Polym. Bull. (2009) 62:679–688
DOI 10.1007/s00289-009-0040-4

ORIGINAL PAPER

Synthesis and characterization of P(MMA-AA) copolymers for targeted oral drug delivery

Anna A. Barba · Annalisa Dalmoro · Felice De Santis · Gaetano Lamberti

Received: 8 September 2008 / Revised: 15 December 2008 / Accepted: 11 January 2009 /
Published online: 20 January 2009

Abstract This paper describes the development of pH-sensitive poly(methyl methacrylate-acrylic acid) copolymers for the enteric coating of pharmaceutical products for oral administration. To obtain the dissolution at the desired pH level, different pH-sensitive polymers are available on the market. Usually, for each desired dissolution pH, an ad hoc polymer is designed. Thus, different dissolution pH values could ask for completely different polymers. Instead, the materials proposed in this work are copolymers of the same two monomers, and the different dissolution pH was obtained by changing the volume fraction of the hydrophobic methyl methacrylate monomer to the hydrophilic acrylic acid monomer. Increasing the volumetric percentage of methyl methacrylate causes the polymer to dissolve at increasing pH, until the dissolution does not take place at all, and it is replaced by a slow swelling phenomenon. The copolymers obtained were characterized by differential scanning calorimetry, in order to evaluate their glass transition temperature, and these latter were related to %MMA. The molecular weights of the pure polymers (PAA, PMMA) were measured by intrinsic viscosity, to further validate the glass transition temperatures observed. The dissolution of the copolymers was carefully tested in buffer solutions for a dense set of pH values. A linear relationship between dissolution pH and volumetric percentage of methyl methacrylate was obtained from these measurements. As a result, for any physiological compartment, the copolymer which dissolves at the pH of interest can be easily synthesized.

Keywords P(MMA-AA) · Drug delivery · Enteric coating

A. A. Barba
Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno,
84084 Fisciano (SA), Italy

A. Dalmoro · F. De Santis · G. Lamberti (✉)
Dipartimento di Ingegneria Chimica e Alimentare, Università degli Studi di Salerno,
84084 Fisciano (SA), Italy
e-mail: glamberti@unisa.it

Introduction

Controlled drug delivery systems, which are intended to deliver drugs at predetermined rates for predefined periods of time, have been used to overcome the shortcomings of conventional drug formulations. It would be highly beneficial if the active agents were delivered by a system that sensed the signal caused by disease, judged the magnitude of signal, and then acted to release the right amount of drug in response. Such a system would require coupling of the drug delivery rate with the physiological need by means of some feedback mechanism [1]. The environment-sensitive polymers, called "smart" polymers, are ideal candidates for developing self-regulated drug delivery systems.

Maybe the most important physiological stimulus is the change in the environment pH. The pH sensitive polymers contain pendant acidic (e.g., carboxylic and sulfonic acids) or basic (e.g., ammonium salts) groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes: polyanions and polycations. The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. The pH-sensitive polymers have been most frequently used to develop enteric coated formulations for oral administration. The pH in the stomach (<3) is quite different from the neutral pH in the intestine, and such a difference is large enough to elicit pH-dependent behavior of polyelectrolyte polymer. Enteric coated products are designed to remain intact in the acidic juices of the stomach and then to release the drug at the higher pH of the small intestine (above pH 5.5) or at the even higher pH in the colon (above pH 6.5): the effectiveness of the drug will be reduced by stomach acids or enzymes if they were left unprotected [2].

Polymers made of poly(acrylic acid) (PAA) or poly(methacrylic acid) (PMA), which are polyanions, can be used to develop formulations that release drugs in a neutral pH environment [3].

Hydrophobic modifications affect both the segmental mobility of polyelectrolytes and the pH range over which the ionization takes place. Different comonomers provide different hydrophobicity to the polymer chain, leading to a different pH-sensitive behavior. Hydrogels made of PMA grafted with poly(ethylene glycol) (PEG) have unique pH-sensitive properties [4]. At low pH, the acidic protons of the carboxyl groups of PMA interact with the ether oxygen of PEG through hydrogen bonding, and such complexation results in shrinkage of the hydrogels. As the carboxyl groups of PMA become ionized at high pH, the resulting de-complexation leads to swelling of the hydrogels.

