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A Novel Composite Membrane for pH Responsive Permeation

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Abstract

Objective(s)
In this study, a kind of pH sensitive composite membrane was prepared and drug permeation through it was investigated in terms of pH. Rationale of this study originated from the fact that a pH change which may be a result of a disease state in the body can trigger drug release.
Materials and Methods
Here, a kind of pH sensitive composite membrane containing different nanoparticle [1:1 n-isopropyl acrylamide (Nipam): metacrylic acid (Maa)] contents in ethylcellulose was prepared by a casting method. Swelling ratios of these nanoparticles and composite membranes with different particle loadings were determined. Permeation of two different drug models with different hydrophilicity and molecular weights, vitamin B_{12} (vit B_{12}) and paracetamol, through these membranes was studied in terms of pH.
Results
It was seen that swelling ratios of nanoparticles and the composite membranes went up as the particle content increased at each pH. Vit B_{12} and paracetamol permeation through the membranes in pH value below the pKa was much higher than that at pHs above it, but this difference was much more pronounced for vit B_{12} compared to paracetamol.
Conclusion
Permeation through these membranes showed a sharp sensitivity to pH changes. Nanoparticles in the composite membranes could act as nanovalves due to their sharp swelling/shrinkage around the pKa of Maa. These membranes could be considered as an ideal stimuli-sensitive barrier for modulating drug release with a small change in pH.

Keywords: Composite membranes, Permeation, Nanoparticles, pH-sensitivity

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Introduction

Research into the area of controlled drug delivery has been focused on the development of systems which result in either zero order drug release or a drug release profile which is a simple function of time (1, 2). It has been recognized for some time, however, that this approach may not be appropriate for certain drugs and it has been suggested that therapeutic efficacy may be improved by the utilization of triggered, pulsed and programmed delivery systems (3). Physiological changes in the body may be utilized as potential triggers for controlled drug delivery. Based on these mechanisms, stimulus–responsive drug delivery systems have developed (4). This partly stems from the observation that several disease states manifest themselves by a change in the physiological parameters of the body, including temperature and pH (5). Tumor cells have been found to possess an intracellular pH differing from the extracellular one. The fabrication of such regulated systems requires the use of stimuli-sensitive materials (6, 7). Stimuli-sensitive materials are essentially hydrogels which can change their hydration and hydrophobicity in response to changes in an external stimulus (8-10). Hydrogels have found increasing applications in stimulus sensitive drug delivery. Many drug therapies which would benefit from a pulsatile delivery regimen involve the administration of peptide or protein drugs. These drugs are typically large compared to conventional ones and most are water soluble. Since most peptides and proteins are impermeable through dense polymers, the type of polymer commonly developed for peptide drug delivery is hydrogels (11). In addition to being permeable to large, water soluble species, the structure and physical properties of hydrogels, particularly polyelectrolyte gels, can also be altered via stimuli such as pH (12), ionic strength, electric field, electric current, temperature and chemical agents (13-17). To increase the response rate, micro- and nanoporous hydrogels have been developed to offer response rates several orders of magnitude higher than non porous gels. Size reduction is another approach to make a fast response (3). Hydrogels with a nanometer size could undergo volume change with a fraction of second upon exposure to a stimulus, because the time for polymer to diffuse is inversely proportional to square of dimension (16). In order to utilize the responsive properties of hydrogels while obtaining good mechanical strength and fast response, several systems have been designed including composite membranes. Turner *et al* prepared a composite – heterogeneous polyelectrolyte gel membranes consisting of polymethacrylic acid (PMAA) gel micro-particles dispersed within a polydimethylsiloxane network. It was found that PMAA gel particles swelled and deswelled in response to external changes similar to homogenous PMAA gels but in much higher level. This can be attributed to the fact that both hydration and percolation mechanisms in composite-heterogenous polyelectrolyte gel membranes have been demonstrated (13).

