SEQUENCE DISTRIBUTIONS IN FREE-RADICAL POLYMERS

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Doctor of Philosophy

The University of Aston in Birmingham

September 1993

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Summary of thesis

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1993

This thesis is concerned with demonstrating how the visual representation of the sequence distribution of individual monomer units, of a polymer, that would be observed upon polymerisation, may be utilised in designing and synthesizing polymers with relatively low cell adhesion characteristics.

The initial part of this thesis is concerned with demonstrating the use of a computer simulation technique, in illustrating the sequence distribution that would be observed upon the polymerisation of a set of monomers. The power of the computer simulation technique has been demonstrated through the simulation of the sequence distributions of some generic contact lens materials. These generic contact lens materials were chosen simply because in the field of biomaterials their compositions are amongst the most systematically regulated and they present a wide range of compositions.

The validity of the computer simulation technique has been assessed through the synthesis and analysis of linear free-radical polymers at different conversions. Two main parameters were examined, that of composition and the number-average sequence lengths of individual monomer units, at various conversions. The polymers were synthesized through the solution polymerisation process. The monomer composition was determined by elemental analysis and ^{13}C nuclear magnetic analysis (NMR). Number-average sequence lengths were determined exclusively through ^{13}C NMR. Although the computer simulation technique provides a visual representation of the monomer sequence distribution up to 100% conversion, these assessments were made on linear polymers at a reasonably high conversion (above 50%) but below 100% conversion for ease of analysis. The analyses proved that the computer simulation technique was reasonably accurate in predicting the sequence distribution of monomer units, upon polymerisation, in the polymer.

An approach has been presented which allows one to manipulate the use of monomers, with their reactivity ratios, thereby enabling us to design polymers with controlled sequence distributions.

Hydrogel membranes, with relatively controlled sequence distributions and polymerised to 100% conversion, were synthesized to represent prospective biomaterials. Cell adhesion studies were used as a biological probe to investigate the susceptibility of the surface of these membranes to cell adhesion. This was necessary in order to assess the surface biocompatibility or biotolerance of these prospective biomaterials.

KEYWORDS: computer simulation, ^{13}C NMR sequence analysis, cell adhesion.

In dear memory of my late mother, whose life expressed compassion and commitment more eloquently than any words.

Acknowledgements

Many thanks to Professor Brian Tighe for his lucid advice and unwavering support throughout the course of this study. Thanks are also due to all my colleagues within the Speciality Materials Research Group for their friendly demeanour and amiable discourse. I am especially grateful to Helen Fitton and Dr. Mohammed Yasin, and last but by no means least to Julie Patterson, our group co-ordinator, for their generous help and encouragement.

I am indebted to Helen Fitton for all her cell adhesion studies on my polymer samples, and for the many exchanges of ideas and thoughts concerning this work.

I would like to acknowledge Dr. S. J. Moss and Dr. P. Corkhill for the development of the computer simulation programs extensively used in this work.

I would like to express my gratitude to Dr. Mike Perry for helpful conversations about ^{13}C NMR and for his time spent on obtaining the many laborious, yet essential spectra.

Words cannot express how grateful I am to my family for their support, encouragement and patience throughout my course of academic study.

My thanks go out to Linh Nguyen for joining me in spending many pleasurable hours taking full advantage of the numerous sporting facilities at Aston.

Financial assistance was kindly provided by SERC and Kodak under the CASE award scheme.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AZBN	Azo-bis-iso-butyronitrile
^{13}C NMR	Carbon-13 nuclear magnetic resonance
DATDAM	N,N-Diallyl-tartardiamide
EGDMA	Ethylene glycol dimethacrylate
EMA	Ethyl methacrylate
EOEMA	Ethoxyethyl methacrylate
EWC	Equilibrium water content
HEA	2-Hydroxyethyl acrylate
HEMA	2-Hydroxyethyl methacrylate
HPA	2-Hydroxypropyl methacrylate
IND	Indene
ITA	Itaconic acid
MMA	Methyl methacrylate
NACM	N-Acryloyl morpholine
NNDMA	N,N-Dimethyl acrylamide
NVC	N-vinyl carbazole
NVI	N-Vinyl Imidazole
NVP	N-Vinyl pyrrolidone
PEG400	Methoxy Poly(ethylene glycol) mono methacrylate
SPE	N,N-Dimethyl-N-methacryloyloxyethyl-N- (3-sulpho propyl) ammonium betaine
STY	Styrene
TAC or TAOTZ	2,4,6-Triallyloxy-s-triazine

CHAPTER ONE

INTRODUCTION

1.0 General Introduction

Up until quite recently most materials currently used in biological environments have been appropriated from the large selection of synthetic materials available, and designed for commodity or engineering application. They have usually been chosen because of ease of fabrication but rarely because they have surface properties similar to a particular natural tissue. Thus, poly (methyl methacrylate) (PMMA) was initially used in contact lenses[1] not only because of its toughness, optical properties and its relatively low physiological activity but mainly because of its ease of fabrication by existing grinding and polishing techniques. It was not, therefore, a purpose designed polymer, but it displayed some important properties, and there were no other serious candidates until the development of hydrogels[2-4]. The story is similar in other areas of biomaterial design. A great need exists for materials whose structures can be tailored to meet the demands of the biological environment.

When designing a new material for use in biological environments one must be fully aware of the relationship between the material and its immediate environment. Consideration of the materials bulk and surface properties, including chemical, physical and biological aspects are important as is the effect of the biological environment on the material. Thus, a good biomaterial which is fully biocompatible, would be one which does not adversely affect the biological environment it is placed in contact with, nor is itself adversely affected by it[5]. This phenomenon of biocompatibility has arisen from the extensive use of man-made materials to replace or augment biological structures *in situ*. It involves the investigation of the interactions between the host tissue and the implanted material(the biomaterial), and its environment.

No single material can be spoken of as being 'biocompatible', this is simply because different biological environments produce somewhat different requirements and no single material meets all of them[6]. For example in the design of a new soft contact lens one must bear in mind the transport, mechanical and surface properties. It is apparent that the universal problem is that of compatibility whether to blood, other body fluids(such as here to tears) or tissue. Surface properties are of paramount importance since they contribute greatly in determining the biocompatibility of the material in its particular biological environment. The transport properties will be governed by the permeability requirements of the cornea. This is because it is avascular it needs to respire directly form the atmosphere, as this is the major source of the oxygen required to maintain its biochemical balance. Since we are dealing with a soft contact lens, it will basically be a hydrogel. In hydrogels the transport properties are governed by the water content of the hydrogel, and a suitably high water content hydrogel may be designed to accommodate the oxygen requirements of the cornea. The presence of this quantity of water in the polymer also affects the mechanical properties of the material. Here the balance of the properties is governed by the eyelid. Although soft materials are, in general, more comfortable to the eyelid, there is a lower limit to the stiffness that can be tolerated. This because the eyelid exerts a fairly considerable deforming force during the blink cycle. Here manipulation of the cross-link density and backbone structure will allow control over the water content of the hydrogel and limit deformation under eyelid load with good elastic recovery. Now, for example, in hip-joint prostheses, where a stainless steel or ceramic ball moves in a polymer cup, we find that mechanical properties here are very important. It is apparent that if the mechanical properties are not reasonably

correct here, then little meaningful evaluation of the other properties can take place.

It is usually the case that the physical nature of the material and its mechanical properties provide the short term barrier to successful application of the biomaterial, in the sense that they are necessary for it to work. Having overcome this hurdle however, the problem that limits the success of the biomaterial in the longer term is usually biocompatibility. The body does not readily tolerate synthetic materials, this is an underlying problem in the great majority of biomedical applications.

1.1 Factors Affecting The Biocompatibility of Biomaterials

As mentioned earlier the surface characteristics of the new biomaterial will predominantly determine its degree of biocompatibility with the biological system it is to be employed in. The underlying processes that govern this interaction are common to many areas where certain materials come into contact with biological solutions. Thus the deposition of tear fluid debris, the clotting of blood on foreign surfaces, the formation of dental plaque, marine fouling and the fouling of membranes used in biochemical separations are all examples of the same fundamental phenomenon. The phenomenon frequently begins with the adsorption of protein at an interface and is followed rapidly by the competitive adsorption of other biochemicals. The initiating processes in all of these interactions are referred to as biological interface conversion processes.

Many factors are known to influence these interface conversion processes, such

as surface energy, surface chemical groups, hydrophobocity, hydrophilicity; equilibrium water content in hydrogels, sequence distribution of monomer units, and the surface topology. It is apparent that no single parameter can be used exclusively to describe the biocompatibility of the surface of the new material. This is simply because most of the parameters listed above are interdependent. Thus for example in a hydrogel material, we may need to increase the Equilibrium Water Content (EWC), this will be achieved through making the material more hydrophilic, e.g., by introducing more hydroxyl groups into the material. This will cause an increase in the polar component of the surface energy of the material and depending upon the reactivity ratios of the constituent monomers, will in all probability change the sequence distribution of the various chemical groups expressed at the surface.

1.11 Surface Energy

Although no single parameter has produced a satisfactory basis for correlation with biocompatibility, the surface energy concept has proved the most useful. This has arisen from the fact that surface forces are exerted by the constituent atoms of solids just as in the case of fluids. This is usually called the critical surface tension of the surface, and is defined as the surface tension of a liquid which will just spread on and wet the surface. The difference between the surface tension of a fluid and the critical surface tension of the surface with which it is in contact with is called the interfacial tension. This takes into account the polar and non-polar contributions to the surface energy mismatch at the surface. This has been put forward as the moderate surface energy hypothesis[7-9]. Which suggests that for a material to exhibit maximum biocompatibility it should have a low interfacial tension with the biological system it is in contact with. Adhesion protein adsorption is generally

considered to be more likely on a surface exhibiting a moderate or high surface energy, whereas surfaces of low energy are less adhesive. It has been noted that the polar component of the surface energy increases with the introduction of hydrophilic, polar, groups such as the hydroxyl group. This is usually accompanied by a proportionate increase in EWC. However, surfaces with very low fractional polarity and low EWC do not all offer the same degree of adhesiveness. For example amorphous polystyrene is non-adhesiveness, whereas crystalline PTFE, polypropylene and polyethylene are cell adhesive[10]. This obviously reflects other differences in surface properties.

1.12 Surface Chemical Groups

The pendant groups exposed to the biological medium depends on the nature of the aqueous environment and on the flexibility of the polymer backbone. Generally polar groups will orientate themselves towards the aqueous environment. The presence and density of various chemical groups affect the adsorption and subsequent conformation of adhesion proteins and hence cell adhesion in serum containing systems. Generally, the introduction of charged groups leads to greater adhesive properties.

We may illustrate the effect of chemical groups on the adhesion proteins and hence cell adhesion by considering the fact that untreated polystyrene (PS) is not generally adhesive in the presence of serum. But if the PS surface is oxidised through treatment with a gas plasma or is glow discharge treated, the surface becomes very adhesive to cells[11]. Work carried out here at Aston, suggested that mild acid treatment of the PS surface introduced hydroxyl groups at the surface of the PS sample. This was found to support extensive cell

adhesion. More severe treatment with hot sulphuric acid or chlorosulphonic acid produced substantial sulphonation and the resulting surface supported some cell attachment but not spreading. But it seems that the hydroxyl groups cannot be the sole factor affecting adhesion since the hydrogel formed from poly(2-hydroxyethyl methacrylate), (PolyHEMA), with a low interfacial energy and rich in surface hydroxyl groups is definitely not cell adhesive. Whereas poly(methyl methacrylate), (PolyMMA), and poly(ethyl methacrylate), (PolyEMA), are cell adhesive in the absence of hydroxyl groups. Investigations of a range of copolymers of HEMA and EMA to determine the relative contributions of the hydroxyl group concentration and the overall physicochemical nature of the substrate showed no linear correlation between cell spreading and hydroxyl group content[10,12,13].

1.13 Hydrophobocity and Hydrophilicity

Hydrophobocity and hydrophilicity are related to the surface energy and chemistry of a surface. Hydrogels based predominantly on monomers like HEMA tend to be very hydrophilic, whereas those based on styrene, also used commonly as a monomer in present biomedical materials, tend to be hydrophobic in nature. In an aqueous medium, hydrophilic substrates tend to have the polar groups exposed at the surface which will hydrogen bond with available water molecules. Hydrophobic surfaces tend to cause an ice like configuration of water molecules at the surface. These water structuring effects may of course be mixed on a surface with polar and non-polar groups exposed, and the complex structures produced may then effect the adsorption of proteins. Generally, It is known that surfaces of a predominantly hydrophobic character cause more denaturation of adsorbed proteins. This is because

proteins once adsorbed are not easily desorbed, and the greater conformational changes this leads to, tends to expose critical binding sequences in these adhesion proteins. Subsequently leading to cell adhesion. In contrast surfaces of a predominantly hydrophilic character are found to allow proteins to desorb much more easily than hydrophobic surfaces, i.e., it seems that the adhesion proteins are bound more loosely to the hydrophilic surfaces[14,17]. This may well explain the non-adhesive qualities of some hydrogels.

1.14 Equilibrium Water Content (EWC) in Hydrogels

Basically hydrogels are water swollen polymers, the simplest being based on the monomer 2-hydroxyethyl methacrylate (HEMA). The water acts almost as a conventional Plasticizer in that it converts a hard, clear and glassy material in its absence, to a clear, flexible elastomeric gel. Thus the properties of the hydrogel are influenced both by the structure of the polymer network and by the water. The water acts as a bridge between the natural and the synthetic systems giving greater biocompatibility, or perhaps more properly biotolerance, and confers membrane properties on the hydrogel, allowing transport of oxygen and water soluble metabolites through the polymer matrix. Copolymerisation of HEMA with other hydrophilic monomers such as N-vinyl pyrrolidone (NVP), the N-alkyl acrylamides and hydroxyalkyl methacrylates/acrylates, allows us to synthesize hydrogel membranes of various water contents and vastly different surface properties[15].

Work done at Aston has demonstrated direct relationships between the EWC and cell adhesion in hydrogels[11]. It has been found that cells will adhere to and spread onto simple HEMA copolymers within the EWC range of 5-35% water.

Higher water contents in the range of 40 - 60% did not support cell adhesion. A further investigation of this phenomenon showed that the non-adhesive zone for cells with respect to the EWC of the hydrogel could be shifted upwards if the hydroxyl groups, present in HEMA, were replaced with charged groups by substituting other hydrophilic monomers e.g. NVP, in place of HEMA. The following trend of functional groups accompanies the upward movement of the non-adhesive zone for cells in terms of the EWC :

-OH(e.g. HEMA) < -CONRR(e.g. NVP) < -CONHR < -$CONH_2$(Acrylamide)

Hydroxyl <Tertiary amide < Secondary amide < Primary amide.

(Where R represents an alkyl group)

The presence of chemical groups at the surface of these hydrophilic materials not only affects the amount and conformation of adsorbed adhesion proteins but gives rise to physicochemical effects such as the reorganisation of water molecules at the interface. The introduction of charged groups into HEMA based hydrogels for example, increases the water structuring effects at the surface. This is especially true of strongly polar groups such as carboxylic acid and amide groups. However, introduction of uncharged MMA into HEMA based hydrogels, also produces an adhesive surface in the absence of charge. This is because MMA and other monomers containing non-polar groups also cause a rearrangement in water structuring at the surface. Thus it seems that the alteration in the water structure at the interface, seen with the presence of various charged and uncharged groups, may indirectly affect the adsorption of adhesion proteins and may be used to explain the cell adhesion characteristics of these various copolymer surfaces. Thus the presence of a dominating structural group, which has the ability to structure water held at the surface, can over-ride any of the effects due to water content[11].

1.15 Sequence Distribution of Surface Groups

In the previous section we see that charged groups at the surface of materials affect the adsorption of adhesion proteins. It would seem to be logical that the charge density and the distribution of this charge at the surface would also affect the adsorption of adhesion proteins[16].

Work done at Aston, has found that polymers with long repeat units or extensive segments of individual monomer units (which may contain charged or uncharged groups), have a greater tendency to produce non-specific protein adsorption than polymers that mimic the molecular architecture of naturally occurring polymers (regular, short sequences of monomers). Thus for example the copolymerisation of a hydrophobic monomer with a hydrophilic monomer, in different relative amounts or with quite different reactivity ratios, will tend to produce a copolymer with a blocky distribution of individual monomer units. This will lead to tiny areas or domains of hydrophobic and hydrophilic structures on the surface of the copolymer. As mentioned above, this will lead to greater protein adsorption at the surface than if we had produced a polymer in which the individual monomer units were more dispersed. Thus the manipulation of the domain size in the synthesis of new biomaterials provides a novel means of controlling non-specific protein adsorption and the subsequent cell adhesion at the interface. This is simply because the organisation of the polymer surface seems to have a great effect on the subsequent protein adsorption. In this thesis we will attempt to show how we may optimise this sequence distribution effect in the synthesis of new biomaterials. Workers investigating the adsorption of adhesion proteins and platelets onto copolymer surfaces using immuno-technology, have shown that preferential adsorption occurs even on the nanometre scale of the surface distribution of groups[18]. They have shown that the surface micro-

domain patterns may be critical in determining adsorption. Cells, depending on type, form adhesive focal or point contacts with the surface, and require a limited space in which to adhere permanently. If the adhesive zone is too small and widely spaced from the next, the cell will be unable to spread, and may not be able to achieve stable adhesion at all. On a smaller scale, protein adhesion required areas of surface chemistry sufficiently large to achieve stable physicochemical interactions between the protein and the material surface[19-21].

1.16 Surface Topology

The topology of a surface has been shown to effect the adsorption of proteins over time. This has been demonstrated for blood proteins and is equally likely to occur within other biological environments such as with tear fluids. Generally the exchange of the first adsorbed protein (usually the one present in the highest bulk concentration, such as albumin in blood) for another of higher affinity is slowed in narrow spaces due to steric hindrance and limited diffusion[22].

In vivo, surface texture has a pronounced effect on the reactive cell population around an implant. Roughened polymer surfaces attract more macrophages and foreign body giant cells for a longer time leading to greater inflammation and subsequent fibrous encapsulation. Superior compatibility is associated with smoother surfaces with no sharp edges[23,24].

1.2 Simulation, Synthesis and Analysis of Polymers with Controlled Sequence Distributions.

As mentioned in the previous section, the sequence distribution of the individual monomer units in the polymer/biomaterial affect the adsorption of

adhesion proteins at the interface, and the subsequent cell adhesion. The following sections will illustrate the factors that affect the sequence distributions seen of the individual monomers, in the synthesized biomaterial. And computer simulation programmes that allow us to illustrate the copolymerisation process, whilst making it possible to easily vary key parameters, such as concentrations of monomers, and to see the effect this has on the overall sequence distribution of the new biomaterial. The final part of this section will show how sequence distributions may be determined/analysed for materials that have been synthesized.

1.21 Copolymerisation and Reactivity Ratios

A polymerisation reaction may be carried out using only one monomer, usually known as homopolymerisation. This is rather limiting in the number of different products that are possible. Rarely does a homopolymer satisfy all the requirements necessary to function as a good biomaterial, for example polyHEMA although being relatively non-adhesive to cells, it possesses an EWC of only 38%. For extended wear contact lenses a much higher EWC than this is required. This is because the transport processes (e.g., of oxygen) in hydrogels are governed by the water content of the hydrogel[25]. We may improve the EWC of a biomaterial by copolymerisation of HEMA with another more hydrophilic monomer, such as N-vinyl pyrrolidone.

Copolymerisation permits the synthesis of an almost unlimited range of polymers and is often used, therefore, to obtain a better balance of properties for the various applications of polymeric materials[26,27]. Copolymers may be synthesized by chain growth and step growth condensation polymerisation

processes. This thesis will deal exclusively with chain growth copolymers, in which one or more types of monomer add to an active centre located on a growing(or live) polymer chain. Chain growth copolymerisation may be done using various active centres, including free radical, ionic and Ziegler-Natta processes. Here, we will only be concerned with active centres derived from free radicals. There are four basic copolymer structures: random, alternating, block and graft. Random copolymers have relatively random distributions of the two monomer units. Alternating copolymers have the two monomer units occurring in an alternating fashion. A block copolymer is a linear copolymer with one or more long uninterrupted sequences of each type of monomer unit. A graft copolymer is a branched copolymer with the main chain and branches having different compositions[28,29]. This thesis will deal mainly with random (statistically random, i.e., obeying some statistical law) copolymers.

The basic hypothesis of simple copolymerisation kinetics is that the reactivity of an active centre only depends upon the monomer unit in the copolymer chain on which the active centre is located. For a binary copolymerisation, the copolymer composition equation describes the growth of copolymer chains, microstructure development and monomer consumption. The equation can be derived from basic copolymerisation kinetics(see chapter 3) and is given below:

$$\boxed{\frac{\partial[M_1]}{\partial[M_2]} = \frac{[M_1]}{[M_2]} \frac{r_1[M_1] + [M_2]}{[M_1] + r_2[M_2]}} \qquad \text{Eqt 3.7}$$

Where, M = monomer ; [ ] = concentration.

The parameters r_1 and r_2 are termed the *monomer reactivity ratios* . Each reactivity ratio is defined as the ratio of the rate constant for a reactive propagating species adding its own type of monomer to the rate constant for its addition of the other monomer. The tendency of two monomers to

copolymerize is noted by r values between zero and unity. An r_1 value greater than unity means that the radical of the monomer unit M_1, preferentially adds M_1 instead of M_2, while an r_1 value less that unity means that the radical of the monomer unit M_1, preferentially adds M_2. From the above equation it can be seen that the main factors which govern the sequence distribution of a polymer are, the concentration of the monomers and their reactivity ratios. Since the concentrations are easily varied this is usually not a problem in helping to achieve a certain sequence distribution. But the reactivity ratios are not easily varied. In fact they are specific for a particular pair of monomers, since they are inherently dependent on the chemical functionality of the monomers concerned. Chapter 3 will show how some common contact lens compositions, that have been synthesized without regard to the reactivity ratios of the constituent monomers, have such poor sequence distributions (long, extended sequences of individual monomer units). This is likely to make them prone to non-specific protein adhesion. Chapter 5 will attempt to illustrate how with the judicious choice of monomers, one may synthesize polymers with relatively good sequence distributions (short, regular sequences of individual monomer units).

1.22 Computer Simulation of Sequence Distributions

To facilitate the design of materials with good sequence distributions, it would be useful if we could in some way visualise/simulate the sequence distribution of the final product formed through the copolymerisation process. This simulation technique would allow us to easily alter the basic factors, mentioned in the above section, that affect the sequence distribution of the synthesized material, whilst also displaying the results in a readily accessible

form. Computer simulation techniques based on various models of the copolymerisation kinetics allow us to demonstrate the sequence distribution that would be seen upon the polymerisation of a set of monomers. Theoretical predictions of sequence distribution in copolymers have been included in the earliest treatments of copolymerisation[30-35], and many theoretical papers on this subject have appeared, suggesting diverse approaches to this problem[36-40].

At Aston we have developed a couple of computer simulation programs, which simulate the sequence distributions that would be seen in the copolymer/terpolymer when two/three monomers were to be polymerized. Both these computer programs, 'COPOL' and 'TERPOL' for copolymerisation and terpolymerisation respectively, are based on the Monte Carlo method (or method of statistical trials)[41]. These computer programs require the concentration and reactivity ratios of the monomers concerned. The programs will at every stage of conversion calculate the probability of addition of each of the monomers to the active centre at the end of the growing chain. A fuller description of these programs may be found in chapter 3, it will suffice here to illustrate one of the programs. The simulated sequence distribution of the contact lens material Etafilcon-A[42], when polymerized can be represented by figure 1.0. Etafilcon-A is composed of monomers with relatively similar reactivity ratios but with quite different concentrations (as shown in figure 1.0). It is a hydrogel type material with an EWC of approximately 58%, and is manufactured and sold under different trade names e.g., as Acuvue by Vistakon (please see table 3.12 in chapter 3 for more details).

When viewing figure 1.0 overleaf, one must bear in mind although the simulated sequence distribution seen does represent the sequence distribution,

from start to 100% conversion, it does not represent the ideally or average copolymer chain in this reaction. The simulated sequence distribution represents a snapshot of, at any particular conversion, the instantaneous sequence distribution of the average copolymer chain in this polymerisation reaction, at that particular level of conversion. The average copolymer composition may also be determined, at this particular level of conversion, since in these simulations the program always starts with an arbitrarily set total of 2000 monomer units. Thus for example if a 50:50 mole ratio of monomer units is required in the initial feed, then the program will carry out the simulation with an initial 1000 units of each monomer. Therefore, the average copolymer composition is easily calculated at any particular stage of conversion, as we can see in the simulated sequence distribution the number of each type of monomer unit that have been polymerized and we know the number of each type of monomer unit present in the initial feed.

Figure 1.0 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with 1% EGDMA cross-linker.

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

1 Mole % of Monomer C, EGDMA

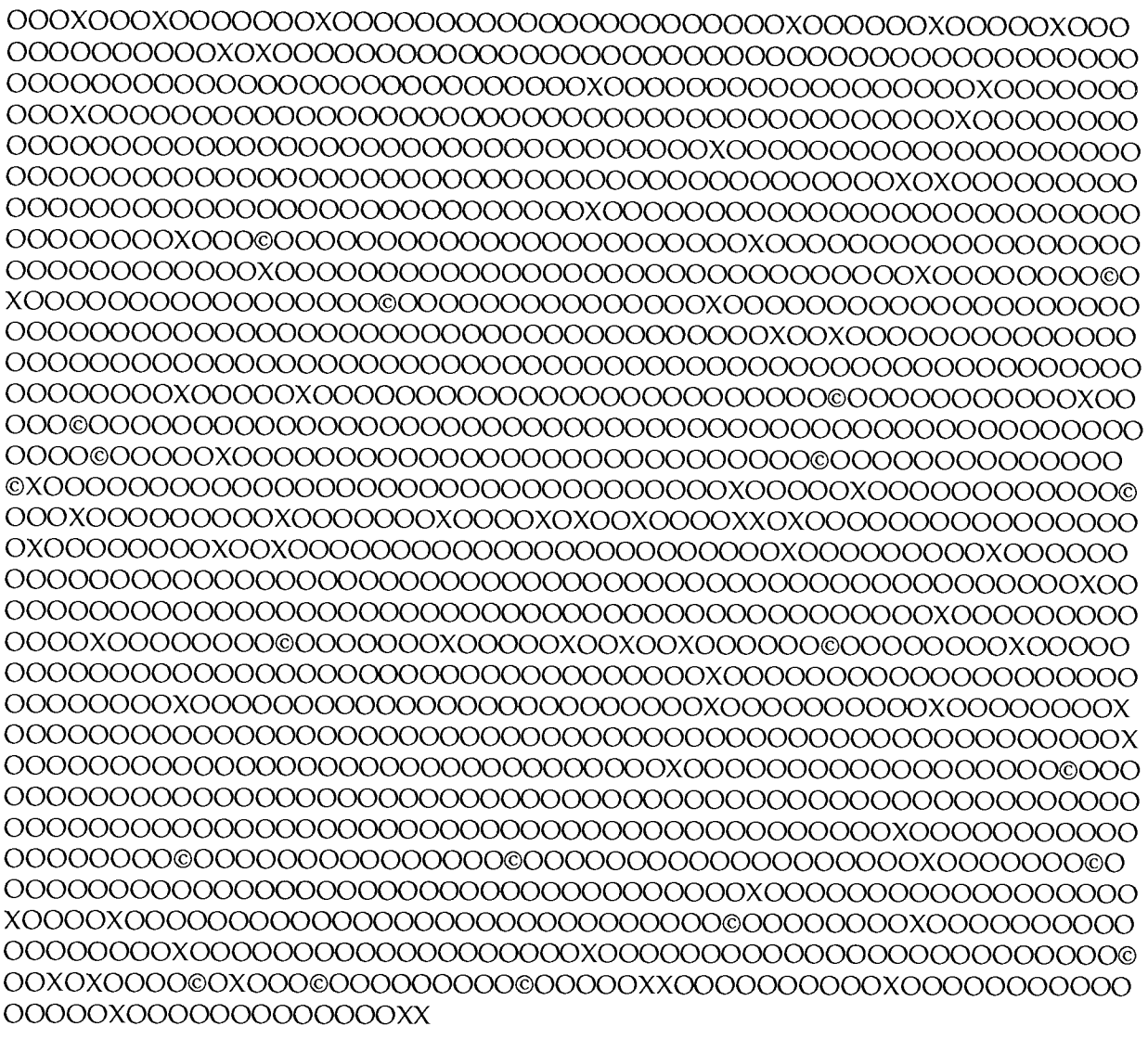
r(AB) = 1.224 r(AC) = 1.882 r(BA) = 0.294

r(BC) = 0.975 r(CA) = 0.388 r(CB) = 0.837

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and EGDMA is represented by © :

XOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 EGDMA units.

