESR continuously increases with pH, in contrast to the discontinuous increase observed for the IPN PAA/PAAM's ESRs.

Thus, it could be concluded that the “extra” α -CH₃ group in PMAA defined a continuous ESR increases as pH increases in contrast to the discontinuous way of ESR increase observed for PAA/PAAM IPNs.

Drug transport in IPNs PAA/PAAM and PMAA/PAAM

In the previous sections it was demonstrated that the replacement of PAA with PMAA into their IPNs with PAAM resulted into: (i) a loss of the temperature responsiveness in the studied temperature region and (ii) a change in the mode of the pH responsiveness from discontinuous to continuous one. Here, the transport mode of the model cationic drug (VPM) in both “acidic” IPNs, differing in their hydrophobicity and smart behavior, will be compared. To this purpose, the Korsmeyer-Peppas model was applied in order to describe the VPM transport in both IPNs, PAA/PAAM and PMAA/PAAM. The main parameters of this model, obtained for both IPNs are presented in Tables 4 and 5, respectively. The dependence of n on the IPNs PAA/PAAM composition is presented in Figure 6A. As it was mentioned above, n values could be used to evaluate the mode of the drug diffusion into the polymer system (Table 3). According to Figure 6A, the VPM diffusion in both SNs PAA and PAAM is *Fickian*. That means that the *mobility of VPM* in these polymeric networks is the rate-limiting step for the drug release as the *drug diffusion rate (R_{drug}) is much slower than the polymer chain relaxation rate (R_{relax})*, i.e. $R_{drug} \gg R_{relax}$. This could be explained by the fact that both components of the IPN (PAA and PAAM) are superabsorbent and their high swelling ability results into a chain relaxation, which is faster than the VPM diffusion.

If we take a look on the IPNs only, a gradual decrease of n with increasing the PAA content is observed (Figure 6A) starting from anomalous for PA19 and changing to Fickian diffusion for all other IPNs samples. This trend well corresponds to the previously observed increase of ESR for IPNs PAA/PAAM with the increase of PAA content in their composition⁸. Thus, only for PA19 (the IPN with the lowest PAA content and the lowest ESR among the studied IPNs PAA/PAAM⁸) the diffusion exponent n has value of 0.542 which reflects the anomalous diffusion of VPM in this sample. Anomalous diffusion means that the rate of the drug diffusion is comparable to the rate of the polymer chains relaxation, i.e. $R_{drug} \approx R_{relax}$ (Table 3). This comparability could be explained by the three peculiarities of the sample, namely: (i) the PAA content is the lowest; it has also (ii) the lowest ESR and (iii) the highest UCST ($\sim 47^\circ\text{C}$, Figure 2) among the studied IPNs of PAA/PAAM. These three parameters define respectively: (i) the weakest interaction between PAA and VPM as the interaction between the drug and the IPN is expected to influence the VPM diffusion in the IPNs and (ii) the slowest among all IPNs samples relaxation of the polymer chains as PA19 has the highest network density and at the same time it is well below (by $\sim 10^\circ\text{C}$) its UCST. As a result, the *drug diffusion rate* in PA19 *is not slowed down* as strong as it is in the other IPNs possessing higher PAA content. At the

same time, the *rate of polymer relaxation* is *slowed down* due to the high density networks as well as to the high number of hydrogen bonds between both components PAA and PAAM. Thus, the *rate of drug diffusion* and the *rate of polymer relaxation* become comparable as acknowledged by $n = 0.542$. The different diffusion modes of VPM in the neat SN PAAM (*Fickian*) and in the IPN with the highest PAAM content PA19 (*anomalous*) are defined by the fact that in PA19 the PAAM chains are interlaced with the PAA ones as compared to the chains of the neat PAAM as well as hydrogen bonds between PAA and PAAM appear. As a result, these two samples have different ESR values and different diffusion modes of the loaded drug.

When one compare PA19 to the other IPNs samples (PA62 to PA23), the latter all exhibit Fickian diffusion of VPM (Figure 6A). In addition, a gradual decrease in their n values is observed as the PAA content increases. Similar is the UCST dependence on the PAA content - it decreases as the PAA content increases (Figure 2). In fact, the UCST for PA41 and PA28 is $\sim 37^{\circ}\text{C}$, which is the temperature at which the VPM release was carried out, i.e. the temperature at which the drug diffusion is evaluated. At the UCST the hydrogen bonds between PAA and PAAM start to disrupt, which means that at this temperature most of PAA's carboxylic groups become free from the PAA-PAAM interaction and thus available for interaction with the VPM molecules. The interaction between VPM and PAA was revealed by IR spectroscopy (see the Supplementary info) to be mainly electrostatic and also via hydrogen bonds. This is in agreement by the reported by other authors ionic interactions between PAA containing IPNs¹⁸ and cationic drugs.

