

Novel Biphasic Hydrogels for Controlled Drug Delivery

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ABSTRACT

The current methods of drug delivery exhibit specific problems in designing a carrier for long-term release. Our aim is to fabricate biphasic hydrogels of predetermined molecular weights as carriers for long-term drug delivery. The rate of drug delivery will be controlled through a control of the morphology. To achieve this goal we have prepared biphasic hydrogels with HEMA segments, which are hydrophilic to impart hydrophilicity and desirable release characteristics, and nBMA hydrophobic segments to increase its mechanical strength.

The overall research goal of this paper was to develop a tunable novel biphasic hydrogel. To accomplish this goal, block polymers with a wide range of block lengths were synthesized with narrow molecular weight distribution using the RAFT (living free radical polymerization technique, and the morphologies correlated with their chain lengths. One of the goals of the research was to study the nanoscopic tuning of the interfacial energies between the blocks; this was achieved and is presented. Since our primary aim is to apply these polymeric films for controlled drug delivery, the transport of water by diffusion in the synthesized polymers was studied.

Keywords: biphasic hydrogels, nanoscopic tuning, living polymerization, RAFT, controlled drug delivery.

1 INTRODUCTION

Biphasic hydrogels are physically crosslinked hydrogels from amphiphilic block and graft copolymers able to self assemble in water. They are successfully used in controlled drug delivery due to their interfacial and transport properties. [1] The component with the lower surface energy is enriched at the air-polymer interface in order to minimize the magnitude of the interfacial energy. Pattern formation caused by instabilities in thin fluid layers has attracted considerable interest because of the technological importance of thin films and also

because these systems allow for the detection and measurement of interfacial forces.

Biphasic hydrogels are characterized by hydrophobic microdomains dispersed throughout and covalently bound to a hydrophilic polymer network. The chemical separation of compatible materials which are synthesized via living polymerization led to the fabrication of these highly blood compatible materials. Primary aims of this project is to provide fabrication of xerogels, with predetermined equilibrium water content values useful in drug delivery device, to design a drug delivery system capable of delivering drug over an extended period using biphasic hydrogels as control release material and Congo red as a model drug.

The device being non-degradable remains intact and is retrievable and is amenable to long term implantation since degradation products are not dispersed throughout the body and active compound is released in relatively controlled manner into the delivery environment. A series of xerogels with diblock polymers with HEMAMI and BMAMI were prepared with different compositions with BMA and HEMA, hydrated to their capacity and their equilibrium water contents are measured.

Sorption experiments are the simplest and commonest methods to investigate the diffusion characteristics. The diffusion coefficient and water content are determined.

1.1 Experimental procedure

There are several reports on the synthesis of controlled – structure HEMA-based (2-hydroxy ethyl methacrylate) block polymers via anionic polymerization chemistry, but this approach requires protection of the alcohol functionality. Beers et al [2-4] came out with the well controlled HEMA polymerization via ATRP (atom transfer radical polymerization) under mild conditions purification of the polymers and removal of the trace material of metal drawback in using ATRP method, Since our aim was to achieve one step strategy for the preparation of functionalized block copolymer of controlled molecular weight, we exploited the unique feature of living free radical procedure via RAFT [5,6](reversible addition fragmentation chain transfer). Preparation of low polydispersity block copolymers of predetermined molar mass containing nBMA (Butyl methacrylate) and HEMA units. Since our aim was to achieve

one-step strategy we exploited the unique feature of living radical polymerization via RAFT. Polymerization were carried out for nBMA MI and HEMA MI (MI refers to macroinitiator) to prepare nBMA MI-b-HEMA and HEMA MI-b-nBMA polymers using different solvents. The molecular weight increases linearly with conversion was observed with narrow molecular weight distribution.

1.2 Sample preparation

Physically cross-linked biphasic hydrogels were prepared by a living free radical polymerization via RAFT. In brief dry diblock copolymers prepared using HEMAMI, BMAMI were placed in petri dish and homogenized by manual mixing with solvents.

The Petri dish was then kept in an vacuum oven at room temperature so that the whole fluid converted into thick semi transparent mass. The dry gel so formed was dried so that it changed into thin film. The film was freed from the unreacted chemicals by equilibrating it with distilled water for a week and drying it at room temperature. The dry film was cut into pieces and stored under vacuum at 27 °C.

