RESEARCH PAPER

Accepted 11 April 2001
Revised 23 March 2001
Received 6 March 2000
Indian J. Pharm. Sci., 2001, 63(3) 222-227

Preparation, Swelling Kinetics and Drug Loading Studies of Cross Linked Polymeric Hydrogel Beads

ARCHANA PATEL AND R. S. R. MURTHY
Pharmacy Department, Faculty of Technology and Engineering,
M. S. University of Baroda, Vadodara-390 001

Co-polymeric hydrogel beads of 2-hydroxy ethyl methacrylae (HEMA) and methyl methacrylic acid (MMA) polymers using four different cross linking agents like EGDMA, DEGDMA, TriEGDMA and TEGDMA were synthesized and characterized by FTIR and DSC studies. Particle size distribution, shape and surface texture studies were conducted by microscopic methods. The 'nd' values subjected to ANOVA indicated no significant influence of the cross-linking agents used in different concentrations. Dynamic swelling studies of polymeric beads conducted in water, methanol and water-methanol mixture (1:1) suggests that the type of cross-linking agents used have very great impact on the permeation of the solvents. The diffussional kinetic exponent (n) values determined for copolymeric hydrogel beads showed a tendency to move towards Fickian transport (close to 0.43) as the hydrophilicity of the cross linking agent increases. Drug loading studies conducted with chlorpheniramine maleate and nifedipine in all batches of co-polymeric beads showed increase in percentage loading of both the drugs in the order of increasing solubility; TriEGDMADEGDMA>EGDMA. Low level of loading with respect to TEGDMA co-polymer (highest solubility) is explained based on the mechanism of liquid penetrant transport in a glassy polymer.

Hydrogels are the polymeric materials that can absorb a significant amount of water (>20% of its weight) while maintaining a distinct three-dimensional structure. In spite of the fact the hydrogels of natural and semi-synthetic origin are available, synthetic hydrogels are used extensively in drug delivery systems due to purity, versatility and reproducibility. High water content co-polymers and hydrogels of varied equilibrium hydration have been studied for use in drug delivery systems and as bio-compatible materials. Low water content hydrogels such as copolymers of 2-hydroxythyl methacrylate (HEMA) and hydrophobic or hydrophilic vinyl polymers have been synthesized as bio-compatible polymers[1]. The poly (hydroxyalky[1] methacrylates) have received great deal of interest ever since Wihchterle and Lim[2] polymerized HEMA in the presence of a cross linking agent under aqueous conditions. The applications and biocompatibility of HEMA based materials have been extensively reviewed[3]. Spurred on by the development of soft contact lenses, the popularity of covalently cross-linked synthetic hydrogels have increased for a variety of bio-medical applications. Polyfunctional cross-linking monomers like ethylenglycol dimethacrylate (EGDMA), N, N-methylene bis acrylamide, di, tri and tetra derivatives of EGMDA (DEGMA, TriEGDMA and TEGDMA) 2,2' - (P-phenylenedioxy) diethyl dimethacrylate have been used to adjust hydrogel properties particularly swelling, premeability and mechanical properties. The control of diffusion rate of a solute through a hydrogel network is of importance when it has potential use in the fabrication of drug delivery device. The diffusion rate of solute being governed both by the physical structure and the chemical nature of the polymer[4], its composition in terms of monomer and the cross linking agent used in its preparation is a deciding factor.

* For correspondence

In the present communication, preparation, characterization and swelling kinetic studies of various batches of co-polymeric hydrogel beads of HEMA and methyl methacrylic acid (MMA) using four different cross linking agents EGDMA, DEGDMA, TriEGDMA and TEGDMA has been described. The percentage loading of co-polymers with highly water soluble drug; chlorpheniramine maleate (CPM) and sparingly water soluble drug; nifedipine have also been studied and the resutls are compared with the swelling characteristics of the co-polymeric beads.