Thus, it could be summarized that the diffusion of VPM in IPNs PAA/PAAM as PAA content increases is slowed down as compared to the polymer chain relaxation rates due to: (i) the enhanced interaction between the drug (VPM) and PAA as well as to (ii) the gradual change of the inner structure of the IPN hydrogels as the IPN's composition changes.

The slowdown of the VPM in the IPN as the PAA content increases is better illustrated in Figure 6B, where the dependence of the VPM's diffusion coefficient (D) on the IPN's composition is presented. As PAA content in the IPNs increases, the diffusion coefficient of VPM gradually decreases, i.e. the VPM molecules diffuse slower and slower (Figure 6B). This is related to the enhanced interaction between the cationic drug VPM and the acidic component of the IPN (PAA) as the content of the latter increases.

It should be mentioned that in this study we have preferably studied the VPM transport in IPNs with low PAA content because according to our previous investigations⁸, exactly these IPNs' compositions were better performing as VPM sustained release systems, PA19 being the best one among them. This fact was explained there by the optimal combination of functionality (in terms of PAA content)

and network density (in terms of PAA/PAAM ratio, defining the interlacing and hydrogen bond formation between them). Thus, for higher PAA content (when it was in an excess to PAAM), the VPM release was far from 100% - between 40 and 70% depending on the exact PAA amount⁸. Here, by studying the VPM transport in these IPN samples, we have found that the best performing for VPM sustained release PA19 defines VPM's anomalous diffusion in contrast to the VPM's Fickian diffusion observed for all other IPNs PAA/PAAM.

Thus it could be concluded that the diffusion of VPM in IPNs of PAA/PAAM changes from anomalous to Fickian as the IPN's composition changes, i.e. as PAA content increases and UCST decreases, due to the enhanced VPM-PAA interaction as well as to the IPN's inner structure's change.

Table 5 summarizes the results obtained by the Korsmeyer-Peppas model for the VPM's diffusion in the IPNs PMAA/PAAM. The dependences of the VPM's diffusion exponent **n** and diffusion coefficient **D** of on the IPN's composition are presented in Figures 7A and 7B.

For these IPNs, there is no clear dependence of the diffusion exponent **n** on the IPNs PMAA/PAAM composition. All of the **n** values are in the range of or below the Fickian diffusion, even the **n** value for PMA71, which also falls into the 95% confidential range as Fickian diffusion. The same lack of a clear trend for IPNs' composition dependence is observed for the VPM's diffusion coefficients (Figure 7B).

The non-clear trend of **n** and **D** as a function of the IPNs PMAA/PAAM composition could be related to the enhanced hydrophobicity of the PMAA as compared to PAA. Thus, besides the already discussed for the IPNs PAA/PAAM factors influencing the VPM diffusion, the hydrophobicity is an additional characteristics of the PMAA based IPNs. So many factors playing together and acting in different directions resulted into the described above loss of temperature sensitivity, continuous change in the pH dependence as well as in the lack of a clear **n** and **D** dependence on the IPNs' composition.

The very low **n** values (~ 0.2), observed for PMA39, PMA30 and PMA71, could be related to the VPM's subdiffusion in these IPN's samples. The subdiffusion is typically observed in e.g. living cells, where it is usually related to the following reasons: (a) geometrical obstructions, due to the molecular crowding; (b) delays, caused by the viscoelasticity of the media and (c) incidental trapping of molecules in possible binding places¹⁹. Subdiffusion has been reported for e.g. ibuprofen diffusion in cyclodextrine hydrogels. There, this subdiffusion mode was explained by the presence of nanopores, defined by the cyclodextrine²⁰.