1.3 Swelling experiments

All chosen block polymers of specific chain lengths of required molecular weight and low polydispersity were taken for this analysis as in Table 1 and were characterized by their swelling behavior, because the degree of swelling can elucidate the effect of phase separation on the formed net work structure. Dynamic swelling measurements were done by gravimetric method. Dry film with fixed surface areas and thickness was weighed before being placed in vial containing distilled water. The vial was put into water at 37 °C. Swelled gels were periodically removed, quickly blotted of surface water using filter paper, weighed on an analytical balance (accuracy ±0.0002), and returned to the swelling medium. The swelling ratio was calculated from the equation.

$$\text{Swelling ratio} = \frac{\text{swollen weight of the sample}}{\text{dry weight of the sample}}$$

(1)

The water absorbed by the hydrated network is quantitatively represented by the equilibrium water content (EWC), the ratio of weight of water in the hydrogel to the weight of the hydrogel at equilibrium hydration as percentage.

1.4 Polymer Characterization

Number and weight average molecular weights, M_n and M_w , respectively, and molecular weight distribution, M_w

$/M_n$, were determined at 25 °C using gel permeation chromatography (GPC), with columns calibrated against linear polystyrene standards and N, N'-dimethylacetamide as eluent. GPC was used because this technique gives access to the number-average molar mass and to the molar mass distribution of a sample (polydispersity index, PDI). This last information is crucial to show control of the free radical polymerization. The number average molar mass M_n is defined as the sum of the products of the molar mass of each fraction multiplied by its mole fraction. The weight average molar mass M_w is the sum of the products of the molar mass of each fraction multiplied by its weight fraction. The ratio M_w/M_n represents the polydispersity index PDI of the sample. Polymer compositions were determined with ^{13}C , ^1H NMR and ATR-FTIR.

2. RESULTS

2.1 Analysis of dynamic sorption data

The phenomenon of water sorption by a hydrogel depends mechanistically on the diffusion of water molecules into the gel matrix and subsequent relaxation of macromolecular chains of the hydrogel⁹. Water transport mechanism in a swelling hydrogel is greatly contributed by numerous factors such as equilibrium water content, swelling arte, chemical composition of the system, etc. the dynamic water sorption experiment was performed and the data in terms of diffusion coefficient 'D' summarized in Table.1

Diffusion of water into the hydrogels has a Fickian character. This can be explained by the hydrophilicity of the polymer chains causing the diffusion to be concentration-dependent indicating that the hydrophilic hydroxyl groups which would slow the relaxation than does the size or bulkiness of the side groups which would slow the relaxation (swelling) rate of the hydrogel matrix creating a non-Fickian characteristic.

The nature of the curve indicating the water transport mechanism is Fickian type. i.e. diffusion controlled. Fitting the data to the Frisch equation determined that Fickian diffusion was taking place. As the HEMA composition in the polymers was reduced, the diffusion coefficients and EWC values also decreased.

F_{HEMA}	HEMAMI-b-BMA $D(\text{m}^2/\text{sec})$	BMAMI-b-HEMA $D(\text{m}^2/\text{sec})$
0.04		1×10^{-7}
0.05		4×10^{-7}
0.18		2×10^{-7}

0.50		1×10^{-7}
0.20	1.1×10^{-8}	
0.60	8.0×10^{-7}	
0.67	9.5×10^{-7}	
0.90	2.4×10^{-7}	
0.95	2.43×10^{-7}	

Table 1: Diffusion coefficient for distilled water in BMAMI-b-HEMA and HEMAMI-b- block polymers

Figure 1a, 1b: Water uptake measurements

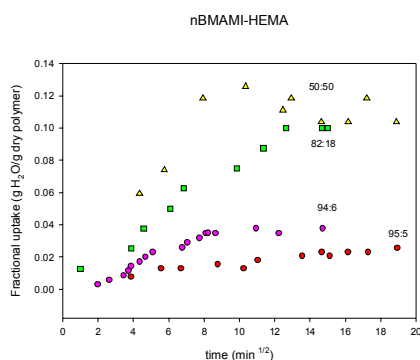
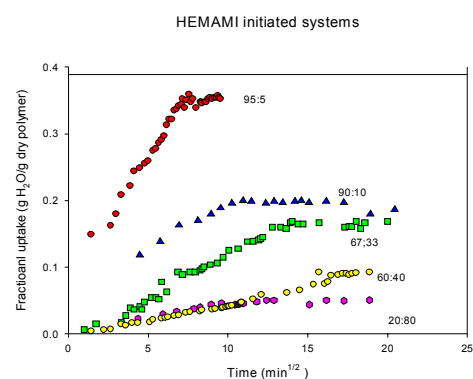
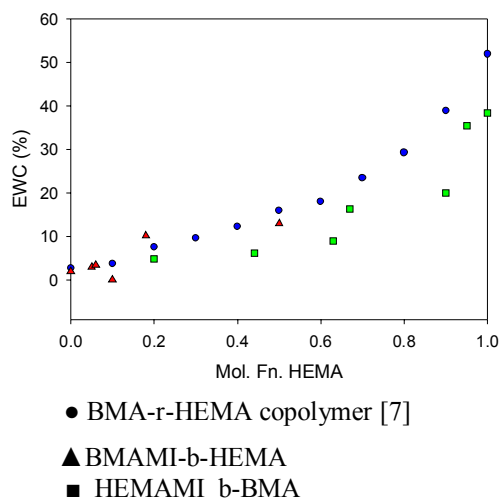