EXPERIMENTAL

Hydroxy ethyl methacrylate (HEMA) was obtained from Merck, Germany and was vacuum distilled at 80° under 5 mm Hg. Methy1 methacrylate (MMA) was obtained from Polymer unit, GSFC, Baroda was purified by extraction with 0.5% NaOH solution. Ethylene glycol dimethacrylate, diethylene glycol dimethacrylate and triethylene glycol dimethacrylate were obtained from Polymer unit, GSFC, Baroda and were used as obtained. Tetraethylene glycol dimethacrylate procured from Fluka, Switezerland was used as obtained. Azo bis isobutyronitrile (AIBN) obtained from National Chemicals, Baroda was used after recrystallization in methanol. Nitrogen gas cylinder was obtained from M/s Shivam Enterprises, New Delhi. CPM and nifedipine were obtained as gift samples from M/s. Alembic Chemical Works, Baroda. All other chemicals were of AR grade and used as obtained.

Preparation of Hydrogel beads:

Co-polymeric hydrogel beads of HEMA and MMA using four cross - linking agents EGDMA, DEGDMA, TriEGDMA and TEGDMA were synthesized by the suspension polymerization method[5]. Sodium chloride solution (180g of 20% aqueous solution) was mixed with 11.5 g of magnesium chloride ($MgCl_2$;$6H_2O$) while being agitated at 500-600 rpm. The temperature was brought to 70° and the system was purged with N_2. To this solution was added drop wise 61.5 ml of 1 N sodium hydroxide solution until a fine gelatiunous precipitate of magnesium hydroxide was formed. The agitation was reduced to 300 rpm and added with the aqueous solution containing HEMA, MMA and cross-linking agents in calculated ratios (Table 1). Azobisisobutyronitrile (AIBN, 0.1% w/w) was added as initiator. The suspension was maintained at 70° for 3 h and then at 90° for 1 h. The final product was cooled under agitation and the remaining Mg (OH_2 was dissolved by the addition of 5 ml of

TABLE 1: PARTICLE SIZE ANALYSIS OF VARIOUS BATCHES OF CROSS LINKED CO-POLYMERIC BEADS

Conc. of. CLA	HEMA:MMA ratio (Molar)	Batch No@. (Arithmetic mean dia. inμm)				Calculated 'F' value	Table 'F' value at P<0.05
		EGDMA	DEGDMA	TriEGDMA	TEGDMA		
0.005	0.75 : 0.25	EP1 (269)	DPI (271)	TrP1(257)	TP1(262)	0.011541	3.29
	0.25 : 0.75	EP2 (264)	DP2 (268)	TrP2 (261)	TP2 (259)	0.002421	3.29
	0.50 : 0.50	EP3 (264)	DP3 (270)	TrP3 (261)	TP3 (268)	0.016662	3.29
	1.00 : Nil	EHI (265)	DHI (271)	TrH1(260)	TH1(270)	0.011880	3.18
0.010	0.75 : 0.25	EP4 (271)	DP4 (264)	TrP4 (263)	TP4 (269)	0.008357	3.29
	0.25 : 0.75	EP5 (263)	DP5 (271)	TrP5 (270)	TP5 (260)	0.009389	3.29
	0.50 : 0.50	EP6 (264)	DP6 (266)	TrP6 (263)	TP6 (264)	0.009138	3.29
	1.00 :Nil	EH2 (270)	DH2 (269)	TrH2 (263)	TH2 (270)	0.005787	3.18
0.050	0.75 : 0.25	EP7 (267)	DP7 (267)	TrP7(264)	TP7 (266)	0.004801	3.18
	0.25 : 0.75	EP8 (266)	DP8 (268)	TrP8 (261)	TP8 (269)	0.002932	3.18
	0.50 : 0.50	EP9 (270)	DP9 (265)	TrP9 (268)	TP9 (265)	0.012355	3.18
	1.00 : Nil	EH3 (263)	DH3 (269)	TrH3 (264)	TH3 (260)	0.013002	3.18

Concentration of cross - linking agent (CLA) is in terms of moles of CLA per mole of monomer mixture. Batches of polymeric beads (@) were prepared using ethylenglycol dimethacrylate (EGDMA), diethyleneglycol dimethacrylate (DEGMA), triethyleneglycol dimethacrylate (TriEGDMA) and Tetraethyleneglycol dimethacrylate (TEGDMA).

