# A monomer feed system for producing narrow composition range copolymers from comonomers of widely differing reactivities

**I. N. Askill and D. K. Gilding***
*ICI/University of Liverpool Joint Laboratory, Bioengineering Unit, P.O. Box* 147,
*Liverpool L*69 3*BX, UK*

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The development of a method of synthesis designed to produce narrow composition range, random copolymers from monomers of widely differing reactivities is described. The structures and properties of these copolymers of methyl methacrylate and acrylic acid are exhaustively characterized and contrasted with their broad composition analogues. The implications of these properties for studies of biocompatibility are discussed.

## INTRODUCTION

The search for bioactive polymers that interact in a positive way with natural tissues led us to synthesize a series of acrylic copolymers as model structures[1-3]. The acrylic family was chosen because it allowed a matrix of materials to be developed of varying hydrophobic/hydrophilic balance, charge, (direction and density) and counter ion.

In order to study the effect of polymer composition on the complex sequence of events occurring in the healing wound, it is necessary to have as broad a range as possible of samples with different compositions, each with as narrow a distribution of compositions as possible. A narrow composition distribution has two major advantages. Firstly, there will be no overlap between the compositions of individual members and any trends will be more definitive. Secondly, domain formation will be unlikely and since these copolymers are amorphous, surface and bulk compositions should be identical. Such narrow compositions do not preclude association between polar or ionic groups causing these copolymer surfaces to be more hydrophobic than might be expected.

## MONOMER FEED METHOD

The composition of a copolymer formed from a given mixture of monomers 1 and 2, of reactivity ratios $r_A$, $r_B$, can be calculated from:

$$\frac{A}{B} = \frac{r_A \frac{a}{b} + 1}{r_B \frac{b}{a} + 1} \qquad (1)$$

'*A*' and '*a*' in equation 1 are the molar concentrations of monomer 1 in the copolymers and monomer mixture respectively — ('*B*' and '*b*' are the same for comonomer 2)[5,6].

Copolymers of methyl methacrylate (MMA) and acrylic acid (AA) are examples of comonomers with widely differing reactivities i.e. $r_{\mathrm{MMA}} = 2.3$ and $r_{\mathrm{AA}} = 0.31$ (ref 4).

The net result is that MMA tends to be incorporated into blocks in the copolymer chain, whereas AA is incorporated individually. This causes a preferential depletion of MMA and results in the formation of a copolymer with a broad distribution of compositions.

If $r_{\mathrm{MMA}}$ and $r_{\mathrm{AA}}$ are substituted into equation 1, with a starting comonomer molar composition of 80:20 for MMA/AA, for example, it is possible to calculate the composition of the initially formed copolymer. In this case the initial copolymer contains 9.5 m% AA. If we allow the reaction to go to 5% conversion, assuming no change in copolymer composition, it is possible to calculate the degree of depletion of MMA. If the same calculation is carried out using the adjusted comonomer composition the copolymer will have a higher AA content. Continuing this procedure in steps of 5% conversion allows the theoretical composition distribution of the 80:20 MMA/AA to be generated, (*Figure 1*). This copolymer contains chains with AA contents ranging from 9.5 to 100 m%.

The theoretical distribution of compositions shown in *Figure 1* represents the narrowest possible composition range and assumes constant and continuous rates of initiation and termination throughout the course of the

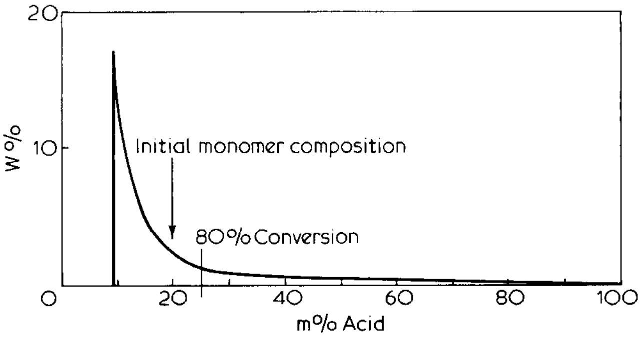

*Figure 1* Theoretical composition distribution for 80 : 20 MMA/AA copolymer

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* Current Address: Millipore Corporation, Ashby Road, Beford, MA 01730 USA