Table 1.0 : Sequence lengths seen in the simulated sequence distribution of figure 1.0.

Sequence Distributions:

Length	HEMA	MA	EGDMA
1	7	74	20
2	6	3	0
3	4	0	0
4	4	0	0

5	7	0	0
6	3	0	0
7	4	0	0
8	6	0	0
9	3	0	0
10	3	0	0
11	1	0	0
12	1	0	0
13	3	0	0
14	1	0	0
15	2	0	0
16	1	0	0
17	2	0	0
18	4	0	0
19	3	0	0
22	1	0	0
23	1	0	0
24	1	0	0
25	3	0	0
28	2	0	0
29	1	0	0
30	1	0	0
31	1	0	0
32	1	0	0
33	1	0	0
34	1	0	0
36	1	0	0
37	2	0	0
39	1	0	0
42	2	0	0
47	1	0	0
54	1	0	0
55	1	0	0
57	1	0	0
58	1	0	0
63	1	0	0
70	1	0	0
77	1	0	0
101	1	0	0
178	1	0	0

It is apparent from this simulation, that the formulation of this Etafilcon-A contact lens results in a very poor sequence distribution for this product (i.e., we have long, extended sequences of individual monomer units). This is unfortunate since here the monomer units have relatively similar reactivity ratios, but the large difference in their relative concentrations in the initial feed precludes the formation of a relatively good sequence distribution (regular, short sequences of monomer units). On purely a sequence distribution effect we would expect this contact lens material to be susceptible to non-specific protein adhesion. The presence of the methacrylic acid monomer produces a negatively charged surface in an aqueous environment this will also have an effect upon the absorption of surface proteins and will thus modify the effect produced by the sequence distribution of individual monomer units, of this material, upon its surface properties.

Thus computer simulation programs can be a valuable tool in understanding how various factors will affect the final sequence distribution, of the monomers, seen in the new biomaterial. This may help us to predict the relative biotolerance of this new material.

1.23 Analysis of the Computer Simulated Sequence Distributions

Accurate analysis of the composition of a copolymer may be made, in principle, by the employment of a number of techniques. The most widely used technique for the composition analysis of a copolymer is elemental analysis. This technique is very accurate, but for it to be useful in the first instance there must be a significant difference in the elemental composition of the monomers concerned.

A technique that has proved to be the most useful method of copolymer analysis, both for composition analysis and for probing the connectivity and stereo-regularity of monomer units is ^{13}C nuclear magnetic resonance (^{13}C NMR). The principal advantage of ^{13}C NMR, is in its sensitivity towards subtle structural features whilst displaying this information in an accessible form. Chemical shift differences are observed in ^{13}C NMR polymer spectra for carbon skeleton rearrangements of repeat units and for configurational sequences. Therefore an interpretation of ^{13}C NMR polymer spectra can be a complex problem in itself. But with modern data acquisition techniques combined with spectral integration and curve fitting (to obtain peak areas), followed by accurate peak assignments will give us valuable information concerning the sequence distribution of the synthesized copolymer[43-47]. Please see chapter 4 for further information concerning ^{13}C NMR and its application in the analyses of copolymer sequence distributions.

It is generally true to say that cells will only adhere to a surface likely to deposit proteins. Since it is also known that non-specific protein adhesion is affected by the sequence distribution of the monomer units, which is reflected in the combination of charged and uncharged groups expressed at the surface of the new biomaterial. Thus cell adhesion studies provides us with a remarkably sensitive probe for investigating the deposition qualities of a surface, with respect to the sequence distribution of monomer units in the new biomaterial, as cells will respond to literally a few molecules of protein. Please see chapter 6 for results of such cell adhesion studies on polymers containing controlled sequence distributions of monomer units.

1.3 Summary of Introduction

It is apparent that there are two main problems that occur when we try to substitute a synthetic material for a natural tissue. Firstly there is the difficulty in actually designing a material which will essentially be inert and structurally fairly simple, compared to the living, structurally complex and highly responsive natural tissue it will be replacing; secondly, when we place such a structurally simple and relatively unresponsive synthetic material in a biological environment, we create a dynamic interface. This usually results in the phenomenon known as interface conversion, as previously mentioned. Thus, it is invariably found that biological environments are extremely sensitive to synthetic materials and very aggressive in their response to them.

The advent of hydrophilic polymeric materials, e.g. the methacrylic hydrogels[2], for use in biomedical applications, has improved the soft tissue compatibility and the transport properties of these synthetic materials. But as seen in this chapter, synthetic polymers will only enjoy limited success as biomaterials until we can develop an improved understanding of the interfacial phenomena that affect the biocompatibility of these materials. This will subsequently allow us to design and synthesize interfacially responsive materials, which are more biocompatible. We believe this may only be achieved from understanding how the structure of natural materials influences their properties and thus by subsequently synthesizing and replacing them with materials which have analogous behaviour.

This thesis will be concerned with assessing one of the factors, the sequence distribution of individual monomer units in the material, that affects the interfacial properties and the subsequent biocompatibility of these materials.

1.4 Scope and Objectives of this Thesis

(i) To demonstrate the use of Monte-Carlo based computer simulation programs in illustrating the sequence distributions that would be seen in the final polymers, when a set of monomers were to be polymerized.

(ii) To determine the precision of these computer simulation programs, through reconciliation of sequence distribution data from ^{13}C nuclear magnetic resonance analysis of a synthesized polymer with that predicted by the computer simulation programs.

(iii) To illustrate how design of polymeric materials with controlled sequence distributions of monomers, may be aided by the use of these computer simulation programs.

(iv) To study the affects of synthesized polymeric materials, containing controlled sequence distributions of monomer units, on cell adhesion in a serum containing environment. In order to assess the biocompatibility or perhaps the biotolerance of these materials, thereby aiding the evaluation of these materials for future use in biological environments.

CHAPTER TWO

MATERIALS AND EXPERIMENTAL

2.0 Materials and Experimental

2.1 Reagents

All monomers were purified by reduced pressure distillation, with the exception of HEMA. This was bought as optical grade high purity monomer. Because of the importance of the polymers of HEMA in biomedical applications, the commercially available monomer is usually purified to a high degree to remove EGDMA and Methacrylic acid which are usually present. EGDMA may be removed through its solubility in Hexane, whilst HEMA remains insoluble. Thus the normal procedure involves, the dissolution of HEMA in four volumes of water and EGDMA is extracted with hexane. Then the aqueous solution of HEMA is salted to complex methacrylic acid. HEMA is extracted with diethyl ether, the solution is dried, and HEMA is distilled under vacuum[48].

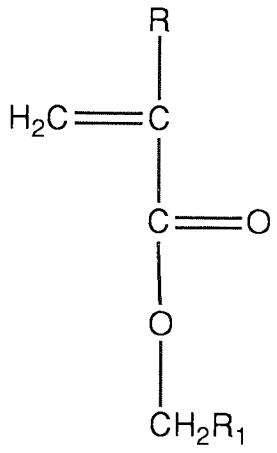
NNDMA which is stabilised with an inhibitor, besides containing traces of acrylic acid and water, is first treated with anhydrous potassium hydroxide to neutralise the acrylic acid and then dried over anhydrous magnesium sulphate. It is then distilled under reduced pressure. Any traces of inhibitor which co-distilled with the monomer (determined through GLC analysis) were removed by prepolymerizing to 20 percent conversion, the residual monomer being then distilled off[49].

Table 2.1 overleaf shows the monomers used and table 2.2 shows the cross-linking agents and initiator used.

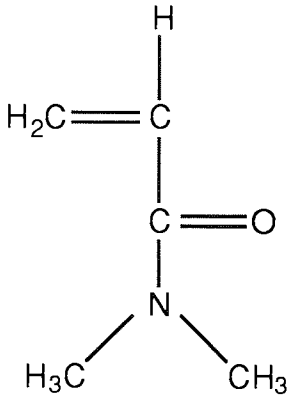
Table 2.11: Molecular Weights and Suppliers of Monomers

Monomer	MWt.(g/mol)	Abbreviation	Supplier
2-Hydroxyethyl methacrylate	130.14	HEMA	Ubichem Ltd.
Methyl methacrylate	100.12	MMA	B.D.H.
N-Vinyl pyrrolidone	111.14	NVP	B.D.H.
N,N-Dimethyl acrylamide	99.13	NNDMA	Fluka
2-Hydroxypropyl methacrylate	144.17	HPA	Polysciences
2-Hydroxyethyl acrylate	116.12	HEA	Fluka
Ethoxyethyl methacrylate	158.19	EOEMA	Fluka
Ethyl methacrylate	114.12	EMA	Aldrich
Styrene	104.15	STY	B.D.H.
Itaconic acid	130.10	ITA	B.D.H.
N,N-Dimethyl-N-methacryloyloxyethyl-N-(3-sulpho propyl) ammonium betaine	279.35	SPE	Monomer-Polymer Labs.
Indene	116.16	IND	Aldrich
N-Vinyl Imidazole	94.12	NVI	Aldrich
Methoxy Poly(ethylene glycol)mono methacrylate	500.12	PEG400	Polysciences

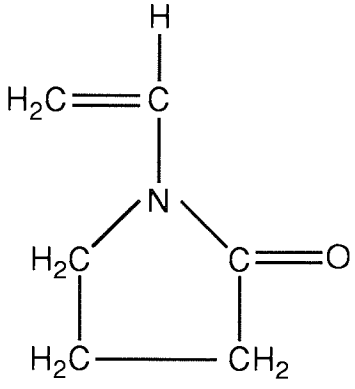
Figure 2.11: Structure of reagents listed in table 2.11



$R = CH_3$	$R_1 = H$	Methyl methacrylate
$R = CH_3$	$R_1 = CH_3$	Ethyl methacrylate
$R = CH_3$	$R_1 = CH_2OH$	2-Hydroxyethyl methacrylate
$R = CH_3$	$R_1 = CH_2OC_2H_5$	2-Ethoxyethyl methacrylate
$R = H$	$R_1 = CH_2OH$	2-Hydroxyethyl acrylate

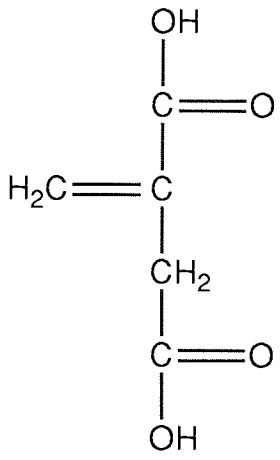


N, N-Dimethyl acrylamide

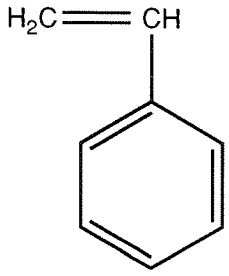


N-Vinyl pyrrolidone

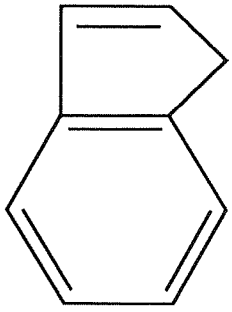
Figure 2.11: Structure of reagents listed in table 2.11(continued)



Itaconic acid

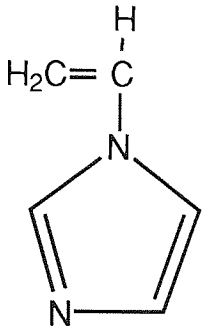


Styrene

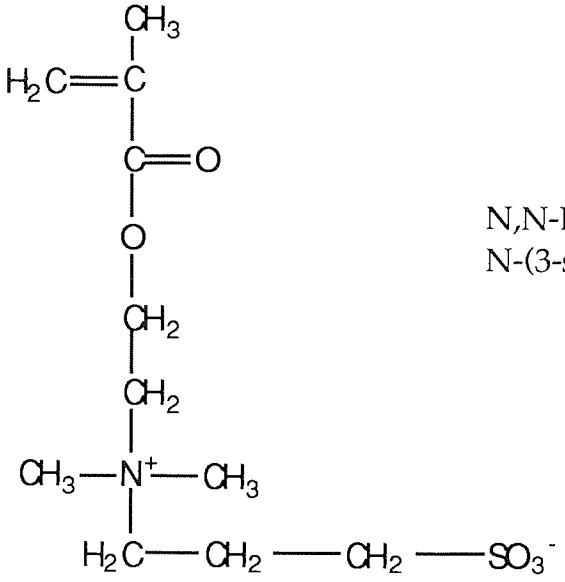


Indene

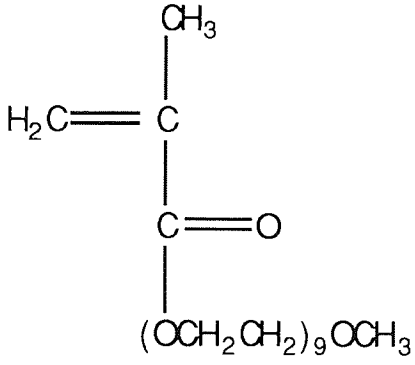
Figure 2.11: Structure of reagents listed in table 2.11(continued)



N-Vinyl imidazole



N,N-Dimethyl-N-methacryloyloxyethyl-N-(3-sulpho propyl) ammonium betaine

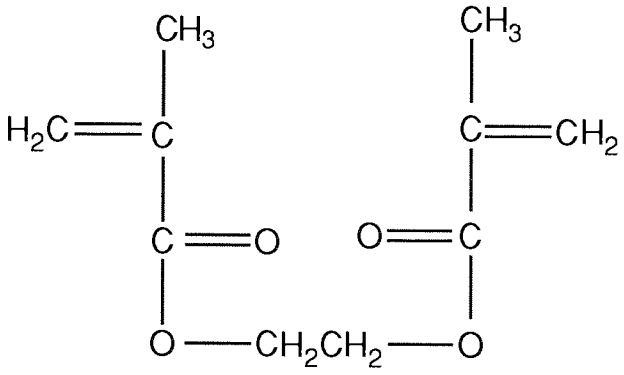


Methoxy poly(ethylene glycol) $_{400}$ -mono methacrylate

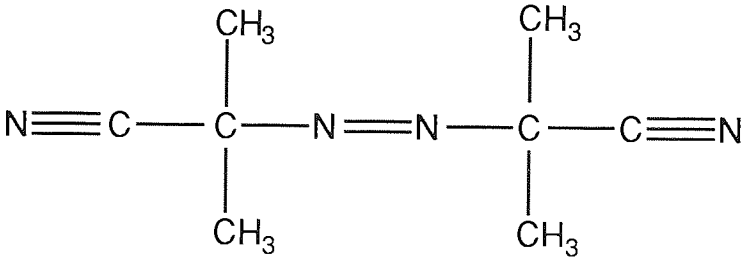
Table 2.12 : Molecular Weights And Suppliers of Crosslinking Agents

Reagent	MWt.(g/mol)	Abbreviation	Supplier
Ethylene glycol dimethacrylate	198.22	EGDMA	B.D.H.
Azo-bis-iso-butyronitrile	164	AZBN	B.D.H.
N-vinyl carbazole	193.25	NVC	Fluka
2,4,6-Triallyloxy-s-triazine	249.27	TAOTZ or TAC	Aldrich
N,N-Diallyl-tartardiamide	228.25	DATDAM	Aldrich

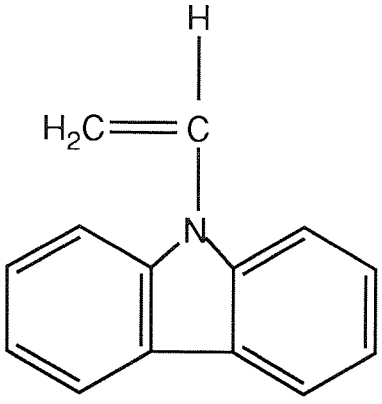
Figure 2.12: Structure of reagents listed in table 2.12



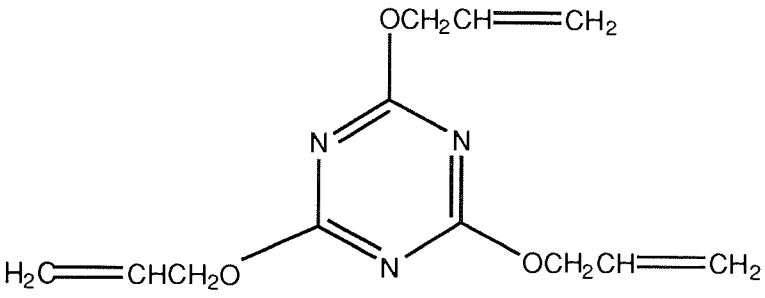
Ethylene glycol-dimethacrylate



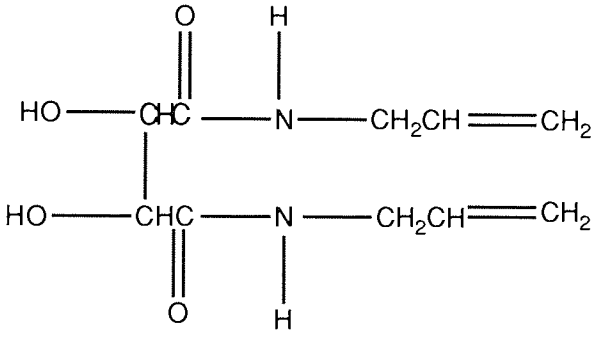
Azo-bis-isobutyronitrile



N-Vinyl carbazole



2,4,6-Triallyloxy-s-triazine



N,N`-Diallyltartardiamide

2.2 Polymer Synthesis

2.21 Solution Polymerisation

This is the process which was used to carry out free radical polymerisation on a 1 litre scale. The polymerisation reaction was carried out in a five necked 1 litre resin flask, which was equipped with a water condenser & air condenser, stirrer, thermometer, pressure equalised dropping funnel and a nitrogen bleed, all in a water bath (see Figure 2.21 overleaf for diagram of set-up). Before beginning the experiment the entire equipment was de-gassed using a nitrogen bleed. During reaction this same nitrogen bleed was used to maintain a nitrogen blanket over the reaction mixture[50-52].

Thus for a typical reaction, such as that between HEMA and MMA, we would start by adding 400mls of methanol to the reaction flask and raise its temperature to 60°C. Once this temperature had been attained, 50 gms of the monomers (HEMA and MMA) and 0.5% initiator (AZBN), by weight, dissolved in 100 mls methanol, were added drop-wise to the reaction flask. After addition was complete the temperature was raised to 65°C and the mixture was refluxed for 12 hours. After this period of time the contents of the flask were allowed to cool and then were added drop-wise to 2.0 litres of ether, cooled with solid CO_2, to give a granular white precipitate. The precipitate was filtered and after three washings with ether, dried in a vacuum oven at 60°C. For ^{13}C NMR sequence analysis and elemental analysis samples were taken during the solution polymerisation reaction using a 25 cm^3 pipette. Once removed from the reaction vessel, the samples were immediately pipetted into a beaker containing a mixture of ether, cooled with solid CO_2. A white precipitate of the polymer was seen. This was now filtered in a pre-weighed sintered-glass funnel

under pressure. The precipitate was washed with more ether, and then dried in a vacuum oven at 60°C for 24 hours, before being weighed. The percentage conversion can now be determined using these gravimetric values.

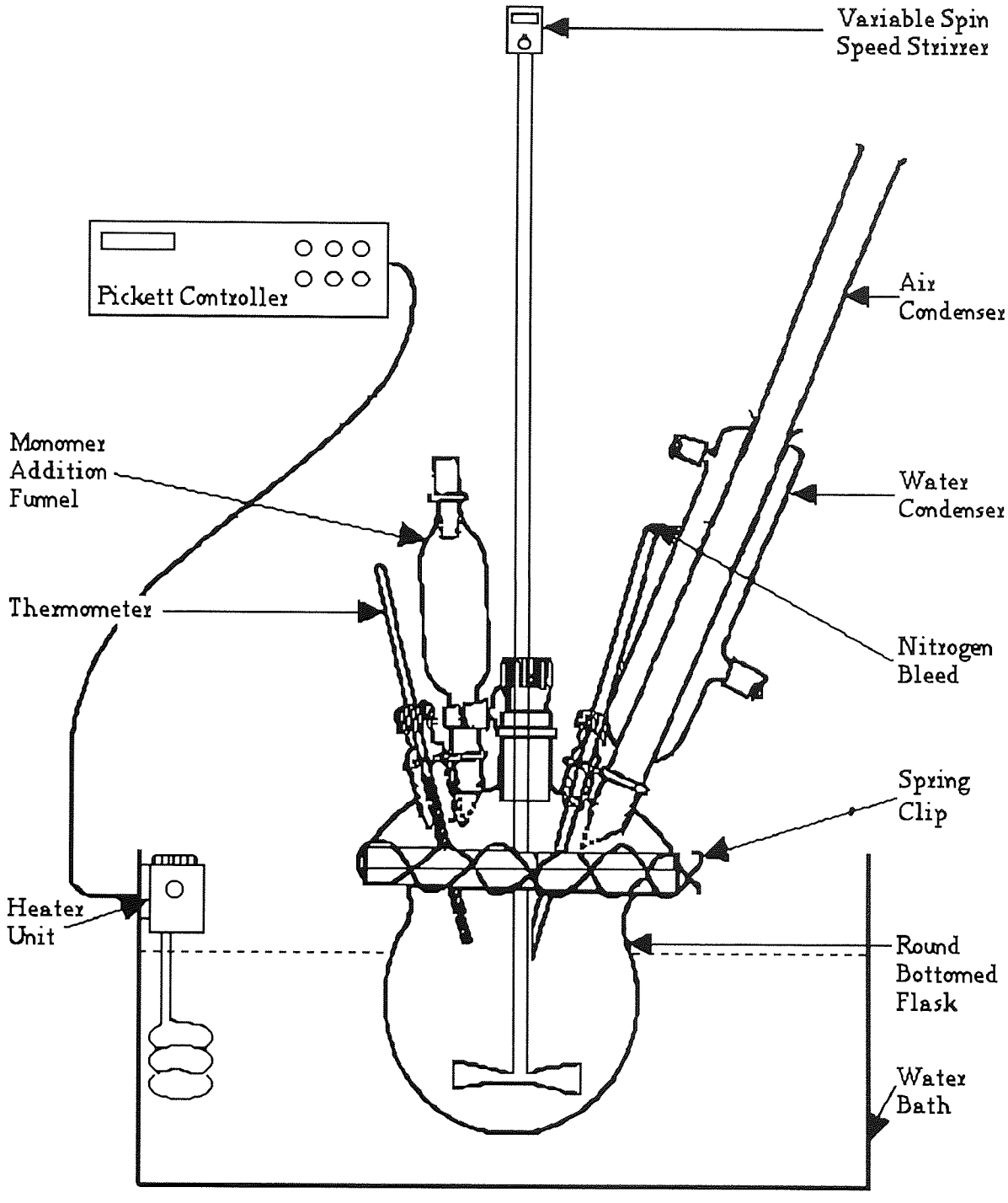
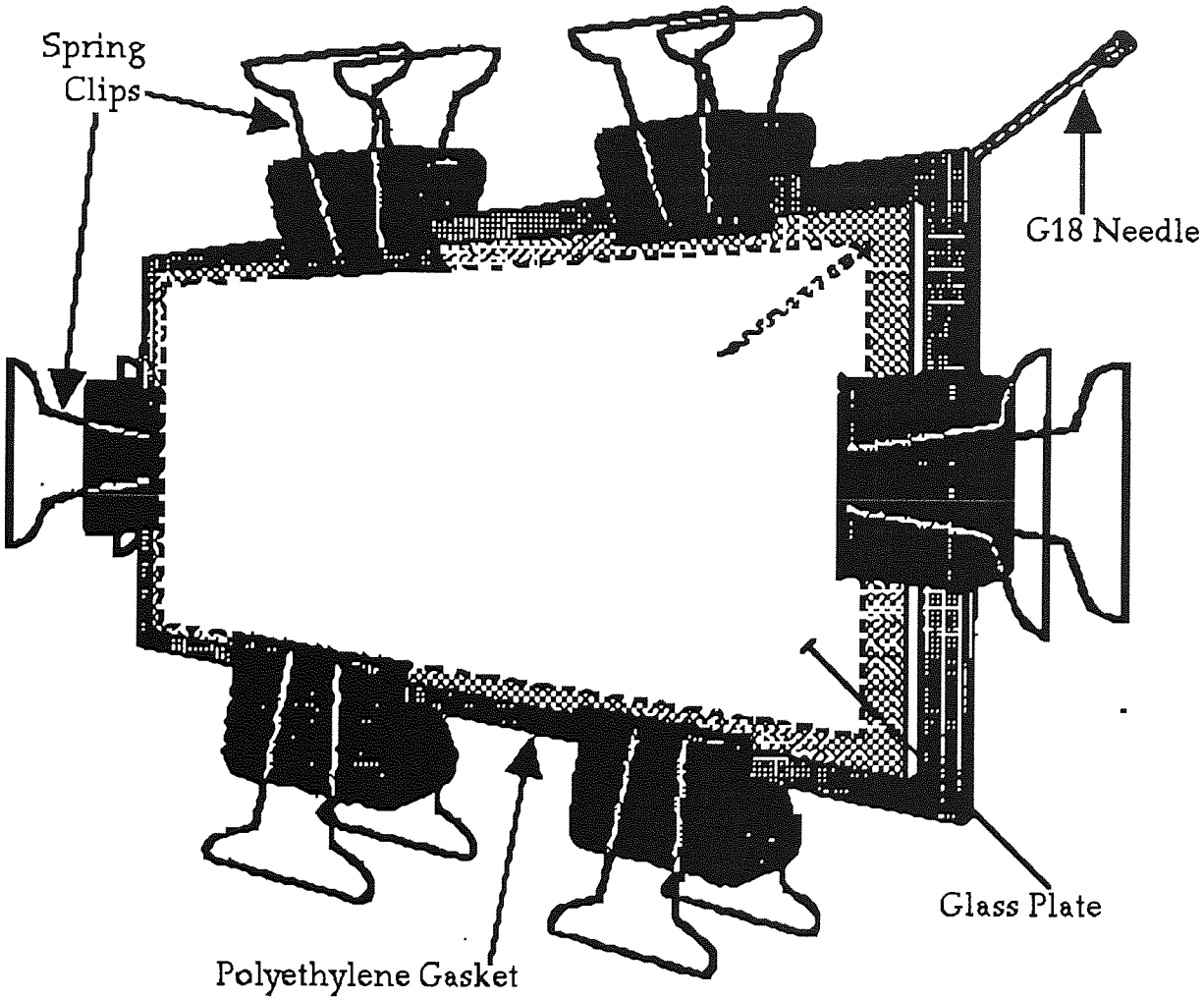


Figure 2.21: Laboratory Solution Polymerisation Apparatus

2.22 Membrane Preparation

Membranes were produced by the polymerisation of approximately 5 gms of the monomer mixture within a glass mould. Two glass plates (15 cm x 10 cm) were each covered by a Melinex (polyethylene terephthalate) sheet to permit easy separation of the plates, as shown below in Figure 2.22:

Figure 2.22: Representation of a Membrane Mould



To further facilitate easy separation of the mould, the Melinex sheets were attached to the glass plates using a spray-mount adhesive. This was to prevent the monomers from coming in between the Melinex sheet and glass plate

during polymerisation, as this would cause the Melinex sheet to stick to the glass plate. Thus making separation as difficult as without the Melinex sheets in the first instance. The plates were placed together with two polyethylene gaskets (each 0.2 mm thick) separating the Melinex sheets. Spring clips were used to hold the mould together leaving sufficient space for the insertion of a G18 syringe needle for the injection of monomer mixture into the mould cavity[53].

In a typical copolymer composition 5 gms of the monomers were mixed together with ethylene glycol dimethacrylate 1.0 % (w/w) and azo-bis-isobutyronitrile 0.5 % (w/w), until a homogeneous solution was obtained. Once dissolution had occurred the mixture was de-gassed with nitrogen before being injected into the mould using a syringe. The mould was then placed in an oven at 60°C for three days followed by two hours postcure at 90°C. After two hours postcure the spring clips were removed and after opening the mould the membrane was separated from the Melinex sheets, then placed in distilled water to hydrate for at least a week. Studies with a variety of monomer combinations showed that, provided the hydration medium was changed daily, constant values of equilibrium water content were obtained in four or five days. This period of time was sufficient both to reach equilibrium hydration and to extract any of the water soluble residuals such as unreacted monomers (as detected by the appropriate GLC technique used in initial assessments of monomer purity).

For cell adhesion studies it is important to maintain the sterility of the membrane. Thus a section of the membrane was placed in a sealed glass bottle

containing a mixture of distilled water and ethanol (to prevent algae & bacterial growth).

