Development of a Statistical Model for the Formation of Poly [Acryloyl Hydroxyethyl Starch] Microspheres

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Purpose. To develop a mathematical model for predicting the molecular weight between crosslinks, Mc, of poly[Acryloyl Hydroxyethyl Starch] (Ac-HES) microspheres system and to identify and evaluate the key microsphere preparation parameters which affect the Mc of the formed microsphere structure based on the developed model.
Methods. Link probability generating functions (LPGFs) based on the classical branching theory were used to derive a model for the calculation of Mc for the Ac-HES system. Based on the developed model, simulation was made to study the effects of the microsphere preparation variables on Mc of the formed microspheres. The process variables were the degree of derivatization (DD) of the Ac-HES, the molar ratio (MR) of the Ac-HES to acrylamide monomer, the fractional conversion of the unsaturation (α), the initiator efficiency (f), the molar concentration of initiator (I), the fraction of intramolecular cyclization (c), and the total weight of the reactable monomer and polymer (s).
Results. A model to describe the crosslinking reaction of Ac-HES system and predict Mc was developed. Simulation based on the model showed that Mc decreased as α increased and reached a limiting value before total conversion. At constant α, Mc initially decreased with MR to a minimum and then increased with MR; while Mc decreased monotonically with DD. I and c affected Mc only at very low α and changes in s and f had no effect on Mc.
Conclusions. Simulation based on the model suggested that the most important microsphere preparation parameters influencing Mc of the Ac-HES system are the number of functional groups on the Ac-HES (DD) and the stoichiometry (MR) of the crosslinking reaction.

KEY WORDS: poly(Acryloyl Hydroxyethyl Starch) microspheres; molecular weight between crosslinks (Mc); degree of derivatization (DD); molar ratio (MR); link probability generating function (LPGF).

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ABBREVIATIONS: Ac-HES, (poly) Acryloyl Hydroxyethyl Starch; EANC, Elastically Active Network Chains; HES, Hydroxyethyl Starch; LPGFs, Link Probability Generating Functions; lmMc, Line of minimum Mc; MRmMc, MR at minimum Mc.

SYMBOLS: α, fractional conversion of unsaturation; θ_1, dummy variable for a bond with Ac-NH_2 unit; θ_2, dummy variable for a bond with Ac-HES unit; ρ, fraction of initial unsaturation contributed by Ac-HES; c, fraction of intramolecular cyclization; DD, degree of derivatization; f, initiator efficiency; h, number of double bonds in Ac-HES molecule; [I], molar concentration of initiator; k_d, decomposition rate constant of initiator; k_p, propagation rate constant of monomer; [M], concentration of monomer; M, average molecular weight of the reaction system; Mc, molecular weight between crosslinks; MR, molar ratio of Ac-HES polymer to acrylamide monomer; n, mole fraction of reaction components; p, probability of a radical to add one more unit before termination; s, total weight of reactable polymer and monomer per 100 ml; T, probability generating function describing the distribution of monomer units with bonds leading to gel; v, extinction probability describing the probability that a bond has no continuation to the infinite network.

INTRODUCTION

Poly [Acryloyl hydroxyethyl starch] (Ac-HES) microspheres and several polymeric systems (1–3) have been designed for drug delivery applications. These systems are commonly formed by the polymerization reaction of a monovinyl monomer with a multivinyl polymer, a reaction system complicated due to the multitude of parameters that could affect the final properties of the formed polymer. The concentration of initiator and monomer, the molar ratio (MR) of multivinyl polymer to monomer, the degree of derivatization (DD) of the multivinyl polymer, and the reaction temperature are important variables in the process.