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*Table 1* Simple polymerizations to obtain kinetic data

| %AA monomer calculated | %AA initial copolymer |  | Rate of polymerization |  |
|---|---|---|---|---|
|  | Theoretical | Experimental (~10% conversion) | % conversion $min^{-1}$ | g $min^{-1}$ |
| 21 | 10 | 10.2 | 0.74 | 1.47 |
| 38 | 20 | 20.6 | 0.74 | 1.47 |

polymerization. In practice non-equilibrium effects due to reduced diffusion rates and 'monomer starvation' are likely, both tending to broaden the composition distribution. However, if, as shown in *Figure 1*, the polymerization was taken to 80% conversion, the compositions would range from 9.5 to 25 m% AA which was unacceptable.

### *Principle of the monomer feed*

The aim of the method is to maintain the concentrations of each monomer and the initiator constant throughout the polymerization. The simplest way to achieve this is to feed monomers in the same ratio as in the copolymer being produced, at the same rate as the copolymer is formed. An attempt was made to maintain initiator levels by introducing initiator with the monomer feed stream at the same concentration as in the initial reaction mixture.

Before such a monomer feed system could be designed, two pieces of information were required. Firstly, the reactivity ratios $r_{MMA}$ and $r_{AA}$ under the reaction conditions used had to be determined in order that the composition of the copolymer being formed could be determined. Secondly, the rate at which the copolymer was formed had to be determined in order to set the feed rate. This type of information was developed from two simple polymerizations.

### *Development of kinetic data*

Simple solution polymerizations of MMA/AA were carried out in butanone at 80°C using azobisisobutyronitrile (AIBN) initiator. A one litre flanged glass reactor was fitted with a reflux condenser, nitrogen bleed, stirrer, thermometer and sampling port and set up in a thermostated water bath maintained at 85°C. The reaction temperature was 80–82°C and was held constant by the refluxing butanone.

Two polymerizations were carried out to determine reaction rates at each end of the composition range of interest, i.e. 10 and 20 m% AA. Value for $r_{MMA}$ and $r_{AA}$ were taken from the literature[4], and the monomer ratios required to produce an initial composition of 10 and 20 m% AA were calculated, see *Table 1*.

A typical reaction sequences was as follows. 300 ml of stirred butanone was brought to reflux and 200 g of total monomer containing 0.2 g of dissolved AIBN was added. Samples were taken every 5 min for the first hour and every 15 min thereafter. The polymer was precipitated in petroleum ether 60–80°C, weighed to obtain % conversion, and titrated[7,8] to obtain AA content.

Conversion rate is constant up to 25% conversion, and is independent of composition between 10 and 20 m% AA. Each reaction showed a 6 min lag prior to onset. This is presumably caused by the cold monomers coming to reaction temperature. The relevant kinetic data for setting up the monomer feed method is shown in *Table 1* together with the compositional data. The close similarity of the theoretical and experimental AA contents of the copolymers confirm the validity of the literature values[4] of $r_{MMA}$ and $r_{AA}$ for the polymerization conditions used.

### *MMA/AA copolymers with broad composition ranges from simple polymerization*

In order to investigate the effectiveness of the monomer feed polymerization it was necessary to synthesize broad composition range copolymers with equivalent compositions to their narrow range analogues. This was done using the same equipment and scale of polymerization as described above, using identical total monomer and initiator concentrations. Samples were withdrawn every 10 min for the first hour and every 30 min thereafter until the reaction was terminated after ~5 h. The samples were quenched in vials surrounded by solid $CO_2$/methanol and stored in a freezer.

Real time analysis was obtained by determining residual monomer contents relative to the butanone using gas chromatography (g.c.). A stainless steel column, 12′ × 1/8″, containing Chromosorb 101 with 3% carbowax 20 M and a precolumn containing PTFE wool was used at 165°C for this analysis. The method was adequate for the analysis of early samples, but became less useful as polymer content increased.

The % conversion and composition of the time samples was determined more accurately by careful precipitation followed by weighing and titration[7,8]. The copolymers were coded on the basis of m% negatively charged AA with a suffix N denoting non-feed, i.e. 17.5-N denotes 17.5 m% AA copolymer produced by non-feed. The average composition for the 17.5-N copolymer shows an increase in AA content with time.

