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Polymeric composite membranes for temperature and pH-responsive delivery of doxorubicin hydrochloride

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ABSTRACT:
Objective(s): Nowadays hydrogels are one of the upcoming classes of polymer-based controlled-release drug delivery systems. Temperature and pH-responsive delivery systems have drawn much attention because some diseases reveal themselves by a change in temperature and/or pH. The objective of this work is to prepare and characterize composite membrane using responsive nanoparticles into a polymer matrix.
Materials and Methods: These nanoparticles were made of the copolymer poly (N-isopropylacrylamide-co-methaçrylic acid) by an aqueous dispersion polymerization process and are responsible for dual sensitivity to temperature and pH. Morphology study with SEM, swelling behavior with Dynamic Light Scattering Technique, in vitro drug release behavior with side-by-side Diffusion Cells were also investigated in this paper. Doxorubicin hydrochloride was used as a model solute.
Results: The study on the release of doxorubicin hydrochloride showed that the release rate was higher at pH 5 than pH 7.4, increased with the increase of temperature. Nevertheless, ionic strength only poses a minor direct effect at higher pH.
Conclusion: Such system may be potentially used as a tumor-targeting doxorubicin hydrochloride delivery in the body.

Keywords: *Doxorubicin hydrochloride, Nanoparticles, N-isopropylacrylamide-co-methaçrylic acid, Temperature and pH-responsive delivery systems*

INTRODUCTION

Drug delivery systems are defined as mechanisms which mainly aim to transport therapeutic compounds to a specific site in the human body until it is no longer necessary.Throughout history, scientists have explored various controlled drug delivery systems, which can be broadly divided into three major eras: 1950-1970, which is the period of extended drug release and systems containing hydrophobic polymers; 1970-1990, during which zero-order release, drug targeting, and biotechnology were emphasized; and post 1990, when considerable efforts were expended in order to develop novel polymeric carriers, and biomacromolecule delivery systems [1]. Each era contributed to the devel-opment of appropriate drug delivery systems, however, the era of developing hydrogels was the most challenging one. The structural framework of hydrogel is formed from three-dimensional networks of randomly cross-linked polymeric chains [2]. The hydrogels undergoing swelling changes in response to environmental stimuli are called stimulus-responsive, smart, or intelligent hydrogels. These changes occur while the hydrogels are exposed to environmental changes such as pH, temperature, electric field, and other stimuli.Temperature and pH are the most widely-used triggering signals for modulated intelligent systems, since some diseases including cancer manifest themselves by a change in temperature and/or pH [3]. Poly(N-isopropylacrylamide) or PNIPA-Am hydrogels are quite useful for biomedical applications, since its lower critical solution temperature (LCST) (approximately 32°C) is very close to the body temperature (37°C), and therefore, it has been vastly studied. However, copolymerization of PNIPAAm with hydrophilic or hydrophobic monomers drastically changes its LCST [4]. The most commonly