Several theories based on polymerization reaction kinetics have been developed to describe the crosslinking reaction and to predict the structural properties of formed polymers (4–12). For example, Miller and Macosko (4) derived finite chain probabilities as a function of the extent of reaction from which post gel properties including Mc, the molecular weight between crosslinks, were estimated using a simple recursive method. Mikos *et al.* (5), developed a kinetic model for the free-radical polymerization/crosslinking of a monovinyl-divinyl monomer system which described the kinetics in terms of the concentrations of the monovinyl, divinyl, and pendent vinyl species. Post gel properties such as Mc were calculated from the moments of the molecular weight distribution of the crosslinked copolymer. Mikos and Peppas (6) later applied this model to the formation of ethylene glycol dimethacrylate (EGDMA) crosslinked to poly [2-hydroxyethylmethacrylate] (PHEMA) microparticles produced by suspension polymerization. Miller (7) presented computational formulae and included a simple FORTRAN program for the calculation of network parameters such as gel point, weight fraction soluble, weight fraction pendent, weight fraction effective, etc., for the crosslinking of polymeric chains with length and site distribution. Scranton and Peppas (8), applying the original classical theory of probability generating functions of Gordon *et al.* (9–11), in combination with the treatment of the number of elastically active network chains (EANC) by Dusek (12), derived a statistical model for the free-radical copolymerization and crosslinking of the HEMA-EGDMA (2-hydroxyethylmethacrylate and ethylene glycol dimethacrylate) system.

None of these existing models, however, apply to systems which simultaneously involve the chain polymerization and crosslinking between a monovinyl monomer and multivinyl polymer and therefore, are not directly applicable to the Ac-HES reaction system. The purpose of this work was to develop a mathematical model to predict the Mc of the microsphere network that is considered to be crucial in regulating the release of bioactive agents and to identify and evaluate the key microsphere preparation parameters which affect the Mc of the formed microspheres. This model was developed based on that described by Scranton and Peppas (8).

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METHODS

The preparation method for the Ac-HES system was that described in detail by Rypacek and DeLuca (1). Briefly, the linear chain of the precursor, HES, was derivatized by attaching double bonds at the hydroxyl groups on the glucose units. The ratio of the number of double bonds attached per glucose unit was defined as the degree of derivatization. The Ac-HES thus obtained was reacted with acrylamide in aqueous solution via free radical polymerization. The system is similar to that of a copolymerization between a vinyl monomer and divinyl crosslinking agent with exception that a multivinyl macromolecule, Ac-HES, is copolymerized with a vinyl monomer. Thus, to develop a mathematical model for predicting the structure of Ac-HES microspheres, the technique which Scranton and Peppas (8) used to derive a model for the copolymerization of monovinyl monomer with divinyl crosslinking agent was followed.

The derivation starts with the formulation of link probability generating functions (LPGFs) based on the classical branching theory of Gordon *et al.* (9), followed by various mathematical operations to generate a final working equation for the calculation of Mc of the crosslinked structure. The development of LPGFs from the original branching theory arose from the need to estimate the structural properties of the random crosslinking or vulcanization of liner chain polymers. Therefore, it should be applicable to the Ac-HES system which also involves a crosslinking reaction of linear chains of large molecules.

The link probability generating functions are the probability of the number and distribution of bonds generated by the monomer units; a summation of all the possible bonded states. A monomer unit before participating in reaction is labeled as being the zeroth topological generation. Any monomer unit directly bonded to this unit is in the first topological generation, and so on. The link probability generating function, $\mathbf{F}_0(\theta)$, describes the distribution of bonds between the zeroth and first generations, and the generating function $\mathbf{F}(\theta)$, describes the distribution of bonds for all other generations. The bold-face letter represents the vectorial form of the function in which the number of the function is dependent on the number of components involved in the reaction.

Derivation of the Mathematical Model

The LPGFs

For the copolymerization of a 2 functional monomer(i.e. one vinyl group) (type 1) and x functional monomer (i.e., more than two vinyl groups) (type 2), Gordon *et al.* (9), gave the LPGF as follows:

for zeroth generation,

$$F_{01}(\theta) = [1 - p + p(1 - \rho)\theta_1 + p\rho\theta_2]^2 \quad (1)$$

$$F_{02}(\theta) = [1 - p + p(1 - \rho)\theta_1 + p\rho\theta_2]^x \quad (2)$$

and for all generations higher than the zeroth,

$$F_{11}(\theta) = 1 - p + p(1 - \rho)\theta_1 + p\rho\theta_2 \quad (3)$$

$$F_{12}(\theta) = [1 - p + p(1 - \rho)\theta_1 + p\rho\theta_2]^{x-1} \quad (4)$$

where p denotes the probability that a radical will add at least one more unit before termination. Mathematically, it is the ratio of the steady-state propagation rate to the sum of the steady-state propagation and termination rates (10). ρ is the fraction of the initial unsaturation belonging to the type 2 unit (here Ac-HES), θ_1 is the dummy variable for a bond with an Ac-NH_2 unit, and θ_2 is that for a bond with an Ac-HES unit.