Molecular characterization of the time samples was carried out using gel permeation chromatography (g.p.c.) with $10^5$ and $10^3$ Å Styragel$^{R}$ columns and anhydrous dimethyl acetamide (DMAc) containing 0.2% LiBr to overcome polyelectrolyte effects[2,9]. Weight and number average molecular weights $\bar{M}_w$ and $\bar{M}_n$ of the 17.5-N copolymer are shown as a function of conversion in *Figure 2*. The measurements were distorted by traces of residual water in the samples introducing a negative peak onto the low *MW* tail of the g.p.c. chromatogram. This increases the apparent $\bar{M}_n$ since it is only possible to calculate *MW* averages based on the positive peak.

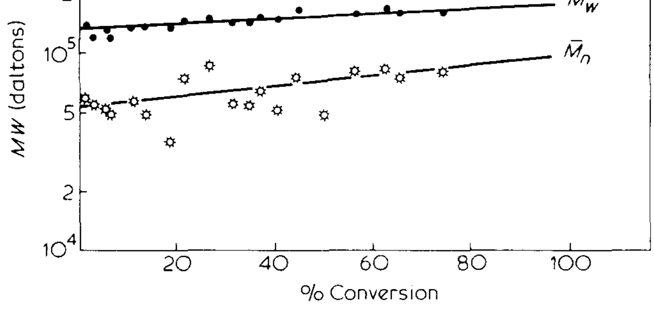

*Figure 2* Average molecular weights as a function of % conversion

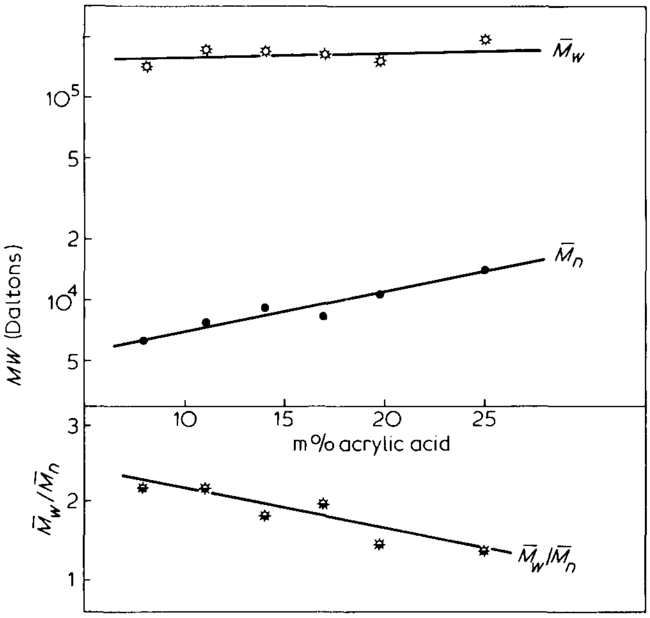

*Figure 3* Molecular parameters for non-feed MMA/AA copolymers

*Table 2* MMA/AA copolymers with broad composition ranges

| Copolymer Code name | M% AA monomers | M% AA initial copolymer | M% AA in final copolymer | |
|---|---|---|---|---|
| | | | theoretical | experimental |
| 10-N | 15 | 7 | 15 | 11 |
| 15-N | 18 | 8.5 | 18 | 14 |
| 17.5-N | 22.3 | 10.8 | 22.3 | 17 |
| 20-N | 25 | 12.3 | 25 | 19.5 |

$\bar{M}_w/\bar{M}_n$ narrows with time which is unexpected, however, as the higher AA content copolymers tend to be removed by solubilization in water during purification, this observation can be explained. This explanation is confirmed in *Figure 3* where $\bar{M}_w$, $\bar{M}_n$ and $\bar{M}_w/\bar{M}_n$ are shown as a function of AA content. $\bar{M}_w$ is found to be independent, $\bar{M}_n$ rises and $\bar{M}_n/\bar{M}_w$ falls as acrylic acid content increases within the family of copolymers. After $\sim 5$ h, the reaction mixture was diluted to 1000 ml with butanone (to improve the ease of handling of the precipitate), and quenched in solid CO$_2$/methanol. The polymer was purified by precipitation in excess petroleum ether 60–80°C to remove MMA residues and initiator. The polymer was redissolved in acetone, reprecipitated in water to remove acrylic acid and finally dried under vacuum at 60°C.

This phase of the work consisted of six polymerizations, the details of the four relevant ones are shown in *Table 2*.