Figure 2: EWC with Mol.Fn HEMA



2.2 Effect of hydrophilic block in chain length

Non- cross-linked hydrophilic homopolymers would be expected to have large pore size and greatest ability to swell, but ultimately, may tend to dissolve. The addition of hydrophobic monomer to would limit the swellability there by limiting the expansion of the interstitial space. When the chain length of PHEMA is increased in the reaction mixture from 0-1 a constant increase in the swelling ratio is found as shown in fig.

The observed large swelling ratio can be explained by the fact that increased PHEMA content in their hydrogel renders the network more hydrophilic such that when the polymer matrix contacts the dissolution medium, the molecules of water penetrates the gel and swells the macromolecular chains. Molecularly, individual chains originally found in the unperturbed state, absorb water so that their end-to-end distance and radius of gyration expand to the new solvated state.

2.3 Effect of the hydrophobic block in the biphasic hydrogel

Mechanical properties of these biphasic hydrogels are very important for pharmaceutical application. A drug delivery system designed to protect a sensitive therapeutic agent until it is released out of the system. Factors affecting the swelling of the physically crosslinked hydrogels The chemical structure of the diblock polymer may also affect the swelling ratio of the hydrogels. Theses biphasic hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus minimising their exposure to the water molecule. As a result, the hydrogels will swell much less compared to the one containing hydrophilic groups. Hence, there

is an optimum length of hydrophobic polymer segment is required to achieve a relatively strong and yet elastic hydrogel. Copolymerizations has been utilized to achieve the desired mechanical properties of hydrogels Incorporating a comonomer that will contribute to H-bonding can increase the strength of these hydrogels. The effect of hydrophobic commoner on water-sorption capacity of hydrogel has been studied by varying the BMA in the range of 0.5-0.95. The results are shown in Figure: 2, where the EWC of the blok copolymers being compated with the Crandom copolymers [7] Which clearly indicate the increasing concentration of hydrophobic monomer ratio results in a substantial fall in the swelling ratio of the hydrogel which may be explained by the fact that an increasing concentration of BMA results in a reduction in mesh size of voids available between the net work chains. This obviously leads to a slow diffusion of water molecules into the network and restricted relaxation of the network chains resulting in a fall in the water sorption capacity of the network. With increasing BMA content results in a slow relaxation and gives rise to a lower water sorption of the hydrogel.

CONCLUSION

In this study, (Poly (2-hydroxyethyl methacrylate-b-butyl methacrylate), and Poly (butyl methacrylate-b-hydroxyethyl methacrylate) hydrogel were prepared by living free radical Polymerization via RAFT. These biphasic hydrogel were prepared in water and swollen to equilibrium in water. Equilibrium swelling values were used for the determination of diffusional behavior of water of the hydrogel systems.

From the above study the following conclusions may be drawn,

The water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion controlled.

With increase in Hydrophilic composition in the biphasic hydrogel the swelling ratio was increased

Of the two macroinitiator initiated hydrogel i.e, nBMAMI, and HEMAMI, the latter seems to have more swelling than the former.

Results reveal that diblock polymeric hydrogels with tailored water uptake was achieved with balanced hydrophobicity /hydrophilicity.

REFERENCES

- [1] Okano, T.,; Aoyagi, T.; Kattaoka, K.; Park, K.D.; Nakahama, S.; Suzuki, K.; Kim .S.W. *Transaction* **1987**, *33*, 596.
- [2] Matyjaszewski, K. *Macromol Symp* **2000**, *152*, 29.
- [3] Matyjaszewski, K. *Advances in Controlled/Living Radical Polymerization*; Oxford University Press: Portland, 2003.
- [4] Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev* **2001**, *101*, 3689
- [5] Moad, G.; Chiefari, J.; Chong, Y. K.; Krstina, J.; Mayadunne, R. T. A.; Postma, A.; Rizzardo, E.; Thang, S. H. *Polym. Int* **2000**, *49*, 993.
- [6] Rizzardo, E.; Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, G.; Thang, S. H. *Macromol. Symp* **1999**, *143*, 291.
- [7] Hill, D. J. T., ; Moss, N.G.; Pomery, P.J.; Whittaker, A.K. *Polymer* **1999**, *41*, 1287.