According to the previous studies, a heterogeneous composite membrane (HCM) containing both pH (Maa) and thermal (Nipam) sensitive segments with a mutual action to pH and temperature was prepared (4, 5). This novel membrane has a heterogeneous structure containing 1:1 Nipam: Maa nanoparticles dispersed in an inert hydrophobic media called ethylcellulose. The effect of different ratios of Nipam to Maa on its pH and temperature sensitivity had been studied before (5). It had been observed that the more Maa content was in the membrane, the better pH sensitivity was achieved; however these previous experiments had focused more on studying temperature sensitivity rather than pH sensitivity in terms of variations in media and ionic strength (4, 5, 18). In this study 1:1 Nipam: Maa nanoparticles, which had been observed to have the most pH sensitivity, were chosen to be studied. pH sensitivity of HCMs prepared from these nanoparticles to different drug models was examined. pH responsivity of different HCMs with different particle contents were also, studied and compared

together. As stimuli sensitive drug delivery is used more for peptid and protein delivery, vit B_{12} which is a good model of these therapeutic agents (due to its hydrophilic nature and high molecular weight) was used here as one of drug models (5,16). paracetamole as a hydrophobic and low molecular weight model was also used here in order to give some valuable information about the mechanisms involved in pH sensitivity of these HCMs.

Materials and Methods

Methacrylic acid (Aldrich, USA) was made inhibitor free by distillation. N-isopropylacrylamide (Nipam, Aldrich,) was purified by recrystallization from hexane and toluene. N,N-methylenebisacrylamide (Bis, Aldrich), sodium dodecyl sulfate (SDS, Mallinckrodt, USA), potassium persulfate (KPS, Aldrich) and ethylcellulose (viscosity 45, Dow Chemical Company, USA) were used as received. Vit B_{12} and paracetamol purchased from Sigma, USA.

Preparation of the HCMs

A solution casting method was employed for preparation of the HCMs. 1:1 Nipam:Maa nanoparticles were prepared according to a dispersion polymerization method described in the previous studies (5). A purified suspension of 1:1 Nipam:Maa nanoparticles in distillated water was dried in an oven at 50-60°C. It was further dried in a vacuum oven (Model 280, Fisher Scientific, USA) at room temperature for one day. Dried nanoparticles were dispersed with ethylcellulose in 100% ethanol. The ratio of nanoparticles to ethylcellulose varied to obtain different particle contents (i.e. 31, 35, 40% w/w). In a typical preparation, 0.31 g of dried nanoparticles and 0.69 g of ethylcellulose were mixed with 14 g of 100% ethanol. The mixture was cast inside a glass ring placed on a Mylar sheet and kept in desiccators until most solvent evaporated. The produced membrane rinsed with distillated water and stored there until usage. A dried membrane had a thickness around 0.12 mm.

Swelling studies

Swelling studies were done for both nanoparticles and HCMs (with different particle contents) in 0.15 M phosphate buffer solution (PBS) and 0.15 M citrate buffer solution (CBS) of different pHs (i.e. 5, 6, 7.4). Dynamic light scattering was conducted to determine the hydrodynamic size of nanoparticles. An aliquot of nanoparticles was transferred to a 6 × 50 mm disposable borosilicate glass culture tube (Kimble). The sample was then diluted with 0.15 M PBS and CBS of different pHs (i.e., 5, 6, and 7.4). These media were first filtered using a 0.22 μm syringe filter (Millex-GP) to eliminate dust particles. The hydrodynamic size of the particles was measured with a submicron particle size analyzer (NICOMP mode1 370) connected to a computer which correlates the light intensity with particle diameters. The data obtained were automatically fitted according to a gaussian distribution function. The intensity-weighed average diameters and their standard deviations were recorded as the results. Diameter of dried nanoparticles is measured by a modern Transmission Electron Microscopy (TEM) (Hitachi H-7000, Nissei Sangyo, USA). A dilute suspension of nanoparticles in distillated water was prepared. A 0.3 ml sample sandwiched between thin copper specimen carriers and frozen in slush nitrogen. The sample fractured in vacuum condition below -170°C by knocking the upper specimen carrier in a freeze-fracture apparatus (JFD-9010, JEOL Ltd., Tokyo, Japan). Particle size was determined according to the TEM images of dried nanoparticles. Swelling Ratio (SR) was determined by dividing the final swelled volume of nanoparticles by the dried one. SRs of HCMs with different nanoparticle contents were also determined by a gravimetric method.

As the molecules could hardly diffuse through the membranes with a particle concentration of lower that 20 wt% and the membranes with particle content of bigger than 40 wt% had low mechanical strength and got easily torn, 30-40 wt% was chosen as the best range of particle contents to be studied.