Copolymers of methacrylic acid (MAA) have shown conformational transition that shifted progressively towards higher pH values with increasing hydrophobicity and/or content of hydrophobic co-monomers (e.g., styrene or alkyl(meth)acrylate derivatives) [5].

The enteric coating polymers commonly available on the market are anionic polymethacrylates, that is copolymers of MAA and either methylmethacrylate or ethyl acrylate (Eudragit®, Kollicoat®); cellulose based polymers, e.g., cellulose

acetate phthalate or CAP (Aquateric®) and polyvinyl derivatives, e.g., polyvinyl acetate phthalate (Coateric®).

Polymers with different chemical structure were available to give the dissolution at different pH values. Therefore, to obtain the release in different body compartments, different polymer formulations have to be chosen. It would be better to have a single class of copolymers, of similar physical properties, which can dissolve at tailored pH values, giving the drug release in correspondence of the desired target.

Aim of this work is to propose and to characterize a class of copolymers obtained from two monomers, which gives the desired dissolution pH simply changing the volume ratio of the hydrophobic to hydrophilic monomer. Thus, the class of copolymers produced and characterized in this work should be able to fulfill the requirement mentioned above.

Experimental

Materials

For the co-polymer synthesis: methylmethacrylate (MMA, CAS number: 80-62-6) and acrylic acid (AA, CAS number: 79-10-7) were purchased from Sigma-Aldrich, Initiator 2,2′-azobis 2,4-dimethylvaleronitrile (AMVN, CAS number: 4419-11-8) was a Cayman Chemical Company product. Potassium biphthalate (CAS number: 877-24-7), hydrochloric acid (HCl, CAS number: 7647-01-0), sodium hydroxide (NaOH, CAS number: 1310-73-2) and monobasic potassium phosphate (CAS number: 7778-77-0), were used for buffer solution preparation; Acetone (CAS number: 67-64-1), for viscosity measurements; all purchased from Sigma-Aldrich.

Methods

Synthesis

The poly(MMA-AA) copolymers were obtained by a free radical polymerization method described by Abusafieh et al. [6], where they developed a cross-linked poly(MMA-AA) copolymer for potential applications in bone implants. The polymerization was carried out in bulk, using AMVN as initiator whose amount was fixed at 0.4 g/100 mL of total mixture. The initiator was added to various volumetric ratios of MMA/AA monomers and mixed thoroughly by sonication (Vibra-Cell™ Ultrasonic Processor, Sonics, Newtown, CT). The reaction mixture was poured into glass tubes, sealed and placed vertically in a water bath which provided a uniform and accurate temperature control. The assembly was maintained at 30 °C for 5 h, then the temperature was raised gradually (5 °C/h) to 70 °C and kept at this temperature for 10 h, this step was followed by overnight cooling. The tubes were then taken out from the bath and broken under slight clamp pressure. The samples were removed from the glass tubes and placed in an oven in which

the temperature was raised slowly (1 °C/min) to 150 °C and left for 3 h, followed by overnight cooling. The samples were crushed and stored at room temperature.

T_g measurements

Differential scanning calorimeter (DSC, Mettler Toledo 822) was used to measure the glass transition temperatures (T_g) of the synthesized samples. The thermal cycle was characterized by a first heating stage from 0 to 170 °C at a rate of 10 °C/min, then the temperature of 170 °C was kept for 5 min, a cooling stage from 170 to 0 °C at a rate of 10 °C/min came after, the temperature of 0 °C was maintained for 5 min after the cooling step and at the end a second heating stage from 0 to 170 °C at a rate of 10 °C/min was imposed.

Viscosity measurements

The viscosity measurements of polymers' dilute solution, carried out following the standard ASTM D2857-95, were made with a Cannon Ubbelohde B409 dilution viscometer (instrument constant $c_v = 0.002110$ cS/s, calibrated at 40 °C). Two polymeric solutions were prepared: PMMA in acetone and PAA in sodium hydroxide water solution, 2 M.

For each couple solute/solvent, the efflux time (t) was measured out starting with 15 mL of 0.002 g/mL solution, then adding 3 mL of solvent (the concentration was thus reduced to 0.00167 g/mL), then adding 3 mL of solvent once more (obtaining a concentration of 0.00143 g/mL). Therefore, the efflux times for three different concentrations were obtained. All the runs were carried out in triplicate.