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studied ionic polymer for pH-responsive behavior is poly (methacrylic acid) or PMAA, which is originated from carboxyl as an ionic pendant groups. In aqueous media, with the pH higher than the pK_a of the carboxylic group, the pendant groups ionize and develop fixed charges on the polymer network, generating electrostatic repulsive forces, responsible for pH-dependent swelling or de-swelling of the hydrogel [5].Main benefits of hydrogels include biocompatibility and biodegradability, while its major limitations are low mechanical strength and slow response to stimuli [6]. Bulk hydrogels have very low mechanical strength, therefore, in order to achieve a good mechanical strength and a fast response, grafted porous membranes were developed [7]. Yam et al. developed a polymeric composite membrane with temperature and pH sensitivity, by dispersing poly (NIPAAm-co-MAA) nan-oparticles (NPs) in a hydrophobic polymer. Solute permeability across this membrane increased with increasing temperature or decreasing pH, namely positive thermo-responsiveness or negative pH responsiveness [8]. In addition, the composite membrane systems showed fast swelling/shrinking properties in response to changes in temperature within a minute. In these systems, the increased permea-bility with increased temperature or lower pH was credited to the shrinkage of PNIPAAm or poly(NIPAAm-co-MAA) NPs [9]. Osada and Takeuchi proposed a novel mechanochemical polymeric membrane, based on the drastic conformational shri-nkage of poly(methacrylic acid) [10]. Hirokawa and Tanaka reported a sharp volume-phase transition in the non ionic N isopropylacrylamide gel [11]. Tsuji et al. synthesized a thermo-sensitive mem-brane, composed of n-isopropylacryamide, and elucidated the permeation mechanism of the membrane [12]. Coughlan et al. reported that the nature of a loaded drug, crosslinker concentration, and drug intera-ction with the polymer have significant effects on the rate of drug release from PNIPAAm gels [13, 14]. Jhon et al. found salt to lower the LCST, due to the Hofmeister effect of salt on the structure of water molecules [15]. Dinarvand et al. prepared a thermo-responsive membrane of P(NIPAAm–AAm). They found that the permeation of molecules increased with increasing temperature above the LCST of hydrogel [16]. Moreover, Zhang et al. prepared NPs of poly (N-isopropylacrylamide-co-metha-crylic acid) of various NIPAAm:MAA ratios, dispersed in a matrix of a hydrophobic polymer. They focused on the analysis of temperature and pH-responsive polymeric composite membranes (17). Permeability of the solutes across the membranes increased with increasing temperature or particle concentration, while it reduced with increasing pH and the molecular size of the solutes. In addition, membranes containing NPs of more NIPAAm units exhibited higher thermal sensitivity, and those with higher MAA content showed more pH responsiveness [8, 9, 17, 18].Important factors determining solute permeability and the swelling of NPs are pH, temperature, and ionic strength of the buffer species; as the ionic strength increases, the diameter decreases [19]. In the current study, we aimed to prepare an ethyl cellulose (EC) membrane, containing P(NIPPAM–MAA) NPs as a doxorubicin (DOX) delivery system. DOX is an anti-cancer drug, extensively used for the treatment of various malignancies, such as breast, lung, and ovary cancers, and soft tissue sarcoma. Considering the broad adverse effects of DOX, particularly the most serious and life-threatening ones, developing controlled release drugs and smart delivery systems, which target cancer cells, is desirable.

MATERIALS AND METHODS

In the present study, methacrylic acid (Aldrich, USA), N-isopropylacrylamide (Aldrich, USA), N,N-methylenebisacryl-amide (Aldrich, USA), sodium dodecyl sulfate (Mallinckrodt, USA), potassium persulfate (Aldrich, USA) and ethyl cellulose (viscosity of 45 cps, Dow Chemical Company, USA) were used as received. Also, doxorubicin hydrochloride was purchased from Sigma, USA.

Preparation of nanoparticles (NPs)

NPs, composed of NIPAAm and MAA, were prepared using the dispersion polymerization technique in an aqueous medium[9]. NIPAAm and MAA with a molar ratio of 1:1 and a monomer concentration of 135 mM were dispersed into the deionized water. The cross-linking agent, BIS (4.59 mM) and the surfactant SDS (0.4 mM) were added. The mixture was stirred at the rate of 200 rpm at 70 °C in a water bath, while it was being bubbled with nitrogen for about 30 min to remove the oxygen prior to copolymerization. The reaction was initiated by adding a concentrated solution of KPS (2.1 mM) to the mixture. Copolymerization was accomplished under a nitrogen blanket at 70 °C for 4 h with a constant stirring rate of 200 rpm. The NPs were entirely

purified using Sigma 12-kDa cut-off dialysis tubes against demineralized water for a week.