In the case of IPN PMAA/PAAM, we have detected in a previous study small hydrophobic clusters formed by the PMAA chains²¹ evenly dispersed within the IPN. It is known from the literature that

the presence of filler particles in a polymer matrix retards the diffusion of small molecules into the polymeric composites. Similar is the behavior of the molecules diffusing in semi-crystalline polymers – the crystal domains are impervious to the penetrating in the polymer matrix molecules and the latter diffuse only in the amorphous regions. The hydrophobic regions in the polymers are also assumed to restrict the diffusive pathways²². Thus, the drug transport through media with complex structure is usually *not well described by the Fickian law*²³. In this way, the specific structure of IPNs PMAA/PAAM due to the hydrophobic PMAA cluster makes them a medium with obstacles, similar to the polymer composites and semi crystalline polymers. The small PMAA domains are less permeable to VPM molecules and hence the pathway of the drug molecules becomes more complicated. Therefore VPM diffuses through IPN PMAA/PAAM slower (i.e. subdiffusion takes place) as compared to the IPN PAA/PAAM due to the geometrical obstructions, formed by PMAA. Most of the IPNs PMAA/PAAM do not release the whole amount of the loaded VPM over the studied time period⁹ also partially due to the VPM subdiffusion.

In summary, both IPNs PAA/PAAM and PMAA/PAAM ensured the best VPM sustained release at compositions where the PAAM prevails^{8,9}. The reasons behind this best performance, however, are different according to our current study. For **IPNs PAA/PAAM**, the reason is the anomalous diffusion of VPM in the PA19 as compared to the Fickian diffusion observed for the others IPN PAA/PAAM compositions. For the **IPNs PMAA/PAAM**, the reason is the Fickian diffusion of VPM in PMA20 as compared to the trend for subdiffusion of VPM in the others IPN PMAA/PAAM.

The results obtained within the current study confirm and also explain the mechanism behind the best performing systems for sustained VPM release from both IPNs of PAA/PAAM and PMAA/PAAM. If one compares the best performing PAA/PAAM IPN and PMAA/PAAM IPN, it could be concluded that the anomalous diffusion of VPM in PA19 combined with its “smart” characteristics define better performance as VPM extended release vehicle as compared to PMA20.

CONCLUSIONS

The drug diffusion into IPNs of PAAM with poly (acrylic acid) and poly(methacrylic acid) is governed by the IPNs components nature as well as by the IPNs’ composition. The replacement of the hydrophilic PAA with the more hydrophobic PMAA resulted into a loss of the IPNs’ temperature sensitivity in the studied temperature region, change of the pH responsiveness mode and also into a loss of a clear diffusion exponent dependence on the IPNs’ composition. Thus, the appropriate choice of the IPNs’ components and composition could be used to finely tune their structure, properties and hence their characteristics as drug delivery systems.

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Table 1. IPNs PAA/PAAM with different composition, φ^{PAA} .

Sample	PAA	PA62	PA41	PA28	PA23	PA19	PAAM
φ^{PAA}	1	0.62	0.41	0.28	0.23	0.19	0

Table 2. IPNs PMAA/PAAm with different composition, ϕ^{PMAA} .

Sample	PMAA	PMA86	PMA71	PMA52	PMA39	PMA30	PMA26	PMA20	PAAM
ϕ^{PMAA}	1	0.86	0.71	0.52	0.39	0.30	0.26	0.20	0

Table 3. Diffusion exponent n value and the mode of diffusion in *cylindrical* sample¹³.

Diffusion exponent (n)	Diffusion mode
0.45	Fickian
$0.45 < n < 0.89$	Anomalous transport
0.89	Non-Fickian (Case II) transport

Table 4. VPM's diffusion characteristics in IPNs PAA/PAAM, according to the Korsmeyer-Peppas model.

Parameters	PAA ($\varphi^{\text{PAA}}=1$)	PA62 ($\varphi^{\text{PAA}}=0,62$)	PA41 ($\varphi^{\text{PAA}}=0,41$)	PA28 ($\varphi^{\text{PAA}}=0,28$)	PA23 ($\varphi^{\text{PAA}}=0,23$)	PA19 ($\varphi^{\text{PAA}}=0,19$)
K_{KP}	0.178±0.016	0.376±0.022	0.335±0.010	0.250±0.016	0.264±0.020	0.215±0.018
n	0.282±0.039	0.325±0.047	0.368±0.028	0.413±0.041	0.430±0.048	0.542±0.054
R^2	0.880	0.940	0.986	0.963	0.954	0.968
$D \text{ [m}^2/\text{s]}$	$7,43 \cdot 10^{-14}$	$3,2 \cdot 10^{-12}$	$5,46 \cdot 10^{-12}$	$5,6 \cdot 10^{-12}$	$8,3 \cdot 10^{-12}$	$2,1 \cdot 10^{-11}$

Table 5. VPM's transport characteristics in IPNs PMAA/PAAM, according to the Korsmeyer-Peppas model.