Starting from the efflux time measurements, the solution viscosity η can be evaluated as the product between the efflux time (t) and instrument constant ($c_v = 0.002110$ cS/s); then the solution reduced viscosity, η_r (also called "viscosity number") can be calculated as:

$$\eta_r = \frac{\eta - \eta_0}{c \times \eta_0} \tag{1}$$

where η_0 is solvent viscosity and c is the solution polymer concentration. Then, the intrinsic viscosity, η_{int} (also called "limiting viscosity number"), can be calculated, since it is defined as:

$$\eta_{int} = \lim_{c \to 0} \frac{\eta - \eta_0}{c \times \eta_0} \tag{2}$$

The value of η_{int} can be easily evaluated from the intercept of a straight line fitting the η_r versus c values. At last, the polymer molecular weight, M_W can be calculated through Mark-Houwink-Sakurada equation (MHS):

$$\eta_{int} = K_W \times M_W^a \tag{3}$$

whose costants (K_W, a), reported in Table 1, were taken from section VII of "Polymer handbook" [7]. Both the ASTM D2857 and the Polymer Handbook define the concentration range (no more than 0.002 g/mL) to be used to avoid the non-newtonian effect of polymer solutions, and the tests were performed accordingly.

Table 1 Values of Mark-Houwink-Sakurada equation constants [7]

	T_{rif} (°C)	$K_W \times 10^3$ (mL/g)	a
PMMA in acetone	25	9.6	0.69
PAA in NaOH 2 M	25	42.2	0.64

Dissolution measurements

Measurements of pH for dissolution and swelling, in order to study the influence of the hydrophilic/hydrophobic ratios on the behavior of the synthesized copolymers, were performed in standard buffer solutions prepared according to USP 28. A dense range of pH values from 4 to 8 was investigated. Table 2 describes buffer solutions preparation. All the pH values were confirmed by Crison GLP 22 pH-meter.

The measure of dissolution pH was performed by putting a small amount (of the order of 1 g) of copolymer powder in a beaker containing 50 mL of any buffer solutions, at room temperature, in presence of a magnetic stirrer. After 24 h of stirring, for each sample: (1) the complete dissolution was assumed if there were not any trace of copolymer in solution; (2) the swelling was assumed if the powder were given up to swelled grains (increase in size and formation of a transparent surface layer of gel); (3) the copolymer was taken as pH-resistant if the powder was found un-dissolved.

Results and discussions

Synthesis

Several copolymers with different volumetric ratios of AA and MMA were synthesized and they were reported in Table 3. All synthesized samples exhibited high levels of transparency; while pure PMMA samples were colorless, pure PAA

Table 2 Composition of standard buffer solutions according to USP 28

Acid phthalate buffer												
Place 50 mL of the potassium biphthalate solution in a 200 mL volumetric flask, add the specified volume of HCl solution, then add water to volume												
pH	4.0											
0.2 M HCl (mL)	0.1											
Neutralized phthalate buffer												
Place 50 mL of the potassium biphthalate solution in a 200 mL volumetric flask, add the specified volume of NaOH solution, then add water to volume												
pH	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8			
0.2 M NaOH (mL)	3.0	6.6	11.1	16.5	22.6	28.8	34.1	38.8	42.3			
Phosphate buffer												
Place 50 mL of the monobasic potassium phosphate solution in a 200 mL volumetric flask, add the specified volume of NaOH solution, then add water to volume												
pH	5.8	6	6.2	6.4	6.6	6.8	7	7.2	7.4	7.6	7.8	8
0.2 M NaOH (mL)	3.6	5.6	8.1	11.6	16.4	22.4	29.1	34.7	39.1	42.4	44.5	46.1

Table 3 Compositions of samples prepared along this work

Sample	Volumetric %								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
MMA	0	25	30	40	50	60	70	75	100
AA	100	75	70	60	50	40	30	25	0

samples had a dark yellow color. The copolymer samples appeared yellow with the intensity of the color increasing with the amount of AA in the copolymer.

T_g measurements

Samples glass transition temperature was measured by DSC. Figure 1 shows the DSC signals for all samples recorded during the second heating step (the thermal history was summarized in the "Methods"). This choice is due to the fact that, in the first heating step, for polymers containing hydrophilic groups, a confusing peak due to adsorbed water can be found, of course this one disappears in the second heating [8].