After inserting the parameters of fractional conversion of the unsaturation, α (10), and fraction of the growing chains that form intramolecular cyclization, c (8), equations 1–4 were modified:

$$F_{01}(\theta) = 1 - \alpha + \alpha\{(1 - p) + p[(1 - \rho)\theta_1 + \rho(1 - c)\theta_2 + \rho c]\}^2 \quad (5)$$

$$F_{02}(\theta) = [F_{01}(\theta)]^h \quad (6)$$

$$F_{11}(\theta) = 1 - p + p[(1 - \rho)\theta_1 + \rho(1 - c)\theta_2 + \rho c] \quad (7)$$

$$F_{12}(\theta) = F_{11}(\theta)[F_{01}(\theta)]^{h-1} \quad (8)$$

h is the number of double bonds in the Ac-HES molecule and is equal to x/2 since every double bond accounts for 2 functionalities.

It should be noted that use of these LPGFs assumes the following for the polymerization/crosslinking reactions (8,9): 1. All double bonds in the system have the same reactivity irrespective of the size or shape of molecules. 2. The double bonds of the crosslinking agent react independently. 3. The number of chains still propagating is negligible compared to the number of dead chains. 4. The termination step of the reaction occurs by disproportionation. A further assumption is that the molecular weight distribution of Ac-HES is monodispersed.

The LPGFs obtained from equation 5–8 can be used in combination with the general equations developed by Gordon *et al.* (9,10), to derive expressions for many structural averages including the critical conversion for gelation, the number and weight average molecular weights, the sol and gel weight fractions, the number of EANC, and the Mc for the reaction system of Ac-HES and Ac-NH_2. For the purpose of studying the crosslinked structure, i.e., the post-gel properties, only the expressions of EANC and Mc were required.

Calculation of Mc

The Mc for a crosslinked structure of polymer is:

$$Mc = \{0.5n_1T_1''(0) + n_2[T_2'(1) - T_2'(0) - 0.5T_2''(0)]\}M/Ne \quad (9)$$

where,

M	is the average molecular weight of the system
n	is the mole fraction
1, 2	denotes acrylamide and Ac-HES, respectively
T	is the probability generating function that describes the distribution of monomer units with bonds leading to the gel
Ne	is the number of EANC per mole of crosslinking agent
′,″	denote first and second derivatives

The average molecular weight of the system, M, can be written as:

$$M = \frac{n_1M_1 + n_2M_2}{n_1 + n_2} \quad (10)$$

T is mathematically expressed as (12):

$$\mathbf{T}(\theta) = [T_1(\theta), T_2(\theta)] = \mathbf{F}_0(\mathbf{v} + (1 - \mathbf{v})\theta) \quad (11)$$

The bold-face parameters designate the vectorial form of the functions. Therefore, equation 11 is in essence equal to the following two equations,

$$T_1(\theta) = F_{01}\{v_1 + (1 - v_1)\theta_1, v_2 + (1 - v_2)\theta_2\} \quad (12)$$

and

$$T_2(\theta) = F_{02}\{v_1 + (1 - v_1)\theta_1, v_2 + (1 - v_2)\theta_2\} \quad (13)$$

which correspond to the replacement of θ_1 and θ_2 in equations 5 and 6 with $v_1 + (1 - v_1)\theta_1$ and $v_2 + (1 - v_2)\theta_2$. v_1 and v_2 are extinction probabilities. They represent the probability that a bond has no continuation to the infinite network (8,13,14). Mathematically, they are the smallest positive roots of the following coupled equations.

$$v_1 = F_{11}(\mathbf{v}) = 1 - p + p[(1 - \rho)v_1 + \rho(1 - c)v_2 + \rho c] \quad (14)$$

$$v_2 = F_{12}(\mathbf{v}) = F_{11}(\mathbf{v})[F_{01}(\mathbf{v})]^{h-1} \quad (15)$$