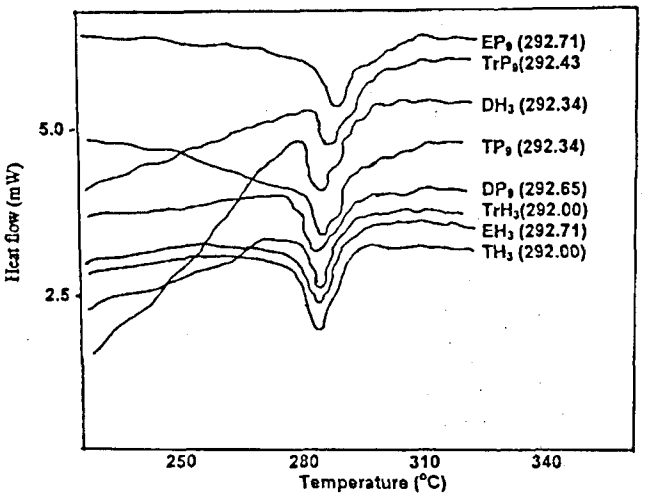

Fig. 1: Thermograms of co-polymers (EP9, DP9, TrP9 & TP9) prepared using HEMA and MMA (0.5:0.5 molar ratio) and homopolymers (EH3, DH3, TrH3 &TH3) of HEMA cross linked with different cross linking agent like EGDMA (EP9) and (EH3), DEGDMA (DP9 and DH3), TriEGDMA (TriP9 and TRH3) and TEGDMA (TP9 and TH3).

concentrated HCl. The beads obtained were recovered, washed several times with water until free from monomers and then dried under vacuum and stored in a desiccator.

Characterization:

All the batches of the co-polymeric hydrogel beads were viewed under a Carl Zeiss Jena microscope (at 40 x and 100 x) to study their shape and were also observed under a WILD MPSIZ Swiss microscope to study their three dimensional structure . Surface characteristics of a representative sample of co-polymeric hydrogel beads were studied using Jeol JSM-T300 Scanning Electron microscope. The sample was coated with gold by metal vaporizing technique in vaccum (10^{-4} torr) and then introduced into the specimen chamber of the microscope. The surface structure was observed under various magnifications (50, 75, 100 and 350) and was photographed)

All the batches of the co-polymeric hydrogel beads were subjected to particle size analysis on the basis of the weight of different size fractions and were also subjected to particle size analysis using a VJ-12 light microscope at a magnification of 100x. The arithmetic mean