Higher AA contents were used in the monomer mixture than a polymerization taken to 100% conversion would require. This was done in an attempt to offset the loss of the higher AA content species by the second precipitation and extensive water washing. The monomer compositions required to produce a desired average copolymer composition were determined empirically as the samples and data were produced[11].

## MONOMER FEED POLYMERIZATION

The same polymerization reactor as described above was used with the addition of a 'Drayton R.Q.' metering pump set up to deliver the feed stream from a stirred reservoir cooled in ice/water. The feed was delivered into the reflux condenser. All monomer contact points were glass, stainless steel or PTFE (stainless steel balls are required as valves in the pump because of corrosion by AA). The pump was calibrated before each reaction with each specific mixture of chilled monomers to eliminate any variations in rates that might occur due to variations in the viscosity of the monomer stream.

Each polymer was synthesized by adding 200 g of monomers + 0.2 g AIBN to 300 ml of refluxing butanone. The monomer ratio introduced into the reactor was that calculated to produce the desired copolymer composition immediately the reaction started i.e. that composition calculated from equation 1. Six minutes were allowed for thermal equilibration and commencement of the reaction before the metering pump was started. The monomer feed stream, containing monomer in the same ratio as being consumed in the polymerization with 0.1% AIBN, was delivered at a rate of 1.47 g of total monomer/min (*Table 1*).

Four monomer feed polymerizations were carried out as this part of the series, relevant polymerization data is shown in *Table 3*.

As in the non feed series, samples were taken from the reactor at 10 min intervals for the first hour, half hourly thereafter, and analysed as described previously by g.c., g.p.c., precipitation and titration. Real time analysis by g.c. was particularly important from the monomer feed runs, as the ratio of MMA and AA must remain constant throughout the reaction, if the feed control is to be successful. In the first polymerization some adjustment of flow was necessary however, using g.c. analysis, control was achieved within 15 min. The other members of the series required no adjustment.

The samples were coded as before, with the suffix 'F' denoting the product of a monomer feed reaction. The average composition of the 17.5-F copolymer as a function of % conversion is shown in *Figure 4* and its $\bar{M}_w$ and $\bar{M}_n$ as a function of % conversion in *Figure 5*. These sets of results show two differences to those shown in *Figure 2* in that the composition remains constant, and the *MWD*

*Table 3* Polymerization data for monomer feed polymerizations

| Copolymer code name | M% AA | Initial monomers (g) | | Feed monomers (g) | |
|---|---|---|---|---|---|
| | | MMA | AA | MMA | AA |
| 10-F | 10 | 168.1 | 31.9 | 227.8 | 22.2 |
| 15-F | 15 | 153.2 | 46.8 | 266.2 | 33.8 |
| 17.5-F | 17.5 | 145.9 | 54.1 | 347.0 | 53.0 |
| 20-F | 20 | 138.9 | 61.1 | 254.2 | 45.8 |

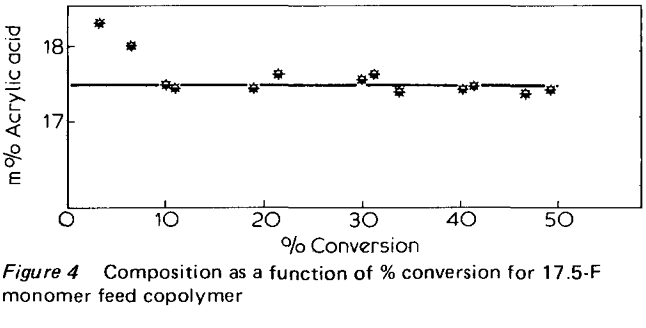

*Figure 4* Composition as a function of % conversion for 17.5-F monomer feed copolymer

remains narrow throughout the course of the polymerization, whereas previously both parameters, i.e. composition and *MWD*'s broadened.

The polymerization was taken to 200 g of copolymer, before being diluted, quenched and purified as described above. In this type of polymerization only the amount of monomer equivalent to that delivered in the feed is converted to copolymer, therefore an amount equivalent to the initial monomer charge in the reactor remains unconverted. No attempt has been made here to optimize the economics of the reaction. However, this can be achieved firstly by reducing the initial charge to as low a level as possible, consistent with maintenance of reaction control; and secondly, by removing the copolymer as it is formed. Both these operations are relatively simple to achieve on a larger scale process. The present process has been sufficient to demonstrate the differences between a simple copolymer and the purely random one formed by the monomer feed process. Both series of polymers have been used in implantation studies[3,10] and marked differences have been shown between narrow and broad composition ranged samples of equivalent average compositions.