HCMs were soaked in each media for about 48 hrs and then at predetermined intervals, were taken out, padded and quickly weighed. Each measurement was repeated eight times for different samples. Average reported as the mean swollen weight of HCMs. Membranes were then taken out and dried in an oven at 50-60°C and then further dried in a vacuum oven (Model 280, Fisher Scientific, USA) at room temperature for one day, till to get a constant weight. The SRs of HCMs were determined by dividing the final swollen weight by the dried one (13):

SR_{HCM}= swelled HCM weight/dried HCM weight

Permeation studies

All permeation studies were carried out at 37 °C using a two-compartment, side-by-side glass diffusion cell with a water jacket (DC-100SC50, Crown Glass Co., UK). The temperature of the solution within the cells was controlled by connecting the cell jacket to a water bath (Haake Model D8). Vit B_{12} (MW=1355) and paracetamol (MW=158) with different molecular weights and hydrophobicity were used as model drugs in order to study the permeation mechanism better. The presoaked HCMs (for at least 24 hrs in PBS) were mounted between the two half cells and the whole assembly was held together with a clamp plus styrofoam between the cells and the clamp. The volume of each cell was 3.4 ml and the area for permeation measured 0.635 cm^2. After leakage checking, a medium and a stock drug solution of 5 mg/ml were introduced to the receptor and the donor cell, respectively, each containing a stirring bar for mixing. In order to meet the requirement of the reservoir-membrane model, the solute concentration in the donor cell was kept at least 100-fold greater than that in the receptor cell, during the entire experiment. A peristaltic pump (Masterflex @ Cole Parmer Instrument Co.) and Teflon tubing were used to transport solution out of the receiver compartment to a quartz flow-cell and then back to the receiver compartment. The concentration of drugs measured with a diode array spectrophotometer (Hewlett Packard Model 8452A). The wavelengths of measurement for vit B_{12} and paracetamol in 0.15 PBS were 361 nm and 243 nm, respectively. Solute permeability, P= DK/h; was calculated according to the following equation based on Fick's first law of diffusion with assumptions including: (1) steady state is reached in the membrane after a lag time, t_L; (2) the area for permeation, S, and solute concentration in the donor cell, Cd; are constant; (3) sink condition is maintained at the receptor side.

$$M_t = PSC_d (t - t_L)$$

Where M_t is the mass of a drug permeated till time t; P is the permeation coefficient of the drug; h is the thickness of the membrane. The *P* value was calculated from the slope of the curve of M_t vs. t at the steady state.

Results

Swelling Ratios of nanoparticles and HCMs with different particle contents

Figure 1 shows the TEM image of dried 1:1 Nipam: Maa nanoparticles. This image shows the nanoparticles are monodispersed and spherical, with their mean dried sizes about 170.48±7.72 nm.

Particle diameters, Size distributions and SRs of swollen 1:1 Nipam:Maa nanoparticles in 0.15 M, PBS and CBS at different pHs are summarized in Table 1.

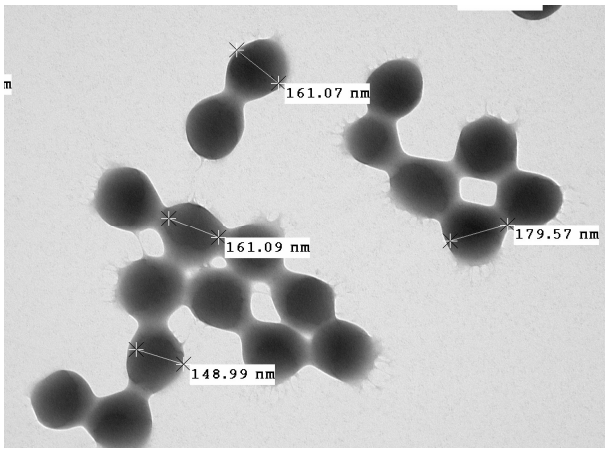

Figure 1. TEM images of dried 1:1 Nipam:Maa nanoparticles

Table 1. Diameters and SRs±standard deviations of nanoparticles in 0.15 M PBS and CBS of different pHs (n=3).

pH	Diameter in PBS±SD	SR in PBS	Diameter in CBS±SD	SR in CBS
5.00	303.90±31.64	5.61±0.57	319.07±56.12	6.48±0.11
6.00	486.83±114.41	23.06±0.44	471.87±160.24	21.00±1.28
7.40	513.40±80.84	27.05±0.01	497.60±120	24.63±5.43