2.3 Equilibrium Water Content

The EWC was measured by weight differences as follows. Samples were cut from a hydrated sheet of hydrogel with a size seven cork borer. Any surface water was removed with filter paper before the samples were transferred to a preweighed sample bottle. Five to ten samples were used in order to give a reasonable total hydrated weight[53] (ca. 0.2g).

The samples, once weighed, were dehydrated in a microwave oven for 10 minutes. Upon removal from the oven the samples were immediately reweighed to obtain their dehydrated sample weight and the EWC was calculated using equation 2.3. The final quoted EWC was obtained from an average of at least 3 samples.

$$EWC = \frac{\text{Weight of water in gel}}{\text{Total weight of hydrated gel}} \times 100\% \qquad \text{Eqt. 2.3}$$

The accuracy of this technique depends on the assumption that upon dehydration no water remains within the sample. This was validated by exposing dehydrated samples to the atmosphere and measuring their EWC's. The samples were dehydrated once more and their EWC's re-determined. A second dehydration was performed and again the EWC's were obtained. The values obtained were found to be identical thus proving the accuracy of the values determined.

2.4 Spin Coating

Spin coating is the technique used to produce a very thin uniform coating of a polymer film onto a glass cover-slip. The polymer film, which contains the Ultra-Violet activated photoresist N-Vinyl carbazole (NVC), can then be effectively cross-linked by exposure to U.V. radiation. This whole procedure is a pre-requisite to cell adhesion and non-specific protein deposition studies on the linear polymers formed through the solution polymerisation experiments.

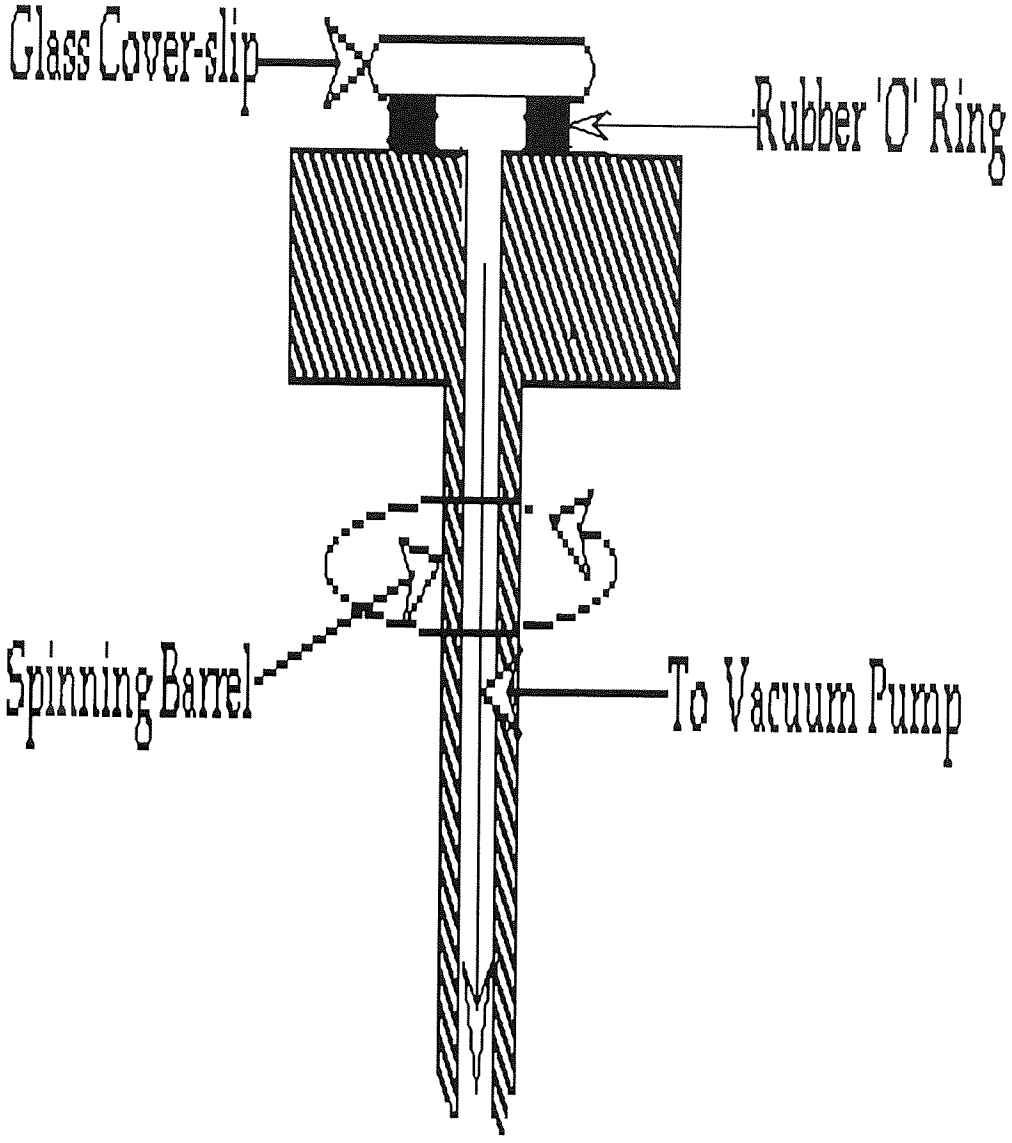
The glass cover-slips are approximately 10 mm in diameter and have previously been treated with a "gas plasma'. Methoxyethanol is used as the main solvent, as previous studies[7] have shown the need for a slow evaporating solvent, to get a good uniform coating of the glass cover slip.

The spinner is a G.E.C. spinner, whose cross-section is shown in Figure 2.4. It basically consists of a hollow barrel shaft the top of which supports a rubber 'o' ring, on top of which is placed the glass cover-slip. The hollow shaft facilitates the application of a vacuum, which holds down the glass cover-slip as the barrel is spun at high speed.

The speed of the spinner is important, if it is too slow the coating will be uneven and if it is too fast the polymer will spin off the glass cover-slip. The viscosity of the polymer solution is also very important, if the viscosity is too high then very thick films with excessive edge beads are formed. If the viscosity is too low then a non-uniform layer results due to uneven evaporation of the solvent[54,55]. Thus by a trial and error method the best spinning conditions were found to be at a spin speed of 4500 rpm for two minutes. With a polymer

solution of similar viscosity to 2 g of polymer in 7 mls methoxyethanol, 1.5 mls ethanol and 1% N-vinyl carbazole (w/w).

Figure 2.4 : A Diagrammatic Representation of a G.E.C. Spinner



Thus in a typical spin-coating experiment a polymer solution would be made up as above. A glass cover-slip would be placed on the 'o' ring of the spinner and a vacuum applied. Now three-to-five drops of the polymer solution would

be dropped onto the glass cover-slip and the spinner would gradually be increased in speed to 4500 rpm, and would be left spinning for two minutes at this speed. This procedure would be repeated ten times to produce ten coated glass cover-slips for each polymer solution. Now all these coated glass cover-slips would be exposed to U.V. radiation for 30 minutes to activate the photopolymerisable photoresist, N-vinyl carbazole, present in this coated polymer film. Finally all these glass cover-slips are pre-baked for 30 minutes to remove any remaining solvent. Now these coated glass cover-slips are ready for cell adhesion studies. Cell adhesion studies were carried out in these laboratories by Helen Fitton.

CHAPTER THREE

COMPUTER SIMULATION OF SEQUENCE DISTRIBUTIONS

3.0 Computer Simulation of Sequence Distributions

Computer simulation of the sequence distributions that would be seen when a set of monomers were to be polymerised allows us to easily make empirical observations about the system, whilst permitting control over more sources of variation than direct study of the system would allow. Thus providing for much easier manipulation of the system. Computer simulations bring into perspective the relevance of various parameters to the system and may provide a framework for testing the desirability of system modifications. This leads to an improved understanding of the system and is generally achieved at a much lower cost, compared to the real system.

Computer simulation of the sequence distributions was carried out through the use of the following two computer programs. Firstly, the 'Copol' program, this simulates the sequence distribution that would be seen in the copolymer when a pair of monomers where to be polymerised. Secondly, the 'Terpol' program, which simulates the sequence distribution that would be seen in the terpolymer when three monomers were to be polymerised (Please see Appendices II and III for listings of these programs).

Both programs are based on the Monte Carlo method. The Monte Carlo method (or method of statistical trials) essentially consists of solving problems of computational mathematics by means of the construction of some random process for each such problem. The parameters of this random process are equal to the required quantities of the problem. These quantities are then determined by means of observations of the random process and the computation of its

statistical characteristics, which are approximately equal to the required parameters[56,57].

3.1 Development of the Computer Simulation Model

The development of the model upon which the computer simulation programs are based may be illustrated by considering a simple copolymerisation system. The basic hypothesis of simple copolymerisation kinetics is that the reactivity of an active centre only depends upon the monomer unit in the copolymer chain on which the active centre is located. Therefore, for a binary copolymerisation, the growth of copolymer chains, microstructure development and monomer consumption are uniquely described by the four propagation reactions[33]:

$$\sim\sim\sim M_1\bullet + M_1 \text{ -----> } M_1\bullet \qquad Rate_{11} = k_{11}[M_1\bullet][M_1] \qquad \text{Eqt 3.1}$$

$$\sim\sim\sim M_1\bullet + M_2 \text{ -----> } M_2\bullet \qquad Rate_{12} = k_{12}[M_1\bullet][M_2] \qquad \text{Eqt 3.2}$$

$$\sim\sim\sim M_2\bullet + M_1 \text{ -----> } M_1\bullet \qquad Rate_{21} = k_{21}[M_2\bullet][M_1] \qquad \text{Eqt 3.3}$$

$$\sim\sim\sim M_2\bullet + M_2 \text{ -----> } M_2\bullet \qquad Rate_{22} = k_{22}[M_2\bullet][M_2] \qquad \text{Eqt 3.4}$$

Where, M = monomer ; $\sim\sim\sim M\bullet$ = monomer radical on end of polymer chain ; k = rate constant; [ ] = concentration.

Let us consider the reaction channels involving the polymer chains ending in the M_1 radical. The overall rate for these reactions is given by :

$$R_1 = Rate_{11} + Rate_{12}$$

And, the fraction of these polymer chains that will add the same type of monomer, as that at the end of the polymer chain is given by :

$$f_{11} = \frac{\text{Rate}_{11}}{R_1}$$

Substituting by the above equations :

$$f_{11} = \frac{k_{11}[A]}{k_{11}[A] + k_{12}[B]}$$

Simplification gives :

$$f_{11} = \frac{1}{1 + \frac{k_{12}}{k_{11}}\frac{[B]}{[A]}}$$

Let us define $r_1 = \frac{k_{11}}{k_{12}}$ and $r_2 = \frac{k_{22}}{k_{21}}$, where r_1 and r_2 are the Reactivity Ratios of the monomers M_1 and M_2, respectively.

Substituting for $\frac{k_{12}}{k_{11}}$ in the above equation, gives :

$f_{11} = \frac{1}{1 + \frac{1}{r_1}\frac{[B]}{[A]}}$, multiplying through by $r_1 \frac{[A]}{[B]}$ gives :

$$f_{11} = \frac{r_1 \frac{[A]}{[B]}}{r_1 \frac{[A]}{[B]} + 1}$$ Eqt 3.5, similarly it follows: $$f_{22} = \frac{r_2 \frac{[B]}{[A]}}{r_2 \frac{[B]}{[A]} + 1}$$ Eqt 3.6

Thus, if the initial concentrations of the monomers and the reactivity ratios, are known, then we can calculate f_{11} , the fraction of polymer chains ending in the radical of monomer M_1 that will add the same type of monomer. We can illustrate f_{11} and f_{12} as ranges on a number-line :

<----------f_{11}----------><--------f_{12}----->

0==========1.0

(here assuming f_{11} is greater than f_{12}).

The computer simulation programs will at each step generate a random number (RN) within this range (0 - 1), which will be compared with f_{11}. If $f_{11} \geq$ RN, then the program will add another M_1 monomer unit to the growing polymer chain. If $f_{11} <$ RN, then the program will add an M_2 monomer unit to the growing polymer chain, and will now switch over to the reaction channels involving the M_2 monomer radical. This same basic procedure has been extended in the development of the terpolymer simulation program.

3.2 Copolymer Composition and Sequence Distribution

Interpretation of the computer simulation data, is usually carried out through the two primary structural variables that are used to describe polymer chains, namely copolymer composition and comonomer sequence distribution. The products of free radical copolymerisations are predominantly determined by the kinetics of the chain growth process. The problem of predicting copolymer composition and sequence distribution requires a kinetic model of the copolymerisation process, and several such models have been described in the copolymerisation literature. The following section examines the fundamental bases of the most important of these models, including the terminal model upon which our computer simulation programs are based, and assesses the degree to which such models can account for experimentally observed copolymerisation behaviour.

3.21 The Terminal Model

The standard kinetic treatment of free radical copolymerisation was introduced during the second world war[33,58]. The central idea of the model was that the rate constant for addition of each monomer was assumed to be dependent on the identity of the terminal unit on the growing chain. Four elementary propagation steps were considered (see equations 3.1 - 3.4). Which simplify to the equation 3.7:

$$\frac{\partial[M_1]}{\partial[M_2]} = \frac{[M_1]}{[M_2]} \frac{r_1[M_1] + [M_2]}{[M_1] + r_2[M_2]} \qquad \text{Eqt 3.7}$$

From this expression some interesting patterns are seen:

(i) When $r_1 \approx r_2 \approx 1$. Neither radical centre shows substantial preference for either M_1 or M_2 so that the relative rates of monomer consumption are determined only by the relative monomer concentrations in the feed mixture. Thus equation 3.7 simplifies to :

$$\frac{\partial[M_1]}{\partial[M_2]} = \frac{[M_1]}{[M_2]}$$

and the copolymer and monomer feed compositions are thus identical.

(ii) When $r_1 \approx r_2 \approx 0$. Each of the radical centres shows a strong preference for cross-propagation. In the extreme case, the copolymer is perfectly alternating and of 1:1 composition, regardless of the composition of the monomer feed mixture. Thus equation 3.7 becomes:

$$\frac{\partial[M_1]}{\partial[M_2]} = \frac{[M_1][M_2]}{[M_2][M_1]} = 1$$

(iii) When $r_1 > 1$ & $r_2 < 1$. Each radical centre prefers to add M_1, so that the copolymer is always enriched in M_1 relative to the feed ratio. This situation arises most frequently in free radical copolymerisation. A special case is that in

which $r_1r_2 = 1$, i.e. both active centres show the same preference for addition of one of the monomers. This behaviour is often termed Ideal Copolymerisation, as the monomer units are arranged at random along the chain in the relative amounts determined by the reactivities and concentrations of the monomers.

(iv) When $r_1<1$ & $r_2<1$. Each of the radical centres prefers cross-propagation but the preference is not absolute. This results in a tendency towards alternation, which grows stronger as r_1 & r_2 approach zero. A characteristic of such copolymerisations is the existence of an azeotropic condition, at which the copolymer and monomer feed compositions are equal. This situation arises when:

$$\frac{\partial[M_1]}{\partial[M_2]} = \frac{[M_1]}{[M_2]}, \qquad \text{therefore: } \frac{r_1[M_1] + [M_2]}{[M_1] + r_2[M_2]} = 1$$

at the azeotropic point. The azeotropic composition is of some practical significance in that at this point compositional drift with conversion may be neglected.

The patterns of copolymerisation behaviour discussed above can be summarised in the form of composition curves in which copolymer composition (e.g. as mole fraction M_1 in the copolymer) is plotted as a function of the monomer feed composition (as the mole fraction M_1 in the feed), as below in Figure 3.1:

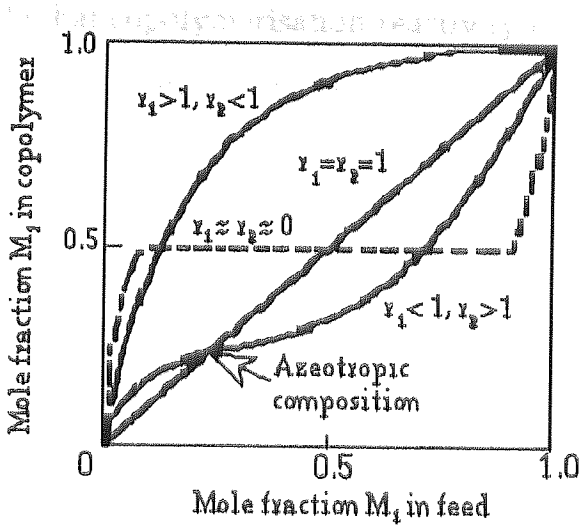


Figure 3.1: Copolymer composition as a function of monomer feed composition for various reactivity ratio combinations

Analysis of the terminal model is readily extended to the predictions of copolymer sequence distributions. Sequence distributions are most generally and conveniently specified in terms of the number fractions of uninterrupted sequences of a given monomer (M_1 or M_2) that are of a particular length. The number fraction (as given by f_{11} in Eqt 3.5, f_{22} in Eqt 3.6) is identical to the probability that a given uninterrupted sequence, selected at random, is of that length. These equations, Eqt 3.5 and Eqt 3.6, allow us to calculate the comonomer sequence distribution from a knowledge of the terminal model reactivity ratios and the monomer feed compositions.

3.22 The Penultimate Model

The basic principle of the terminal model, i.e. that the reactivity of the growing radical is determined only by the identity of the last-added monomer unit, is equivalent to the assumption that the relative rates of monomer addition are insensitive to substitution at positions more remote than that beta to the radical centre. Remote substituent effects are well known in organic chemistry,

and it is thus plausible that copolymerisation reactivity ratios should be affected by units that precede the terminal residue on the propagating macro-radical. Thus it was suggested that a proper description of the propagation step should take into account four distinct active centres, which are defined by the identities of their terminal and the penultimate units, giving us eight propagation steps[59]:

$$\sim\sim M_1M_1^{\bullet} + M_1 \xrightarrow{k_{111}} \sim\sim M_1M_1M_1^{\bullet}$$

$$\sim\sim M_1M_1^{\bullet} + M_2 \xrightarrow{k_{112}} \sim\sim M_1M_1M_2^{\bullet}$$

$$\sim\sim M_2M_1^{\bullet} + M_1 \xrightarrow{k_{211}} \sim\sim M_2M_1M_1^{\bullet}$$

$$\sim\sim M_2M_1^{\bullet} + M_2 \xrightarrow{k_{212}} \sim\sim M_2M_1M_2^{\bullet}$$

$$\sim\sim M_1M_2^{\bullet} + M_1 \xrightarrow{k_{121}} \sim\sim M_1M_2M_1^{\bullet}$$

$$\sim\sim M_1M_2^{\bullet} + M_2 \xrightarrow{k_{122}} \sim\sim M_1M_2M_2^{\bullet}$$

$$\sim\sim M_2M_2^{\bullet} + M_1 \xrightarrow{k_{221}} \sim\sim M_2M_2M_1^{\bullet}$$

$$\sim\sim M_2M_2^{\bullet} + M_2 \xrightarrow{k_{222}} \sim\sim M_2M_2M_2^{\bullet}$$

This will obviously complicate the kinetics some what, but an expression for $\partial[M_1]/\partial[M_2]$ can be found in a similar fashion to that for the terminal model. Prediction of the monomer sequence lengths by the penultimate model is conceptually identical to that described previously for the terminal model. Therefore with a knowledge of the copolymerisation reactivity ratios we can calculate the copolymer compositions and sequence distributions as functions of the ratio of monomer concentrations in the feed.

3.23 The Complex Participation Model

Radical copolymerisation of electron rich alkenes with electron poor alkenes are anomalous in several aspects. Such monomer pairs often afford alternating copolymers over the entire range of feed compositions and often such systems

show a marked sensitivity of the overall composition rate to temperature, solvent and monomer concentration[60].

A mechanistic scheme that accounts for this behaviour invokes the participation of 1:1 alkene electron donor-acceptor (EDA) complexes in the propagation step. Specifically it was proposed that the 1:1 complex, (M1M2), competes with free monomers for the growing chain end. Modification of the terminal model in this way requires consideration of eight propagation steps, including the four equations, 3.1 - 3.4, and the following four:

$$\sim\sim M_1^{\bullet} + (M_1M_2) \text{------}k_{1(11)}\text{---}> \sim\sim M_1M_1M_2^{\bullet}$$

$$\sim\sim M_1^{\bullet} + (M_2M_1) \text{------}k_{1(21)}\text{---}> \sim\sim M_1M_2M_1^{\bullet}$$

$$\sim\sim M_2^{\bullet} + (M_1M_2) \text{------}k_{2(12)}\text{---}> \sim\sim M_2M_1M_2^{\bullet}$$

$$\sim\sim M_2^{\bullet} + (M_2M_1) \text{------}k_{2(21)}\text{---}> \sim\sim M_2M_2M_1^{\bullet}$$

and if radical additions to each 'side' of the complex are regarded as distinct, a complexation equilibrium:

$$M_1 + M_2 <\text{====}K\text{====}> (M_1M_2)$$

Thus again analysis of these equations will allow us to predict copolymer composition and sequence distributions as functions of the feed composition.

3.24 Model Discrimination

Thus the terminal model is extraordinarily useful as a context in which to describe the compositions of copolymers prepared from vinyl monomers of widely varying structure and reactivity. On the other hand, it has been shown in literature that the penultimate and/or complex participation models are slightly more accurate in detailed descriptions of the copolymer microstructure[5]. Therefore the complexity of the use of the individual models

must be counter-balanced with the requirements of the analysis. If the analysis of the copolymer microstructure is required to a very high degree of precision then the penultimate and/or complex participation models should be used. But if only a reasonable idea of the copolymer microstructure is required with additional compositional data, then it is perfectly adequate and much simpler to employ the terminal model[61].

3.3 Reactivity Ratios and the Q-e scheme

For extensive modelling of sequence distributions through the computer simulation programs we require a large source of pairs of monomers whose reactivity ratios have been determined experimentally. Often this is not possible as we may be required to use monomers whose reactivity ratios are not known. A reasonable approximation of the reactivity ratios may be arrived at through the use of the Q-e scheme[62,63]. This scheme was developed to help quantify the different extents to which polar and resonance stabilisation effects influence copolymerisation reactions. The two reactants in a radical/monomer addition were assigned e values, e_1 and e_2, respectively, to represent their charges, identical charges being assumed for a monomer and its derived radical. The general reactivities of radicals and monomers were denoted by P and Q respectively. The rate of reaction was considered to be determined by the four quantities P_1, Q_1, e_1 and e_2 as indicated by the equation below:

$$k_{12} = P_1 Q_2 \exp(-e_1 e_2)$$

four such equations (representing each propagation step) allow us to arrive at:

$$r_1 = (Q_1/Q_2)\exp[-e_1(e_1-e_2)]$$

$$r_2 = (Q_2/Q_1)\exp[-e_2(e_1-e_2)]$$

$$r_1 r_2 = \exp[-(e_1-e_2)2]$$

Thus the Q-e scheme allows predictions to be made about reactivity ratios in systems which have not been studied experimentally. For this purpose it was necessary to assign characteristic Q and e values to monomers on the basis of copolymerisation experiments with a limited number of reference monomers[64-66]. Styrene has been chosen as the reference monomer and has been assigned Q=1 and e=-0.8. Examples of some common monomers and their Q and e values can be seen in table 3.1 below :

Table 3.1: Q-e values for some selected monomers

Monomer	Q value	e value
STY	1.0	-0.8
MMA	0.78	0.40
HEMA	1.78	-0.39
MA	0.40	-0.05
NNDMA	0.41	-0.26
NVP	0.088	-1.62

A program has been written which uses the equations overleaf, with the Q-e values to calculate the reactivity ratios. By studying the Q-e values given for numerous monomers in the literature, we may make reasonable approximations of the Q-e values for monomers with no data available, based on comparisons of the structures of these monomers with the structures of monomers whose Q-e values are known. This is a reasonable assumption since

the Q-e scheme itself is based upon the properties of the structures of the monomers involved. This will then allow us to derive the reactivity ratio values for these monomers with the other monomers to be used in the computer simulation programs. For example no Q-e data is available for the commonly used cross-linker ethylene glycol dimethacrylate (EGDMA). From its structure it can be seen that it contains two vinyl moieties. A reasonable approximation for the reactivity of the first vinyl bond would be to use the Q-e values of ethyl methacrylate (EMA), a relatively reactive methacrylate. For the second vinyl bond it is more appropriate to use the Q-e values of a much more sterically restricted methacrylate/acrylate, such as octadecyl methacrylate (ODMA).

3.4 Computer Simulated Sequence Distributions

The computer simulation programs may be simply illustrated by considering the sequence distributions seen for a few common contact lens materials. Besides being commercially important biomaterials, the formulations of these materials provides a wide range of compositions and monomer types, which would allow us to adequately illustrate the power of these computer simulation programs. For example, we may start with a relatively simple material, essentially a copolymer, such as *Etafilcon-A which is based on two monomer units, and then move onto more complex materials such *Xylofilcon-A, which is based on three different monomer units including cyclohexyl methacrylate (CMA). *Table 3.12 below gives more details about these materials and their nomenclature.

These contact lens materials are essentially all hydrogels and are regulated by different national authorities. The most systematic approach has been in the

United States. They have devised United States Adopted Name Council (USAN) names for generic materials such that they become like paracetomol or aspirin and almost as well characterised. This is the nomenclature that has been adopted in this thesis. The various manufacturers then use their own trade names for the subsequently manufactured contact lenses based on these materials, thus Acuvue & Surevue are trade names for contact lenses manufactured by Johnson & Johnson, both are based on the material Etafilcon-A.

Table 3.12 : Contact Lens Material Data and Nomenclature.

USAN Nomenclature	Trade Name	Manufacturer /supplier	Principal components	EWC (%)
Etafilcon-A	Acuvue	Vistakon	HEMA,MA	58
Surfilcon-A	Permaflex	Pilkington Barnes-Hind	MMA, NVP	74
Tetrafilcon-A	Aquaflex	UCO optics	HEMA, NVP,MMA	42.5
Xylofilcon-A	Igel-68	Igel optics	MMA, NVP, CMA	68

All of the above materials also contain 1% EGDMA used as a cross-linker.

In studying the simulated sequence distributions of the above contact lens materials, we may add an extra variation in order to see how these sequence distributions are altered by replacing the commonly used cross-linker EGDMA, with firstly N, N`-diallyltartardiamide (DATDAM), and secondly with 2, 4, 6-triallyloxy-s-triazine (triallyl cyanurate, TAC) (see Chapter 2, for structures of these cross-linkers). This is simply because it is well established that the concentration and distribution of a cross-linker in a polymeric material has a significant affect upon that materials properties, such as the EWC, tensile

strength, etc. Thus it would be very interesting to observe how different cross-linkers affect the simulated sequence distributions of these commercially important biomaterials.

Table 3.2, below, shows the cross-linkers used, and if any equivalent monomer Q - e values were used to calculate the reactivity ratios of the first and second vinyl bond additions, of these cross-linkers with the monomers in the proceeding contact lens formulations. One must remember that when making an estimate for the addition of the first vinyl bond of a particular cross-linker, we may take the cross-linker molecule as being distinct. But when we come to consider an estimate for the addition of the second vinyl bond we have a more complex situation. Here the portion of the cross-linker molecule containing the vinyl bond that has already reacted may in all probability be attached to a fairly large polymer molecule. Thus generally the second vinyl bond of a particular cross-linker tends to be of a lower reactivity than the first vinyl bond.

Table 3.2: Cross-linkers and equivalent Monomers used

Cross-Linkers	Equivalent Monomers used for the 1st and 2nd vinyl bonds of the cross-linker	
	1st vinyl bond	2nd vinyl bond
EGDMA	Ethyl methacrylate	Octadecyl methacrylate
DATDAM	Allyl acrylate	N, N-Diallyl stearamide
TAC	Triallyl cyanurate	Triallyl isocyanurate

3.41: Etafilcon-A contact lens material (HEMA : MA : EGDMA :: 95 : 4 : 1)

We may satisfactorily start to illustrate the principle of the computer simulation programs through the use of the contact lens material Etafilcon-A. This is because Etafilcon-A is a rather simple copolymeric material and the monomers which constitute this material have relatively similar reactivity ratios. Etafilcon-A is a transparent hydrogel with an EWC of approximately 58%. Figures 3.21 to 3.26 show the computer simulated sequence distributions for Etafilcon-A contact lens material with various cross-linkers. Tables 3.21 to 3.26 show the sequence lengths seen in figures 3.21 to 3.26, respectively.