In order to estimate the glass transition temperature, a Boltzmann equation (Eq. 4, with A_1, A_2, T_0 and dT as fitting parameters) was used to fit the DSC signal. The temperature corresponding to the center of the Boltzmann curve (the parameter T_0) was taken as T_g, as shown in Fig. 2 for a copolymer containing the 40% in volume of MMA (sample S4). Usually, the T_g is identified as the onset or as the midpoint of the transition. Here the center was selected as the most easily reliable data. However, in the following discussion the data obtained in this work will be

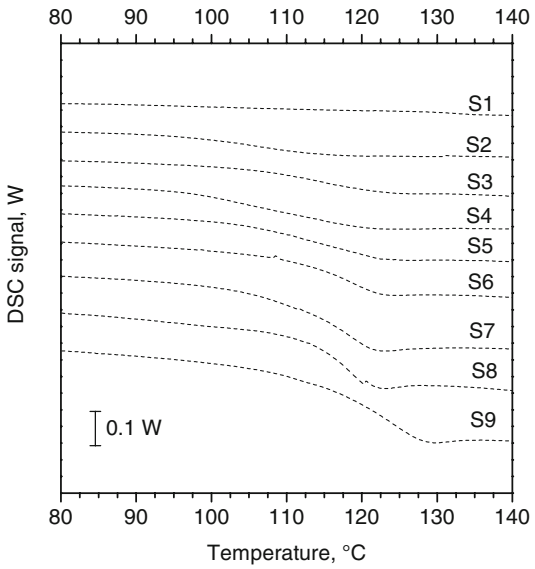

Fig. 1 DSC signal versus temperature, the graph is parametric in % of MMA

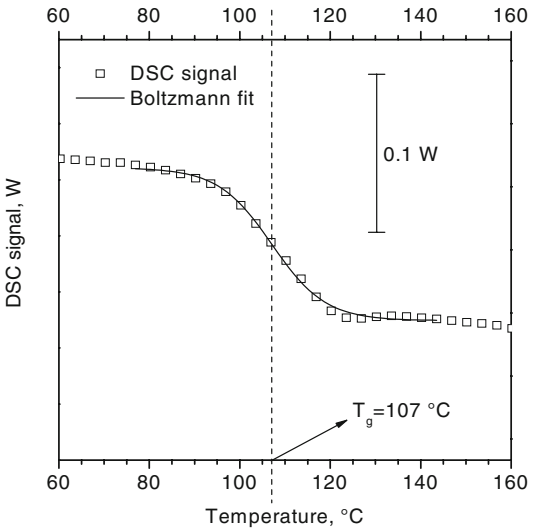

Fig. 2 DSC signal and Boltzmann fit for a copolymer with 40% (v/v) of MMA (S4)

critically compared with data from different source, accounting for the different method to estimate T_g

$$\mathrm{DSC} = \frac{A_1 - A_2}{1 + \exp\left(\frac{T - T_0}{\mathrm{d}T}\right)} + A_2. \tag{4}$$

The values of T_g as function of volumetric percentage of MMA were plotted in Fig. 3. These values for the copolymers were in good agreement with the values computed from the glass transition temperatures of the constituent homopolymers using the inverse weighted average rule:

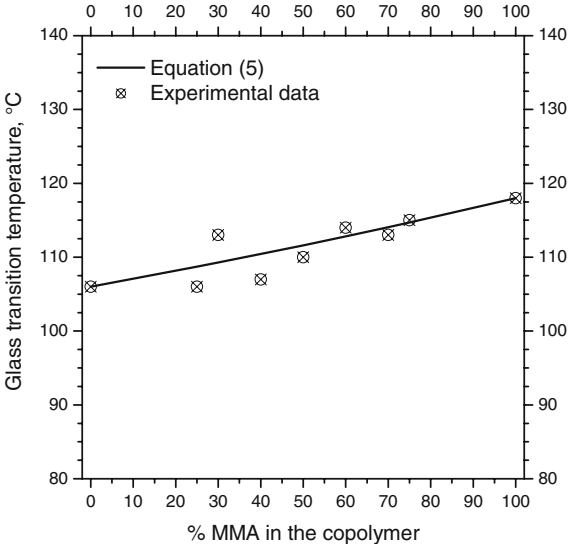

Fig. 3 Inverse weighted average rule (Eq. 5) and measured T_g values versus volumetric percentage of MMA in the copolymer

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \tag{5}$$

where w_1 and w_2 are the weight fractions of the monomer, and T_{g1} and T_{g2} are the glass transition temperatures of pure PMMA ($T_{g1} = 118$ °C) and of pure PAA ($T_{g2} = 106$ °C).