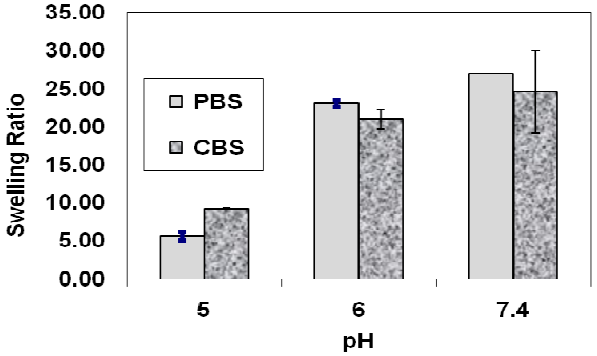

Figure 2. SRs of 1:1 Nipam:Maa nanoparticles at different pHs of PBS and CBS at 37°C (n=3).

As can be seen Figure 2, swelling ratios of nanoparticles jumped to several orders of magnitude with a small change in pH (from 5.61 at pH=5 to 23.06 at pH=6 for PBS and from 6.48 at pH=5 to 21.00 at pH=6 for CBS), whereas such a big change in swelling ratios and diameters in terms of pH was not observed with changing media from pH=6 to pH=7.4. This abrupt jump in SRs and diameters of nanoparticles with such a small change in pH was a result of ionization/deionization of the carboxylic acid groups in Maa segment of nanoparticles. Figure 3 indicated that diameters of 1:1 Nipam:Maa nanoparticles, correlated linearly to the concentration of H^+ in the media as ionization and deionization of carboxylic groups was the main mechanism of swelling and shrinkage in nanoparticles. This is so helpful because one can know the swelling degree of nanoparticles in each pH of PBS and CBS.

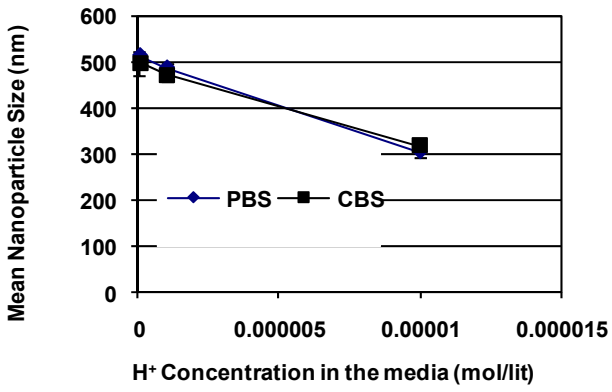

Figure 3. Relationship between nanoparticle diameters and H+ concentration in the media (n=3).

Figure 4 shows SRs of HCMs with 31, 35 and 40 wt% nanoparticle content in PBS of different pHs. It is clear that the SRs of HCMs increased as the particle content rose in both pHs. This could be easily attributed to an increase in hydrophilic part of HCMs versus hydrophobic part (ethylcellulose) as the particle content went up from 31 wt% to 40 wt%.

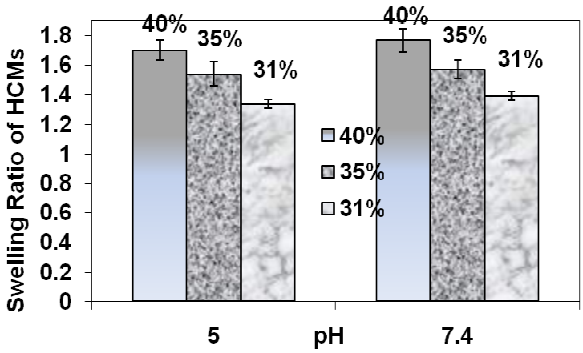

Figure 4. SRs of HCMs with different particle contents in terms of pH (n=8).

Figure 5 presents the correlation between particle content and SR which is linear and helped us to know the SRs of HCMs with knowing their particle content in each pH.

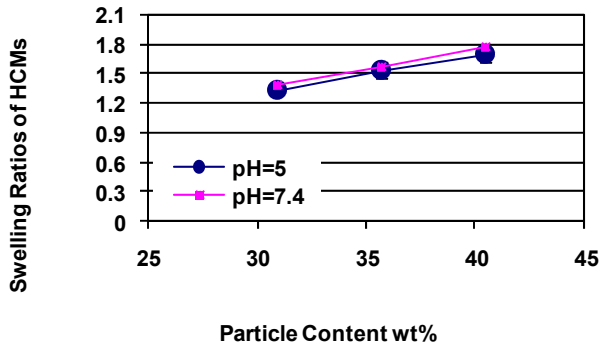

Figure 5. Relationship between SRs of HCMs and their particle content at different pHs of phosphate buffer solutions.