*Fractionation*

Additional information was developed by fractional dissolution in methanol/butanone mixtures of increasing butanone content. Methanol was selected in preference to a non-polar, non-solvent such as petroleum ether 60 80 C since AA was expected to be more abundant in the lower *MW* species, and hence fractionation on the basis of *MW* with composition working as an additive rather than a subtractive effect could be achieved using a polar non-solvent.

10 g of the purified copolymers were refluxed with the extractant for ~ 1 h with stirring, at which point heating was discontinued but stirring maintained for another hour. The mixture was allowed to cool to 4 C over 24 h, at which point the solution was syphoned off and evaporated to dryness in a weighed Rotovap$^R$ flask. Enriched extractant was added to the remaining polymer and the process was repeated until 10 15 fractions had been taken and the total polymer dissolved.

Cumulative distributions of, for example, the 17.5-N and 17.5-F copolymers are shown as a function of solubility of *Figure 6*. The Figure shows that the solubility range of the non-feed polymerizations is broader for the non-feed copolymer than the feed which was expected.

Each fraction was titrated[7,8] to yield acid content, and molecularly characterized by g.p.c. The results are tabulated in *Table 4* for the 17.5-N and 17.5-F fractions.

The fractionation data in *Table 4* was summed to obtain average composition as a function of *MW*. In order to do this it was assumed that composition is constant across the *MWD* of each fraction. Each g.p.c. was normalized firstly on the basis of total area, and secondly by wt% of the specific fraction relative to the total sample. The average composition at each *MW* was then computed from the summation of normalized heights of the chromatograms, e.g.:

$$A_{M_i} = \frac{[A_1.h_1 + A_2.h_2 + A_3.h_3 + \quad ]_{M_i}}{[h_1 + h_2 + h_3 \quad ]_{M_i}}$$

where $A_{M_i}$ is the m% of acrylic acid at molecular weight $M_i$, $A_1$, $A_2$, $A_3$, etc. are the AA contents of fractions 1, 2, 3, etc., and $h_1$, $h_2$, $h_3$ are the normalized heights of the

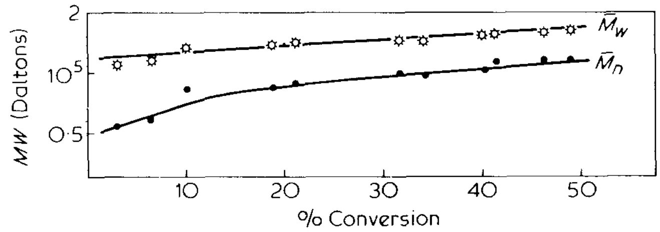

*Figure 5* Average molecular weights as a function of % conversion for 17.5-F monomer feed copolymer

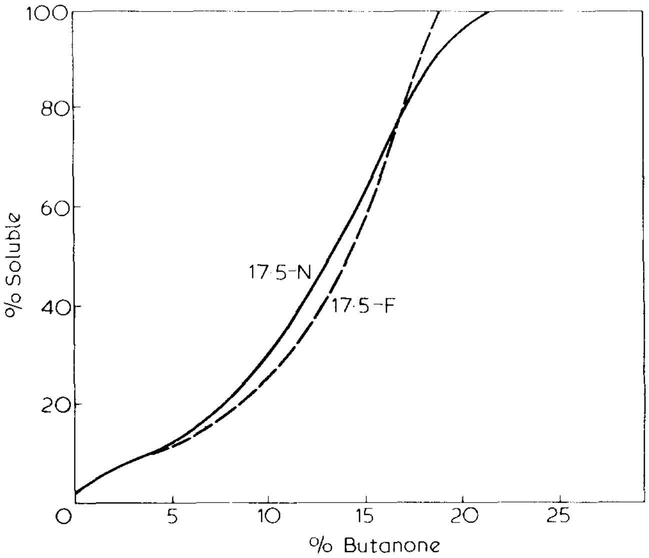

*Figure 6* Fractional solubility of 17.5-F and 17.5-N copolymers in butanone/methanol mixtures