Figure 3.21 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with EGDMA (showing only the addition of the first vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

1 Mole % of Monomer C, EGDMA

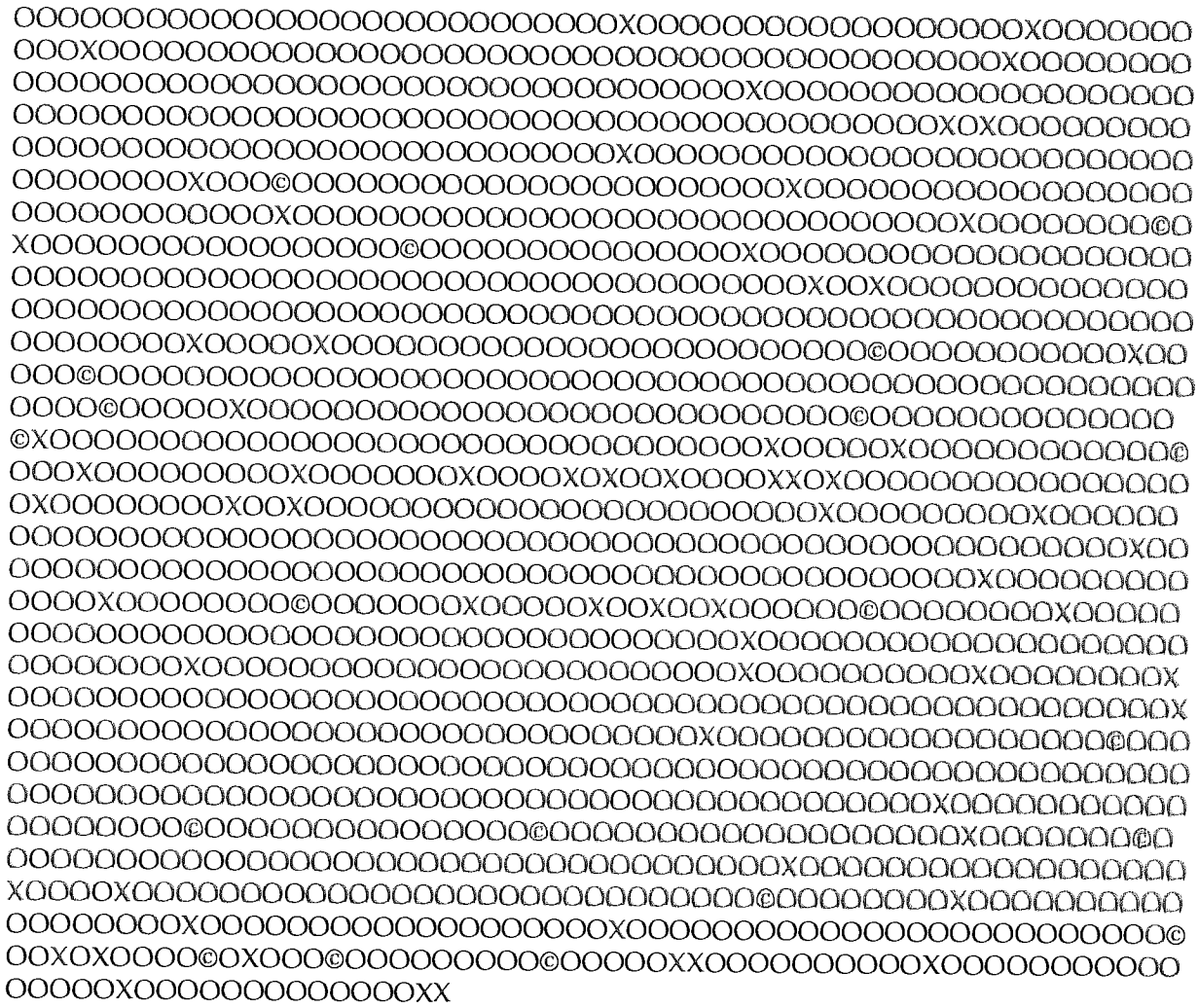
r(AB) = 1.224 r(AC) = 1.882 r(BA) = 0.294

r(BC) = 0.975 r(CA) = 0.388 r(CB) = 0.837

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and EGDMA is represented by © :

XOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOXOOOXOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOXOOOOOXOOOOXOOO
OOOOOOOOOOXOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 EMA units.

Table 3.21 : Sequence lengths seen in the simulated sequence distribution of figure 3.21.

Sequence Distributions:

Length	HEMA	MA	EGDMA
1	7	74	20
2	6	3	0
3	4	0	0
4	4	0	0
5	7	0	0
6	3	0	0
7	4	0	0
8	6	0	0

9	3	0	0
10	3	0	0
11	1	0	0
12	1	0	0
13	3	0	0
14	1	0	0
15	2	0	0
16	1	0	0
17	2	0	0
18	4	0	0
19	3	0	0
22	1	0	0
23	1	0	0
24	1	0	0
25	3	0	0
28	2	0	0
29	1	0	0
30	1	0	0
31	1	0	0
32	1	0	0
33	1	0	0
34	1	0	0
36	1	0	0
37	2	0	0
39	1	0	0
42	2	0	0
47	1	0	0
54	1	0	0
55	1	0	0
57	1	0	0
58	1	0	0
63	1	0	0
70	1	0	0
77	1	0	0
101	1	0	0
178	1	0	0

Figure 3.22 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with EGDMA (showing only the addition of the second vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

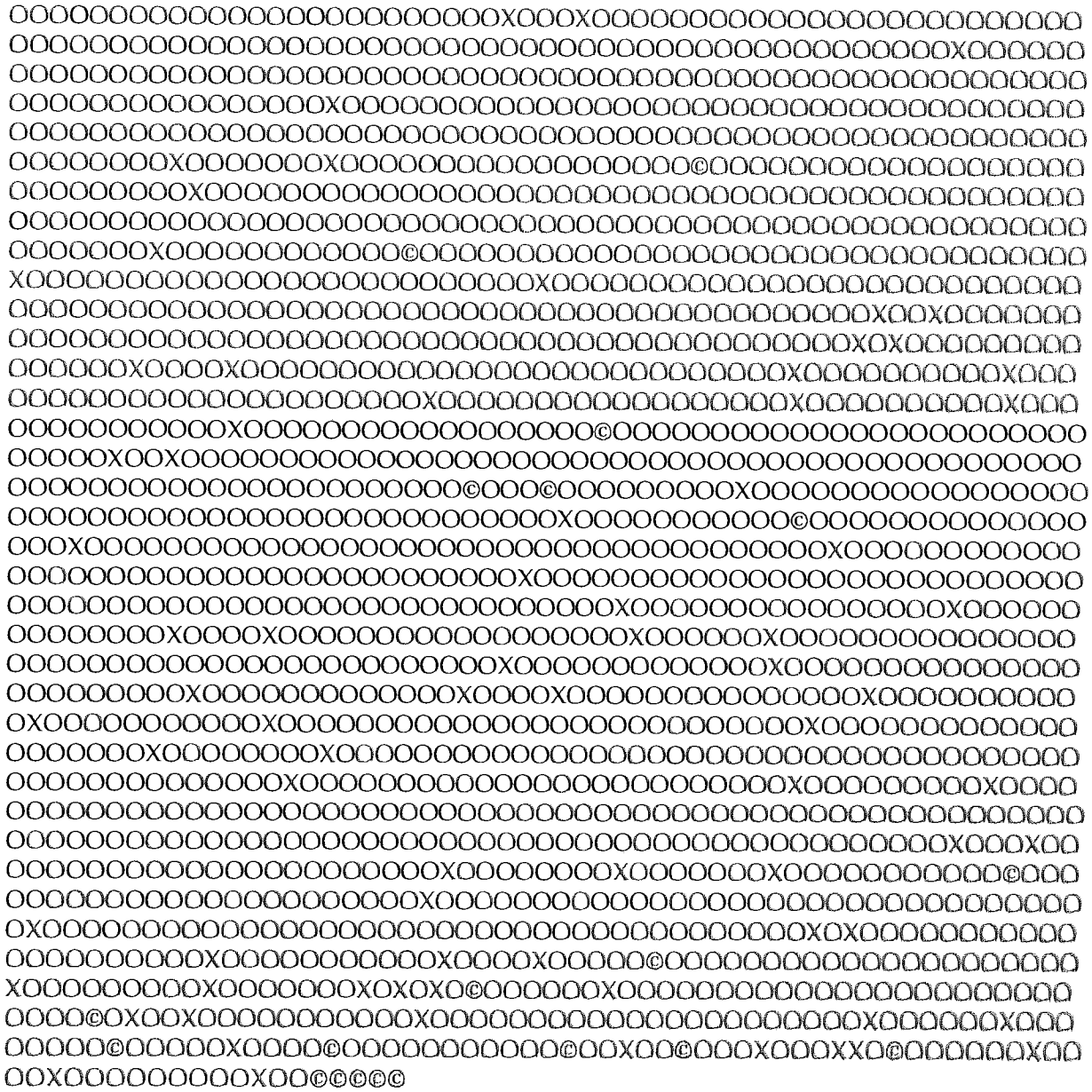
1 Mole % of Monomer C, EGDMA

r(AB) = 1.224 r(AC) = 2.834 r(BA) = 0.294

r(BC) = 4.416 r(CA) = 0.023 r(CB) = 0.15

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and EGDMA is represented by © :



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 EGDMA units.

Table 3.22 : Sequence lengths seen in the simulated sequence distribution of figure 3.22.

Sequence Distributions:

Length	HEMA	MA	EGDMA
1	7	78	15
2	6	1	0
3	5	0	0
4	6	0	0
5	2	0	1
6	4	0	0
7	3	0	0
8	3	0	0
9	4	0	0
10	2	0	0
11	7	0	0
12	1	0	0
13	2	0	0
14	2	0	0
15	2	0	0
16	1	0	0
17	1	0	0
18	4	0	0
20	1	0	0
21	2	0	0
22	1	0	0
24	4	0	0
25	2	0	0
26	1	0	0
27	2	0	0
28	2	0	0
29	1	0	0
34	2	0	0
38	2	0	0
39	1	0	0
40	1	0	0
45	1	0	0
50	1	0	0

52	1	0	0
59	1	0	0
69	1	0	0
71	1	0	0
73	1	0	0
77	1	0	0
101	1	0	0
107	2	0	0

Figure 3.23 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with DATDAM (showing only the addition of the first vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

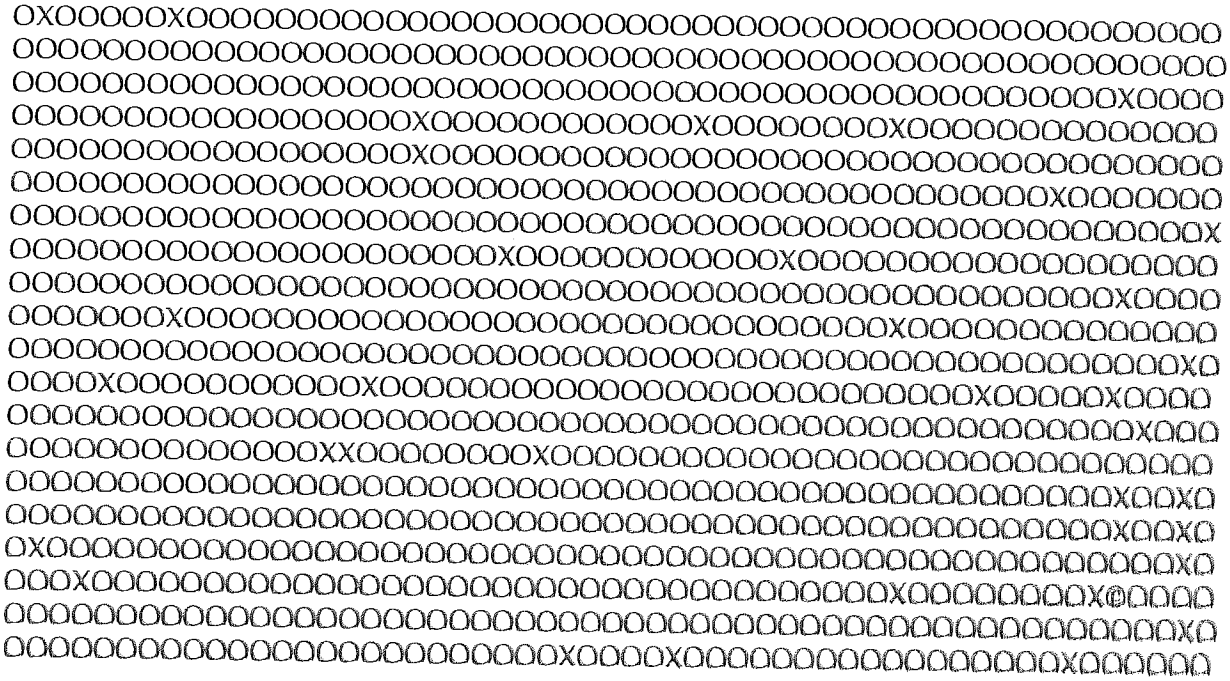
1 Mole % of Monomer C, DATDAM

r(AB) = 1.224 r(AC) = 9.67 r(BA) = 0.294

r(BC) = 1.432 r(CA) = 0.065 r(CB) = 0.04

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and DATDAM is represented by © :



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 DATDAM units.

Table 3.23 : Sequence lengths seen in the simulated sequence distribution of figure 3.23.

Sequence Distributions:

Length	HEMA	MA	DATDAM
1	3	78	6
2	5	1	0
3	3	0	0
4	7	0	0
5	3	0	0
6	2	0	0
7	1	0	0
8	4	0	0
9	3	0	0
10	2	0	0
11	2	0	0
12	3	0	0
13	1	0	0
14	2	0	1
15	3	0	0
16	1	0	0
17	2	0	0
18	2	0	0

19	2	0	0
21	3	0	0
22	3	0	0
25	2	0	0
26	2	0	0
27	1	0	0
32	4	0	0
33	1	0	0
36	3	0	0
40	1	0	0
50	1	0	0
51	3	0	0
55	1	0	0
57	1	0	0
61	1	0	0
67	1	0	0
69	1	0	0
75	1	0	0
80	1	0	0
83	1	0	0
152	1	0	0

Figure 3.24 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with DATDAM (showing only the addition of the second vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

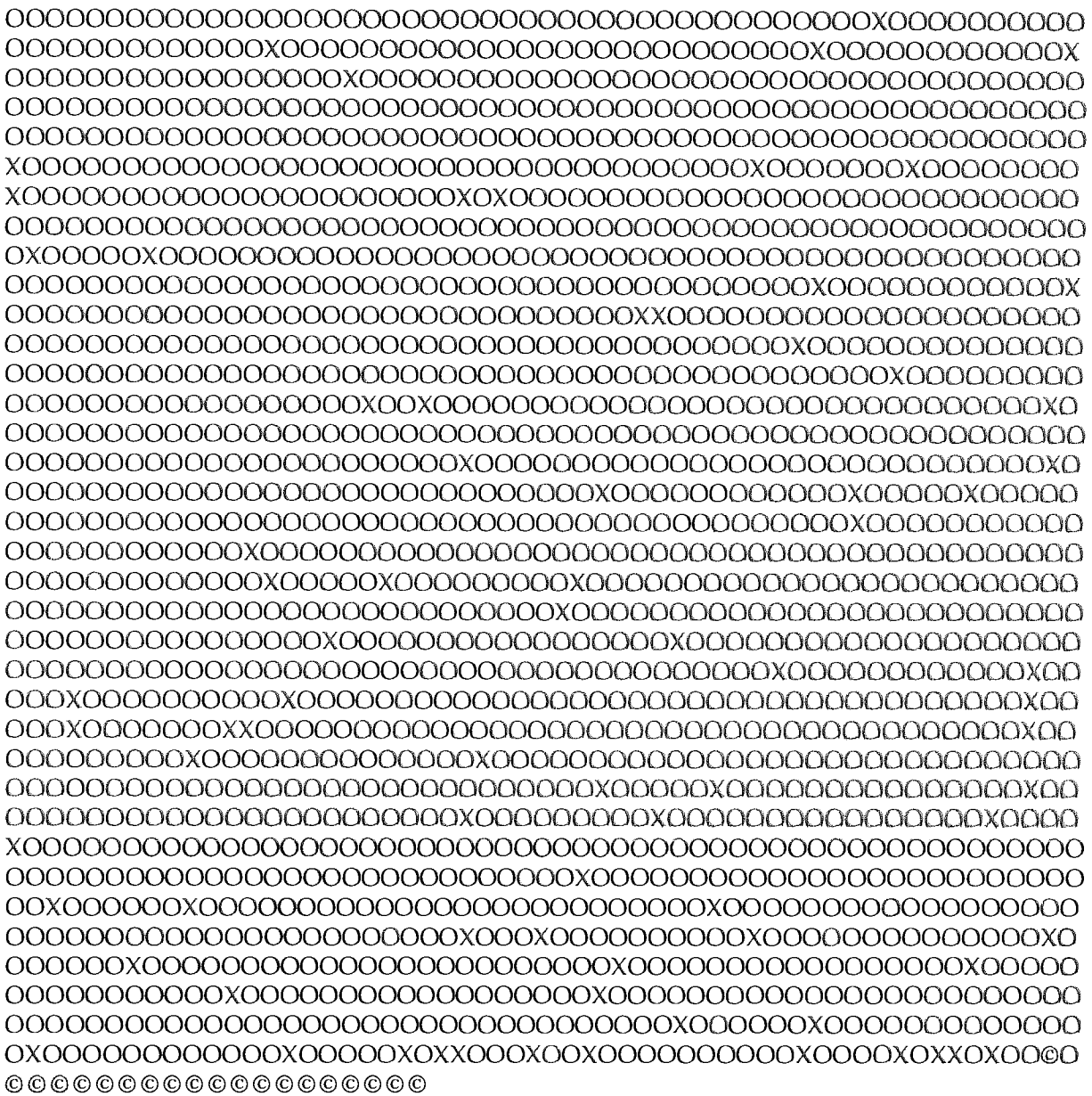
1 Mole % of Monomer C, DATDAM

r(AB) = 1.224 r(AC) = 74.747 r(BA) = 0.294

r(BC) = 21.561 r(CA) = 0.013 r(CB) = 0.016

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and DATDAM is represented by © :



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 DATDAM units.

Table 3.24 : Sequence lengths seen in the simulated sequence distribution of figure 3.24.

Sequence Distributions:

Length	HEMA	MA	DATDAM
1	5	72	1
2	3	4	0
3	2	0	0

4	2	0	0
5	7	0	0
6	2	0	0
7	3	0	0
8	1	0	0
9	2	0	0
10	3	0	0
11	1	0	0
12	5	0	0
14	3	0	0
15	1	0	0
16	2	0	0
17	3	0	0
18	1	0	0
19	0	0	1
22	1	0	0
23	2	0	0
24	1	0	0
25	1	0	0
26	1	0	0
27	3	0	0
29	1	0	0
31	2	0	0
32	1	0	0
37	2	0	0
39	1	0	0
41	1	0	0
42	1	0	0
44	1	0	0
48	1	0	0
53	1	0	0
55	1	0	0
58	1	0	0
59	2	0	0
60	1	0	0
61	1	0	0
79	1	0	0
83	1	0	0
85	1	0	0
88	1	0	0
147	1	0	0

Figure 3.25 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with TAC (showing only the addition of the first vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

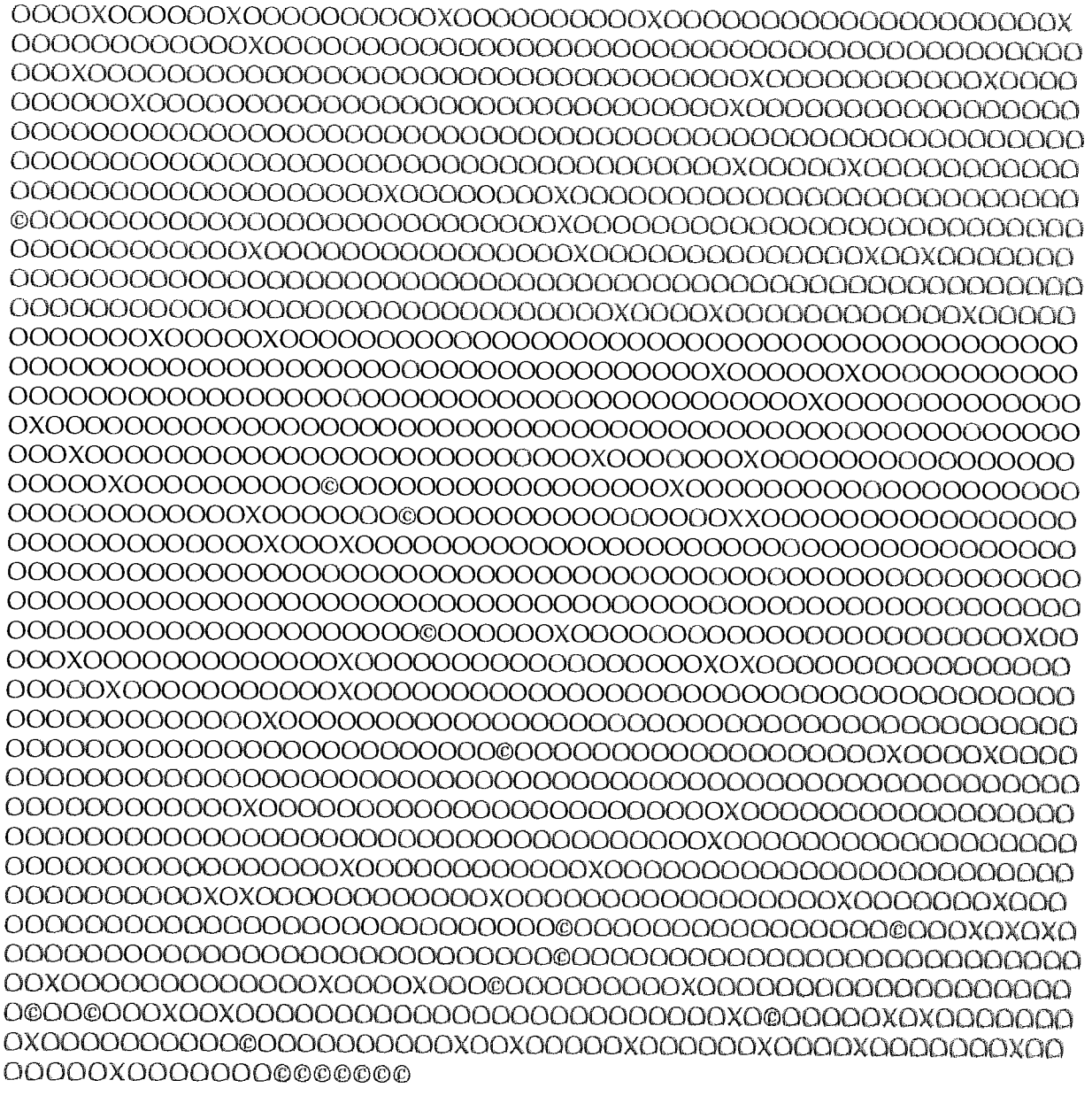
1 Mole % of Monomer C, TAC

r(AB) = 1.224 r(AC) = 4.266 r(BA) = 0.294

r(BC) = 21.236 r(CA) = 0.001 r(CB) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and TAC is represented by © :



The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 TAC units.

Table 3.25 : Sequence lengths seen in the simulated sequence distribution of figure 3.25.

Sequence Distributions:

Length	HEMA	MA	TAC
1	6	78	13
2	4	1	0
3	4	0	0
4	5	0	0
5	5	0	0
6	4	0	0
7	6	0	1
8	2	0	0
9	1	0	0
10	6	0	0
11	2	0	0
12	5	0	0
13	2	0	0
14	2	0	0
16	3	0	0
17	2	0	0
18	1	0	0
19	1	0	0
20	2	0	0
21	2	0	0
23	1	0	0
24	1	0	0
25	1	0	0
26	2	0	0
27	1	0	0
28	1	0	0
29	2	0	0
30	2	0	0
31	1	0	0
32	1	0	0
34	2	0	0
35	1	0	0
38	1	0	0

45	1	0	0
50	1	0	0
52	1	0	0
53	1	0	0
56	1	0	0
66	1	0	0
71	1	0	0
77	1	0	0
93	1	0	0
109	1	0	0
168	1	0	0

Figure 3.26 : Computer simulated sequence distribution of Etafilcon-A contact lens formulation with TAC (showing only the addition of the second vinyl bond).

95 Mole % of Monomer A, HEMA

4 Mole % of Monomer B, MA

1 Mole % of Monomer C, TAC

r(AB) = 1.224 r(AC) = 47.78 r(BA) = 0.294

r(BC) = 16.53 r(CA) = 0.02 r(CB) = 0.029

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MA is represented by X and TAC is represented by © :

OOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOXOOOOOOOOOOOOOOOOOOOOXOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOO
OOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOOOXOOOOOOXOXOOOOOOOOOX
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOXOOOOOOOOOOOOOOXOOOOOOOXOOOOOOOOOOOOOOOOOXO
OOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOXOOOOXOOOOOOOOXOOOOOOOOOOOOXOXOOOOOOOOOXOOOOOOOOOOXO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOXOOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOXOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
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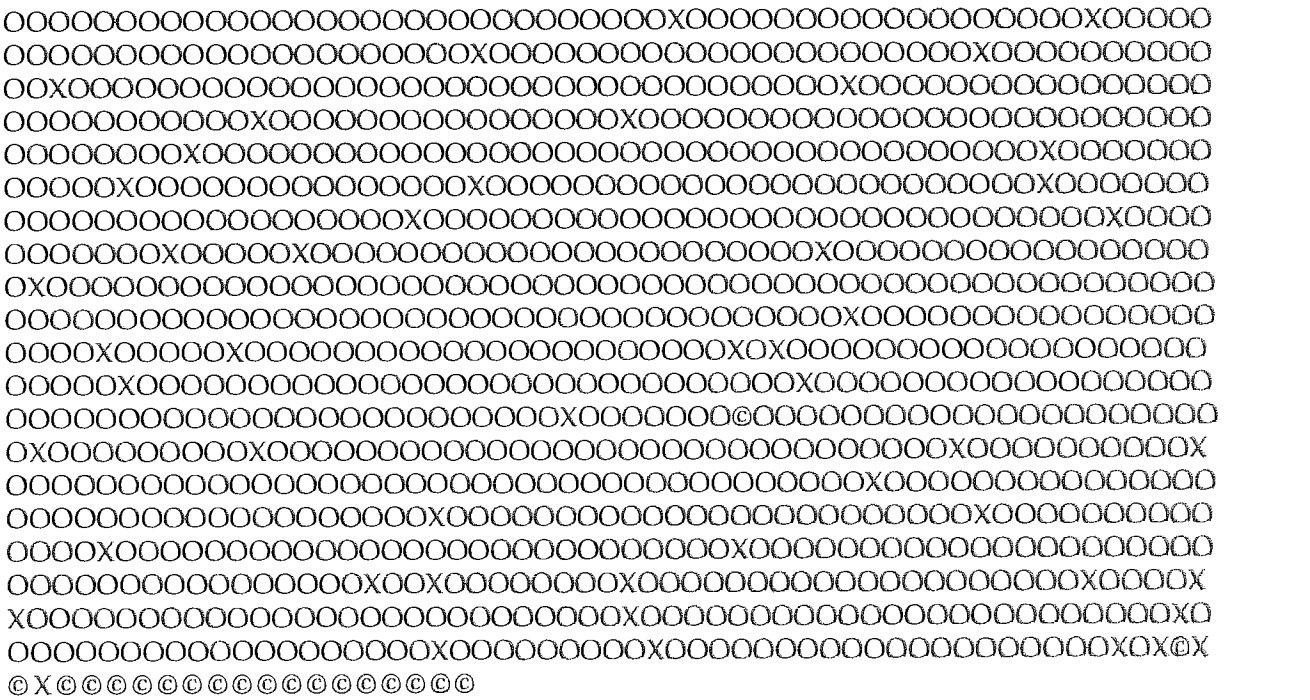

The simulated terpolymer contains 1900 HEMA units, 80 MA units and 20 TAC units.

Table 3.26 : Sequence lengths seen in the simulated sequence distribution of figure 3.26.