TABLE 2: ANALYSIS OF DYNAMIC SWELLING STUDIES OF VARIOUS BATCHES OF CROSS LINKED CO-POLYMERIC BEADS IN VARIOUS MEDIA

Conc. of. CLA	Swelling kinetic exponent (n) values of different batches				'F' values calculated for various batches in groups A, B & C *		
	EGDMA	DEGDMA	TriEGDMA	TEGDMA	Water	Methanol	W:M (1:1)
0.005	EP1 (0.5882)	DPI (0.5247)	TrP1(0.4813)	TP1(0.4181)	77.347	43.769	141.839
(Group A)	EP2 (0.6225)	DP2 (0.5424)	TrP2 (0.5074)	TP2 (0.4422)	(x)	(x)	(x)
	EP3 (0.6036)	DP3 (0.5357)	TrP3 (0.4928)	TP3 (0.4333)	2.794	5.297	8.161
	EHI (0.5669)	DHI (0.5234)	TrH1(0.4699)	TH1(0.4156)	(y)	(y)	(y)
0.010	EP4 (0.5781)	DP4 (0.5313)	TrP4 (0.4852)	TP4 (0.4285)	158.668	50.354	360.900
(Group B)	EP5 (0.6293)	DP5 (0.5610)	TrP5 (0.5117)	TP5 (0.4456)	(x)	(x)	(x)
	EP6 (0.6104)	DP6 (0.5442)	TrP6 (0.4960)	TP6 (0.4358)	7.847	14.872	24.395
	EH2 (0.5727)	DH2 (0.5727)	TrH2 (0.4746)	TH2 (0.4219)	(y)	(y)	(y)
0.050	EP7 (0.6086)	DP7 (0.5367)	TrP7(0.4882)	TP7 (0.4314)	380.320	156.090	447.700
(Group C)	EP8 (0.6329)	DP8 (0.5723)	TrP8 (0.5150)	TP8 (0.4433)	(x)	(x)	(x)
	EP9 (0.6174)	DP9 (0.5510)	TrP9 (0.5005)	TP9 (0.4326)	17.5572	22.423	28.84
	EH3 (0.5851)	DH3 (0.5289)	TrH3 (0.4782)	TH3 (0.4244)	(y)	(y)	(y)

Table 'F' values in all cases is 2.262 at P<0.05.* 'F' values calculated out of 'n' values for various batches in groups A, B and C. 'x' represents 'F' values calculated between batches containing different cross linking agents in the same concentration, while 'y' indicates 'F' value calculated between batches containing different monomer ratio.

TABLE 3: PERCENTAGE SWELLING AND DRUG LOADING STUDIES OF DIFFERENT BATCHES OF CO-POLYMERIC HYDROGEL BEADS

Batch	Percentage swelling in 60 min (%Sw), % Drug (CPM, nifed) loading in co-polymers with cross linking agents (X=E, D, Tr, T).											
	EGDMA (X=E)			DEGDMA (X=D)			TriEGDMA (X=Tr)			TEGDMA (X=T)		
	%Sw	CPM	Nifed	% Sw	CPM	Nifed	%Sw	CPM	Nifed	%Sw	CPM	Nifed
XP1	40.26	8.937	7.625	42.26	9.059	8.235	44.51	10.293	8.416	46.37	7.938	7.652
XP2	39.24	7.349	6.973	41.24	6.576	8.104	43.49	10.116	8.333	46.37	7.817	7.576
XP3	39.75	7.472	6.642	41.75	7.498	7.899	44.01	9.943	8.211	45.72	7.833	7.466
XH1	39.75	9.311	9.147	42.53	9.141	8.431	46.80	10.563	8.456	46.71	8.003	7.741
XP4	40.16	8.645	8.163	42.11	8.741	7.845	44.26	9.576	7.989	46.21	7.746	7.313
XP5	38.94	7.963	6.943	41.04	8.013	7.786	44.13	9.613	7.854	45.06	7.649	7.296
XP6	39.50	7.641	6.761	41.35	7.672	7.663	43.81	9.341	7.813	45.53	7.473	7.103
XH2	40.80	8.831	8.344	42.32	8.921	7.944	44.69	9.677	8.124	46.62	7.896	7.411
XP7	40.07	8.323	7.157	41.95	7.435	7.542	44.06	9.217	8.022	46.07	7.201	6.873
XP8	38.65	7.676	6.421	40.86	6.791	7.502	42.98	8.936	7.625	44.95	6.983	6.742
XP9	39.26	6.817	6.661	41.01	6.644	7.426	43.62	8.863	7.541	45.32	6.466	6.616
XH3	40.51	8.395	7.472	42.32	7.669	7.773	44.62	9.332	8.337	46.47	7.306	6.943

CPM represents chlorpheniramine maleate while Nifed indicates nifedipine

diameter for each batch was calculated[6] and is shown in Table 1.