Ne, the number of EANC per mole of crosslinking agent, was given by Dusek (12) and Scranton (8) as,

$$Ne = [T_2'(1) - T_2'(0) - T_2''(0)]/2 \quad (16)$$

From equations 12 and 13, the derivatives of $\mathbf{T}(\theta)$ can be written:

$$T_2'(1) = 2h\alpha p[(1 - \rho)(1 - v_1) + \rho(1 - c)(1 - v_2)] \quad (17)$$

$$\begin{aligned} T_2'(0) = h[1 - \alpha + \alpha\{(1 - p) \\ + p[(1 - \rho)v_1 + \rho(1 - c)v_2 + \rho c]\}^2]^{h-1} \\ \times 2\alpha p\{(1 - p) + p[(1 - \rho)v_1 + \rho(1 - c)v_2 + \rho c]\} \\ \times \{(1 - \rho)(1 - v_1) + \rho(1 - c)(1 - v_2)\} \end{aligned} \quad (18)$$

$$T_2''(0) = h[T_1(0)]^{h-1}T_1''(0) + T_1'(0)h\{(h - 1)[T_1(0)]^{h-2}T_1'(0)\} \quad (19)$$

where,

$$\begin{aligned} T_1(0) = 1 - \alpha + \alpha\{(1 - p) + p[(1 - \rho)v_1 \\ + \rho(1 - c)v_2 + \rho c]\}^2 \end{aligned} \quad (20)$$

$$\begin{aligned} T_1'(0) = 2\alpha p\{(1 - p) + p[(1 - \rho)v_1 + \rho(1 - c)v_2 + \rho c]\} \\ \times \{(1 - \rho)(1 - v_1) + \rho(1 - c)(1 - v_2)\} \end{aligned} \quad (21)$$

and

$$T_1''(0) = 2\alpha p^2\{(1 - \rho)(1 - v_1) + \rho(1 - c)(1 - v_2)\}^2 \quad (22)$$

Therefore, logically, the calculation of Mc can be made by first solving equations 14 and 15 to obtain v_1 and v_2. From these values, various derivatives of T's can be evaluated from equations 17 to 22. The calculated T values are then substituted into equation 16 to obtain Ne, and finally into equation 9 for Mc.

The p Value

The probability, p, in above equations is the ratio of the steady-state propagation rate to the sum of the steady-state propagation and termination rates (17). It can be estimated from the kinetic data for the homopolymerization of monomer, acrylamide, as follows

$$p = \frac{1}{1 + \frac{2\sqrt{k_tk_d f[I]}}{k_p[M]}} \quad (23)$$

where

- k_d is the decomposition rate constant of initiator I, ammonium peroxydisulfate, and is equal to 1.034×10^{-8} (sec^{-1}) at 25°C (15).
- k_t is the termination rate constant of monomer acrylamide (16).
- k_p is the propagation rate constant of monomer acrylamide, $k_t^{0.5}/k_p = 0.33(M\text{-}min.)^{0.5}$ at 25°C.
- f is the initiator efficiency, equal to 0.6 to 1.0 for most reactions (17).
- [I] is the molar concentration of initiator.
- [M] is the molar concentration of monomer.

p is a function of f, [I], and [M] according to equation 23 provided the polymerization/crosslinking reaction is at a constant temperature. It should be noted that the monomer concentration is dependent of the s and MR of the reaction system through the following equation:

$$[M] = \frac{ab \times s}{(b \times MR + a)} \times 10 \quad (24)$$

where $a = 5.208 \times 10^{-3}$, b = 1/71.08, and s is the total weight of reactable monomer and polymer in 100 ml. The derivation of equation 24 is included in Appendix A. With [M] as a function of two variables, p becomes a function of four variables; f, [I], MR, and s.

The Simulation

The calculation of Mc involves 5 independent variables; α, p, c, MR, and DD. Although not explicitly shown in equation 9, the effect of MR on the calculation is through the respective mole fraction of acrylamide, n_1, and of Ac-HES, n_2, while the influence of DD is through h in the various derivatives in equations 17 to 19. Since p is a function of 4 parameters, the total number of independent variables for the calculation of Mc is actually 7, provided the reaction is at constant temperature.

$$Mc \cong \text{Function}(\alpha, f, c, MR, DD, [I], s) \quad (25)$$

Among these parameters, MR, DD, [I], and s are adjustable and controllable during the microsphere preparation process, while α, f, and c are dependent on the nature and extent of the reaction. The plan of the simulation was to first identify the key parameters from these 7 variables that affect Mc and then to focus on the influence of the key parameters on Mc.