Viscosity measurements

The characterization of the polymers synthesized requires, at least, an estimation of their molecular weight. It can be done by MHS equation (Eq. 3), once the intrinsic viscosity, η_{int}, was measured. The constants in MHS equation were known for the two homopolymers (Table 1), thus the measurement is possible only for them (samples S1, S9). The intrinsic viscosity values found were 63.2 mL/g for PAA (S1) and 44.5 mL/g for PMMA (S9). By MHS equation the average molecular weight values found were 92,000 for PAA and 217,000 for PMMA.

For commercial PAAs it is reported a glass transition temperature which is independent upon molecular weight on the value of 106 °C for polymers in the M_w range from 1,800 to 4,000,000 (materials with code numbers 323667, 181293, 181285, 306215, 306223, 306231 in the Sigma-Aldrich web-catalog), the same value of T_g we found for a M_w 92,000 (which falls in the M_w range mentioned above). Thus the molecular weight is coherent with the glass transition temperature.

The dependence of glass transition temperature upon the molecular weight for PMMA is roughly described by a straight line in the plane T_g versus $\log(M_w)$. In Fig. 4 a graph of such kind is reported, with several data for commercial PMMAs (taken from Sigma-Aldrich web-catalog, the code numbers are reported on the data point themselves). For three materials the onset of glass transition is reported, along with the molecular weight as determined by GPC (closed squares). From these three data points, the linear relationship was found (the continuous line), and then a line (dashed) with the same slope was assumed to describe the dependence of (midpoint of) T_g upon $\log(M_w)$. Of course this line has to pass through the single data available for the midpoint of T_g, the sample no. SA 445746, with $M_w = 350{,}000$ and $T_g = 122$ °C. The sample S9 produced in this work has to fall on the same line, and it nicely fits in. Thus, the molecular weight and the glass transition temperature were mutually strengthened.

Dissolution measurements

The results of dissolution measurements were shown in Fig. 5, in which the closed triangles identify the polymer dissolution, the open squares the polymer full swelling and the (lower) y-error bar identify the incipient swelling.

As expected, the increase of hydrophobic monomer (MMA) causes an increase of pH at which the copolymer swells or dissolves. For example, the copolymer containing the 60% (v/v) of MMA (sample S6) dissolves at pH = 6.2 (triangle), strongly swells at pH = 5.8 (square), but the swelling was observed up to pH = 5.6, as indicated by the error bar: under this pH value the polymer kept un-dissolved. For

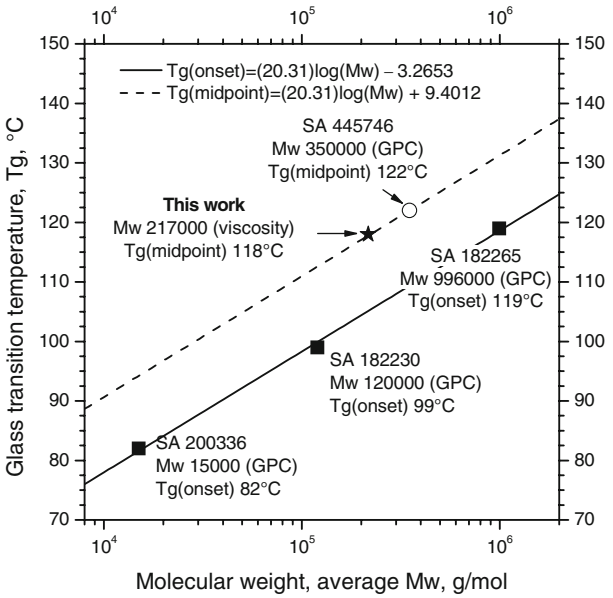

Fig. 4 Relationship between the glass transition temperature (onset or midpoint) and log (molecular weight), for some commercial PMMAs (SA, i.e., from Sigma Aldrich) and for the one obtained in this work