The FTIR spectra of representative batches of co-polymeric hydrogel beads were studied. The spectra of the different batches were studied for the evidence to confirm polymerization. Thermograms were obtained for representative batches using a PERKIN-ELMER DSC7. Differential Scanning Calorimeter. The heat flow was being maintained at a rate of 20°/ min. The representative thermograms are shown in fig.1.

Dynamic Swelling Studies:

Dynamic swelling of all the co-polymeric hydrogel beads were performed in three solvent systems-water, methanol, and 1:1 mixture of water and methanol. The dynamic change in the diameter of the beads was observed under a VJ-12 light microscope at a magnification of 100 x for different time intervals (5, 10, 20, 30 and 60 min) in all the three solvent systems. Analysis of the transport mechanism of the solvent using the empirical equation[7] was achieved by calculating the values of the exponent "n" using the equation.

$D_t/D_- = Kt^n$

Where, D_t/D_- = fractional increase in the diameter at time t, K= diffusional kinetic constant and n= diffusional kinetic exponent.

The "n" values calculated for all the co-polymeric hydrogel bead in all the three solvent systems is recorded in Table 2. The above data were subjected to ANOVA and the calculated 'F' values, are compared with the table 'F' value at $P<0.05$ and are recorded in Table 2.

Drug loading studies:

Co-polymeric hydrogel beads (10 G) in the size range of 250-355 μm were soaked in methanolic drug solution (5% w/v CPM; 2.5% w/v nifedipine) and allowed to equilibrate for 24 h. The swollen beads were then filtered, rinsed with methanol and dried in the vaccum oven at 50° under 25 mm Hg pressure. The dried beads were again rinsed with methanol and dried to remove the absorbed drug. The loaded beads were allowed evaluated for percentage drug loading by allowing 100 mg of loaded beads were allowed to swell in a 25 ml aliquots of methanol for 24 h, filtered and allowed to swell in another aliquot of fresh methanol. The filtrates collected after repeated such extraction for sufficient number of times previously validated were pooled and estimated for the drug content by the method described below. The results are tabulated in Table 3.

Analytical method:

Estimation of CPM was carried out by an UV Spec-

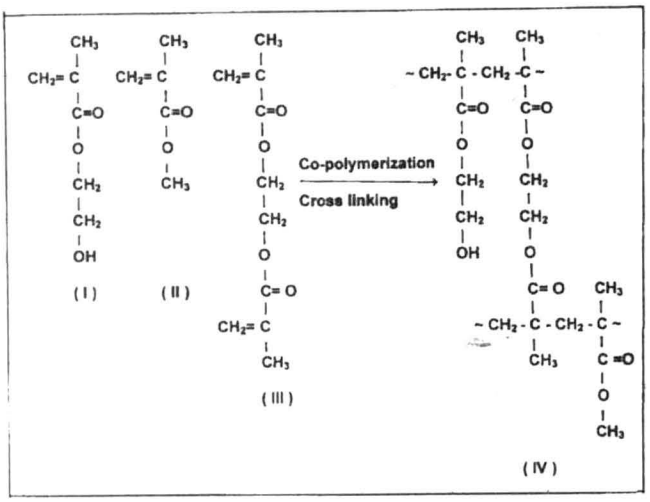

Fig. 2: Co-polymerization and cross linking reaction of HEMA (I), MMA (II) and EGDMA (III) to form cross linked co-polymer (IV), Note the sign (~) indicates the position of attachment

trophotometric method[8]. Suitable aliquot of the sample was transferred to calibrated volumetric flasks and the volume made up to 10 ml with distilled water so as to obtain the drug concentration in the range of 1-100 µg/ml. The absorbence was read at 261 nm using distilled water as blank. The drug concentration was calculated using the regressed calibration curve developed for the purpose. Similarly nifedipine was estimated[9] in the concentration range 1-100 µg/ml (in methanolic media) at the λ_{max} of 269 nm using methanol as blank. The drug concentration was calculated using the regressed calibration curve developed for the purpose.