Design of experiment (DOE) and statistical analysis

Using a multi-level full factorial design, the effects of pH (3 levels), buffer ionic strength (2 levels), and temperature (2 levels) on the size and drug permeation coefficient (P_c) were evaluated. The factors and their levels are shown in table 1. Based on these factors and levels, a 12-run experimental design was applied using Minitab 14 software (Table II). The effects of factors on each experimental response (y) were analyzed and modeled, using a second order polynomial equation (equation 1):

$$y = c + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_1^2 + b_5x_2^2 + b_6x_3^2 + b_7x_1x_2 + b_8x_2x_3 + b_9x_1x_3 + b_{10}x_1x_2x_3$$

Models were simplified with a backward, stepwise linear regression technique; only significant terms were selected for the final model (P<0.05). Modeling was performed using SPSS *v*16.0, and related surface plots were obtained by Statgraphics (version X).

Table 1. Design summary

Factors	Levels		
	-1	0	+1
Temperature (°C)	25	-	37
pH	5	6	7.4
Ionic strength	0.05	-	0.15

Evaluation of the size of NPs

The effects of temperature (25 and 37 °C), pH (5, 6, and 7.4), and ionic strength (0.05 and 0.15 M) of the solvent on the mean diameter and size distribution of NPs were investigated using dynamic light scattering (DLS). The test was conducted using Malvern Zetasizer Nano ZS (Malvern Instruments Ltd., Malvern, UK), with a detection angle of 90° and at a wavelength of 633 nm.

Preparation of membranes

Membranes were fabricated using a casting method [20]. Briefly, the emulsion of NPs was dried in an oven at 50-60°C, and the obtained film was grinded by a mortar grinding machine.The NPs were dispersed in absolute ethanol (0.03 g/ml) and stirred at room temperature overnight.EC dispersion in ethanol (6% w/v) with a weight ratio of 1.5:1 (EC:NP) was added, and the mixture containing 0.75g solid material was cast onto a glass Petri dish on a Mylar sheet. The membranes were formed within a couple of days after incubation at 35°C. The thickness of the dried membranes was deter-mined using a vernier caliper as 60 µm.

Scanning Electron Microscopy (SEM)

The morphology of membranes, conta-ining NPs, was evaluated by a canning electron microscope (LEO-1350 VP, Germany).The freeze-dried samples were mounted on an aluminum base with an adhesive carbon tape, and coated with 2-5 nm gold under-vacuum for 5 minutes to prevent charging and distortion prior to capturing SEM images.

Drug permeation study

The permeability of DOX through the membrane was investigated using a horizontal side-by-side glass diffusion cell. The membrane was soaked into the buffers (phosphate buffer solutions (PBS) with various pH and ionic strengths), for about 24 hrs prior to the test. Afterwards, it was fixed between two cells of apparatus with a permeation area of 0.92 Cm^2 and chamber volume of 3.4 ml. The apparatus was coated with a water bath to set the temperature at 25 and 37°C. After leakage checking, the donor and receptor chambers were filled with DOX and drug-free solution, respectively, in PBS with various ionic strengths (0.05 M and 0.15M) and pH (5, 6, and 7.4). To provide the sink condition, the drug concentration in the donor cell was kept 100-fold more than the receptor. Also, to avoid boundary layer creation, the solution in each cell was stirred at 100 rpm. During each sampling time, an aliquot of 0.8 ml was taken out from the receptor cell and replaced by the same volume of fresh buffer. The amount of DOX in each sample was then detected using UV spectrophotometer at 232 nm. In order to plot the amounts of permeated drug vs. time, solute permeation was estimated based on Fick's first law of diffusion [21].

RESULTS AND DISCUSSION

A great deal of attention has been paid to smart drug delivery systems due to their special properties such as controlled drug release in response to environmental parameters including pH, temperature, specific molecules, electricity, and magnetism.

Considering the low pH and high temperature of cancerous tumors, these vehicles as targeted delivery systems, which release cytotoxic cargos to the tumor, have been heeded. In this study, we prepared a pH and temperature sensitive composite mem-brane, composed of NIPAAm-co-MAA NPs, incorporated into the EC polymer matrix.