RESULTS AND DISCUSSION

Identification of Key Parameters

The relative effect of the 7 parameters in equation 25 on Mc was evaluated based on the dependence of Mc on α under the influence of every other parameter. Figures 1 and 2 show that Mc decreased as α was increased and reached a limiting value before total conversion (α = 1.0.). Figure 1b shows that Mc decreased monotonically with an increase in DD. Effects of [I] (Figure 2a) and c (Figure 2b) on Mc occurred only at very low α and changes in s (Figure 2c) and f (Figure 2d) had no effect on Mc. Thus, MR and DD showed the greatest influence on Mc-α relationship and the key variables affecting the process can be identified as α, MR, and DD. In other words, the crosslinked structure became tighter as the fractional conversion of double bonds (unsaturation) was increased. This tightness of structure reached a limit at a certain degree of fractional conversion before total conversion. Figure 3 shows that at a constant α, Mc initially decreases with MR to a minimum and then increases with MR.

Combined Effects of DD and MR on Mc and Influence on the Experimental Design

With the identification of the key parameters, it was convenient to study the combined effects of these parameters on the Mc and to examine their effect of the experimental design. In this study α, MR, and DD were varied. The other parameters were held constant; [I] = 0.01M, f = 0.8, c = 0.0, and s = 30%.

As shown in Figure 3 at a DD = 0.1, the effect of varying MR on the crosslinked structure was to gradually reduce the Mc to a minimum value and then progressively increase it. Since DD also has a strong effect on the Mc-α relationship, the minimum Mc value is a function of both DD and MR. Thus, minimum Mc can be defined only by a specific pair of values of DD and MR. This is best demonstrated with Figure 3 where the minimum Mc of about 3000 can only be obtained by selection of MR equal to about 1.0 and DD of 0.1. Any other selected values of MR will cause Mc to shift away from this minimum value. The almost parabolic nature of the dependence of Mc on MR also suggests that in order to obtain a crosslinked structure with Mc higher than its minimum value, one can either increase or decrease MR from the value that gave minimum Mc (MRmMc). Variation of MR from the MRmMc in either direction by about the same scale could lead to approximately the same Mc. For example, to have a crosslinked structure with Mc equal to 10,000 in Figure 3, one can select to use 0.1 or 20 as the value for MR at the conditions for the other parameters.

By including the effect of changing DD on Mc, Figure 4 shows that as the DD increased, the minimum Mc value decreased. However, the corresponding MRmMc was also decreasing. This showed that the minimum Mc was defined by one and only one set of values of DD and MR, which is consistent with the argument made previously. It is interesting that the minimum Mc at various combinations of MR and DD was linear (Figure 4).

The significance of this line of minimum Mc, (lmMc), is two fold. First, the line represents points of minimum Mc. Any point defined by other values of DD and MR located outside of this line will have a higher value of Mc than that on the line. Second, the line defines two regions below and above the line, respectively. The region below the line is designated the stable operation region since variation of DD or MR in this region produces predictable and expected response of Mc change. For example, it could be expected that decreasing DD at constant MR and/or decreasing MR at constant DD caused Mc to increase, and vice versa. For the region above the line, the positive dependence of Mc and MR at constant DD is valid, but the relationship of Mc with DD at constant MR is not distinctly defined. This can be explained by observing Figure 4 in the portion of curves with MR higher than MRmMc that the change of Mc with respect to variation of DD at constant MR was not necessarily positively or negatively dependent. For instance, at MR equal to 10, Mc produced from a DD of 3.0 was higher than that from a DD of 1.0. However, it was lower than that from DD of 0.01. Therefore, the region above the line was defined as unstable because variation of DD might not produce predictable change in Mc. It is recommended that experiments be designed around the stable region, especially when the purpose is to study the effect of DD on Mc.

