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Chemically Crosslinked N-Vinyl-2-Pyrrolidone/2-Hydroxyethyl Methacrylate (VP/HEMA) Copolymer for the Controlled Release of Cyclic Oligopeptide

Bashir AHMAD[1*], Shumaila BASHIR[1], Shams-un NISA[2], M. B. HUGLIN[3]
[1] *Department of Pharmacy University of Peshawar, Peshawar-25120, PAKISTAN*
[2] *Department of Pharmacy and Jinnah College for Women, University of Peshawar, Peshawar-25120, PAKISTAN*
[3] *Institute of Material Research and Chemistry, Salford University, Manchester, UK.*
e-mail: bashirdr2001@yahoo.com

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Crosslinked copolymers of various compositions of N-vinyl-2-pyrrolidone (VP) and 2-hydroxyethyl methacrylate (HEMA) were prepared chemically in the presence of a crosslinking agent. The swelling mechanism was non-Fickian with about 86% conversion of feed composition to crosslinked copolymer. The reactivity ratios $r_1 = 0.045$ and $r_2 = 3.07$ for VP and HEMA indicate that HEMA is more reactive than VP in the reaction. Hydrophilicity, hydrophobicity and monomer composition in the copolymer controlled the drug release from the hydrogels.

Key Words: N-vinyl-2-pyrrolidone, 2-hydroxyethyl methacrylate, Hydrogels, Drug release.

Introduction

Interest in the preparation of hydrogels due to their use in contact lenses, controlled release, biotechnology and other fields of life has increased considerably in recent years[1−6]. However, the number of polymers suitable for controlled release is quite limited compared to the total available synthetic polymers because of the lack of certain properties like biodegradability, swellability and non or less toxicity in specific environments.

We have reported previously[7−9] on the preparation, properties and controlled release of hydrogels based on N-vinyl-2-pyrrolidone (VP) and some others with comonomers. High conversion for copolymerisation was obtained and the overall degree of equilibrium swelling in water was found to cover a wide range according to the nature and content of the comonomer.

HEMA/VP copolymer has been prepared by different methods[10−12] using γ-radiation but due, to a lack of certain properties which are greatly dependent on the monomer contents and crosslinking extents, it

*Correspondence author

could not be used every time for controlled release. However, linear HEMA/VP copolymer was successfully used for the controlled release of certain drugs like theophylline and erythromycin by Koresmeyer and Peppas[4] and Ahmad et al.[8], respectively. Lee[13] studied the release of thiamine HCl, and progesterone from its beads and sheets whereas, Graham et al.[14] prepared pessaries containing prostaglandin E2 in a matrix of the copolymer. The mechanism of release was one of "melting out" of crystallites as a result of swelling. All these applications of polymers and copolymers in medicine enhanced the current interest in controlled release technology.

In the present work VP/HEMA copolymers with varying comonomer compositions were prepared using azo-isobutyronitrile (AIBN) as an initiator and N-N methylene bis acryl amide (MBA) as a crosslinker. These hydrogels were characterised with respect to reactivity ratio, conversion, and swelling/diffusion properties and later evaluated for the potential controlled release of a cyclic oligopeptide called cyclosporine.

Experimental

a) Chemicals

NVP (Aldrich Chemical Co) and HEMA (Sigma Chemical Co) were vacuum distilled at 68 °C/2.0 mmHg and 67 °C/3.5 mmHg, respectively. Cyclosporine A ($C_{62}H_{111}N_{11}O_{12}$) of molecular weight 1202 g/mol was purchased from the Fluke–Aldrich Co. UK, and AIBN, the initiator from Sigma, was purified by recrystallisation from toluene. N, N methylene bis acrylamide was used as a crosslinker without further purification.

b) Polymerisation

Mixtures of NVP and HEMA in the volume ratios 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 were initiated with 0.25 wt% AIBN and 0.35 wt% crosslinker. These ratios of VP/HEMA will be designated hereafter as VP4/HEMA6, VP5/HEMA5, VP6/HEMA4, VP7/HEMA3, VP8/HEMA2 and VP9/HEMA1, respectively. The reaction mixtures were degassed with nitrogen for 15 min to remove the oxygen that acts as a chain-terminating agent. We sealed the vials and bulk co-polymerisation was carried out at 50 ± 0.5 °C for 2 h, at 60 ± 0.5 °C for 3 h, at 70 ± 0.5 °C overnight and at 80 ± 0.5 °C for 12 h in a water bath maintained at polymerisation temperature. After this the vials were removed from the bath, cut away from the glassy polymer and discs 2.0 mm thick were separated/prepared from it.