*Table 4* Comparative data for 17.5 m% AA copolymer fractionations for feed and non feed samples

| | Broad 17.5-N | | | | Narrow 17.5-F | | | |
|---|---|---|---|---|---|---|---|---|
| % Butanone | wt % soluble | % AA | $\bar{M}_w \times 10^{-3}$ | $\bar{M}_n \times 10^{-3}$ | wt % soluble | % AA | $\bar{M}_w \times 10^{-3}$ | $\bar{M}_n \times 10^{-3}$ |
| 0 | 5.2 | 21 | 43 | 9.8 | 5.3 | 18.3 | 72 | 32 |
| 2 | 2.4 | 19.6 | 72 | 19 | 3.1 | 17.9 | 96 | 51 |
| 4 | 3.4 | 18.9 | 95 | 34 | 3.2 | 17.2 | 113 | 71 |
| 6 | 4.3 | 18.7 | 120 | 41 | 3.9 | 17.7 | 119 | 76 |
| 8 | 5.6 | 18.5 | 140 | 76 | 5.3 | 17.6 | 125 | 81 |
| 10 | 12.4 | 17.8 | 150 | 89 | 7.5 | 17.5 | 137 | 94 |
| 12 | 15 | 17.2 | 170 | 100 | 12.4 | 17.5 | 141 | 97 |
| 14 | 14.2 | 16.5 | 170 | 100 | 14.2 | 17.3 | 156 | 109 |
| 16 | 14.8 | 15.3 | 180 | 120 | 25.5 | 17.0 | 171 | 118 |
| 18 | 17.5 | 14.7 | 180 | 120 | 19.6 | 16.8 | 164 | 114 |
| 20 | 5.2 | 13.9 | 180 | 130 | | | | |

*Table 5* Molecular characterization data for MMA/AA copolymers produced by feed and conventional polymerization

| Sample code | m% AA | $\bar{M}_w \times 10^{-3}$ | $\bar{M}_n \times 10^{-3}$ | $M_{max} \times 10^{-3}$ | $M_{min} \times 10^{-3}$ | $\bar{M}_w/\bar{M}_n$ |
|---|---|---|---|---|---|---|
| 10-N | 11 | 170 | 78 | 1250 | 2.4 | 2.2 |
| 15-N | 14 | 170 | 94 | 1250 | 2.8 | 1.8 |
| 17.5-N | 17 | 160 | 81 | 1600 | 4.0 | 2.0 |
| 20-N | 19.5 | 150 | 107 | 810 | 8.4 | 1.4 |
| 10-F | 10 | 160 | 116 | 900 | 13 | 1.4 |
| 15-F | 15 | 150 | 107 | 980 | 15 | 1.4 |
| 17.5-F | 17.5 | 160 | 116 | 900 | 15 | 1.4 |
| 20-F | 20 | 160 | 110 | 900 | 12 | 1.4 |

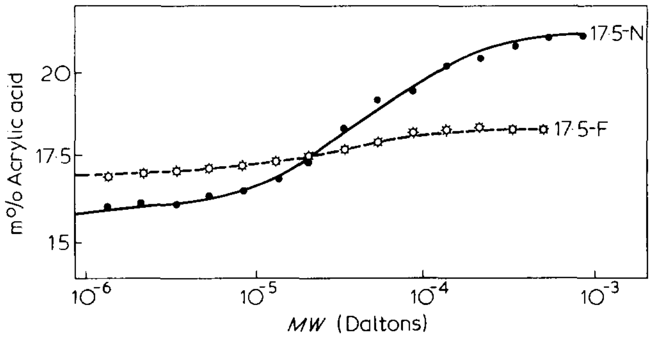

*Figure 7* Variation of composition with *MW* for 17.5-F and 17.5-N MMA/AA copolymers

chromatograms at $MW = M_i$.

The average compositions of, for example, the 17.5-N and 17.5-F samples are shown in *Figure 7*. The data shows a ±0.6 m% variation for the copolymer produced by the feed reaction, with only the species in each tail of the *MWD* showing any deviation from the mean. The copolymer produced by the simple polymerization has higher acid levels for the lower *MW* species with is undesirable because of increased solubility in hydrophilic media, such as the physiological environment.

The molecular characterization data is shown in *Table 5* for the members of each series.