Scanning Electron Microscopy (SEM)

The membrane containing NPs was prepared, and the membrane morphology of the surface and cross-section were investigated by SEM as shown in Fig. 1.The images clearly demonstrate that the particle clusters dispersed through the membrane, and formed water-rich channels. The cross-sectional images of the membrane, obtained by SEM (Fig. 1), confirmed the formation of a porous hydrogel matrix and the layers of accumulated NPs inhabiting it. The surface image indicated an integrated distribution of the NPs.

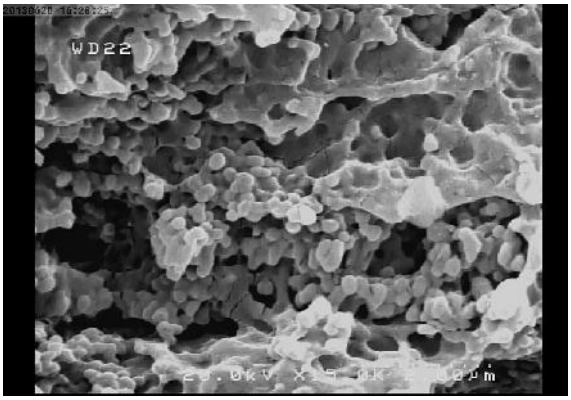
Effects of pH, temperature, and ionic strength on the size of NPs

The effects of temperature, buffer pH and ionic strength on the mean size of NPs are demonstrated in Table 2.Equation 2 is a mathematical model, obtained by the regression analysis of each response.

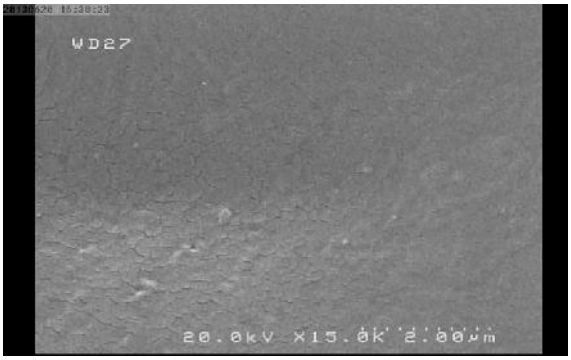
$$S = -2929.599 + 1102.739\,x_2 - 0.117\,x_1^2 - 81.351\,x_2^2 - 36.111\,x_1x_3 + 7.371\,x_1x_2x_3$$

R^2=0.999

How the variables affected the size of NPs is exhibited using surface plots in Fig. 2. All the three variables are present in the size equation; however, ionic strength only persists in an interaction with other factors. The maximum size is obtained around pH 7.4, and it seems acidic condition reduces the size of NPs. In addition, changing the temperature decreases the size of NPs to some extent; nevertheless, ionic strength only poses a minor direct effect at higher pH. The graphs in Fig. 2 demonstrate the effect and interaction of pH and temperature (a), ionic strength and pH (b), and ionic strength and temperature (c). According to the results, an increase in the particle size was observed in pH of >5 (Figs. 2, a and b). Considering the MAA pKa, which is about 5.3-5.7 [19], we assume that the ionization of carboxylic polymer moieties results in the destruction of the intermolecular hydrogen bond (between the hydrogen of MAA carboxylic group and the oxygen of NIPAAm carbonyl group), and increases the freedom of movement in molecules, resulting in water absorption into the NPs, followed by unfolding of the polymer and its swelling. It was also observed that the size of NPs changed by temperature (Figs. 2, a and c). The LCST of NIPAAm was about 32°C (22), however the block copolymer had a higher LCST, due to the carboxylic groups of MAA which add to its hydrophilicity [23, 24]. Below the LCST, the polymer posed hydrophilic properties, and water mole-cules were in hydrogen bonds with amine, hydroxyl and carboxylic moieties. By changing the temperature, hydrogen bonds were destroyed, the entropy of the system increased, and water molecules diffused out of the NPs.Consequently, the polymer chains touched each other and hydrophobic bonds were formed among them. Such swelling and shrinkage below and above the LCST, respectively, were verified by Dynamic Light Scattering (DLS).