The lmMc shown in Figure 4 was obtained when the fractional conversion of unsaturation was 100%. Since it is almost impossible to have complete reaction, it is important to know how lmMc, and thereby the stable region, is affected by variation of fractional conversion. Figure 5 shows that the minimum Mc for Ac-HES polymer of DD equal to 0.1 was elevated as the fractional conversion deviated from total conver-

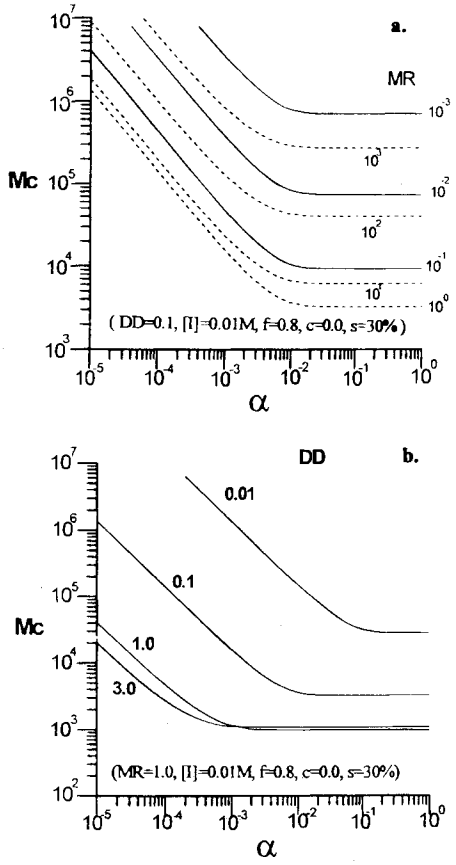

Fig. 1. The dependence of Mc on fractional conversion α at various (a) molar ratios, MR and (b) degrees of derivatization, DD.

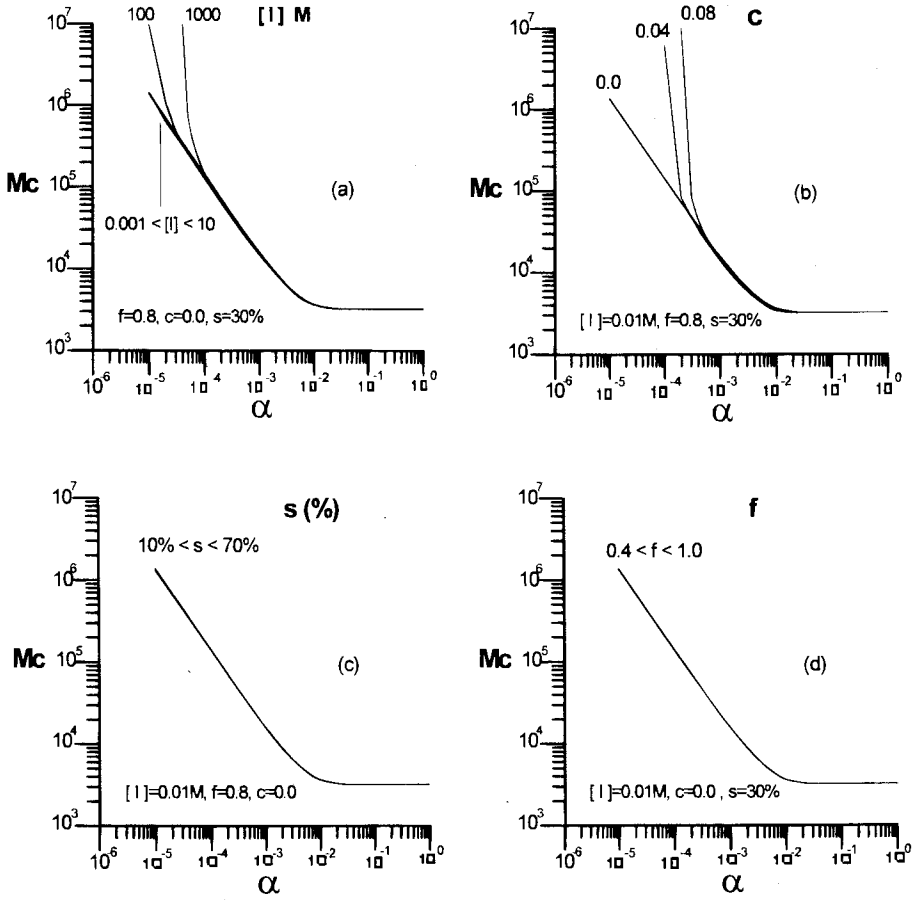

Fig. 2. The dependence of Mc on α at various levels of (a):[I], (b):c, (c):s, and (d):f. (DD = 0.1, MR = 1.0)

sion. In addition, the corresponding MRmMc also increased slightly. When different DD were also considered, it is clear that incomplete conversion causes lmMC to shift from its original position at 100% conversion toward the unstable region as shown in Figure 6. As the reaction becomes less complete, the stable region tends to expand. Since the actual fractional conversion is experimentally difficult to determine and usually unknown for the Ac-HES-acrylamide crosslinking reaction, it is suggested that the stable region bounded by the lmMc from the 100% conversion be used as the working range for experimental design.