The results in *Table 5* show that the *MWD*s of the non-feed copolymers have longer low *MW* tails than the equivalent copolymers produced by the feed method. The polydispersities $\bar{M}_w/\bar{M}_n$ are narrow for polymers produced by free radical mechanisms. AA levels become progressively lower than expected in the non-feed polymers as the average AA content increases indicating that the highest AA species are being lost during precipitation and washing in distilled water.

Solubilization (or leachability) is particularly serious when a polymer is to be implanted into biological tissues as phagocytic cells whose prime purpose is the disposal of soluble species or small particles of foreign bodies within the healing wound environment will be stimulated by the soluble products, and the observed tissue response will be changed. As the copolymers described in this paper are ionized at pH 7 and their degree of hydration will depend to a great extent not only on the AA level, but also the counter cation, equilibrium water measurements were made using tris buffer containing $H^+$, $Na^+$, $K^+$, $Mg^{++}$, $Ca^{++}$ and $Zn^{++}$ cations.

The results in *Figure 8* show a dramatic effect of counter ion on equilibrium water level. The $Na^+$ and $K^+$ forms of 20-F are soluble which is a particularly important observation as no matter which form is used in *in vivo* experiments, ion exchange will occur to the $Na^+$ form and the implant will dissolve. From the point of view of insoluble species 17.5-F is the upper limit of AA, however, the $Na^+$, $K^+$ and $Mg^{++}$ forms are hydrogel-like. The water contents of the broad composition range series are always lower than their narrow range equivalents, this is probably due to the influence of the low AA content species. For AA contents up to 15 m%, the hydrophobicity and $T_g$ of the MMA comonomer is the factor controlling swelling behaviour and mechanical properties.

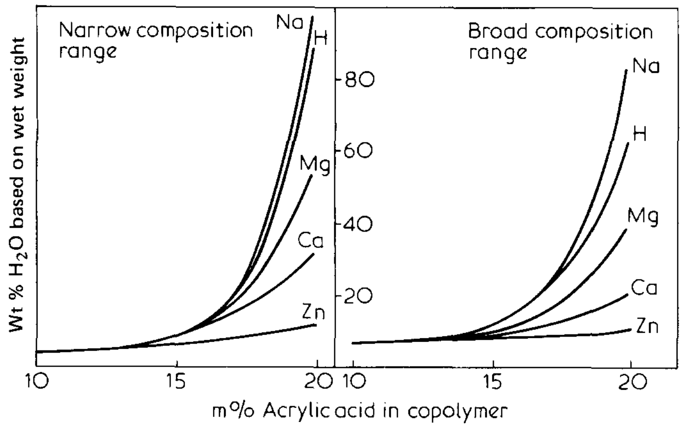

*Figure 8* Water uptake for AA/MMA with counter ions

## CONCLUSIONS

The data presented shows that narrow composition distribution copolymers can be produced from many monomers of widely differing reactivities (providing $r_1 \geqslant 1$ and $r_2 \leqslant 1$) using relatively simple equipment. These copolymers have different properties than their broad composition distribution analogues, as demonstrated by their solubility and swelling behaviour. Further differences in the surface properties of these materials, their behaviour *in vivo*[10], and their effect on protein adsorption and cell adhesion *in vitro* will be demonstrated in later papers in this series.

## REFERENCES

1 Gilding, D. K., Wilson, J. and Pigott, G. H. *J. Biomed. Mater. Res.* to be published
2 Gilding, D. K. and Askill, I. N. *ibid*
3 Wilson, J., Gilding, D. K. and Pigott, G. H. *ibid*
4 'Polymer Handbook' 2nd edn. (Eds J. Brandrup and E. H. Immergut) Wiley 1975; Kerber, R. and Glamann, H. *Makromol Chem.* 1971, **144**, 1
5 Flory, P. J. 'Principles of polymer chemistry', Cornell University Press 1953
6 'Copolymers, High polymers', XVIII, (Ed H. Cram) Wiley, 1964
7 Pohl, H. A. *Anal. Chem.* 1954, **26**, 1614
8 Conix, A. *Makromol. Chem.* 1958, **26**, 226
9 Gilding, D. K., Reed, A. M. and Askill, I. N., *Polymer* 1981
10 Wilson, J., Gilding, D. K., Askill, I. N. and Pratt, I. *J. Biomed. Mater. Res.* to be published
11 Askill, I. N., *PhD Thesis* University of Liverpool, 1981