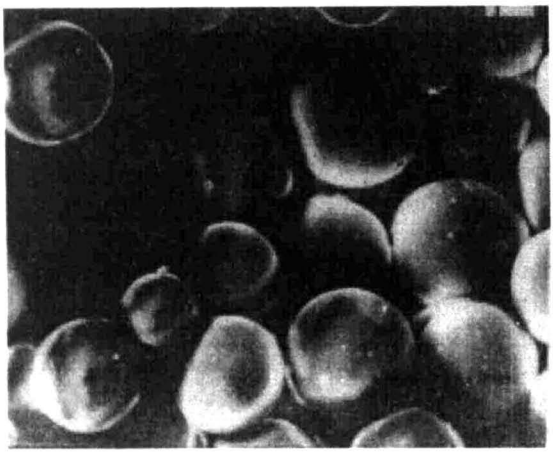

Fig. 3: Scanning electron micrograph of a sample of co-polymeric beads (100x)

RESULTS AND DISCUSSION

A representative reaction with one mole of HEMA and MMA crosslinked with EGDMA is shown in fig. 2. Since Crosslinking takes at -C=C-, the reaction would be similar with the other cross-linking agents also. The co-polymer beads obtained were transparent and spherical with smooth surface structure as confirmed by scanning electron microscopy (fig. 3). Frequency distribution study showed that the particle size distribution of all batches of beads were normal i.e. symmetric around the mean. The 'nd' values were subjected to ANOVA. The calculated 'F' values from different batches of beads compared with the table values at $P<0.05$ (Table 1) indicates no significant influence of the cross-linking agents in different concentrations on the particle size distribution of the beads.

The differential scanning thermograms of the representative batches of co-polymers showed peak at ~ 292°, which is different from the reported value for either HEMA (m.p.12°) or MMA (m.p.48°) monomers indicating the absence of monomers in the product[8]. The peak at ~292° appears in the thermograms of co-polymer prepared with mixture of HEMA and MMA and also with homo-polymer prepared with only HEMA, indicates the possibility of the molecular break at the point of cross linkage[8]. The completion of co-polymerization was further confirmed by FTIR spectra that provided compelling evidences for the carboxy1 and hydroxy1 group.

The analysis of the dynamic swelling data show that the values of the diffusion exponent 'n' lie between 0.43 to 0.66 for all the batches with few exceptions, indicating that the solvent penetration is by anomalous transport. The data on the dynamic swelling study in various media were subjected to ANOVA to study the variation among the batches of the co-polymeric beads. The 'F' value calculated between the groups (x) batches between different cross linking agents in the same concentration and groups (y) batches containing different HEMA:MMA ratio. These value are compared with the table 'F' values at $P<0.05$ (Table 2). Very high 'F' values (calculated) among the group (x) in comparison to table 'F' value (2.262) at $P<0.05$ indicates highly significant difference among the different cross-linking agents in dynamic swelling ability. The 'F' value calculated among group (y) are though higher in comaprison to the table 'F' value (2.262) at $P<0.05$, the values are quite low in comparison to the values for group (x). This indicates that the influence of monomer

composition is not very much important, as compared to that of cross linking agent for dynamic swelling characteristic of this group of co-polymers. However among the media studied the influence was found highest in water: Methanol (1:1) media.

The above observations suggest that the type of cross-linking agents used have a very great impact on the penetration of the solvent in to the beads by diffusion. The greater the cross linking density (0.005<0.01<0.05), higher the difference in the diffusion for the batches with the same monomer ratio. There is however, a comparatively less significant difference in diffusion among the batches with different ratios of monomer mixture at P<0.005.