CONCLUSIONS

A model describing the progress of the crosslinking polymerization reaction of Ac-HES and acrylamide monomer was

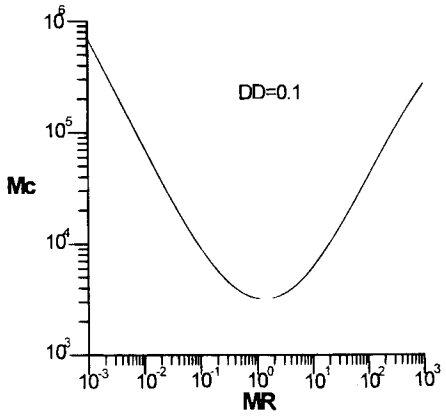

Fig. 3. Effect of molar ratio on Mc at total conversion of unsaturation (α = 1) (DD = 0.1, [I] = 0.01M, f = 0.8, c = 0.0, s = 30%)

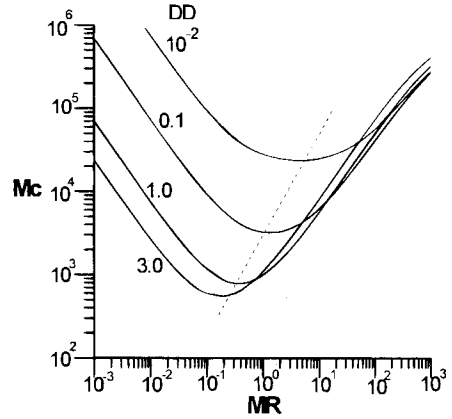

Fig. 4. Effect of molar ratio on Mc at total conversion of unsaturation (α = 1) at various degree of derivatization, DD. The broken line shows points of minimum Mc(lmMc). ([I] = 0.01M, f = 0.8, c = 0.0, s = 30%)

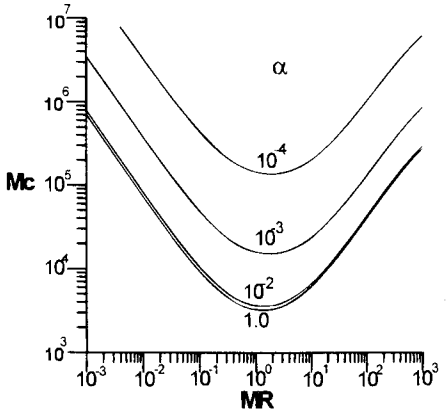

Fig. 5. Effect of fractional conversion on the dependence of Mc on molar ratio. (DD = 0.1, [I] = 0.01M, f = 0.8, c = 0.0, s = 30%)

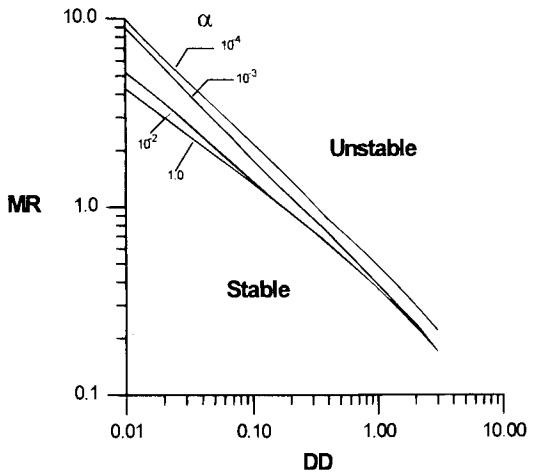

Fig. 6. Effect of fractional conversion on the line of minimum Mc. ([I] = 0.01M, f = 0.8, c = 0.0, s = 30%)

developed. Simulation based on the developed model showed that the most important microsphere preparation parameters influencing the crosslinked structure of the poly[Ac-HES]system are the degree of derivatization of the Ac-HES and the molar ratio of the Ac-HES to acrylamide monomer. For experimental study of poly [Ac-HES] system, it is advantageous and efficient to focus on the effects of these two key parameters. The suitable working rang for the experimental study of the effect of DD on Mc was the region bounded under the line of minimum Mc at 100% conversion in the logarithmic plot of MR against DD.