Sequence Distributions:

Length	HEMA	MA	TAC
1	5	78	3
2	1	1	0
4	2	0	0
5	2	0	0
6	1	0	0
7	2	0	0
8	2	0	0
9	3	0	0
10	2	0	0
11	3	0	0
12	3	0	0
13	1	0	0
14	2	0	0
15	1	0	0

16	2	0	0
17	1	0	1
18	2	0	0
20	5	0	0
22	3	0	0
23	2	0	0
24	3	0	0
25	3	0	0
26	1	0	0
27	3	0	0
28	1	0	0
29	1	0	0
30	1	0	0
31	2	0	0
34	2	0	0
35	1	0	0
37	1	0	0
38	1	0	0
39	1	0	0
43	1	0	0
46	1	0	0
49	2	0	0
51	2	0	0
54	1	0	0
57	1	0	0
71	1	0	0
75	1	0	0
91	1	0	0
113	1	0	0

It is apparent from the formulation of this Etafilcon-A contact lens material that the two monomers that constitute this material have relatively similar reactivity ratios. We would thus expect to see one monomer evenly dispersed throughout the other one, to produce a fairly regular sequence distribution as the reaction proceeds. Although the large difference in the concentration ratios of the two monomers does preclude the possibility of producing a relatively

good sequence distribution(i.e. short, regular sequences of individual monomer units). This is borne out by figures 3.21 to 3.26 and tables 3.21 to 3.26.

In spite of the fact that this material does not produce a relatively good sequence distribution, we observe that one monomer is evenly dispersed throughout the other one. This suggests, here, the distribution of different cross-linkers at 1% concentration, in such a sequence distribution of monomer units, is likely to be fairly uniform throughout the copolymer, and dependent upon the reactivity of the cross-linking agent. For example EGDMA which, of the cross-linkers used, has the most similar reactivity ratios to the main constituent monomers is found to be fairly uniformly distributed throughout the simulated sequence distribution of this material. In contrast both DATDAM and TAC, display much lower reactivities than the main constituent monomers, and are found to be uniformly residual in the simulated sequence distribution. The reaction of the first vinyl bond occurs after 50% conversion, whilst the second vinyl bond comes in after 90% conversion, for both these cross-linkers. Thus, from figures 3.21 to 3.26 we see that EGDMA is the best cross-linker for this contact lens formulation.

3.42: Surfilcon-A contact lens material (MMA : NVP : EGDMA :: 40 : 59 : 1)

Surfilcon-A is also a copolymeric material, like Etafilcon-A, but in contrast to Etafilcon-A the constituent monomers have a large difference in their reactivity ratios. This will produce a quite different sequence distribution to that seen for Etafilcon-A. Surfilcon-A is also a transparent hydrogel and because

it is based mainly on NVP, it has a much higher EWC, approximately 74%, than Etafilcon-A. Figures 3.27 to 3.32 show the computer simulated sequence distributions for the Surfilcon-A contact lens material with various cross-linkers. Tables 3.27 to 3.32 show the sequence lengths seen in figures 3.27 to 3.32, respectively.

Figure 3.27 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with EGDMA (showing only the addition of the first vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

1 Mole % of Monomer C, EGDMA

r(AB) = 4.04 r(AC) = 0.936 r(BA) = 0.01

r(BC) = 0.006 r(CA) = 1.013 r(CB) = 6.37

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and EGDMA is represented by © :

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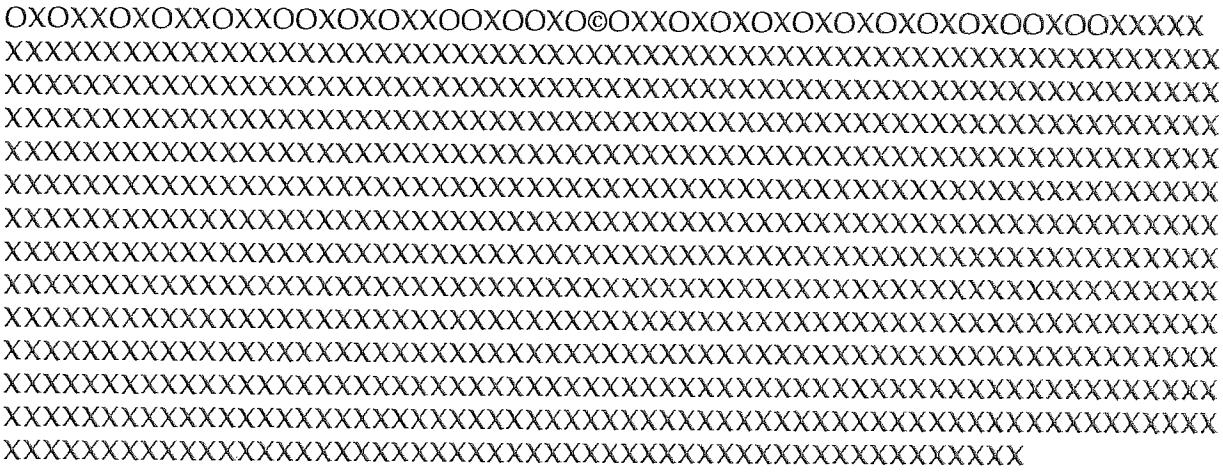

The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 EGDMA units.

Table 3.27 : Sequence lengths seen in the simulated sequence distribution of figure 3.27.

Sequence Distributions:

Length	MMA	NVP	EGDMA
1	169	322	20
2	85	19	0
3	40	2	0
4	19	0	0
5	13	0	0
6	9	0	0
7	5	0	0
8	5	0	0
9	1	0	0
10	2	0	0
11	1	0	0
12	1	0	0
19	1	0	0
814	0	1	0

Figure 3.28 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with EGDMA (showing only the addition of the second vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

1 Mole % of Monomer C, EGDMA

r(AB) = 4.04	r(AC) = 3.334	r(BA) = 0.01
r(BC) = 0.002	r(CA) = 0.143	r(CB) = 0.099

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and EGDMA is represented by © :

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The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 EGDMA units.

Table 3.28 : Sequence lengths seen in the simulated sequence distribution of figure 3.28.

Sequence Distributions:

Length	MMA	NVP	EGDMA
1	153	326	20
2	69	14	0
3	45	1	0
4	26	0	0
5	14	0	0
6	7	0	0
7	11	0	0
8	4	0	0
9	3	0	0
11	2	0	0
823	0	1	0

Figure 3.29 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with DATDAM (showing only the addition of the first vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

1 Mole % of Monomer C, DATDAM

r(AB) = 4.04 r(AC) = 1.805 r(BA) = 0.01

r(BC) = 0.15 r(CA) = 0.063 r(CB) = 4.912

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and DATDAM is represented by © :

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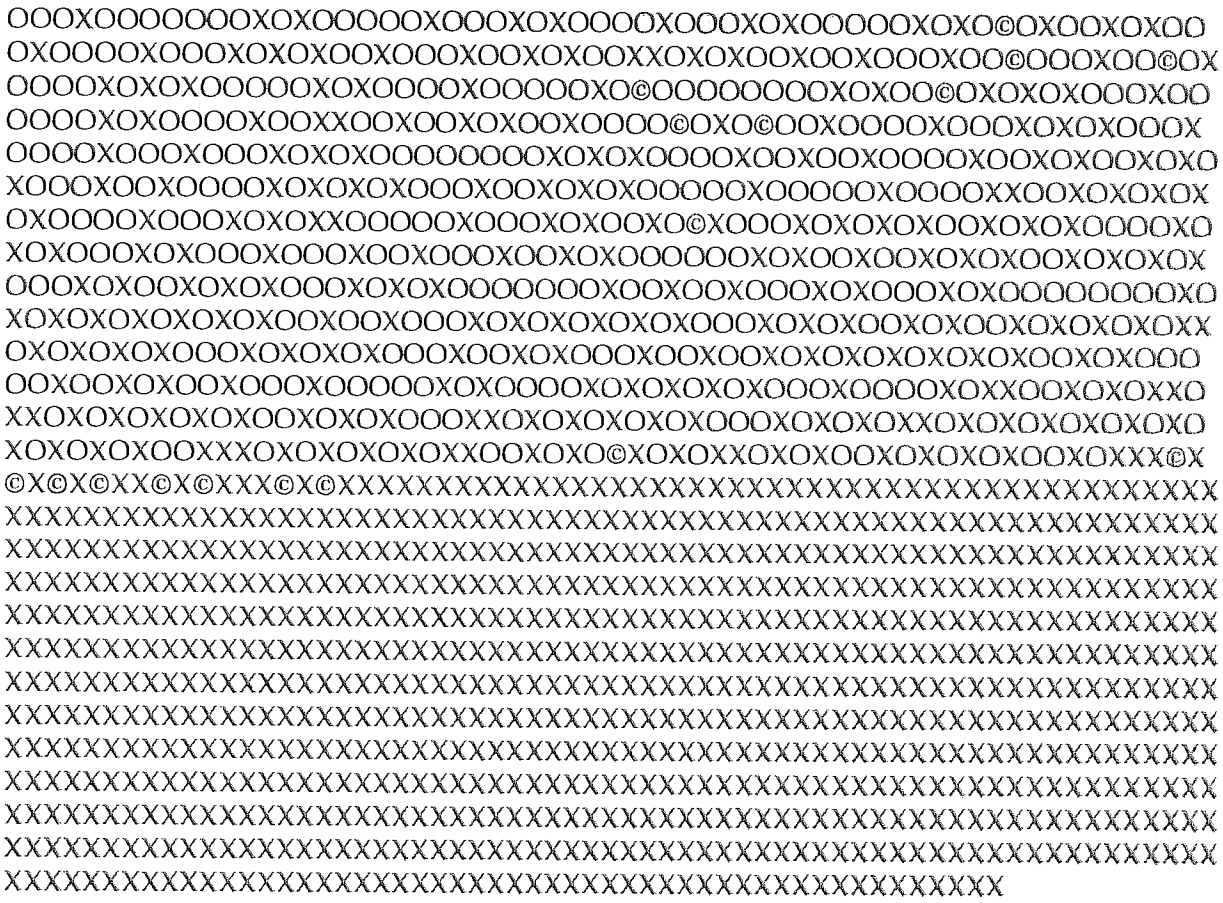


The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 DATDAM units.

Table 3.29 : Sequence lengths seen in the simulated sequence distribution of figure 3.29.

Sequence Distributions:

Length	MMA	NVP	DATDAM
1	188	345	20
2	67	18	0
3	55	3	0
4	25	0	0
5	18	0	0
6	4	0	0
7	5	0	0
8	4	0	0
9	2	0	0
14	1	0	0
790	0	1	0

Figure 3.30 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with DATDAM (showing only the addition of the second vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

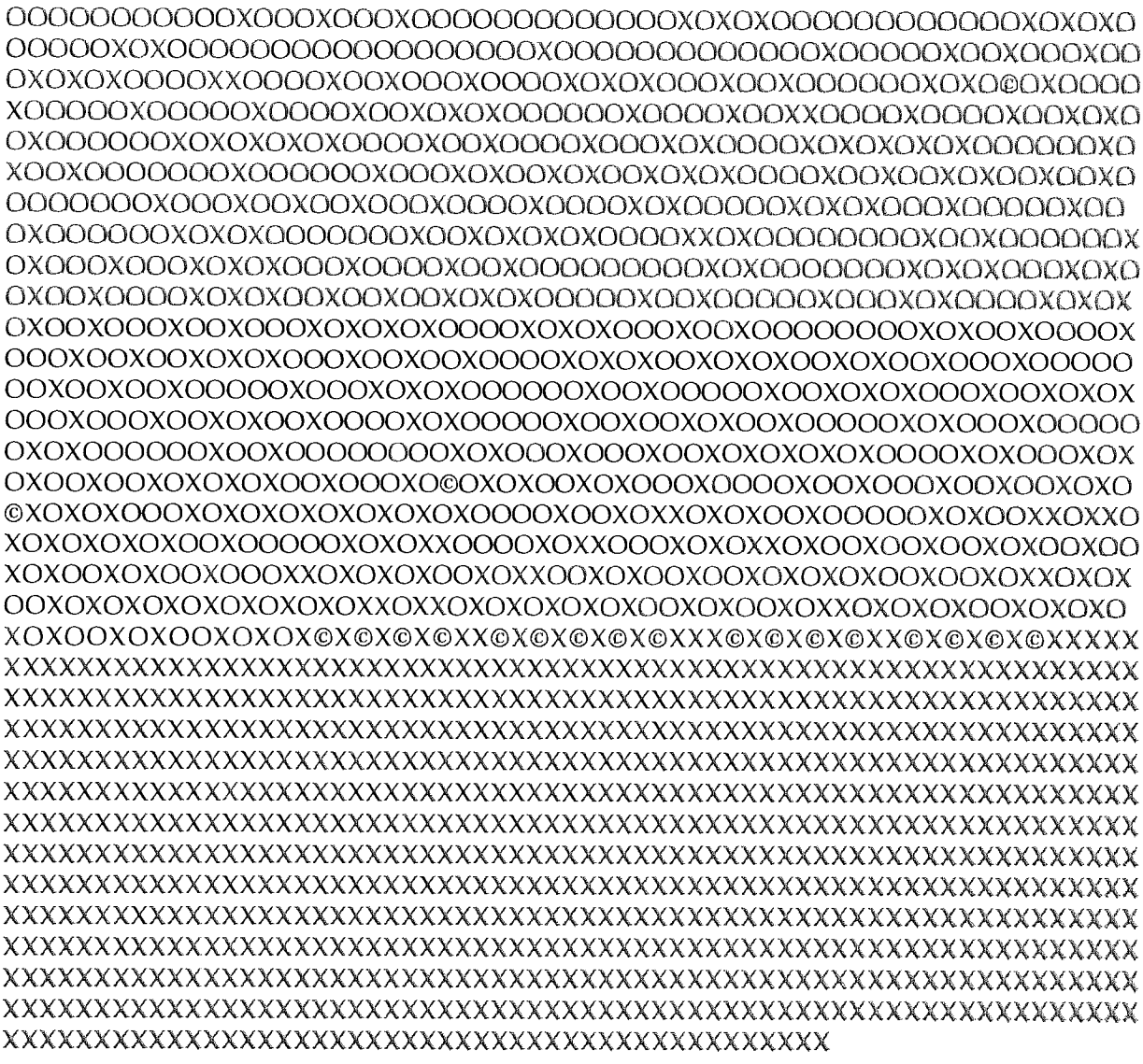
1 Mole % of Monomer C, DATDAM

r(AB) = 4.04 r(AC) = 23.505 r(BA) = 0.01

r(BC) = 0.516 r(CA) = 0.022 r(CB) = 0.447

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and DATDAM is represented by © :



The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 DATDAM units.

Table 3.30 : Sequence lengths seen in the simulated sequence distribution of figure 3.30.

Sequence Distributions:

Length	MMA	NVP	DATDAM
1	160	336	20
2	79	17	0
3	37	1	0
4	26	0	0
5	13	0	0
6	11	0	0
7	4	0	0
8	4	0	0
9	1	0	0
11	1	0	0
12	1	0	0
13	2	0	0
18	1	0	0
807	0	1	0

Figure 3.31 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with TAC (showing only the addition of the first vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.04 r(AC) = 12.449 r(BA) = 0.01

r(BC) = 0.001 r(CA) = 0.001 r(CB) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and TAC is represented by © :

The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 TAC units.

Table 3.31 : Sequence lengths seen in the simulated sequence distribution of figure 3.31.

Sequence Distributions:

Length	MMA	NVP	TAC
1	167	359	20
2	80	9	0
3	46	2	0
4	21	0	0
5	18	0	0
6	6	0	0
7	8	0	0
8	1	0	0
9	3	0	0
10	2	0	0
14	1	0	0
803	0	1	0

Figure 3.32 : Computer simulated sequence distribution of Surfilcon-A contact lens formulation with TAC (showing only the addition of the second vinyl bond).

40 Mole % of Monomer A, MMA

59 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.04 r(AC) = 17.321 r(BA) = 0.01

r(BC) = 0.264 r(CA) = 0.038 r(CB) = 0.547

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and TAC is represented by © :

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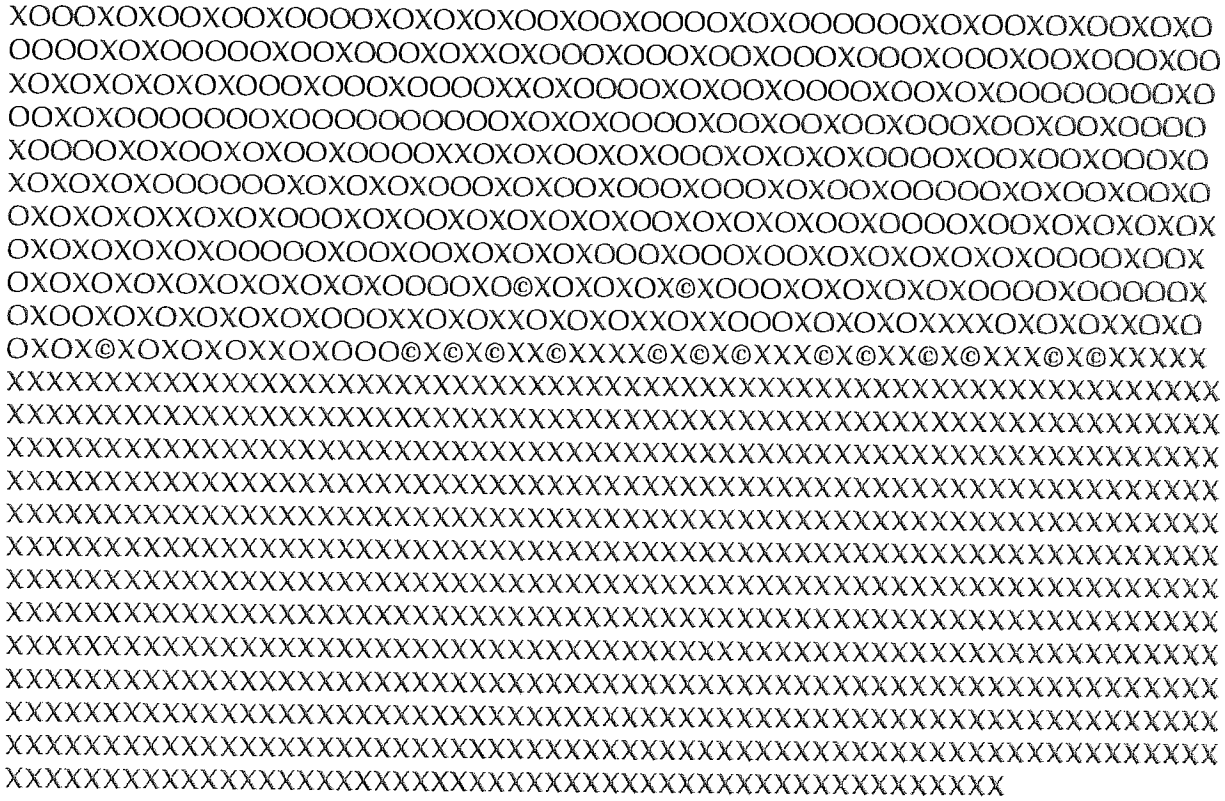

The simulated terpolymer contains 800 MMA units, 1180 NVP units and 20 TAC units.

Table 3.32 : Sequence lengths seen in the simulated sequence distribution of figure 3.32.

Sequence Distributions:

Length	MMA	NVP	TAC
1	152	327	20
2	66	13	0
3	45	2	0
4	32	2	0
5	16	0	0
6	10	0	0
7	4	0	0
8	2	0	0
10	2	0	0
11	1	0	0
12	1	0	0
13	2	0	0
813	0	1	0

Here, it is seen that the Surfilcon-A contact lens material has a better balanced composition than the previous contact lens material Etafilcon-A. Consequently, we would expect to see a much better sequence distribution, if sequence distribution was determined by composition alone. But the big difference in the reactivity ratios of the two main components are such that, in the simulated sequence distributions, we see that up to about 60% conversion we have an average-to-poor sequence distribution, after this we see an immense residual block of NVP. This occurs because NVP is present in greater quantity than MMA and is much less reactive than MMA, which consequently gets used up in the first half of the reaction.

Thus, here, we may note that the distribution of different cross-linkers, even at 1% concentration, in such a sequence distribution of monomer units, is likely to be quite diverse for each type of cross-linker. Thus for example EGDMA, which is more reactive than NVP, is found to be predominantly consumed by 50% conversion. From figures 3.27 and 3.28 we can see that both the vinyl bonds of EGDMA react before 50% conversion, therefore only helping to improve the sequence distribution before 50% conversion and in no way helping to break up the large block of NVP at the end. In contrast both DATDAM and TAC display a similar reactivity towards NVP, and both of these cross-linkers are similar or slightly more reactive towards MMA than NVP. This results in these latter two cross-linkers being more uniformly distributed throughout the simulated sequence distribution seen for Surfilcon-A, in contrast to EGDMA. In both DATDAM and TAC the reaction of the second vinyl bond occurs after 50% conversion, somewhat helping to break up the large block of NVP found at the end of the reaction. Therefore, here it would

appear that DATDAM or even TAC would be better used as cross-linkers for a reasonable sequence distribution and best distribution of cross-links, in contrast to the currently used cross-linker EGDMA.

3.43 Tetrafilcon-A contact lens material (HEMA : NVP : MMA : EGDMA :: 79 : 10 : 10 : 1)

The contact lens material Tetrafilcon-A represents a much more complex composition than that seen in previous simulations. The material is based predominantly on HEMA but it does contain some NVP. Its EWC is approximately 43%. Tetrafilcon-A is instructive in that it illustrates a problem that may arise, when the material whose sequence distribution is to be simulated, contains more than three components. This problem exists, since the computer simulation programs can only run a maximum of three components at any one time. To overcome this problem we must develop a method through which we can reduce the number of components to be simulated in the sequence distribution, down to a maximum of three. This may be achieved by considering the simulated copolymerisation sequence distributions, for reactions between the main individual monomers which constitute Tetrafilcon-A, as shown in figures 3.33 and 3.34:

Figure 3.33 : Computer simulated sequence distribution of a copolymer of HEMA : MMA :: 50 : 50.

50 Mole % of Monomer A, HEMA

50 Mole % of Monomer B, MMA

r(AB) = 0.810

r(BA) = 0.192

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and MMA is represented by X :

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The simulated copolymer contains 1000 HEMA units and 1000 MMA units.

Table 3.33 : Sequence lengths seen in the simulated sequence distribution of figure 3.33.

Sequence Distributions:

Length	HEMA	MMA
1	395	451
2	138	114
3	43	32
4	25	13
5	8	6
6	5	1
7	3	0
9	1	0
12	0	1
125	0	1

Figure 3.34 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 50 : 50.

50 Mole % of Monomer A, HEMA

50 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :

XOOOOOOOOOOOXOOXOOOOOXOOOOOOOXOOXOOOOOOXOOOOOOOOOOXOOOO
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OOOOOOXOOOOOOXOOXOOOOOXOOXOOOOOOXOOOXOOOOOOXOOOOOO
OOOXOOXOOOXOOXOOOOOOOOOXOXOOOOOOOOOOOOOOOOXOOOXOOOXO
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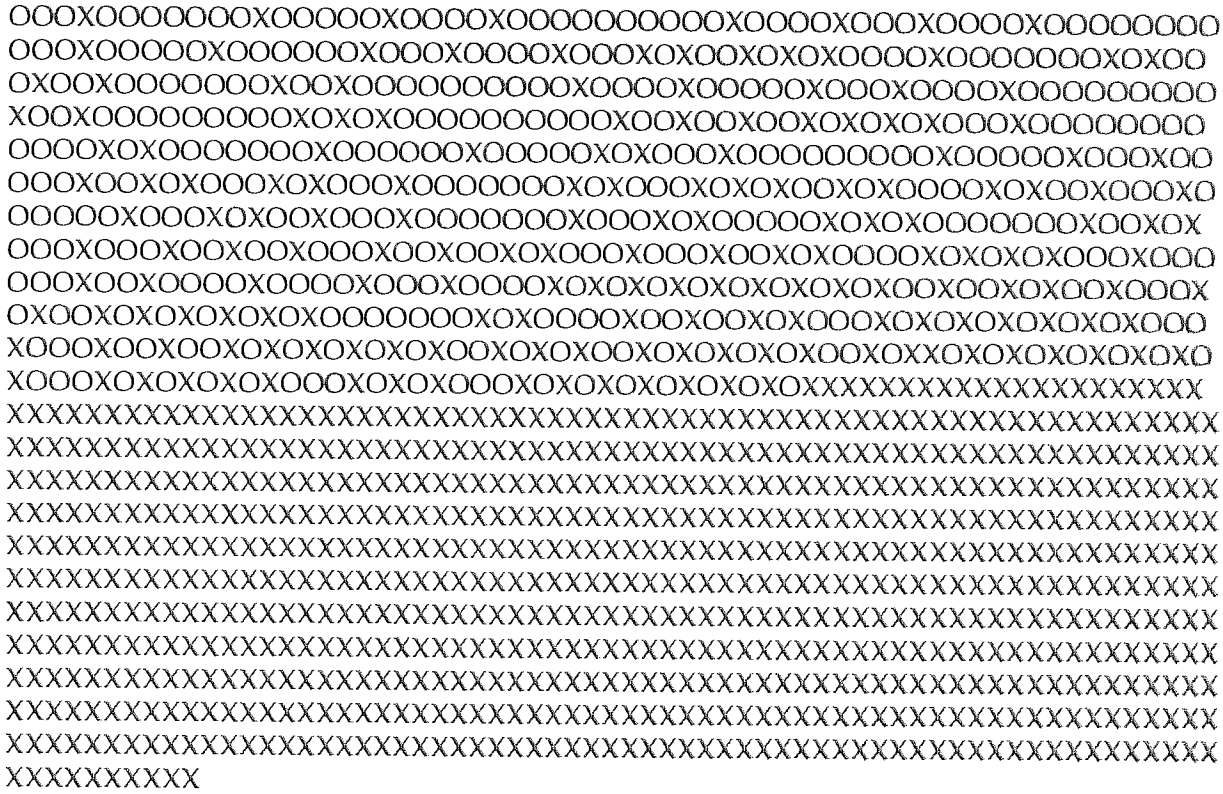
OOXOOOOOXOOOXOOOOOOOOOOXOOOOXOOXOOXOOOOOOXOOOOX



The simulated copolymer contains 1000 HEMA units and 1000 NVP units.

Table 3.34 : Sequence lengths seen in the simulated sequence distribution of figure 3.34.

Sequence Distributions:

Length	HEMA	NVP
1	91	272
2	47	2
3	40	0
4	22	0
5	16	0
6	10	0
7	16	0
8	3	0
9	6	0
10	8	0
11	8	0
12	2	0
13	1	0
16	1	0

17	1	0
18	1	0
21	1	0
724	0	1

From figures 3.33 and 3.34 we can see that the reactivity of HEMA more closely resembles MMA than NVP (nearly three-quarters of the NVP remains unreacted until the end). Therefore it is now possible to run a simulation of the pseudo sequence distribution that represents the contact lens material Tetrafilcon-A. To do this we must substitute MMA in this contact lens formulation by increasing the HEMA content by 10% to account for the absent MMA. Thus, it is now possible to run the terpolymer simulation program to compare the different sequence distributions seen with the different cross-linkers.

Figures 3.35 to 3.40 show the computer simulated sequence distributions for the Tetrafilcon-A contact lens with various cross-linkers. Tables 4.6 to 5.1 show the sequence lengths seen in figures 3.35 to 3.40, respectively.

Figure 3.35 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with EGDMA (showing only the addition of the first vinyl bond).