As illustrated by Figure. 4, for each amount of particle content; 31, 36 or 40 wt%, the swelling ratio of HCMs just varied a little in terms of pH change (for example; the SR of HCMs with 40 wt% nanoparticles changes from 1.77 at pH=7.4 to 1.70 at pH=5). Compared with the particles that their SRs decreased to several orders of magnitude

when pH varied from 7.4 to 5 (Figure 1), this change was considered insignificant.

In vitro permeation studies

Figure 6 shows permeation coefficients of vit B_{12} through HCMs containing different particle loadings in terms of pH. It was seen that vit B_{12} could hardly diffuse through HCMs with 31 and 36 wt% particle content at pH=7.4. Permeability remained undetectable for three days at this pH, while jumped to 1.56×10^{-6} cm/min at pH=5 for HCMs containing 31 wt % particles and to 1.89×10^{-6}cm/min at pH=5 for HCMs with 36 wt% particles. As pH increased from 5 to 7.4, the permeability of vit B_{12} through HCMs containing 40 wt% particles decreased from 2.84×10^{-6} to 1.18×10^{-7}. This could be easily attributed to the special heterogeneous structure of HCMs.

Figure 7 compares the permeation of two different drug models, paracetamol (MW=158) and vit B_{12} (MW=1355), through HCMs containing 35 wt% particles at different pHs. It was indicated that as pH increased from 5 to 7.4, the permeability of vit B_{12} through the HCMs decreased from 1.89×10^{-6} to an amount under detection limitation of the method, whereas the result of paracetamol permeation showed a much smaller and more incomplete on/off response through these HCMs when pH changed from 5 to 7.4.

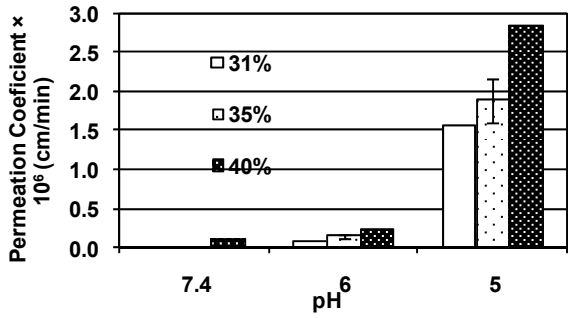

Figure 6. Permeability of vit B_{12} through HCMs with different particle content.

At pH=7.4, the swollen particles occupy the space and the pore size is minimal. Hence, the solutes mainly diffuse through the gel phase of the swollen nanoparticles. As the particles collapse at pH=5, the pores open up for solute to pass through.

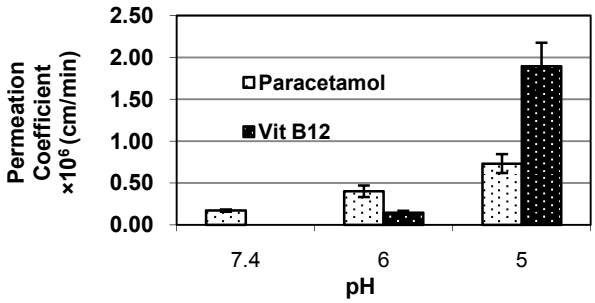

Figure 7. Permeability of vit B_{12} and paracetamol through HCMs with 35 wt% nanoparticles.

Discussion

Swelling Ratios of nanoparticles and HCMs with different particle contents

The TEM image of dried nanoparticles (Figure 1) showed that nanoparticles were so monodispersed. Unlike the emulsion polymerization process, which involves an initial reaction mixture consisting of two separate phases, the dispersion polymerization process employed here started with an initially homogenous solution of the reaction mixture. The particle formation was believed to be governed by a homogenous nucleation process, which could produce a very narrow particle size distribution provided that the particles had been formed very early in the polymerization process and subsequent growth had taken place without the formation of additional particles (18).