APPENDIX A

Derivation of Equation 24

Assuming X g of Ac-NH_2 was mixed with Y g of Ac-HES to make up 1.0 g of total solid. If the total weight of solid per 100 ml of phosphate buffered solution (PBS) was s, the required volume of PBS to dissolve the mixture is 100/s. The corresponding Ac-NH_2 concentration, [M], defined as the mole of Ac-NH_2 in 1000 ml of PBS, is then

$$[M] = \frac{X \div 71.08}{100 \div s} \times 1000$$

$$= \frac{X \times s}{71.08} \times 10 \qquad (A.1)$$

where 71.08 is the molecular weight of Ac-NH_2. When the molar ratio of Y to X is defined as MR, the amount of X is calculated from the solution to the follwoing simultaneous mass balance equations:

$$X + Y = 1.0 \qquad (A.2)$$

$$MR = \frac{Y \div 422{,}000 \times 2198}{X \div 71.08} \qquad (A.3)$$

where 422,000 is the number average molecular weight of Ac-HES polymer, and 2198 is the mumber of glucose units in one mole of Ac-HES polymer.

From equation A.2: Y = 1.0-X substituted into equation A.3 followed by mathematical operation, the X is:

$$X = \frac{5.2083 \times 10^{-3}}{MR \div 71.08 + 5.2083 \times 10^{-3}} \qquad (A.4)$$

$$= \frac{a}{b \times MR + a} \qquad (A.5)$$

where $a = 5.2083 \times 10^{-3}$, and b = 1/71.08

With X from equation A.5, the concentration of monomer [M] in equation A.1 becomes:

$$[M] = \frac{ab \times s}{b \times MR + a} \times 10 \qquad (24)$$

REFERENCES

1. P. P. DeLuca and F. Rypacek. Preparation of biodegradable microspheres useful as carriers for macromolecules. US Patent 4741872, (1988).
2. K. Park. *Biomaterials* **9**:435–441 (1988).
3. P. Artursson, P. Edman, T. Laakso, and I. Sjoholm. *J. Pharm. Sci.* **73**:1507–1513 (1984).
4. D. R. Miller and C. W. Macosko. *Macromolecules* **9**:206–211 (1976).
5. A. G. Mikos, C. G. Takoudis, and N. A. Peppas. *Macromolecules* **19**:2174–2182 (1986).
6. A. G. Mikos and N. A. Peppas. *J. Controlled Rel.* **5**:53–62 (1987).
7. D. R. Miller. *J. Polymer Science:B:Polymer Physics* **26**:1–54 (1988).
8. A. B. Scranton and N. A. Peppas. *J. Polymer Science:A:Polymer Chemistry* **28**:39–57 (1990).
9. M. Gordon and G. N. Malcolm. *P. Roy. Soc. A.* **295**:29–54 (1966).
10. M. Gordon. *P. Roy. Soc.A* **268**:240–259 (1962).
11. G. R. Dobson and M. Gordon. *The J. Chemical Physics* **43**:705–714 (1965).
12. K. Dusek. *Advances in Polymer Science* **78**:1–59 (1986).
13. K. Dusek and J. Spevacek. *Polymer.* **21**:750–756 (1980).
14. K. Dusek and M. Ilavsky. *J. Polymer Sci.: symposium* **53**:57–73 (1975).
15. J. C. Masson. In J. Brandrup and E. H. Immergut (Eds.) *Polymer Handbook.* 3rd ed., pp.II/1-II/59, Wiley, NY. (1989).
16. D. J. Currie, F. S. Dainton, and W. S. Watt. *Polymer.* **6**:451–453 (1965).
17. F. A. Bovey and F. H. Winslow (Eds.) *Macromolecules, an introduction to Polymer Science.*, pp. 36–38, Academic Press, NY. (1979).