Parameters	PMAA ($\varphi^{\text{PMAA}}=1$)	PMA86 ($\varphi^{\text{PMAA}}=0,86$)	PMA71 ($\varphi^{\text{PMAA}}=0,71$)	PMA52 ($\varphi^{\text{PMAA}}=0,52$)	PMA39 ($\varphi^{\text{PMAA}}=0,39$)	PMA30 ($\varphi^{\text{PMAA}}=0,30$)	PMA26 ($\varphi^{\text{PMAA}}=0,26$)	PMA20 ($\varphi^{\text{PMAA}}=0,20$)	PAAM ($\varphi^{\text{PMAA}}=0$)
K_{kp}	0.263± 0.023	0.348± 0.036	0.314± 0.020	0.434	0.321± 0.019	0.381± 0.006	0.273± 0.006	0.282± 0.005	0.264± 0.013
n	0.376± 0.058	0.592± 0.118	0.215± 0.032	0.455	0.198± 0.030	0.144± 0.008	0.345± 0.014	0.382± 0.011	0.364± 0.029
R^2	0.912	0.948	0.875	-	0.873	0.981	0.992	0.997	0.972
$D \text{ [m}^2/\text{s]}$	$3,3 \cdot 10^{-12}$	$7,5 \cdot 10^{-11}$	$3,34 \cdot 10^{-14}$	$3,5 \cdot 10^{-11}$	$1,3 \cdot 10^{-14}$	$3,7 \cdot 10^{-16}$	$1,9 \cdot 10^{-12}$	$4,5 \cdot 10^{-12}$	$2,6 \cdot 10^{-12}$

Scheme 1. Hydrogen bonds between PAA and PAAM (A) and their disruption at (B) $T > UCST$ and (C) $pH > pK_a^{PAA}$.

Figure 1. ESR^{T^0C} dependence on temperature for IPNs PAA/PAAM.

Figure 2. Dependence of the UCST on the composition of IPNs PAA/PAAM.

Figure 3. ESR^{T^0C} of IPNs PAA/PAAM as a function of temperature.

Figure 4. ESR^{pH} as a function of pH for IPNs PAA/PAAM.

Figure 5. ESR^{pH} as a function of pH for IPNs PMAA/PAAM.

A

B

Figure 6. Diffusion exponent **n** (**A**) and diffusion coefficient **D** (**B**) of VPM, released from IPNs PAA/PAAM, as evaluated by the Korsmeyer-Peppas model.

A

B

Figure 7. Diffusion exponent (A) and diffusion coefficient (B) of VPM, released from IPNs PMAA/PAAM, as evaluated by the Korsmeyer-Peppas model.