SRs of nanoparticles jumped to several orders of magnitude with a small change in pH around the pKa of Maa segment (Figure 2). At low pH, usually pH value less than 5.5, which was the pKa of methacrylic acid (Maa), the -COOH groups were not ionized and kept the Maa network at its collapsed state. At high pH values, the -COOH groups ionized, and the charged COO^- groups repeled each other, leading to an increase in the dynamic pressure and nanoparticle swelling. The similar results of swelling ratios in PBS (ionic strength=0.15) and CBS (ionic strength=0.15) showed that swelling phenomenon mainly governed by an alteration in pH and ionic

strength of media and did not affect by the kind of buffer utilized (P >0.05) (16).

Turner *et al* prepared a kind of heterogeneous composite membrane containing pMaa microspheres dispersed in a hydrophobic elastic poly di-methylsiloxane network. Their results showed that a change in pH from pH=5 to pH=7, caused an increase of about three folds in SRs of microspheres. This jump however, was not as much as the amount observed in our study. This might not only be attributed to a difference in polymerization variables but also, to the application of nanoparticles instead of microspheres in our study which made a more pronounced responses to stimuli compared to microparticles (13).

In another report, the effect of pH on thermally induced volume change of Nipam: Maa nanoparticles were studied. It was observed that the transition temperature of nanoparticles shifted to lower degrees when pH decreased. This attributed to an increase in shrinkage of nanoparticles (according to the above mechanism) in lower pH which shifted the phase transition temperature to the lower temperatures (18).

Comparing Figure 2 to Figure 4, one can see that all SRs of HCMs were much lower than those of nanoparticles at the same pH. This could be attributed to the fact that SRs of HCMs were calculated on the basis of weight according to the formula mentioned before. The presence of hydrophobic part (ethylcellulose) in HCMs, significantly reduced the number calculated from dividing swelled HCMs weights by dried ones, which exhibited SRs of membranes relative to SRs of the nanoparticles which have no hydrophobic part (13).

When pH changes from 7.4 to 5, nanoparticles entrapped within the HCMs were shrunken as a result of deionization of carboxylic groups inside the nanoparticles, subsequently water was squeezed from them (as a result of deswelling), but still was retained inside the porous matrix of HCMs. As SRs of HCMs calculated on the basis of weight, retention of the water inside the HCMs when pH changed from 7.4 to 5 caused no significant variation in weights and SRs of HCMs (13).

Such a result was also, indicated in a study done by Yam *et al*. They showed that the SRs of a composite membrane consist of 1:0.1 Nipam: Maa nanoparticles decreased with increasing temperature by a transition around phase transition temperature of nanoparticles. The change in the SR at the transition was less than 10 wt%. Such a small change in SRs was attributed to small portion (≈31wt %) and entrapment of the particles, as well as the retention of the water in the membranes at temperatures above the phase transition temperature (4, 5). Whereas in this study (as can be seen in Figure 3), such a small change in SRs in terms of pH was not only observed for the membranes with a low entrapment of nanoparticles (about 3.73% change in swelling ratio achieved for HCMs with 31 wt% particles when pH changed from 7.4 to 5) but also, was seen to the same value for the ones with high nanoparticle content (about 4.12 % change in SR achieved for HCMs with 40 wt% particles when pH changed from 7.4 to 5). As a conclusion, small changes in SRs of HCMs when pH changed from 7.4 to 5 could not be attributed to the amount of nanoparticle entrapment in the membranes and was only a result of retention of water within HCMs.

In vitro permeation studies

Permeation of vit B_{12} through HCMs at pHs below pKa was much larger than that at pHs above it. This could be the result of heterogeneous structure of HCMs.

Collapsed, dried nanoparticles dispersed in ethylcelluylose media inside the HCMs. When membranes were preparing, because of the difference in hydrophilicity between ethylcelllulose and nanoparticles, the particles tended to aggregate forming clusters resulting in uneven distribution. As the particle concentration increased, the aggregates became bigger. The clusters connected to one another, resulting in water - rich channels served as a primary route for solute diffusion wherase the ethylcellulose part was so dense that it was almost impermeable to drugs.

Then, the nanoparticles distributed throughout the polymer matrix acted as pore forming agents. These particles functioned as nanovalves that controlled the pore size by their volume change in terms of pH. This behavior was a result of ionization/deionization of the carboxylic acid groups in Maa segment of nanoparticles. At low pH, usually pH value less than 5.5, the -COOH groups were not ionized and kept the pMaa network at its collapsed state. At high pH values, the -COOH groups were ionized, and the charged COO^- groups repeled each other, leading to nanoparticles swelling.