89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

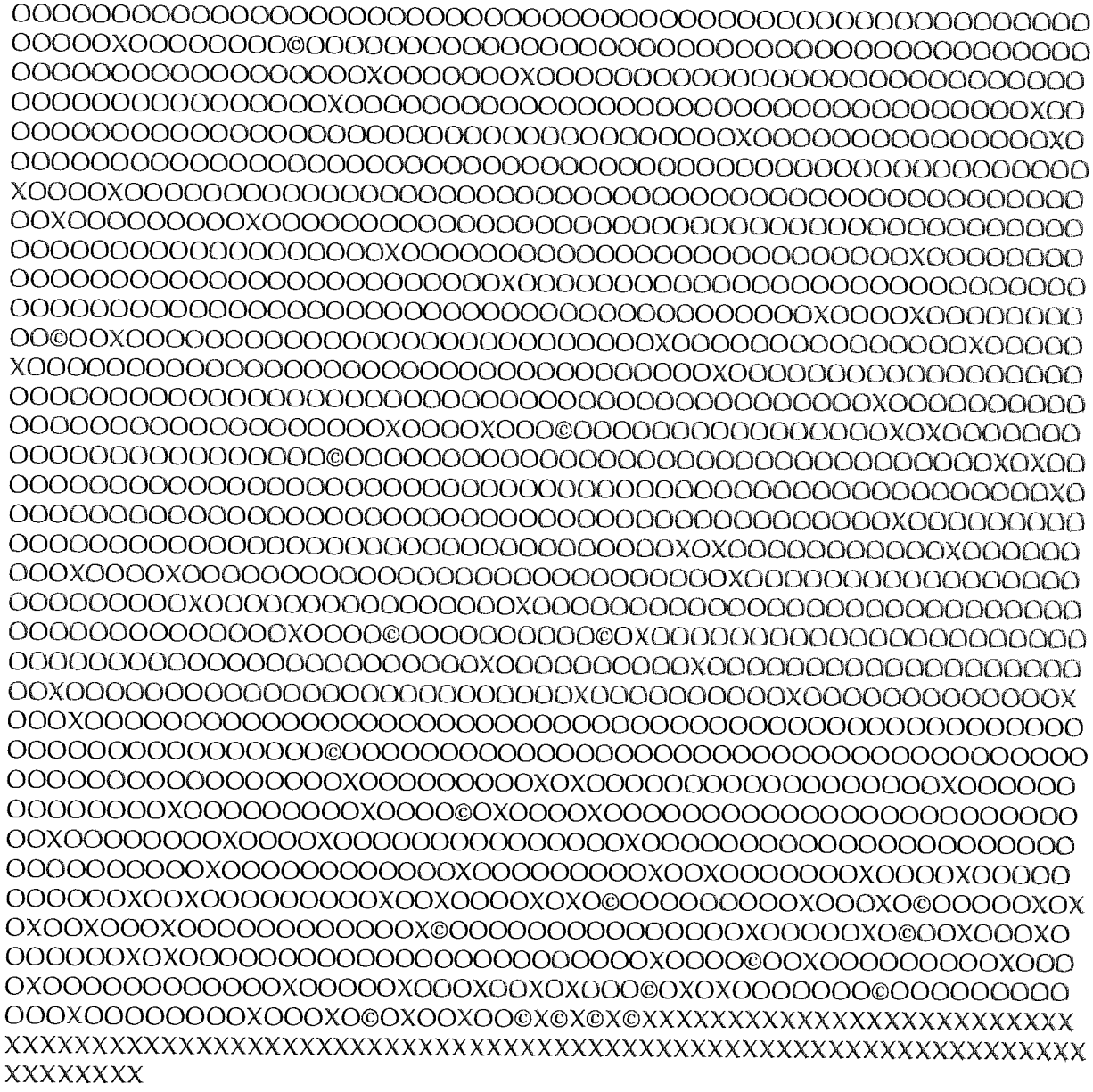
1 Mole % of Monomer C, EGDMA

r(AB) = 4.841 r(AC) = 1.882 r(BA) = 0.001

r(BC) = 0.006 r(CA) = 0.388 r(CB) = 6.37

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and EGDMA is represented by © :



The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 EGDMA units.

Table 3.35 : Sequence lengths seen in the simulated sequence distribution of figure 3.35.

Sequence Distributions:

Length	HEMA	NVP	EGDMA
1	18	104	20
2	10	0	0
3	8	0	0
4	12	0	0
5	4	0	0
7	4	0	0
8	3	0	0
9	8	0	0
10	4	0	0
11	2	0	0
12	4	0	0
13	1	0	0
14	1	0	0
15	4	0	0
16	2	0	0
18	1	0	0
21	1	0	0
23	1	0	0
24	1	0	0
26	4	0	0
27	1	0	0
28	1	0	0
29	1	0	0
32	1	0	0
33	2	0	0
35	2	0	0
39	1	0	0
42	1	0	0
43	1	0	0
44	1	0	0
46	2	0	0
51	1	0	0
55	2	0	0
56	1	0	0
58	1	0	0
60	1	0	0
61	1	0	0
62	1	0	0

67	1	0	0
70	1	0	0
96	0	1	0

Figure 3.36 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with EGDMA (showing only the addition of the second vinyl bond).

89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

1 Mole % of Monomer C, EGDMA

r(AB) = 4.841 r(AC) = 2.834 r(BA) = 0.001

r(BC) = 0.002 r(CA) = 0.023 r(CB) = 0.099

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and EGDMA is represented by © :

XOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOXOO
OOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOO
OOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
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OOOOOOOOOOOOOOOOOO©OOOOOOXOOOOOOOOOOOOOOOOOOOO

The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 EGDMA units.

Table 3.36 : Sequence lengths seen in the simulated sequence distribution of figure 3.36.

Sequence Distributions:

Length	HEMA	NVP	EGDMA
1	11	93	20
2	14	0	0
3	11	0	0
4	7	0	0
5	1	0	0
6	5	0	0
7	8	0	0
8	4	0	0
9	6	0	0
10	4	0	0
11	1	0	0
13	3	0	0
15	1	0	0
16	3	0	0
17	1	0	0
18	1	0	0
19	1	0	0
20	2	0	0
21	2	0	0
22	1	0	0
23	1	0	0

24	2	0	0
25	1	0	0
26	2	0	0
28	1	0	0
29	1	0	0
40	2	0	0
48	1	0	0
49	1	0	0
50	1	0	0
56	2	0	0
65	1	0	0
70	1	0	0
89	1	0	0
94	1	0	0
97	1	0	0
107	0	1	0
233	1	0	0

Figure 3.37 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with DATDAM (showing only the addition of the first vinyl bond).

89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

1 Mole % of Monomer C, DATDAM

r(AB) = 4.841 r(AC) = 9.67 r(BA) = 0.001

r(BC) = 0.15 r(CA) = 0.065 r(CB) = 4.912

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and DATDAM is represented by © :

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OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
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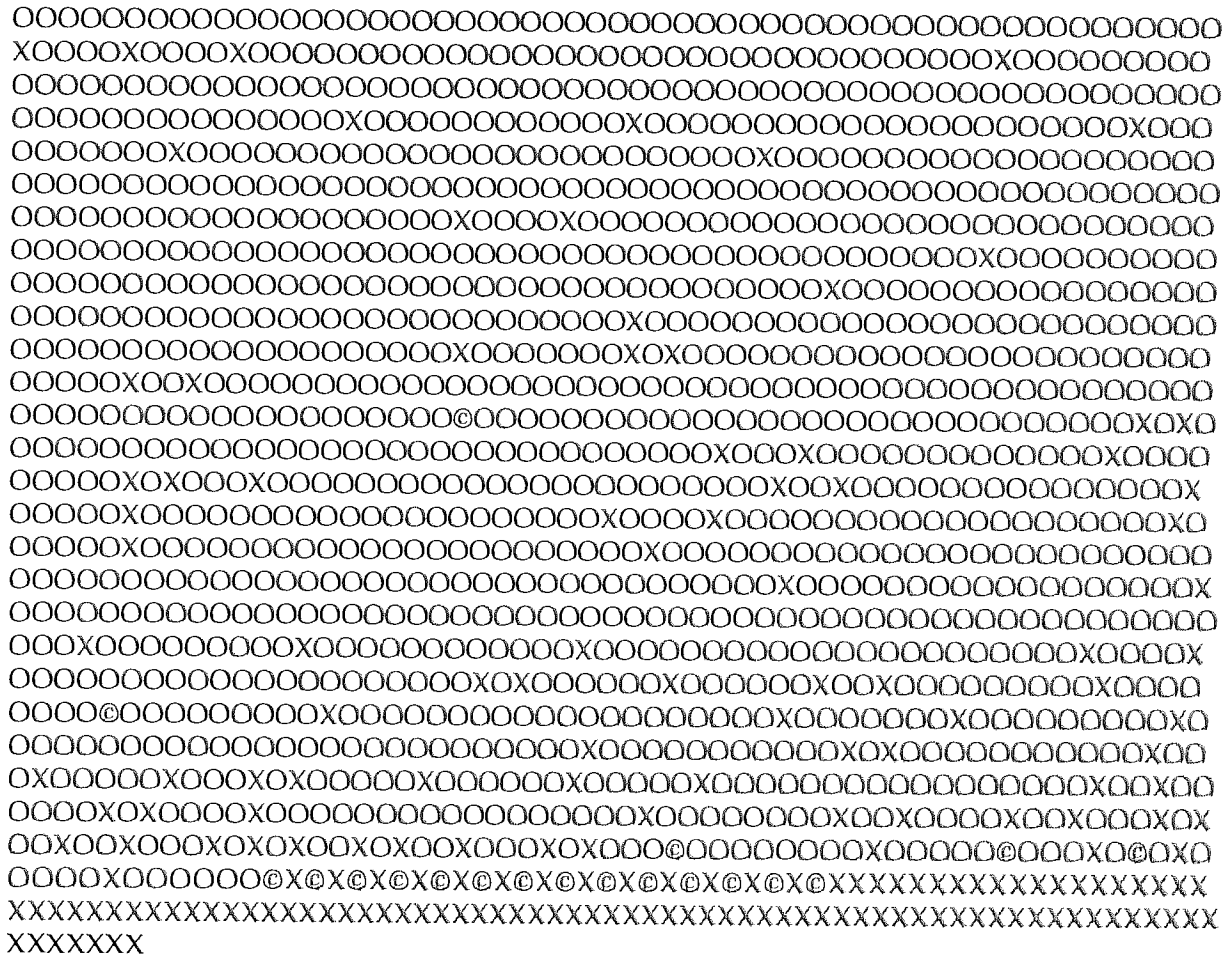


The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 DATDAM units.

Table 3.37 : Sequence lengths seen in the simulated sequence distribution of figure 3.37.

Sequence Distributions:

Length	HEMA	NVP	DATDAM
1	14	111	20
2	12	0	0
3	9	0	0
4	8	0	0
5	6	0	0
6	6	0	0
7	2	0	0
8	3	0	0

9	5	0	0
10	1	0	0
11	2	0	0
12	2	0	0
13	1	0	0
15	1	0	0
17	2	0	0
18	2	0	0
20	2	0	0
21	2	0	0
22	2	0	0
23	2	0	0
26	1	0	0
27	1	0	0
29	1	0	0
30	1	0	0
32	1	0	0
33	1	0	0
34	1	0	0
45	1	0	0
46	1	0	0
47	1	0	0
55	1	0	0
58	1	0	0
60	1	0	0
64	1	0	0
66	1	0	0
73	1	0	0
79	1	0	0
84	1	0	0
89	0	1	0
95	1	0	0
108	1	0	0
117	1	0	0

Figure 3.38 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with DATDAM (showing only the addition of the second vinyl bond).
89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

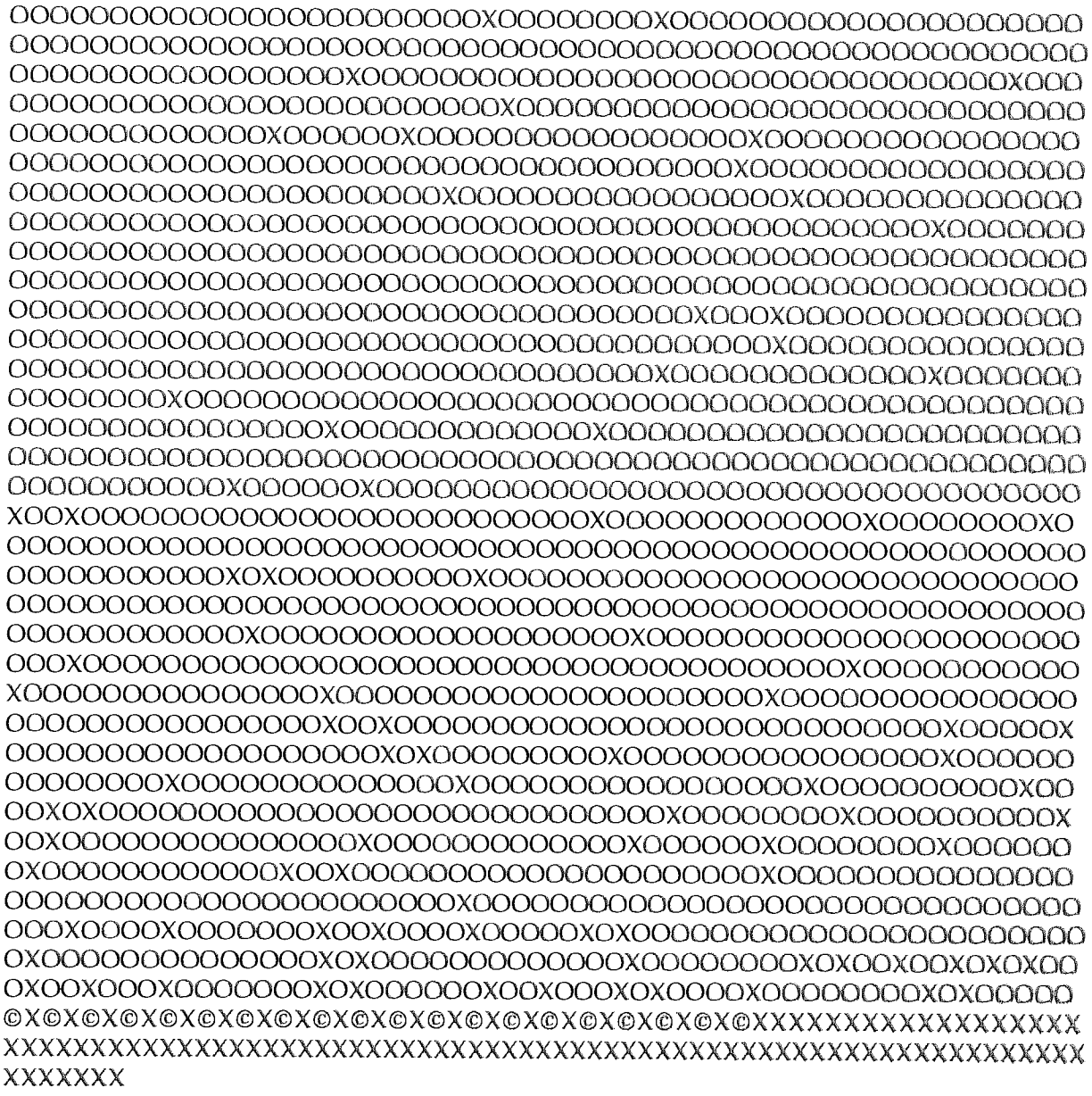
1 Mole % of Monomer C, DATDAM

r(AB) = 4.841 r(AC) = 74.747 r(BA) = 0.001

r(BC) = 0.516 r(CA) = 0.013 r(CB) = 0.477

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and DATDAM is represented by © :



The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 DATDAM units.

Table 3.38 : Sequence lengths seen in the simulated sequence distribution of figure 3.38.

Sequence Distributions:

Length	HEMA	NVP	DATDAM
1	11	112	20
2	9	0	0
3	4	0	0
4	4	0	0
5	3	0	0
6	4	0	0
7	3	0	0
8	6	0	0
9	1	0	0
10	3	0	0
11	1	0	0
12	1	0	0
13	5	0	0
14	3	0	0
15	3	0	0
16	1	0	0
17	3	0	0
19	2	0	0
21	1	0	0
22	1	0	0
24	2	0	0
25	1	0	0
26	1	0	0
28	2	0	0
29	1	0	0
31	1	0	0
33	1	0	0
34	1	0	0
36	1	0	0
38	1	0	0
39	2	0	0
42	1	0	0
48	1	0	0
53	1	0	0
54	1	0	0
61	1	0	0
62	1	0	0
67	1	0	0

88	0	1	0
90	1	0	0
93	1	0	0
97	1	0	0
152	1	0	0

Figure 3.39 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with TAC (showing only the addition of the first vinyl bond).

89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.841 r(AC) = 4.266 r(BA) = 0.001

r(BC) = 0.001 r(CA) = 0.001 r(CB) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and TAC is represented by © :

OOOOOOOOOOOOOOOOOOOOOXOOXOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOXOOOOOOOOOOOOOOOOOOO
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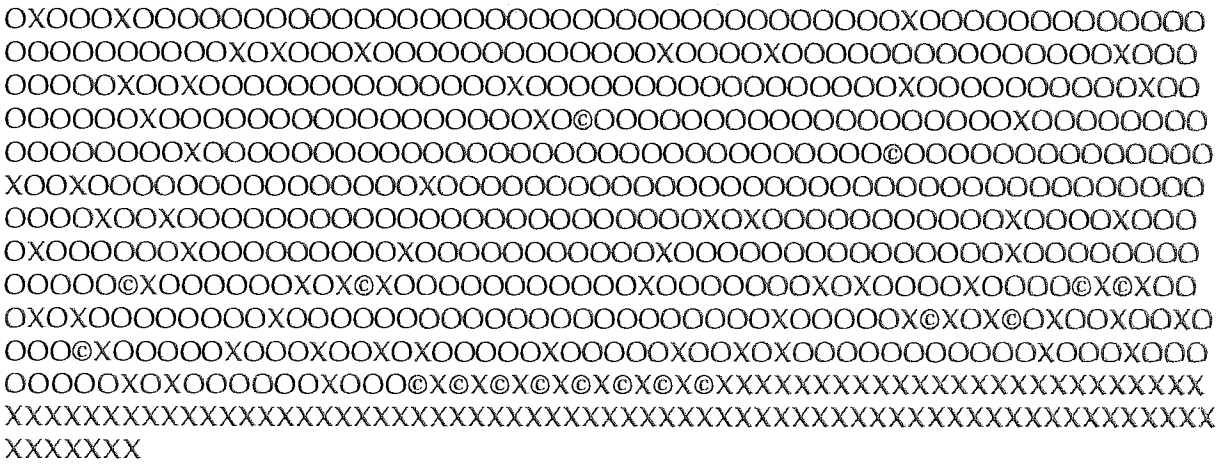


The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 TAC units.

Table 3.39 : Sequence lengths seen in the simulated sequence distribution of figure 3.39.

Sequence Distributions:

Length	HEMA	NVP	TAC
1	11	105	20
2	9	0	0
3	7	0	0
4	6	0	0
5	6	0	0
6	5	0	0
7	1	0	0
8	6	0	0
9	1	0	0
10	1	0	0
11	4	0	0
12	1	0	0
13	2	0	0
14	3	0	0
15	3	0	0
16	2	0	0
17	2	0	0
18	1	0	0
19	1	0	0
21	1	0	0

22	2	0	0
23	2	0	0
24	1	0	0
27	1	0	0
29	1	0	0
30	2	0	0
31	1	0	0
34	2	0	0
35	1	0	0
36	1	0	0
37	1	0	0
38	1	0	0
39	1	0	0
42	1	0	0
44	1	0	0
48	1	0	0
54	1	0	0
58	1	0	0
63	1	0	0
71	1	0	0
95	0	1	0
102	1	0	0
131	1	0	0
152	1	0	0

Figure 3.40 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation with TAC (showing only the addition of the second vinyl bond).

89 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, NVP

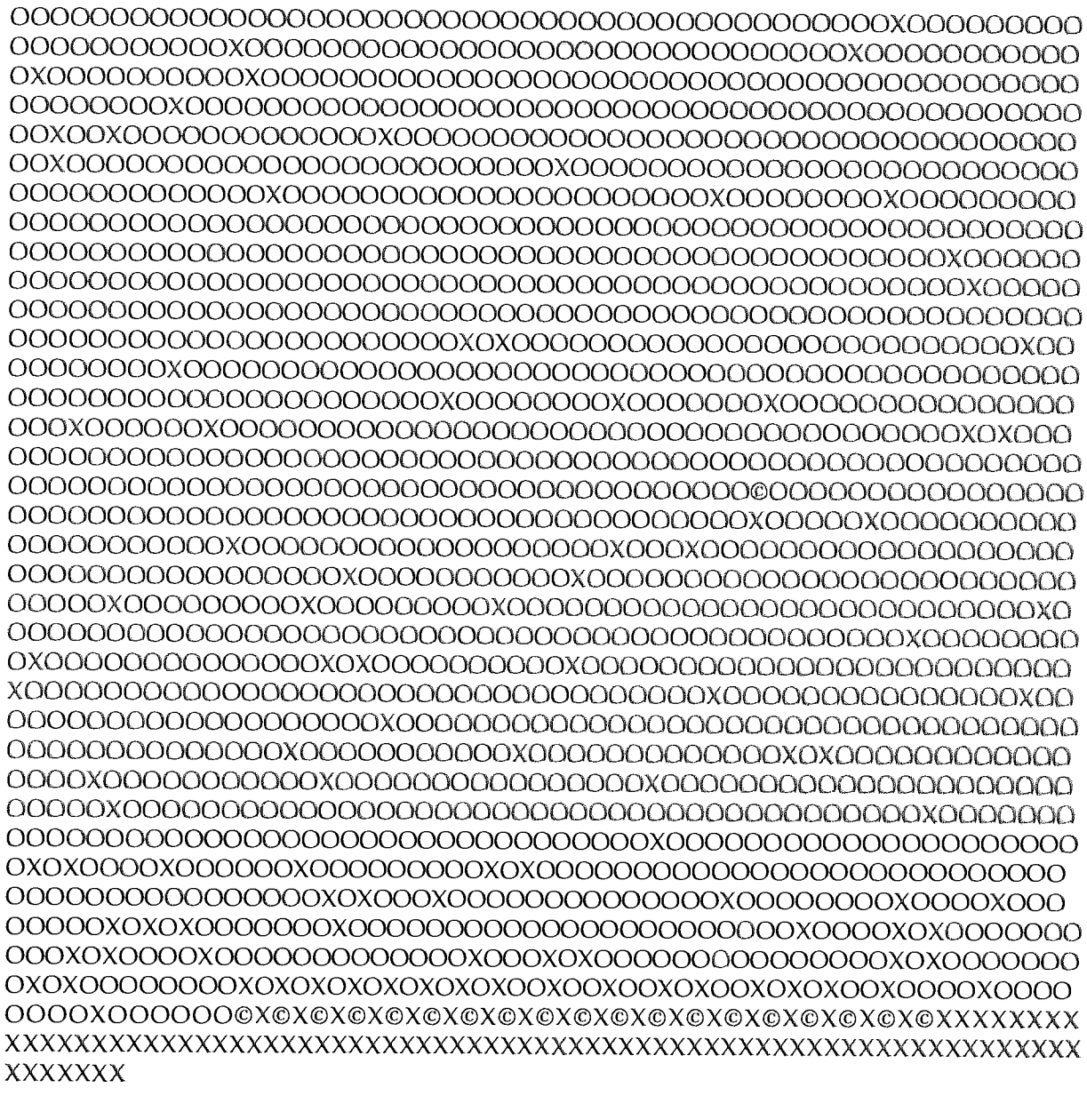
1 Mole % of Monomer C, TAC

r(AB) = 4.841 r(AC) = 47.78 r(BA) = 0.001

r(BC) = 0.264 r(CA) = 0.02 r(CB) = 0.547

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and TAC is represented by © :



The simulated terpolymer contains 1780 HEMA units, 200 NVP units and 20 TAC units.

Table 3.40 : Sequence lengths seen in the simulated sequence distribution of figure 3.40.

Sequence Distributions:

Length	HEMA	NVP	TAC
1	24	122	20
2	6	0	0
3	3	0	0

4	5	0	0
5	1	0	0
6	3	0	0
7	2	0	0
8	7	0	0
9	4	0	0
10	4	0	0
11	3	0	0
12	1	0	0
13	3	0	0
14	2	0	0
15	2	0	0
16	2	0	0
18	1	0	0
19	1	0	0
20	1	0	0
21	2	0	0
22	2	0	0
23	1	0	0
25	2	0	0
26	2	0	0
27	1	0	0
30	1	0	0
31	1	0	0
35	1	0	0
36	1	0	0
37	1	0	0
38	1	0	0
39	1	0	0
40	1	0	0
41	1	0	0
43	1	0	0
45	1	0	0
47	1	0	0
48	1	0	0
49	1	0	0
50	1	0	0
54	1	0	0
55	1	0	0
68	1	0	0
78	0	1	0
83	1	0	0
96	1	0	0
112	1	0	0

Before considering the analysis of the sequence distributions seen in figures 3.35 to 3.40, we must bear in mind that 10% of the HEMA units seen in these sequence distributions actually represent MMA units. Figure 3.41, below, represents the computer simulated sequence distribution of the Tetrafilcon-A contact lens formulation without any cross-linker. This figure and table 3.41 will give us an idea of the whereabouts of the MMA units present in the complete formulation, but absent from figures 3.35 to 3.40, and also what the overall sequence distribution would look like.

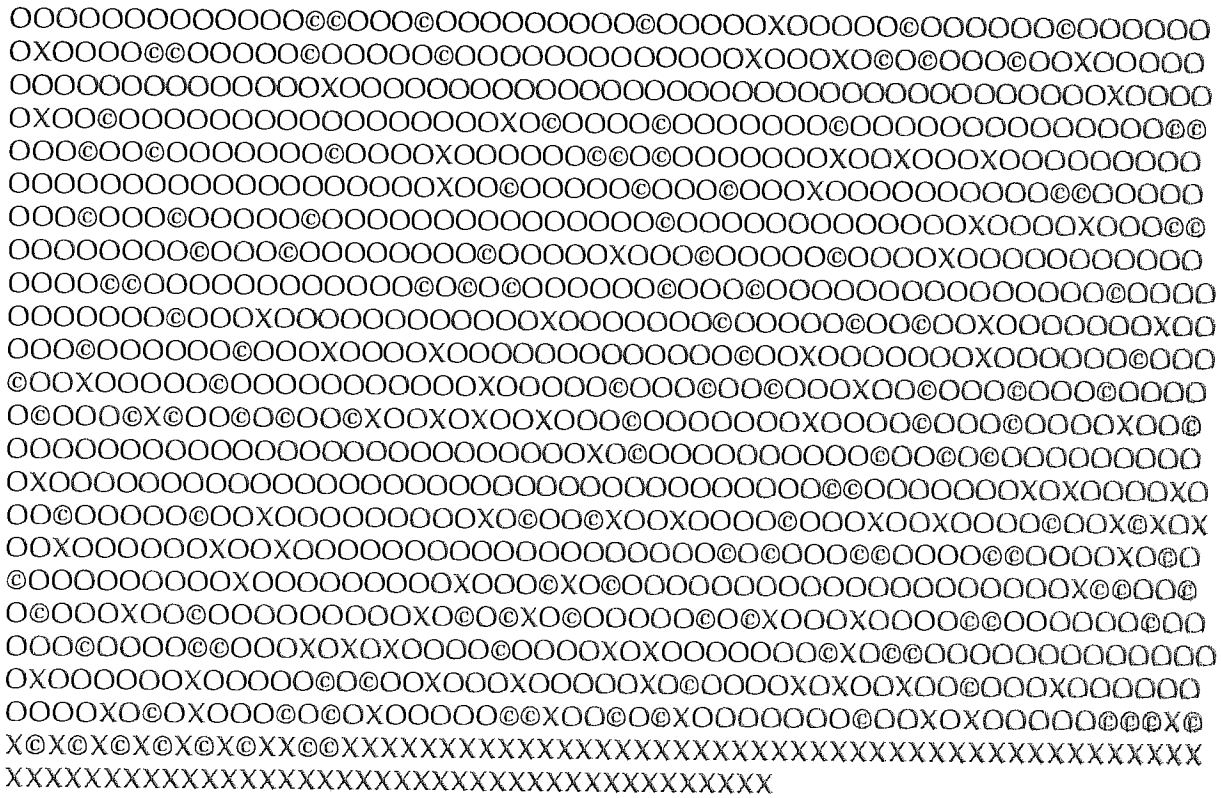
Figure 3.41 : Computer simulated sequence distribution of Tetrafilcon-A contact lens formulation in the absence of any cross-linkers.

80 Mole % of Monomer A, HEMA
10 Mole % of Monomer B, NVP
10 Mole % of Monomer C, MMA

r(AB) = 4.841	r(AC) = 0.810	r(BA) = 0.001
r(BC) = 4.04	r(CA) = 0.192	r(CB) = 0.01

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and MMA is represented by © :



The simulated terpolymer contains 1600 HEMA units, 200 NVP units and 200 MMA units.

Table 3.41 : Sequence lengths seen in the simulated sequence distribution of figure 3.41.

Sequence Distributions:

Length	HEMA	NVP	MMA
1	47	114	157
2	35	1	20
3	40	0	1
4	22	0	0
5	27	0	0
6	12	0	0
7	14	0	0
8	10	0	0
9	5	0	0

10	5	0	0
11	6	0	0
12	2	0	0
13	4	0	0
14	5	0	0
15	4	0	0
16	2	0	0
17	2	0	0
18	4	0	0
19	2	0	0
20	1	0	0
21	2	0	0
23	1	0	0
26	1	0	0
28	2	0	0
34	1	0	0
35	3	0	0
84	0	1	0

From figures 3.35 to 3.40 and figure 3.41 it can be seen that the overall sequence distribution for this Tetrafilcon-A contact lens is not very good, we tend to have too many extended sequences of HEMA monomer units. This is primarily due to the fact that it is present in much greater quantity than either of the other major components in the initial formulation, and to a lesser degree, here, because it is more reactive than the other components.