A



B

Fig.1. Membrane cross section(A)and surface morphology (B)

Table 2. Design runs and results

Temp. (oC)	pH	Ionic strength	Size (nm)
37	5	0.05	392.4
25	5	0.15	484.3
37	5	0.15	393.4
25	6	0.05	700.5
37	6	0.05	607.7
37	7.4	0.05	655.5
25	5	0.05	475.2
25	7.4	0.15	763.4
25	7.4	0.05	724.4
37	6	0.15	640
25	6	0.15	720
37	7.4	0.15	723.6

Effects of variables on drug release through the membrane

DOX release through the membrane was Significantly higher at 37 °C, as shown in Fig. 3. The membrane also showed a pH responsive behavior. As illustrated in Fig. 4, the rate of permeation through the membrane was higher at pH 5.The amount of released drug was negligible at pH 6 and 7.4 until min 90, and just a small portion of the drug was permeated after about 8 h. The effects of different variables such as pH, ionic strength, and temperature on DOX permeability coefficients (P_c) through the membrane are shown in Table 3.Equation 3 is a mathematical model, obtained by the regre-ssion analysis of the permeation coefficient.

$$P_c = 3.093\times10^{-5} - 9.267\times10^{-6}x_2 + 4.260\times 10^{-9}x_1^2 + 7.728\times10^{-7}x_2^2 - 3.701\times10^{-8}x_1x_2$$

$$R^2=0.909$$

The process through which the variables affect P_c is demonstrated using the surface plots in Fig. 5. Although pH and temperature both affected the P_c, the effect of temperature was negligible, and had an interaction with pH. In other words, in an acidic condition, increasing the temperature elevates the P_c and when pH shifts to neutral, no change or a slight decrease in P_c is observed. pH noticeably affects the P_c, in fact, the least P_c was observed at pH 7.4; more pH reduction results in higher P_c.Similar to the DLS results, DOX perm-eation experiment confirmed the pH and thermo sensitivity of the membrane (Figs. 3-5); the results of permeation study were in an adequate correlation with the DLS results. The highest release rate was observed at pH 5, at which the NPs were not in a swollen shape. Although DOX (M.W. 580 g/mol) is not as high enough to inhibit the diffusion of drug through the membrane, it seems it cannot easily diffuse through the membrane while the NPs are swelled and the pores of membrane are closed; this is due to its long structure (Fig. 6) and molecular size (15.7 °A x 8.56 °A), determined by Chem Office software. By the shrinkage of NPs at pH 5, some pores emerged in the composite membrane and it facilitated the permeation of drug through the membrane.Regarding ionic molecules such as DOX, the electrostatic interaction with the membrane also plays an important role in drug permeation. The amine groups of DOX (pKa=8.2) ionize at neutral and acidic conditions. According to the pKa of copolymer carboxylic moieties [5.6]abovethe pH of 5.6, there is an electrostatic interaction with DOX ammonium, therefore the permeation of drug through the membrane significantly drops (25). On the other hand, below the pH of 5.6, the carboxylic moieties are protonated, and DOX easily releases through the membrane. Drug permeation through the membrane also depends on temperature. It was found that at body temperature, the rate of DOX permeation is not the same as the room temperature, but is meaningfully higher. We selected the same mechanism for this phenomenon, as discussed with regard to pH sensitivity. In fact, below the LCST, (the room temperature at which the NPs are in their swollen shape), the drug molecules cannot permeate through the composite membrane; however, above the LCST (e.g. 37 °C) due to the shrinking of NPs and emerging pores, the drug permeation increases [26]. In acidic conditions, carboxylic groups of MAA are protonated and hydrophobic interaction is the contributing factor for the hydrodynamic size of the NPs, so they are more sensitive to temperature [19]. Considering the extracellular acidic pH of tumors and their higher temperature, we suggest that the system is appropriate for targeted anticancer drug delivery. The effect of ionic strength on the hydrodynamic size of NPs participates in an interaction with pH and temperature. The most significant influence of ionic strength alteration is observed at neutral pH, at which the NPs are in maximum swollen state; however, at acidic pH, the NPs are in a shrunk state and there is no remarkable change in the size by ionic strength variations. Additionally, temperature and ionic strength interact with each other; in fact, at lower ionic strengths, the size reduction is more notable by increasing the temperature. These finding are in consistence with previous reported observations by Huang and Wu [19]. Since the prepared NPs possess polyelectrolyte properties, their hydrodynamic size depends on the ionic strength. By increasing the osmotic pressure, the diffusion of water molecules out of the NPs leads to their shrinkage. Nonetheless, the size at ionic strengths of 0.05 and