When pH was below the pKa of COOH groups of nanoparticles, they were in collapse state, this made channels and pores opened inside the membranes and drug could easily diffuse through them. Above the pKa, nanoparticles were in swollen state and as a result, the pores blocked and drug could not diffuse (16).

It was seen that a complete, sharp and ideal on/off permeability ratio (pH/7.4/pH/5) achieved for vit B_{12} permeation through HCMs with 31 and 35 wt% particles content in terms of a small change in pH, whereas vit B_{12} permeation could be detected even in off condition (pH=7.4) of HCMs with 40% particle content. Turner *et al* indicated an on/off ratio of 7 for vit B_{12} permeation through composite membranes containing Maa microspheres dispersed in polydimethyl-siloxan when pH changed from 3 to 7. They also reported just an on/off response of 2 when vit B_{12} permeated through pMaa homogeneous membranes (13). This could easily show that making particles smaller to the size of nano not only made a faster response compared to the micro size and homogeneous hydrogel matrix (3) but also gave a better and more ideal on/off drug delivery.

In comparison with vit B_{12} permeation through HCMs containing 31 and 35% particles, the on/off response for 40% HCMs was not so complete. In the previous studies on temperature sensitivity of Nipam:Maa membranes containing 30-35 wt% particles it was shown that vit B_{12}, a big hydrophilic molecules, could just permeate through the water filled pores of the membranes and could not go through the gel phase of HCMs at all. Regarding this mechanism, at pH= 7.4 when nanoparticles were swelled and the pores were blocked, no vit B_{12} permeation should be detected. The results of vit B_{12} permeation through HCMS containing less than 40 wt % particle were consistent with this mechanism but according to the results obtained from permeation through HCMs containing 40 wt % particles, both gel phase and hydrophilic part of HCMs was now big enough to make an alternative rout for vit B_{12} (4).

Based on the previous experiments on vit B_{12} permeation through HCMs of different particle contents, it was seen that the percolation threshold for permeation through HCMs was about 20 wt% of dry particles. Vit B_{12} could hardly permeate through HCMs containing particles less than 20 wt % (16). This attributed to the low gel volume fraction of these HCMs resulting in little or no increase in gel particle connectivity, despite increase in gel particle medium. At particle loading more than 20 wt%, the gel particles were sufficiently close to one another. The swelling of particles which were initially isolated from each other led to the formation of new connections. This result showed that HCMs with 35 wt % of particles achieved or surpassed the percolation threshold and could be a good amount to achieve a desirable on/off response. Turner *et al* also, demonstrated the dependence of permeability on the dry gel content of composites prepared with pMaa microspheres dispersed in polydimethylsiloxan. They found that permeability increased as the hydrogel content increased, with large changes in permeability occurring in composites containing between 28 wt% and 33 wt% gel particle contents, and attributed this observation to the formation of mutual contacts between gel particles. This was in close agreement with results obtained in our study (13).

According to Figure 5, one could conclude that HCMs with 35 wt% particles content had the best on/off permeation ratio and was the

most ideal one for modulating drug delivery in order to get a pulsatile release.

Based on Figure 7, vit B_{12} permeation through HCMs showed a bigger and more complete response than paracetamol permeation.

There existed two possible pathways, 1) water-filled pores among the particles in a composite membrane, and 2) free spaces in the network of the nanoparticles. The former increased while the latter decreased as the particles shrinked. For small molecules that could diffuse through both pathways, the net change in permeability was small, due to off-set of the two pathways. For big molecules with MWs near a thousand to a few thousands like vit B_{12}, the space among the particles was the main pathway, because the networks in the cross-linked nanoparticles were rather tight for them, hence, the enlargement of the pores among the nanoparticles, due to collapse of the particles led to significant elevation of solute permeation upon exposure to a stimulus (16).

Conclusion

In this study, permeation of different drug models through a kind of pH sensitive composite membrane in terms of pH was examined. Composite membranes prepared by dispersing pH sensitive nanoparticles in an inert media. These pH sensitive nanopartices collapsed when pH decreased below the pKa of COOH groups and this made routes for drug to permeate. These membranes showed an ideal on/off response to pH changes, especially when big hydrophilic drug molecules were chosen as models.

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