c) Conversion

After polymerisation the discs were swollen to equilibrium in deionised water at 37 °C over 3 days during which the water was changed twice a day in order to remove any possible unreacted monomers or linear polymer. These samples were dried to constant weight at 40 °C in an oven and 45 °C in a vacuum oven. The quantity m_1 is the mass of the crosslinked copolymer (xerogel) and the ratio of m_1 to known mass (m_o) of (NVP + HEMA + AIBN) in the feed mixture represents the fractional conversion to crosslinked copolymer. The ratio (r) represents the minimum value of the conversion of monomers.

$$r = m_1/m_o \tag{1}$$

d) Analysis of copolymer

For all the systems, the VP contents were determined by analysis using Tecator Kjeltec autoanalyser on 0.05–0.08 g at the maximum operation temperature. The method adopted in this laboratory is reported elsewhere[15−16]. For the VP/HEMA copolymer, the –OH group content was analysed using a sample of 0.1 g, the procedure being indicated elsewhere[17].

e) Swelling kinetics

The swelling kinetics of the hydrogels was measured gravimetrically. The xerogel of weighing (w_1) was immersed in distilled water, periodically removed from the water, surface dried lightly and weighed (w_2) and water uptake capability was calculated as

$$W_u = 100(w_2 - w_1)/w_e \tag{2}$$

where w_e is the weight of the hydrogel at equilibrium swelling

f) Loading/release of drug

Polymer discs were loaded with cyclosporine in an aqueous/ethanol mixture for longer than the equilibrium swelling time. The concentration of the drug solution was 5–10% wt/wt of the dry polymer xerogel. The swollen drug loaded gels were dried at 25 ± 0.5 °C in a vacuum oven. The drug release experiments were performed in the same medium at a particular temperature, and the drug concentration in release medium was monitored by its absorbance using a Hitachi model U-2000 spectrophotometer.

Results and Discussion

a) Reactivity ratio

The Mayo–Lewis[18], Fineman–Ross[19] and Keler–Tudos[20] graphical methods were used to determine the reactivity ratios r_1 and r_2 for VP/HEMA system and the values are given in Table 1.

Table 1. Reactivity ratio of VP/HEMA copolymer.

	VP / HEMA		
Method	r_1	r_2	Reference
1: Mayo-Lewis	0.018	2.88	present work
2: Fineman–Ross	0.088	3.37	=
3: Kelen–Tudos	0.029	2.95	=
Average value	0.045 ± 0.82	3.07 ± 0.35	
5: Al-Essa	0. 05 ± 0.09	3.12 ± 0.38	15

The values of r_1 and r_2 from method (2) are high but the average values are in good agreement with those reported[15], i.e. $r_1 = 0.05$ and $r_2 = 3.12$. $r_1 = 0.045$ and $r_2 = 3.07$ indicate that HEMA is more reactive in the copolymerisation and the copolymer structure will be random coil in nature.

b) Conversion

The solution copolymerisations with different composition of VP/HEMA afforded a minimum of 85.8% for xerogel of high HEMA mole fraction based on 0.35 wt% MBA. We synthesised (unpublished data) the crosslinked PVP alone with the same crosslinker by inverse suspension polymerisation and conversion was

68%. This high mean HEMA content enhanced the conversion of copolymer. The discs were assessed visually for optical homogeneity and were found clear although there was considerable compositional heterogeneity in the feed mixture. In an earlier report[21] on HEMA/VP copolymerisation involving calculation of compositional heterogeneity via a form of the Skeist procedure[22], a plot was given of fractional conversion vs. composition as expressed by the mole fraction of VP in the copolymer. This showed that HEMA enters the copolymer faster than VP due to its high reactivity, and thus the product has a composition very close to that of PVP homopolymer in the latter stages of conversion. The higher the VP contents in the feed, the lower the conversion at which HEMA is totally consumed.

The swelling behaviour of copolymers with different VP/HEMA compositions was first characterised without a model drug because this swelling is the key factor describing drug diffusion in the gels, the swelling ratio trend with time is shown in figure 1. The rate of water uptake is faster for feed composition (VP9/HEMA1) having higher VP content than for that having lower VP and higher HEMA (VP1/HEMA9). Huglin et al.[23,24] observed that by increasing VP content in copolymers, the cross-linking efficiency decreases, while copolymers of higher HEMA are more crosslinked due to the presence of diester in the HEMA monomer. In the present case, for the same reason of higher hydrophilicity due to VP, the VP9/HEMA1 has higher water uptake and 93% water uptake was reached within 4 h, while for the high content HEMA copolymer VP4/ HEMA6 water uptake was only 15% and hence took longer time.