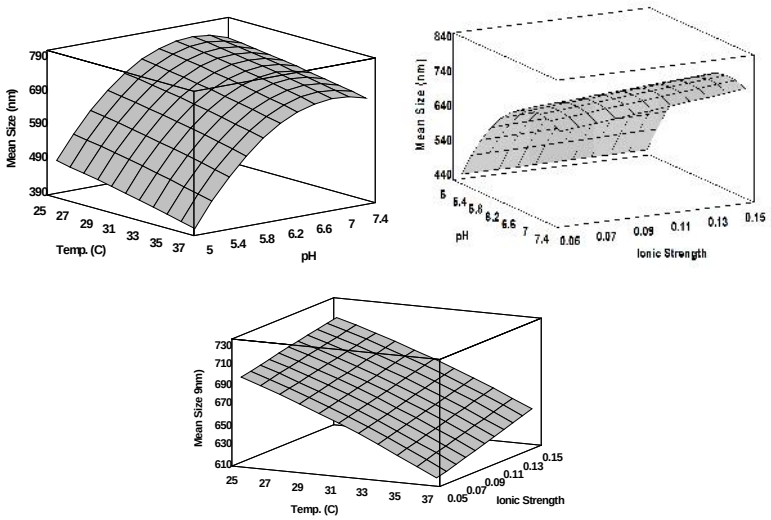


Fig. 2. Effects of pH, temperature (Temp.) and ionic strength on hydrodynamic size of nanoparticles

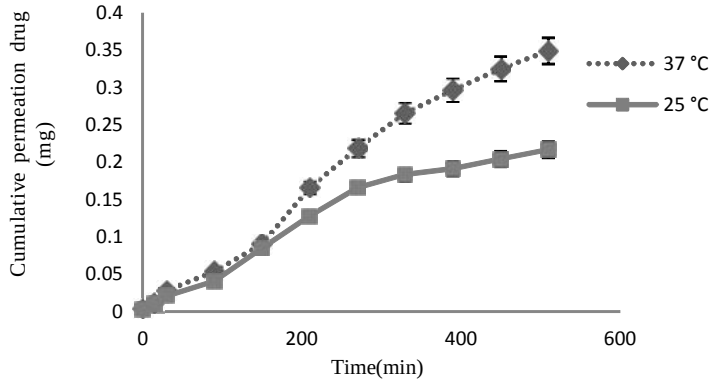


Fig. 3. Effect of temperature on DOX release through the membrane, at pH 5 and ionic strength 0.15 M