Considering the cross-linkers, we see that EGDMA is reasonably well distributed throughout the terpolymer, but both DATDAM and TAC are very poorly distributed throughout the terpolymer and show much higher residual tendencies (both first and second vinyl bonds come in very late, towards the end of the polymerisation). Thus, here it appears that the appropriate cross-linker to use would be EGDMA.

3.44 Xylofilcon-A contact lens material(MMA : NVP : CMA : EGDMA :: 30 : 59 : 10 : 1)

The Xylofilcon-A contact lens material is based predominantly on NVP and has an EWC of approximately 68%. This is much higher than the EWC of Tetrafilcon-A (ca. 43%) simply because Tetrafilcon-A is based predominantly on HEMA which is less hydrophilic than NVP.

Since Xylofilcon-A is composed of four components, a similar procedure to that adopted in section 3.43 must be used to determine which one of the major components of this contact lens formulation may be replaced by increasing the percentage composition of one of the two remaining components, which most closely represents the reactivity of the component being replaced. To aid this, copolymerisation simulations were run between MMA : CMA and NVP : CMA, both at a 50 : 50 mole ratio, computer simulated sequence distributions are shown in figures 3.42 and 3.43, respectively. It must be mentioned that no reactivity ratio or Q-e data was found for cyclohexyl methacrylate (CMA), a reasonable approximation was made using the Q-e values of phenyl methacrylate.

Figure 3.42 : Computer simulated sequence distribution of a copolymer of MMA : CMA :: 50 : 50.
50 Mole % of Monomer A, MMA
50 Mole % of Monomer B, CMA
r(AB) = 0.729
r(BA) = 1.177
Polymerized to 100% Conversion
In the simulated copolymer MMA is represented by O and CMA is represented by X :

XOOXXOXXOOOXXOXOXXXXXOOXXXOXOXXOXOXXXOOOOXOXXXXOXOXXXXOXXOX
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The simulated copolymer contains 1000 MMA units and 1000 CMA units.

Table 3.42 : Sequence lengths seen in the simulated sequence distribution of figure 3.42.

Sequence Distributions:

Length	MMA	CMA
1	252	252
2	116	117
3	65	56
4	30	38
5	20	17
6	6	8

7	3	3
8	3	5
20	1	0

Figure 3.43 : Computer simulated sequence distribution of a copolymer of NVP : CMA :: 50 : 50.

50 Mole % of Monomer A, NVP

50 Mole % of Monomer B, CMA

r(AB) = 0.001

r(BA) = 2.116

Polymerized to 100% Conversion

In the simulated copolymer NVP is represented by O and CMA is represented by X :

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The simulated copolymer contains 1000 NVP units and 1000 CMA units.

Table 3.43 : Sequence lengths seen in the simulated sequence distribution of figure 3.43.

Sequence Distributions:

Length	NVP	CMA
1	463	235
2	2	102
3	0	52
4	0	31
5	0	20
6	0	15
7	0	3
8	0	5
9	0	1
10	0	1
11	0	1
533	1	0

From figures 3.42 and 3.43 we can see that MMA more closely resembles CMA than NVP, but NVP does have a reasonable reaction profile with CMA as seen from the sequence distribution in figure 3.43. Therefore it would be appropriate here to replace CMA in this contact lens formulation by increasing the MMA content by approximately 6% and by increasing the NVP content by approximately 4% to account for the absent CMA (this would also take into account the fact that CMA is slightly less reactive than PMA, whose Q-e values were used to calculate the reactivity ratios for CMA with the other monomers).

It is now possible to run the terpolymer simulation program to compare the different sequence distributions seen with the different cross-linkers for the contact lens material Xylofilcon-A.

Figures 3.44 to 3.49 show the computer simulated sequence distributions for the Xylofilcon-A contact lens material with various cross-linkers. Tables 3.44 to 3.49 show the sequence lengths seen in figures 3.44 to 3.49, respectively.

Figure 3.44 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with EGDMA (showing only the addition of the first vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

1 Mole % of Monomer C, EGDMA

r(AB) = 4.04 r(AC) = 0.936 r(BA) = 0.01

r(BC) = 0.006 r(CA) = 1.013 r(CB) = 6.37

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and EGDMA is represented by © :

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The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 EGDMA units.

Table 3.44 : Sequence lengths seen in the simulated sequence distribution of figure 3.44.

Sequence Distributions:

Length	MMA	NVP	EGDMA
1	198	336	20
2	100	30	0
3	36	2	0
4	17	2	0
5	12	0	0
6	2	0	0
7	4	0	0
8	2	0	0
9	2	0	0
12	1	0	0
858	0	1	0

Figure 3.45 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with EGDMA (showing only the addition of the second vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

1 Mole % of Monomer C, EGDMA

r(AB) = 4.04 r(AC) = 3.334 r(BA) = 0.01

r(BC) = 0.002 r(CA) = 0.143 r(CB) = 0.099

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and EGDMA is represented by © :

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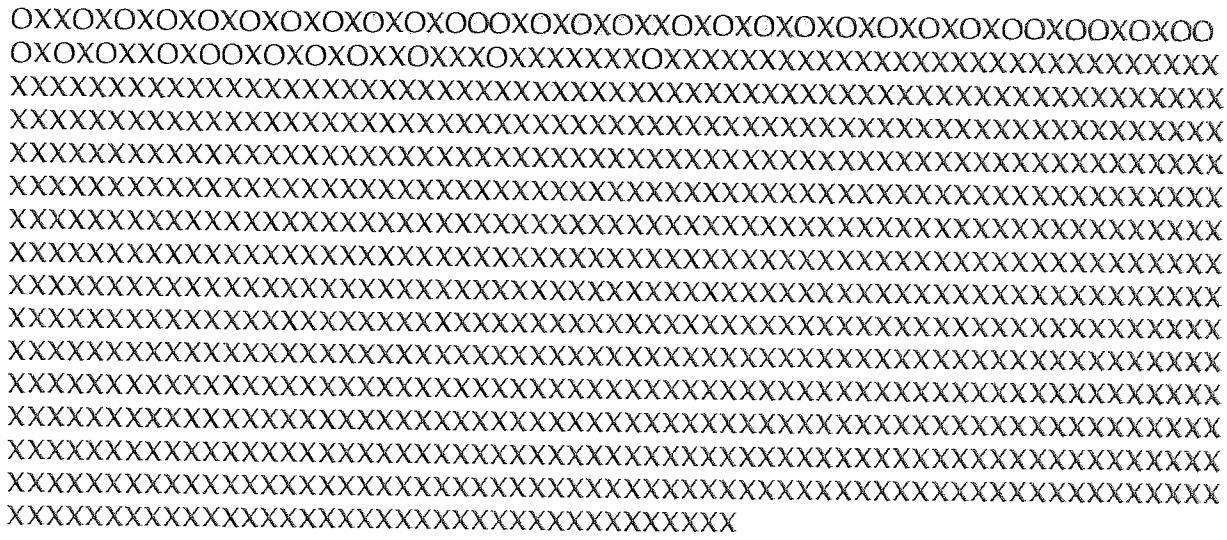


The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 EGDMA units.

Table 3.45 : Sequence lengths seen in the simulated sequence distribution of figure 3.45.

Sequence Distributions:

Length	MMA	NVP	EGDMA
1	174	338	20
2	71	13	0
3	38	1	0
4	27	2	0
5	7	0	0
6	7	0	0
7	5	0	0
8	1	0	0
9	2	0	0
10	2	0	0
12	2	0	0
866	0	1	0

Figure 3.46 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with DATDAM (showing only the addition of the first vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

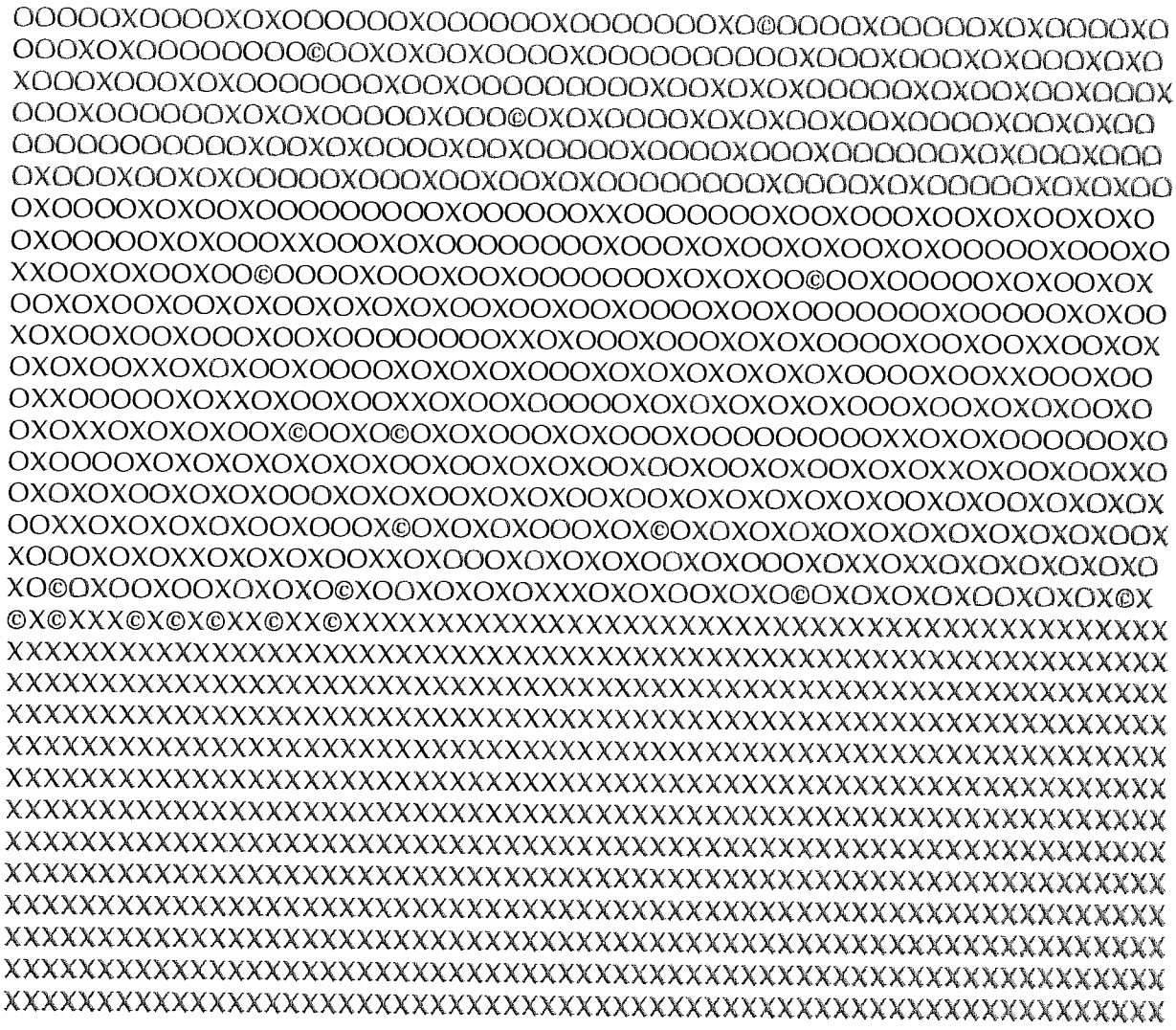
1 Mole % of Monomer C, DATDAM

r(AB) = 4.04 r(AC) = 1.805 r(BA) = 0.01

r(BC) = 0.15 r(CA) = 0.063 r(CB) = 4.912

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and DATDAM is represented by © :



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The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 DATDAM units.

Table 3.46 : Sequence lengths seen in the simulated sequence distribution of figure 3.46.

Sequence Distributions:

Length	MMA	NVP	DATDAM
1	168	308	20
2	80	22	0
3	34	2	0
4	18	2	0
5	13	0	0
6	6	0	0
7	5	0	0
8	4	0	0
9	3	0	0
10	1	0	0
13	1	0	0
902	0	1	0

Figure 3.47 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with DATDAM (showing only the addition of the second vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

1 Mole % of Monomer C, DATDAM

r(AB) = 4.04 r(AC) = 23.505 r(BA) = 0.01

r(BC) = 0.516 r(CA) = 0.022 r(CB) = 0.447

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and DATDAM is represented by © :

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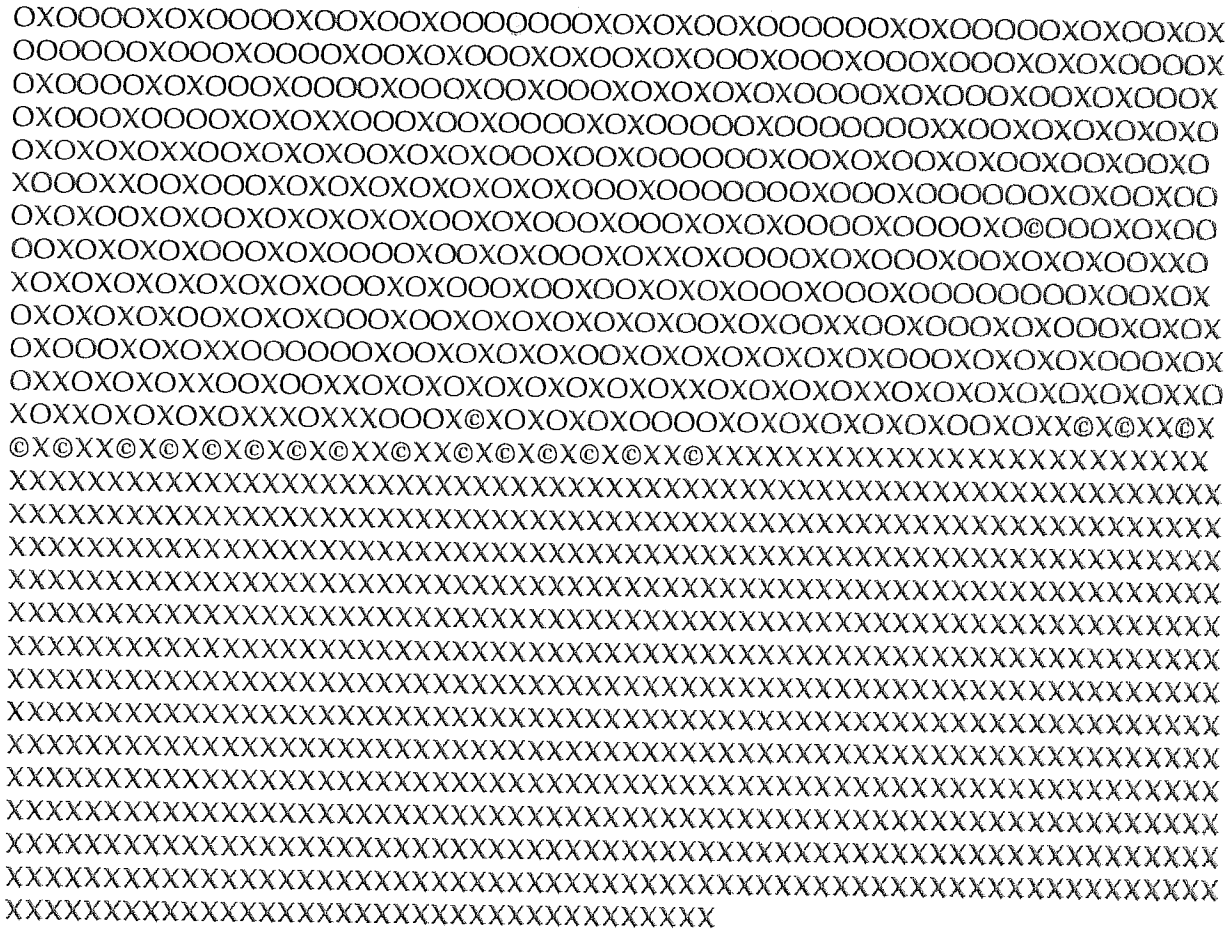

The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 DATDAM units.

Table 3.47 : Sequence lengths seen in the simulated sequence distribution of figure 3.47.

Sequence Distributions:

Length	MMA	NVP	DATDAM
1	179	329	20
2	61	22	0
3	46	2	0
4	19	2	0
5	12	0	0
6	7	0	0
7	3	0	0
8	3	0	0
9	3	0	0

10	2	0	0
11	1	0	0
881	0	1	0

Figure 3.48 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with TAC (showing only the addition of the first vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.04 r(AC) = 12.449 r(BA) = 0.01

r(BC) = 0.001 r(CA) = 0.001 r(CB) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and TAC is represented by © :

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The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 TAC units.

Table 3.48 : Sequence lengths seen in the simulated sequence distribution of figure 3.48.

Sequence Distributions:

Length	MMA	NVP	TAC
1	168	323	20
2	78	18	0
3	30	2	0
4	21	2	0
5	9	0	0
6	9	0	0
7	6	0	0
8	5	0	0
9	2	0	0
11	1	0	0
12	1	0	0
901	0	1	0

Figure 3.49 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation with TAC (showing only the addition of the second vinyl bond).

36 Mole % of Monomer A, MMA

63 Mole % of Monomer B, NVP

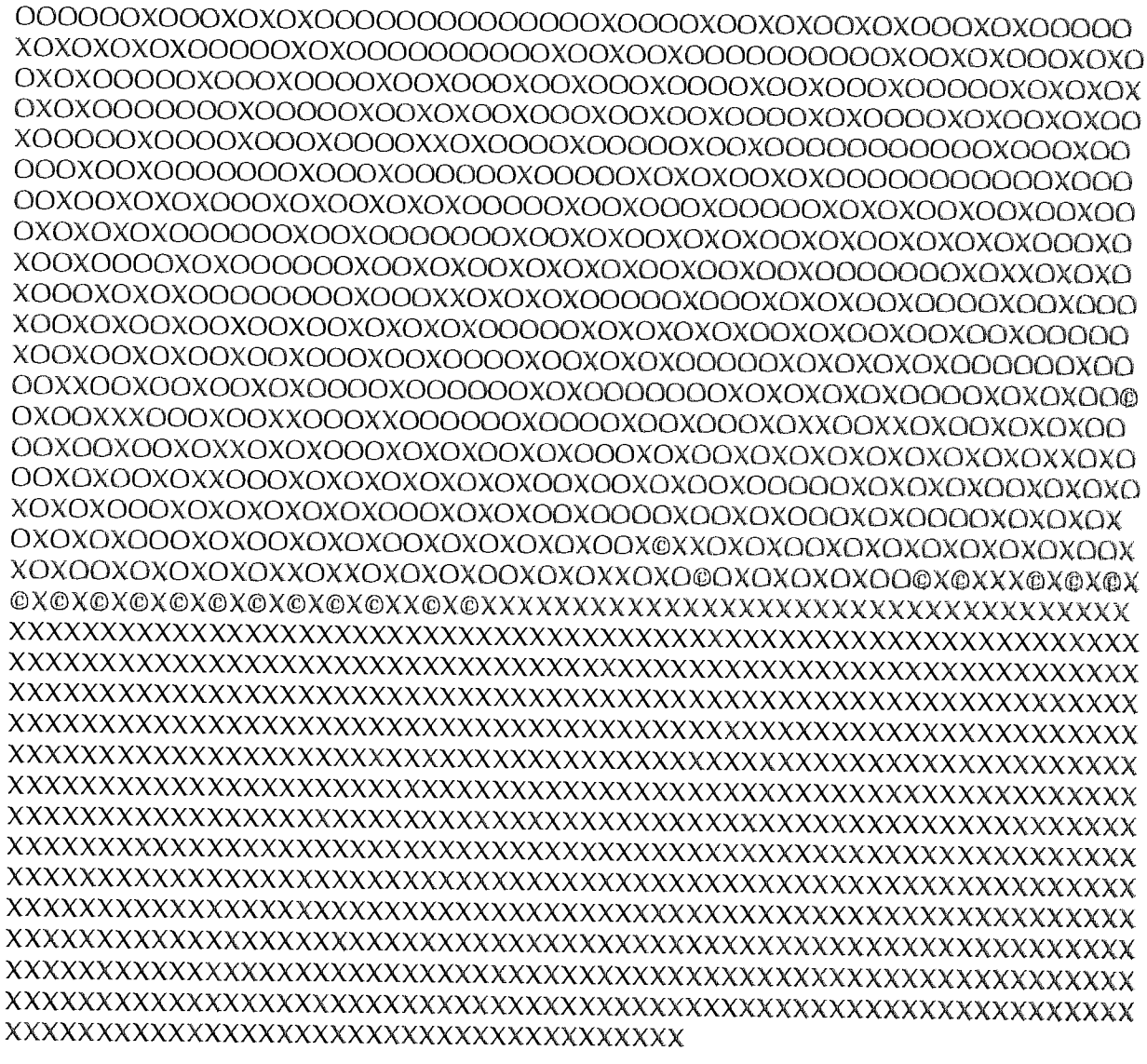
1 Mole % of Monomer C, TAC

r(AB) = 4.04 r(AC) = 17.321 r(BA) = 0.01

r(BC) = 0.264 r(CA) = 0.038 r(CB) = 0.547

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and TAC is represented by © :



The simulated terpolymer contains 720 MMA units, 1260 NVP units and 20 TAC units.

Table 3.49 : Sequence lengths seen in the simulated sequence distribution of figure 3.49.

Sequence Distributions:

Length	MMA	NVP	TAC
1	169	328	20
2	80	17	0
3	31	2	0
4	18	2	0
5	17	0	0
6	7	0	0
7	5	0	0
8	1	0	0
10	2	0	0
11	2	0	0
14	1	0	0
892	0	1	0

Before considering the analysis of the sequence distributions seen in figures 3.44 to 3.49, we must bear in mind that approximately 6% of the MMA units and 4% of the NVP units, seen in these sequence distributions actually represent CMA units. Figure 3.50, below, represents the computer simulated sequence distribution of the Xylofilcon-A contact lens formulation without any cross-linker. This figure and table 3.50 will give us an idea of the whereabouts of the CMA units present in the complete formulation, but absent from figures 3.44 to 3.49, and also what the overall sequence distribution would look like.

Figure 3.50 : Computer simulated sequence distribution of Xylofilcon-A contact lens formulation in the absence of any cross-linkers.

30 Mole % of Monomer A, MMA

60 Mole % of Monomer B, NVP

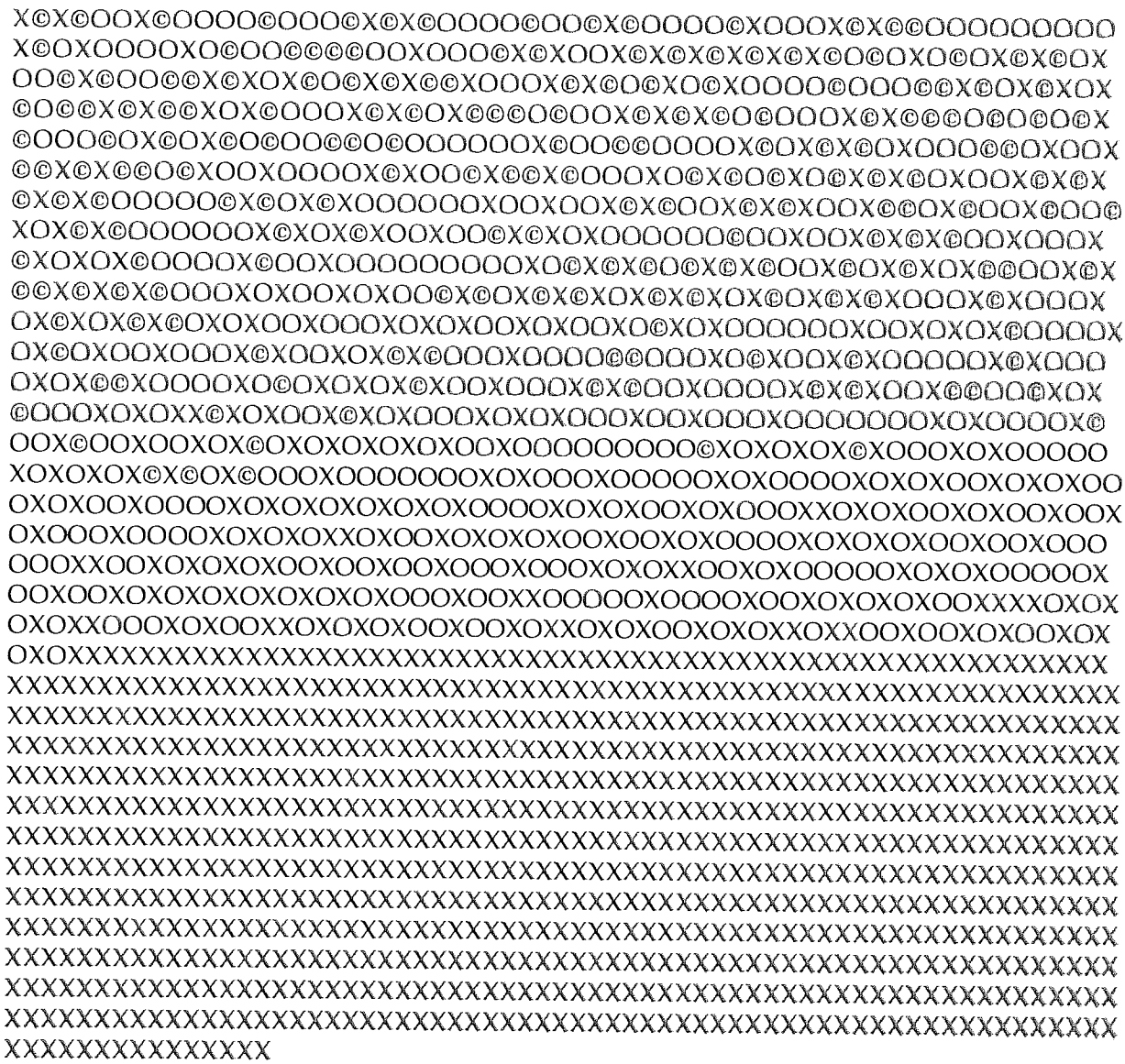
10 Mole % of Monomer C, CMA

r(AB) = 4.04 r(AC) = 0.729 r(BA) = 0.01

r(BC) = 0.001 r(CA) = 1.177 r(CB) = 2.116

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVP is represented by X and CMA is represented by © :



The simulated terpolymer contains 600 MMA units, 1200 NVP units and 200 CMA units.

Table 3.50 : Sequence lengths seen in the simulated sequence distribution of figure 3.50.

Sequence Distributions:

Length	MMA	NVP	CMA
1	159	344	154
2	75	11	18
3	33	0	2
4	20	1	1
5	7	0	0
6	6	0	0
7	2	0	0
9	3	0	0
830	0	1	0

From figures 3.44 to 3.49 and figure 3.50 it can be seen that the overall sequence distribution for this Xylofilcon-A contact lens is not very good. Up to about 50% conversion the sequence distribution is reasonable, but after this point it becomes rapidly poorer and around 60% conversion we have a large block of NVP. This occurs due to two factors: firstly because NVP is present in much greater quantity than either of the other major components in the initial formulation; secondly because it is much less reactive than the other components. These factors together produce a very poor overall sequence distribution for this contact lens formulation.

Considering the cross-linkers shown in figures 3.44 - 3.49, we can see that both the vinyl bonds of EGDMA react before 50% conversion, although they are well distributed throughout this section of the terpolymer, therefore only helping to improve the sequence distribution before 50% conversion and in no way helping to break up the large block of NVP at the end. In contrast DATDAM reacts mainly after 50% conversion, especially the second vinyl bond, which

helps to break up some of the NVP block residue. With TAC, we see that the first vinyl bond predominantly reacts before 40% conversion, whilst the second vinyl bond comes in very late and helps to break up some of the NVP block residue.

Therefore, here it would appear that TAC or even DATDAM would be the best cross-linkers to use for a reasonable sequence distribution and best distribution of cross-links in contrast to the currently used cross-linker EGDMA.

3.5 Discussion of the contact lens sequence distributions

From the examples given in section 3.4 of the sequence distributions of various contact lens formulations, we see that the overall sequence distributions of all these contact lens formulations are very poor i.e., they tend to produce extensive sequences of individual monomer units. Therefore, it may be inferred that the formulations of these generic materials were determined primarily owing to factors other than the relative reactivities of the monomers, which when reacted would produce a characteristic sequence distribution. Perhaps, water contents or tensile properties were the over-riding factors which determined the formulations we see.

It is also patently obvious that the selection of the type of cross-linker used in these generic materials is very important. This is because the reactivity of the cross-linker in relation to the main constituent monomers will have a significant bearing upon determining its distribution throughout the final sequence distribution of monomer units. From the examples given in this chapter we see that the distribution of the different cross-linkers, although only present in 1% mole ratio, can be significantly affected by the sequence distribution of the monomers in the polymer. It is therefore important to bear this in mind, in conjunction with the reactivity ratios of the individual monomer units, when designing polymers with controlled sequence distributions.