REFERENCES AND NOTES

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- ¹ Q. Wang, S. Li, Z. Wang, H. Liu, C. Li; "Preparation and characterization of a positive thermoresponsive hydrogel for drug loading and release", *Journal of Applied Polymer Science*, **2009**, *111*, 1417–1425
 - ² D. E. Owens III, Y. Jian, J. E. Fang, Br. V. Slaughter, Yi-H. Chen, N. A. Peppas; *Macromolecules*, **2007**, *40*, 7306-7310
 - ³ P. Bouilliot, B. Vincent; "A comparison of the swelling behaviour of copolymer and interpenetrating network microgel particles", *Colloid and polymer science*, **2000**, *278* (1), 74-79
 - ⁴ Saruchi, B. S. Kaith, R. Jindal, V. Kumar, M. S. Bhatti; "Optimal response surface design of Gum tragacanth-based poly[(acrylic acid)-co-acrylamide] IPN hydrogel for the controlled release of the antihypertensive drug losartan potassium", *RSC Advances*, **2014**, *4* (75), 39822- 39829
 - ⁵ H. Katono, A. Maruyama, K. Sanui, T. Okano, Y. Sakurai; "Thermo-responsive swelling and drug release switching of interpenetrating polymer networks composed of poly(acrylamide-co-butyl methacrylate) and poly(acrylic acid)", *J. Controlled Release*, **1991**, *16*, 215–227
 - ⁶ H. Katono, K. Sanui, N. Ogata, T. Okano, Y. Sakurai; "Drug release OFF behavior and deswelling kinetics of thermo-responsive IPNs composed of poly(acrylamide-co-butyl methacrylate) and poly(acrylic acid)", *Polymer Journal* , **1991**, *23* (10), 1179-1189
 - ⁷ Q. Wang, S. Li, Z. Wang, H. Liu, C. Li; "Preparation and characterization of a positive thermoresponsive hydrogel for drug loading and release", *Journal of Applied Polymer Science*, **2009**, *111*, 1417–1425
 - ⁸ M. Simeonov, B. Kostova, E. Vassileva; „Interpenetrating Polymer Networks of Poly(Acrylic Acid) and Polyacrylamide for Sustained Verapamil Hydrochloride Release“, *Macromol. Symp.*, **2015**, *358*, 225–231
 - ⁹ M. Simeonov, B. Kostova, E.Vassileva, *Interpenetrating polymer networks of poly(methacrylic acid) and polyacrylamide: synthesis, characterization and potential application for sustained drug delivery*, *RSC Adv.*, **2016**, *6*, 64239-64246
 - ¹⁰ A. Pourjavadi, Gh. R. Mahdavinia; "Superabsorbency, pH-Sensitivity and Swelling Kinetics of Partially Hydrolyzed Chitosan-g poly(Acrylamide) Hydrogels", *Turk J Chem*, **2006**, *30*, 595 – 608
 - ¹¹ R.W. Korsmeyer, R. Gurny, E.M.Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 1983 *15*, 25–35

-
- ¹² P. Costa , J. M. S. Lobo, "Modeling and comparison of dissolution profiles", *Europ. J. Pharm. Sc.* **2001**, 13, 123–133
- ¹³ N. A. Peppas, J. J. Sahlin; "A simple equation for the description of solute release. III. Coupling of diffusion and relaxation", *International Journal of Pharmaceutics*, **1989**, 57, 169-172
- ¹⁴ "Preparation and Properties of Monodisperse Thermo-responsive Microgels" in Smart Hydrogel Functional Materials, L.-Y. Chu, R. Xie, X.-J. Ju, W. Wang, Chemical Industry Press, Beijing and Springer Berlin Heidelberg 2013
- ¹⁵ P. Bouillot, B. Vincent; "A comparison of the swelling behaviour of copolymer and interpenetrating network microgel particles", *Colloid and Polymer Science*, **2000**, 278 (1), 74-79
- ¹⁶ H. Feil, Y.H. Bae, S.W. Kim; "Mutual influence of pH and temperature on the swelling of ionizable and thermosensitive hydrogels", *Macromolecules*, **1992**, 25, 5528–5530
- ¹⁷ S. Hirotsu; "Coexistence of phases and the nature of first-order phase transition in poly(N-isopropylacrylamide) gels", *Adv. Polym. Sci.* , **1993**, 110, 1–26
- ¹⁸ N. A. Peppas, S. L. Wright "Drug diffusion and binding in ionizable interpenetrating networks from poly(vinyl alcohol) and poly(acrylic acid)" *Eur. J. Pharm.&Biopharm.* **46**, 15–29 (1998)
- ¹⁹ T. Miyaguchi, T. Akimoto „Intrinsic randomness of transport coefficient in subdiffusion with static disorder" *Physical Review E* 83, 031926 (2011)
- ²⁰ M. Ferro, F. Castiglione, C. Punta, L. Melone, W. Panzeri, B. Rossi, F. Trotta, A. Mele „Anomalous diffusion of Ibuprofen in cyclodextrin nanosponge hydrogels: an HRMAS NMR study" *Beilstein J. Org. Chem.* 2014, 10, 2715–2723
- ²¹ L. Ruiz-Perez, A. Pryke, M. Sommer, G. Battaglia, I. Soutar, L. Swanson, M. Geoghegan; *Macromolecules*, **2008**, 41, 2203
- ²² M. P. Mullarney, T. A.P. Seery, R.A. Weiss "Drug diffusion in hydrophobically modified N,N-dimethylacrylamide Hydrogels" *Polymer* 47 (2006) 3845–3855
- ²³ D. De Kee, Q. Liu, J. Hinestroza "Viscoelastic (Non-Fickian) Diffusion" *The Canadian Journal of Chemical Engineering* , 83, 913-929 (2005)