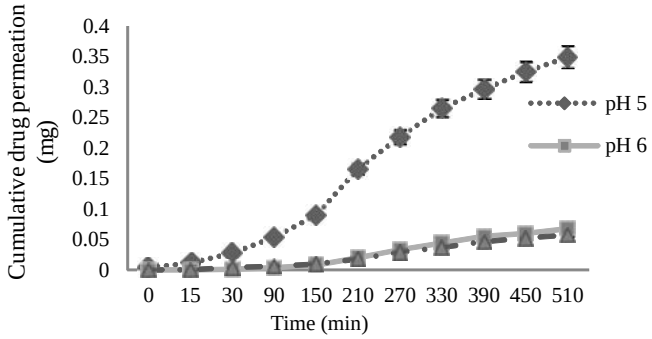


Fig. 4. Effect of pH on DOX release through the membrane. At temperature 37 ºC and ionic strength 0.15 M

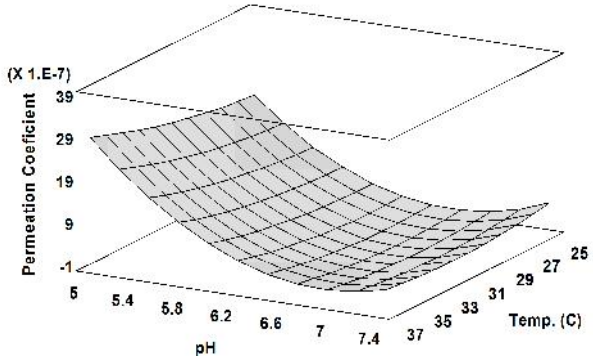


Fig. 5. Effects of pH and temperature on permeation coefficient

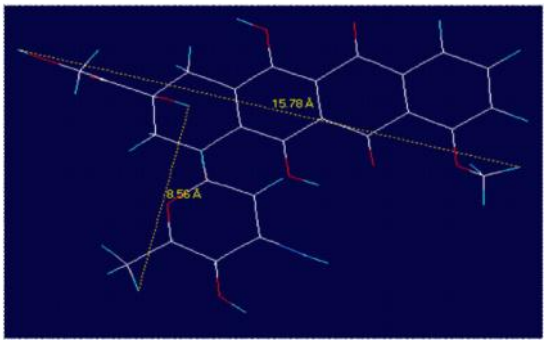


Fig. 6. The DOX structure and molecular size determined by Chem office software

Table 3. Design runs and results

Temp. (°C)	pH	Ionic strength (M)	P_c*10^7 (cm/s)±SD
37	5	0.05	32±9.60
25	5	0.15	16.03±2.85
37	5	0.15	25.7±5.55
25	6	0.05	4.88±0.60
37	6	0.05	5.94±0.90
37	7.4	0.05	4.98±0.15
25	5	0.05	20.49±3.75
25	7.4	0.15	3.82±0.01
25	7.4	0.05	4.14±0.15
37	6	0.15	5.09±0.30
25	6	0.15	4.46±0.30
37	7.4	0.15	4.14±0.15

0.15 M does not reduce. It was supposed that some of the water molecules, participating in stronger interactions with polymers, cannot leave the NPs even at higher osmotic pressure. On the other hand, increasing the ionic strength more than 0.05 M results in the migration of ions through the semi-permeable membrane into NPs. The result of this migration is achieving equilibrium between the two sides of the membrane. The next assumption is the absorption of water molecules from outer layers and their shrinkage, which results in closing water-passing pores. Therefore, the swelling ratio remains constant in the range of 0.05-0.15 M.In the current study, we did not study the effect of osmotic pressure higher than 0.15. However, as Huther et al. reported, we expected that a greater increase in osmotic pressure would finally lead to the departure of NP structure, and conse-quently an abrupt size reduction [27].

CONCLUSION

In this study, the composite membrane of NIPAAm-co-MAA NPs and EC was prepared, and DOX permeation was studied. The membrane showed sensitivity to environmental variables including pH and temperature. The drug permeability variation by pH and temperature is explained by the swelling and shrinking of NPs in response to the variables, and the electrostatic interaction between amine and carboxylic moieties of the drug and MAA, respectively. We suggest that this carrier may be potentially used as a tumor-targeting anticancer drug delivery in normal tissues.

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