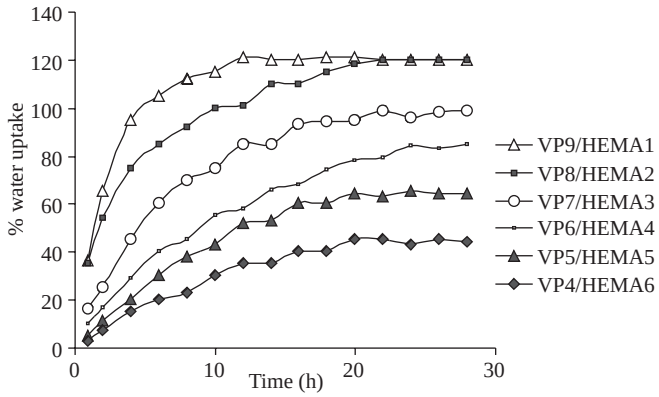

Figure 1. Variation of percentage water uptake with time (h) for various compositions of VP/HEMA copolymer.

The effect of temperature on dimensions was studied for only one particular hydrogel, i.e that prepared in VP6/HEMA4 and measurable decrease of 7.16% was noted over an increase of 310–340 K = 30 K, which corresponds to 0.25% per Kelvin.

Furthermore, the following equation was used to determine the nature of diffusion of water into hydrogel[25]:

$$M_t/M_e = kt^n \tag{3}$$

M_t/M_e is the fractional water uptake, t is the diffusion time, n is the transport mode for the penetrant and k is a constant related to the structure of the network. Value n = 0.45– 0.50 corresponds to Fickian diffusion whereas $0.50 < n > 1.0$ shows non-Fickian diffusion[26]. The values of n obtained from the slope of the plot of log M_t/M_e vs. logt are given in Table 2. For all compositions the value varies between 0.55 and 0.67, showing non-Fickian diffusion.

Drug release

The drug loaded dry gels were equilibrated in the medium and the drug concentration was monitored at 37 °C. It has been assessed[27] that swelling, not only in water but also in ethanol and chloroform, decreases at increasing temperature and the opposite effect prevailed for swelling in nonhydrogen bonding liquids. This behaviour will ultimately affect the release of the drug and so we selected 37 °C, body temperature. The release of cyclosporine from the discs is shown in figure 2. The release is seen to be dependent on copolymer composition. Likewise, the samples containing the smallest amounts of the most hydrophilic NVP component and larger quantities of HEMA exhibit slow release. The release is considerably faster as the NVP content increases, i.e. after 4 h, 66% of the drug is released to the medium for VP9/HEMA1, whereas for VP4/HEMA6 the release is only 11%. At the start, the release is controlled by the PVP fraction due to its rapid swelling, while the later stage is related to the hydrophilic/hydrophobic balance of the residual HEMA rich copolymer and thus permeabilities and diffusion parameters have to be taken into account. The release is independent of the incubation time. A cyclosporine release experiment was recently undertaken by Gallardo et al.[28] through a linear uncross linked copolymer on the basis of solubility difference and microstructural distribution but the burst effect of the linear copolymer with high HEMA content restricts its use for controlled release. The crosslinked VP/HEMA copolymer is stable as reported[4] for the release of theophylline.

Table 2. Diffusion coefficient values for different systems.

	System	n	correlation coefficient
1	VP4/HEMA6	0.55	0.9993
2	VP5/HEMA5	0.56	0.9995
3	VP6/HEMA4	0.58	0.9951
4	VP7/HEMA3	0.59	0.9981
5	VP8/HEMA2	0.62	0.9972
6	VP9/HEMA1	0.67	0.9985

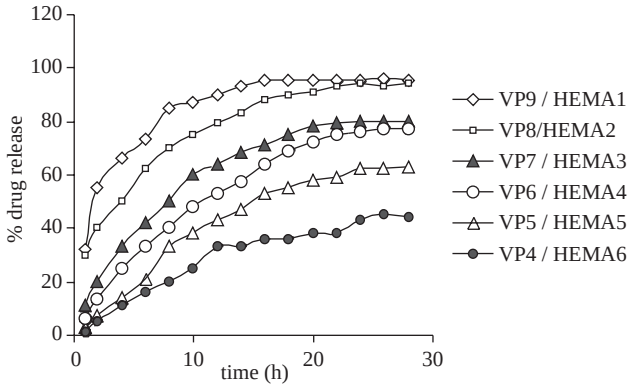

Figure 2. Variation of drug release with time (h) for different compositions of VP/ HEMA copolymer at 37 °C.

Conclusion

1. VP/HEMA copolymer was crosslinked by a chemical method rather than by the γ-radiation commonly used.

2. 86% conversion of feed composition into crosslinked copolymer was obtained.
3. The reactivity ratio for VP/HEMA is $r_1 = 0.045$ and $r_2 = 3.07$.
4. The diffusion coefficient values for all compositions are above 0.55, indicating non-Fickian mode of diffusion.
5. The VP/HEMA contents of the copolymer controlled the release of cyclosporine in the initial and later stages respectively.

Acknowledgements

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