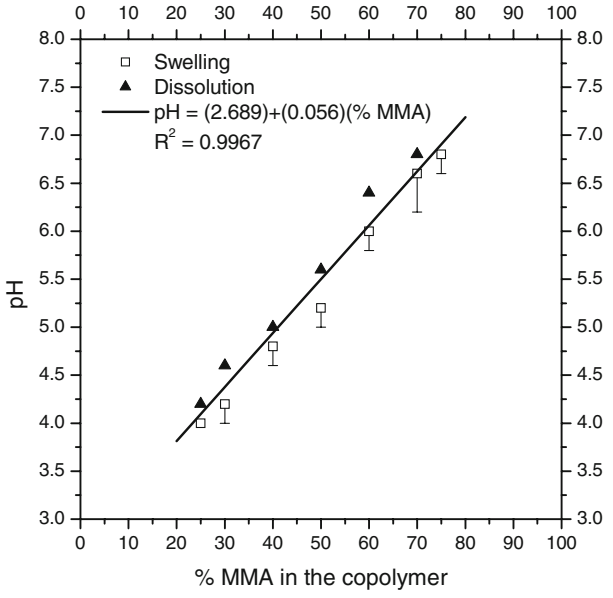

Fig. 5 Swelling and dissolution pH versus volumetric percentage of MMA in the copolymer

the sample S8 [the 75% (v/v) of MMA copolymer], only swelling was observed (from pH = 6.5 to 6.8): dissolution was not observed in the investigated range, that is up to pH = 8.

The pH interval between the swelling and dissolution is small and it is hard to investigate, since the two phenomena take place simultaneously. Thus, an arithmetic mean between the swelling and the dissolution pH values was taken as the measure of "incipient" dissolution, and these average data points (not reported in the graph) were taken as the basis for a linear fit, reported as a continuous line in Fig. 5. The equation is:

$$\mathrm{pH} = a + b \times \%\mathrm{MMA} \tag{6}$$

where $a = 2.689$, $b = 0.056$ and the values of R^2 was 0.9967. Therefore the desired pH of dissolution of a poly(methyl methacrylate-acrylic acid) copolymer (wished pH for targeted drug release) can be chosen in function of its MMA volumetric percentage by this linear equation.

Conclusions

In this work, copolymers of poly(methyl methacrylate-acrylic acid) with various ratios of the hydrophobic to hydrophilic monomers were synthesized and characterized. The glass transition temperature of each copolymer follows the inverse weighted average rule, confirming the production of copolymers with the right composition. The viscosity of the pure-polymer solution well agrees with the molecular weight expected on the basis of glass transition temperature measurements. The dissolution and swelling pH values were carefully determined, and a linear relationship was found between the %MMA in the copolymer and the dissolution pH. Thus, the copolymer which dissolves at the desired pH, for targeted oral drug delivery, can be easily prepared by using Fig. 5.

References

1. Qiu Y, Park K (2001) Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 53:321
2. Maharaj I, Nairn JG, Campbell JB (1984) Simple rapid method for the preparation of enteric-coated microspheres. J Pharm Sci 73:39
3. Brannon-Peppas L, Peppas NA (1990) Dynamic and equilibrium swelling behavior of pH sensitive hydrogels containing 2-Hydroxyethyl methacrylate. Biomaterials 11:635
4. Peppas NA, Klier J (1991) Controlled release using P(EG-g-MAA) hydrogels. J Control Release 16:203
5. Yessine MA, Lafleur M, Petereit HU, Meier C, Leroux JC (2003) Characterization of the membrane-destabilizing properties of different pH-sensitive methacrylic acid copolymers. Biophys Biochim Acta 1613:28
6. Abusafieh A, Gobran R, Kalidindi SR (1997) Synthesis and characterization of a poly(methyl methacrylate-acrylic acid) copolymer for bioimplant applications. J Appl Polym Sci 63:75
7. Brandrup J, Immergut EH, Grulke EA (1999) Polymer handbook, 4th edn. Wiley, New York
8. Turner DT, Schwartz A, Graper, Sugg H (1986) Highly swollen hydrogels: vinyl pyrrolidone copolymers. Polymer 27:1619