The 'n" values of the co-polymeric hydrogel beads shows a tendency of the hydrogel to move towards the Fickian transport (closer to 0.43) as the hydrophilicity of the cross linking agent increases. This suggests that the relaxation of the co-polymer is faster than the diffusion of the penetrant in the order : TEGDMA > TriEGDMA > DEGDMA >EGDMA, for different cross linkers. The dynamic swelling studies performed showed methanol to induce maximum swelling in case of all the co-polymeric hydrogel beads, indicating it to be a better thermodynamic solvent suitable for drug loading in beads. The results of the percentage loading of different batches of beads with CPM and nifedipine individually are given in Table 3. No significant difference in percentage loading was observed between CPM and nifedipine in all the batches of beads indicating the fact, that the solubility of the penetrant solute is not an influencing parameter in drug loading. A marginal increase in the percent drug loading was observed from co-polymeric beads cross-linked with EGDMA to TriEGDMA through DEGDMA, which is in conformity with the increase in hydrophilicity of the co-polymers in the same order. It is interesting to note a sudden drop in the percentage loading of both the drugs in all the batches of beads cross-linked with TEGDMA in spite of the fact that this cross-linked polymer is the most hydrophilic among the polymers studied. This indicates that hydrophilicity is not the only parameter controlling the percentage drug loading in the hydrogel matrix.

The above result may be interpreted based on the mechanism of liquid penetrant transport in glassy polymers which is associated with state transition from the glassy to the rubbery state due to increased mobility of macromolecular chain in presence of a compatible liquid penetrant. This state transition is accompanied by considerable relaxation of the macromolecular chain and increase in the radius of gyration and end to end distance of the polymer molecules, which is seen microscopically as swelling[13]. Cross linking with a long chain cross linking agent, more than the critical length (TEGDMA in the present context) increase the end to end distance of the polymer molecule which may exhibit high rate of passage for the solution penetrated during rinsing and drying resulting in drug leakage. Selection of cross-linking agents for hydrogel matrix devices based on the above criteria may be useful as in case of these devices it is generally recommended to load drugs by equilibration method of the prepared polymeric matrix than during polymerization.

ACKNOWLEDGEMENTS

The authors acknowledge M/s Alembic Chemical Works, Baroda for financial assistance to the first author during the tenure of the project.

REFERENCES

1. Mack E.J., Okona,T. and Kim, S.W., In; Peppas, N.A., Eds., Hydrogels in Medicine and Pharmacy, Vol. II, CRC Press, Inc., Boca Ration, Florida, 1987, 65.
2. Wichterle, O. and Lim, D., **Nature,** 1960, 185, 117.
3. Ratner, B.D., and Hoffman, A.S., In; Andrade, J.D., Eds., Hydrogels for Medical and Related applications, ACS Symp Series, 1976,1.
4. Wood, J.M., Attwood, D. and Collett, J.M., **Drug Dev. Ind. Pharm.**, 1983, 9, 93.
5. Robert, C.C.R. and Buri, P.A., **J. Control Release**, 1987, 5, 151,.
6. Edmundson, I.C., In; Bean H.S. Carless, J.E. and Beckett, A.H., Eds., Advances in Pharmaceutical sciences, Vol. II, Academic Press, London, 1967, 75.
7. Robert, C.C.R., Buri, P.A. and Peppas, N.A., **J. Appl. Polym, Sci.,** 1985, 30, 301,
8. Eckhart, C.G. and McCorckle, T., In; Florery K., Eds., Analytical profile of drug substances, Vol. 7, Academic press, New York,1978, 43.
9. Ali, S.L. In; Florey K., Eds., Analytical profie of drug substances, Vol. 18, Academic Press, New York, 1989, 221.
10. Sanghavi, N.M., Sheikh, F. and Fruitwala M., **Drug Dev. Ind. Pharm.,** 1994, 20, 1923.
11. Peppas, N.A., and Barr-Howell, B.D., In; Peppas, N.A., Eds., Hydrogels in Medicine and Pharmacy, Vol. I, CRC Press, Inc., Boca Ration Florida,
12. Ritzer, P.L., and Peppas, N.A., **J. Control Release,** 1987, 5, 37.
13. Davidson III, G.W.P. and Peppas, N.A., **J. Control Release**, 1986, 3, 243.