Thus it is apparent that the sequence distribution of the monomers in the contact lens materials studied, was not considered in the formulation of these generic contact lens materials. This may perhaps be one factor which contributes to the high sales of de-proteination tablets sold to wearers of contact lenses. Since it has been shown at Aston, that polymers with long repeat units or extensive segments of individual monomers have a greater tendency to produce non-specific adsorption than polymers with regular, short sequences of individual monomer units.

Chapter 5 will illustrate an approach in which reactivity ratios may be used to the design polymers with improved sequence distributions of monomer units. In chapter 6 we will consider the response of cell adhesion on polymers that have been designed with controlled sequence distributions.

CHAPTER FOUR

VERIFICATION OF COMPUTER SIMULATIONS

4.0 Verification Of Computer Simulations

In contrast to the large number of studies of the polymerisation of copolymers and of the possible copolymerisation mechanisms, investigations with aim of establishing the general sequence distributions of monomers in the copolymers are some what fewer. Analysis of the composition of a copolymer, may in principle be made through the employment of any convenient method[67]. However, the most useful and widely applied methods are elemental analysis and Nuclear Magnetic Resonance(NMR) based analysis. Provided the ever-present problems of obtaining a solvent- and monomer-free sample of high enough molecular weight, and any possible contamination from homopolymer, are taken into account, then the former would be the preferred technique. However, the elemental composition of many common monomers does not vary all that much, and prove sufficiently similar to limit the accuracy of the final results. The successful use of NMR also depends on significant differences being present in the comonomers, in their structure, which will provide resonances characteristic of each[68,69]. ^{1}H NMR is probably the more convenient commonly available technique, but signal resolution is often limited by concentration effects in polymer solutions and ^{13}C NMR is usually the enforced choice, though even here resolution limits will be found. The need to calibrate ^{13}C NMR resonances with respect to concentration requires appropriate homopolymer standards, but modern data acquisition and spectral subtraction routines can facilitate the subsequent analysis.

4.1 ^{13}C Nuclear Magnetic Resonance

^{13}C Nuclear magnetic resonance has undoubtedly proved the most versatile method of copolymer analysis, both for composition analysis and for probing the connectivity and stereo-regularity of monomer units. In polymer structural determinations the NMR spectrum represents directly and completely the "average molecule". No extinction coefficients are required and each resonance area is directly proportional to the number of contributory species. The NMR spectrum, as recorded, is a result of accumulations of responses from millions of individual polymer molecules. Thus we see and interpret results from a final summation that represents directly the average polymer chain. The principal of advantage of ^{13}C NMR, however, is a sensitivity towards subtle structural features displayed in an accessible form[70-74].

Chemical shift differences are observed in ^{13}C polymer spectra for carbon skeleton rearrangements of repeat units, inversions in head-to-tail monomer additions and for configurational sequences. An interpretation of ^{13}C NMR polymer spectra can, therefore, be a perplexing analytical problem. Spectral responses associated with stereo-chemical configurations are often superimposed upon a corresponding response to the polymer carbon skeleton. Thus when describing polymer structure, we customarily divide the polymer backbone conceptually into a succession of individual monomer units, even though after a polymer has formed, the source of any particular backbone carbon may be arbitrary. But one must be able to relate observed, complex ^{13}C NMR spectral patterns to successions of monomer additions.

^{13}C NMR spectra are usually obtained with ^{1}H-^{13}C spin-spin coupling completely removed by broad band or noise decoupling at the proton resonance frequency. Under these conditions, energy transfer can occur among ^{1}H and ^{13}C nuclear spin levels. For these particular nuclei an enhancement called the Nuclear Overhauser Effect (NOE) is observed for the intensities of the ^{13}C resonances. In small molecules with unrestricted segmental mobilities, NOE varies from factors of one to three according to the structural environments. In polymers it has been shown that NOE's are generally the same throughout because of restricted segmental mobilities[75].

Intensity measurements in ^{13}C NMR polymer spectra can be made using either relative peak heights or peak areas. Peak heights can be used reliably if there is no overlap and if the peaks measured have the same line width at one-half the maximum peak height. These criteria are not often met in ^{13}C NMR polymer spectra because of a characteristic ^{13}C sensitivity to subtle structural features, thus intensity measurements are more reliable if based on relative peak areas. Spectral integration, cutting and weighing and curve fitting can be used to obtain relative peak areas, the best approach is usually through curve fitting to avoid unwanted contributions from peak overlap.

Polymers prepared by addition polymerisation are necessarily characterised by over-simplified representations. As monomers may add to a growing polymer chain in more than one manner. Thus for some polymers this is no more than a difference in monomer unit configuration, for others it may be a skeletal rearrangement. Thus only average structure, however, can be determined. These may not reflect the sequencing of monomer units or the structural variabilities possible form one polymer chain to another. Thus a true structural

determination that would describe the monomer sequences or sequence distributions for each chain length is really not possible, only a final average structural picture is obtained. But it is possible to describe average sequence distributions.

4.11 Determination of Number-Average Sequence Lengths

In its simplest form, structural information about monomer distribution may be expressed as the ratio of monomer A to monomer B in a copolymer. Sequencing information may be obtained through the calculation of number-average sequence lengths for each monomer type, within the copolymer.

If we consider triad concentrations, then the derivation for number-average sequence lengths may be developed through an intuitive approach as follows: Let 0 represent the units of monomer A in the copolymer, and 1 represent the units of monomer B within the copolymer.

Now the total number of 0 units is equal to the triad concentrations $N_{101} + N_{001} + N_{000}$, because these triads represent all the possible arrangements where 0 is the central unit. The number of runs is simply $N_{101} + 1/2\, N_{001}$. The factor 1/2 appears because there are two N_{001} triads for each run containing two or more consecutive 0's. The number-average sequence length, $\overline{n_0}$, therefore is given by:

$$\overline{n_0} = \frac{N_{101} + N_{001} + N_{000}}{N_{101} + 1/2\, N_{001}} \qquad \text{Eqt. 4.11}$$

Similarly, for 1 sequences :

$$\overline{n_1} = \frac{N010 + N110 + N111}{N010 + 1/2\,N110} \qquad \text{Eqt. 4.12}$$

Where $\overline{n_0}$ and $\overline{n_1}$ represent the number-average sequence lengths for 0 centred units and 1 centred units, respectively.

Some essentially random copolymers of HEMA with NVP, and MMA with NVP were synthesized by conventional free radical polymerisation techniques, as described in chapter 2, section 2.21. The compositions of the copolymers were obtained from elemental analysis and compared with those obtained from j-Modulated spin echo ^{13}C NMR spectra. ^{13}C NMR spectra of the copolymers were recorded on a 10% w/v solutions in d-DMSO, by using a Bruker AC 300, at a probe temperature of 373 K. Other relevant parameters were: a sweep width of approximately 18,000 Hz; acquisition time 0.916 secs; number of pulses approximately 14,000; additional delay between pulses 3.0 secs; proton decoupling was accomplished by the use a composite pulse decoupling technique.

Relative peak areas were measured by using spectral integration and curve fitting and/or cutting and weighing. It was initially found that cutting and weighing provided similar results for relative peak areas compared to those obtained through the curve fitting approach. The best approach is usually through curve fitting since it avoids unwanted contributions from peak overlap, through the deconvolution of overlapped peak components, and matching these with generated peaks of Lorentzian shape. This is because NMR peak shapes, theoretically are Lorentzian[76] and a Lorentzian shape will be observed if the peak widths are determined by the transverse or T_2 relaxation process rather than field inhomogeneity. Contributions to the line widths from

magnetic field inhomogeneity usually produce Gaussian peak shapes. Line widths in ^{13}C NMR polymer spectra are generally 2 Hz or larger. Contributions from field inhomogeneity, if the field is well tuned, will only be a few tenths of a hertz; thus polymer line shapes are predominantly Lorentzian. Thus the curve fitting method produces the most accurate results for use in calculation of the number-average sequence lengths and configurational monomer distributions. In all cases, comparisons were made only between areas of peaks arising from carbons in similar chemical environments.

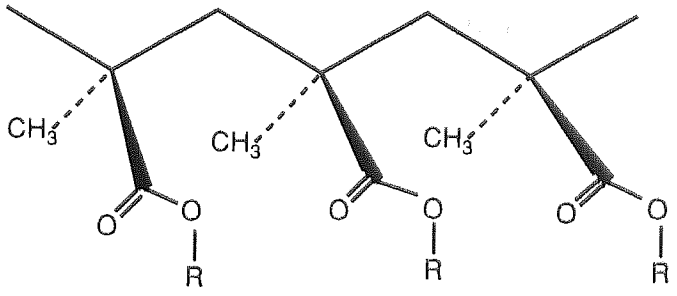
4.12 Carbon-type identification and peak assignments

The chemical shift in ^{13}C NMR polymer spectra are related to the number, type, and relative configuration of nearest-neighbour carbon atoms. The three carbon atoms nearest a carbon of interest strongly affect the chemical shift while weaker contributions arise from carbons in the fourth and fifth positions away[77]. Sizeable chemical shift differences (10-40 ppm), therefore, can be produced by the skeletal arrangement. Configurational arrangements also lead to chemical shift differences but only by an order of 1 or 2 ppm or less[78].

The technique of off-resonance decoupling is used to identify the carbon type, that is, whether it is a methyl, methylene, methine or quarternary. A single ^{1}H decoupling frequency, which offset 100-200 Hz from the resonance of interest, is employed. The net result is that ^{1}H-^{13}C splittings are observed as multiplets of only a few Hertz and can be used to identify the type of carbon from which the signal arises. Thus, a methyl resonance is identified through the appearance of a quartet, the methylene resonance by a triplet, and the methine resonance by a doublet. Of course this information will be complicated by the various configurational placements that each carbon type may be found in. Off-

resonance decoupling is a valuable tool for carbon-type assignments in ^{13}C NMR spectra of most polymers and copolymers. It will not lead, however, to a discrimination of the same carbon type in different structural environments. An interpretation of the result after off-resonance decoupling can still be ambiguous if the lines overlap. Other techniques or methods are still needed. The most valuable have been assignments based on, firstly established chemical shift behaviour, i.e., using some form of empirical method for ^{13}C NMR chemical shift assignments, such as the Grant and Paul Rules[77]; secondly, through comparison with the corresponding spectrum of a polymer containing similar chemical moieties or carbon atoms in similar chemical environments. Here, we must also consider the possible electronic interactions between the central monomer unit and its immediate neighbours, this information will allow us to differentiate between resonances due to tacticity effects from resonances due to monomer sequence effects. To illustrate this we may, for example, consider a copolymer of MMA-NVP. Free radical polymerized PMMA is primarily syndiotactic. In the -CO carbon resonance the most upfield peaks have been assigned to the isotactic (*mm*)* triad[79]. [* The m,r system to depict individual monomer unit configurations along a polymer chain was developed by Bovey[80,81]. This system elegantly accounts for relative configurational differences without inferring chirality. Adjacent monomer pairs with the same relative methine configurations are called *meso* (*m*) dyads while those with opposite configurations are called *racemic* (*r*) dyads. Thus an isotactic triad would be represented by *mm* and a syndiotactic triad by *rr*].

The preferred conformation of the isotactic alkyl methacrylate chain is[82-87] :



Where R = -CH_3, -C_2H_5, -C_2H_4OH, etc., and in this case interactions between the oxygen of the -CO group and the hydrogen of the alkyl group can take place. The initial deshielding effect on the -CO carbon is decreased because of these interactions and by the diamagnetic shielding effects from the anisotropy of the immediate -CO neighbours. This kind of interaction cannot take place in the syndiotactic (*rr*) triad and the *rr* triad appears down field. PNVP prepared by free radical polymerisation is also predominantly syndiotactic in nature. Therefore, although the carbonyl group in NVP is part of a five-membered ring, the peak assignments are based on the occurrence of similar interactions between the carbonyl oxygen of one ring and the hydrogens of an adjacent ring, like those found and described above in PMMA, but these interactions will occur to a slightly lesser degree due to the inherent stability of the five-membered ring. Thus the most down field peak has been assigned to the syndiotactic (*rr*) triad and the most upfield peak to the isotactic (*mm*) triad.

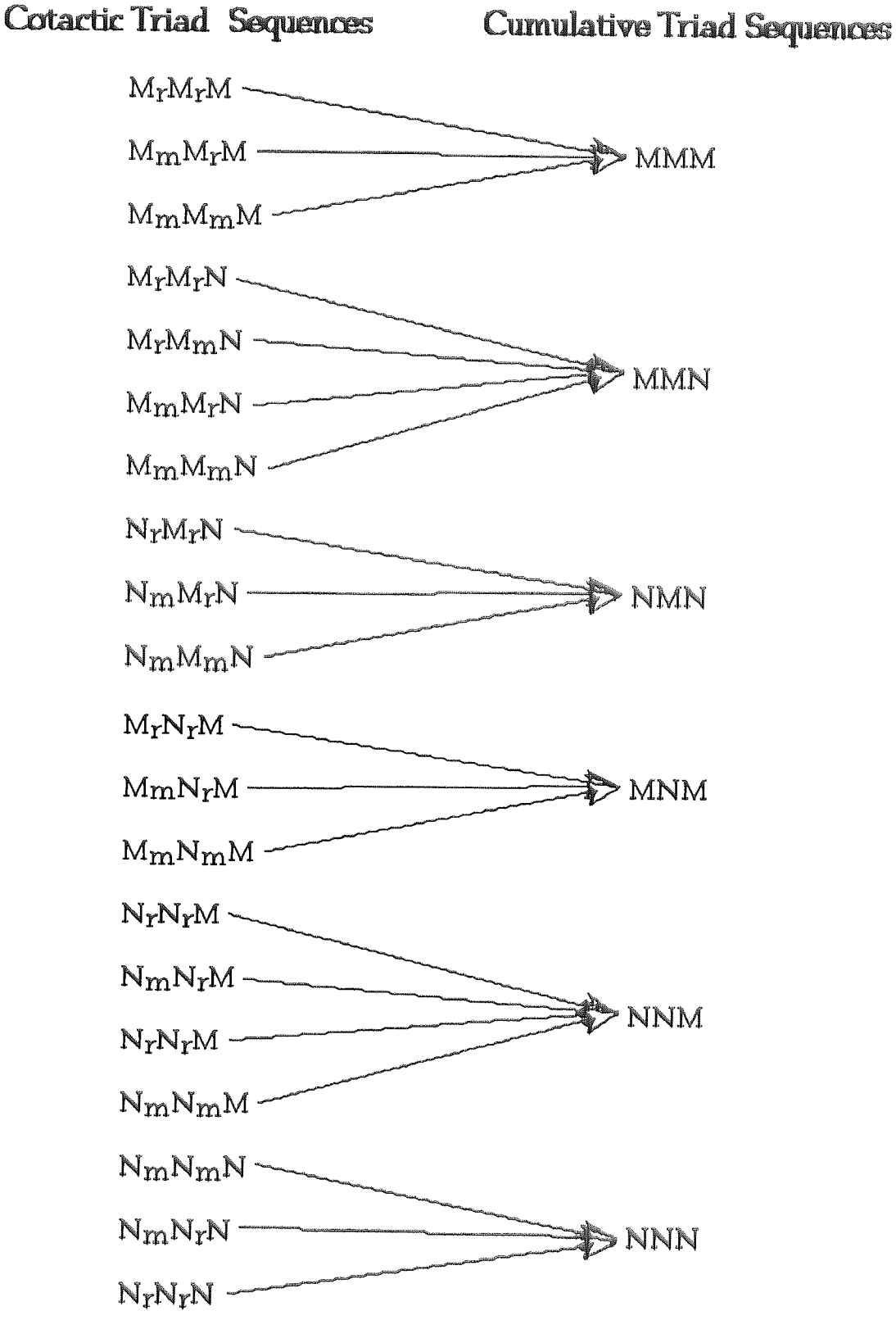
Now, let M, represent a monomer unit of MMA within the copolymer, and N, represent a monomer unit of NVP within the copolymer. A subscript of r/m will indicate the configuration of the preceding monomer unit to the following one. While making the peak assignments in the case of different cotactic sequences for the MMN, NMN, NNM and MNM monomer triads, we must bear in mind that the central carbonyl carbon in an M monomer unit and an N monomer unit will not have the same sensitivity to the tacticity of an adjacent N monomer because of the various electronic interactions involved between

the central monomer unit and its immediate neighbours in different triad sequences. These interactions may lead to a varying degree of shielding or deshielding effect on the carbonyl carbon of the central monomer unit depending on the configurations of the adjacent M and N unit.

In the case of the MMN triad, the central -CO carbon will have a diamagnetic shielding effect from a M unit in *m* configuration as in PMMA. Similarly an N unit attached to a central M unit in *m* configuration will result in the interaction between the hydrogen of $-OCH_3$ protons and the oxygen of the -CO group in the ring of the N unit. This interaction again leads to the increased electron density on the central -CO carbon. This kind of interaction is not possible in an MrMrN cotactic triad sequence and hence there is no induced diamagnetic shielding effect. This cotactic triad is expected to appear most downfield out of the four possible cotactic sequences. Out of M_mM_rN and M_rM_mN sequences, the central -CO carbon will have interactions with M and N units in the respective sequences. The electron in-booting effect in the case of M_mM- is greater, as compared to the $-M_mN$ sequence and is supported by the chemical shift values for different tactic triad sequences in homopolymers. Consequently, the M_mM_rN triad will appear upfield as compared to the M_rM_mN triad. Thus using this information, lines corresponding to the MMN sequences can be assigned to the various cotacticities that may occur within these sequences. Considering similar kinds of interactions and their relative effects, the lines of the -CO carbon resonance for the NMN sequence may also be assigned to the various cotacticities that may occur within these sequences. Using similar procedures to those adopted for the M-centered sequences, we may assign the various cotactic sequences that are possible, to the lines arising from the -CO carbon resonance for the N-centered sequences.

Summation of the individual cotactic sequences for a particular triad sequence, will give its overall concentration, as shown below in Figure 4.1. These triad values may then be used to calculate the number-average sequence lengths for the individual monomer units within the copolymer, as indicated earlier.

Figure 4.1: Summation of Cotactic Triad Sequences



4.13 Statistical Analysis of Monomer Distributions

A technique frequently practised when making ^{13}C NMR chemical shift assignments is the inspection of observed comonomer distributions for conformity to a statistical model. Bovey[88] and Price[38] pioneered the development of statistical analyses of polymers. The most frequently used statistical models are Bernoullian and first-order Markov. Bernoullian models describe a random distribution of monomer units where the probability of a monomer addition is independent of the outcome of any previous addition. A Bernoullian distribution is a common occurrence in vinyl homopolymers as well as in some copolymers. All first- (and higher -) order Markovian models describe those circumstances where a probability of an addition is dependent upon previous events: a first-order Markov model depends upon a single preceding event; a second-order Markov model depends upon the outcome of two previous events, and so on[89-92]. Comonomer distributions may then be defined by probability expressions for complete sets of mole fractions, that is, normalised dyad or triad, etc., concentrations. For distinguishing first-order Markovian from Bernoullian behaviour, we may compare a calculated versus observed *n*-ad comonomer distribution for both cases (or calculated versus observed number-average sequence lengths), or through the inspection of the triad ratios, 001/010 and 110/101, which should equal 2.0 for Bernoullian behaviour. Both Bernoullian and first-order Markov models will be examined in the following analyses of copolymer ^{13}C NMR spectra.

4.2 Analysis of ^{13}C NMR Copolymer Spectra in Comparison with their Computer Simulations

4.21 Analysis of a HEMA : NVP :: 60 : 40 copolymer

From the reactivity ratios(HEMA = 4.841, NVP = 0.001), it can be seen that the HEMA radical much prefers to add to its own monomer against adding the NVP monomer. The NVP radical prefers to cross-propagate by adding to the HEMA monomer, rather than adding its own monomer. Also we have a 3:2 ratio of HEMA : NVP in the initial feed. We would expect this to lead to a copolymer with large blocks of HEMA monomer units interspersed with the occasional NVP monomer unit. Thus the HEMA monomer would be used-up through the early period of the polymerisation and a large block of the remaining NVP monomer units would be added at the end. If we look at the computer simulation of this copolymer, as shown in figure 4.21, with this initial composition ratio, we see a quite reasonable approximation of what we predicted:

Figure 4.21 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 60 : 40.

60 Mole % of Monomer A, HEMA

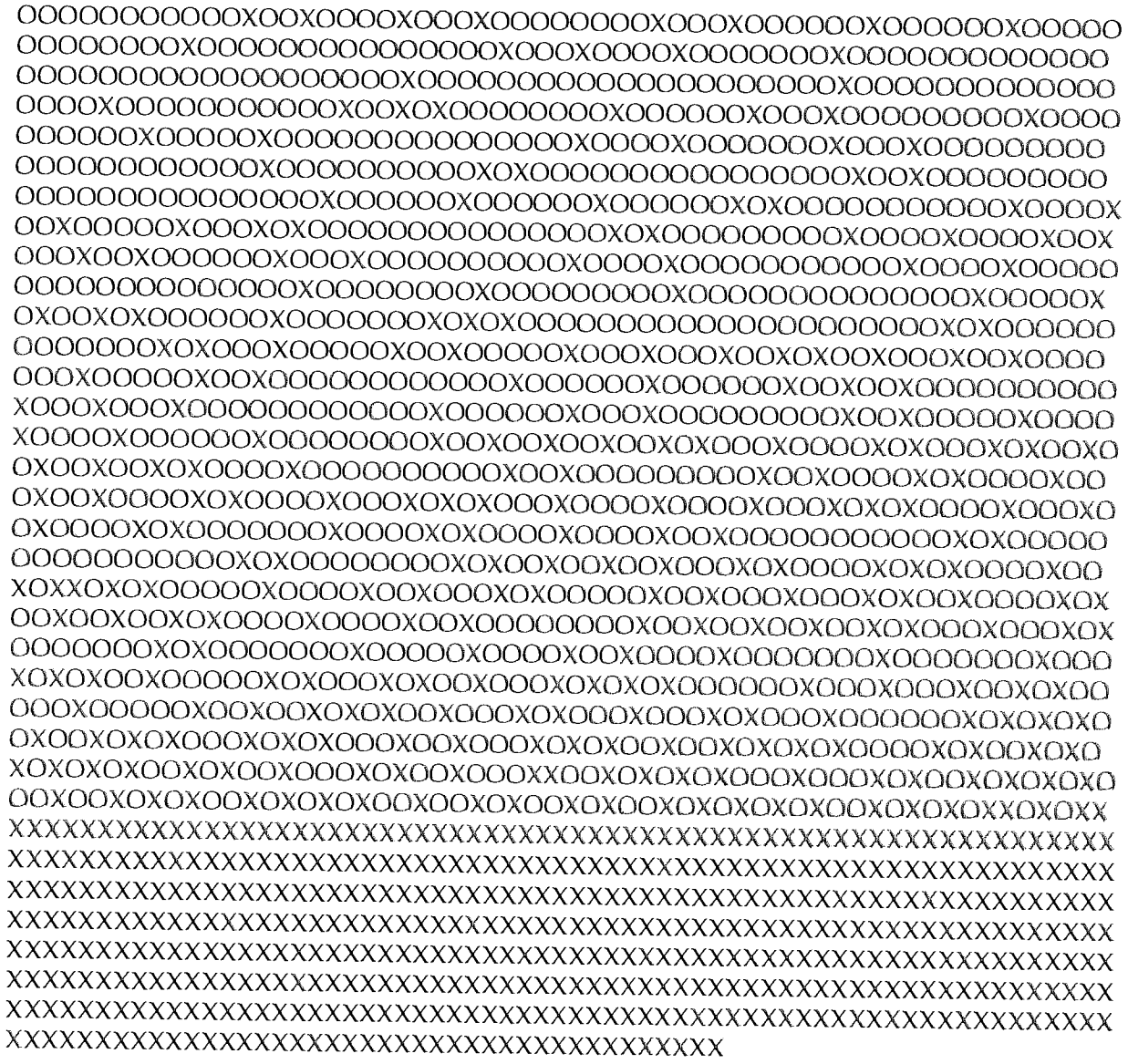
40 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :



The simulated copolymer contains 1200 HEMA units and 800 NVP units.

Table 4.21 : Sequence lengths seen in the simulated sequence distribution of figure 4.21.

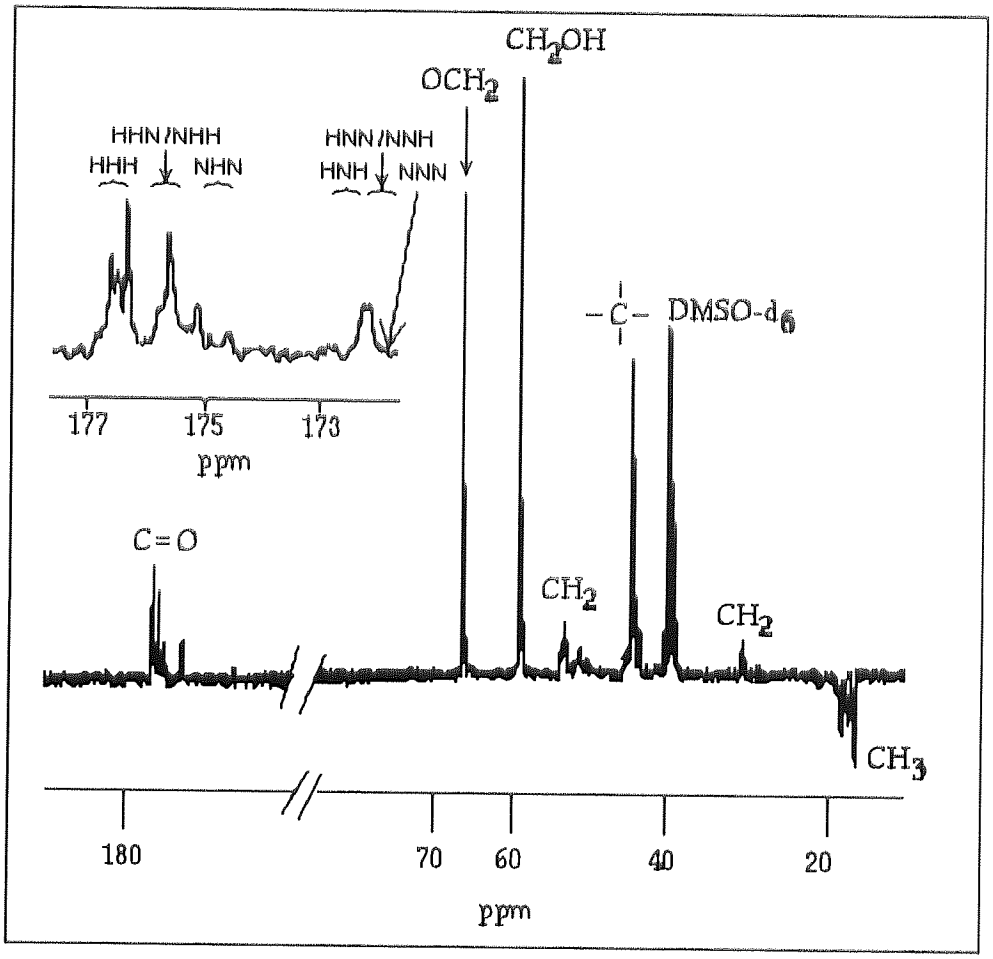
Sequence Distributions:

Length	HEMA	NVP
1	95	310
2	68	3
3	45	0
4	32	0
5	13	0

6	14	0
7	9	0
8	6	0
9	5	0
10	5	0
11	5	0
12	2	0
13	2	0
14	1	0
15	3	0
16	2	0
17	1	0
19	1	0
21	3	0
24	1	0
32	1	0
484	0	1

4.211 A HEMA : NVP :: 60:40 Copolymer sampled at 37% Conversion

Figure 4.211: ^{13}C NMR Spectrum of a HEMA:NVP :: 60:40 Copolymer at 37% Conversion



Where 'H' represents a HEMA monomer unit and 'N' represents a NVP monomer unit in the copolymer.

Analysis of the above HEMA : NVP :: 60:40 copolymer ^{13}C NMR spectrum, by methods described earlier in section 4.1, leads to the following comonomer triad fractions, shown in Table 4.211:

Table 4.211: Observed Triad Distributions for a HEMA : NVP :: 60:40 Copolymer sampled at 37% Conversion

Triad Sequences	Observed Fraction
000	0.651
001/100	0.189
101	0.027
010	0.110
110/011	0.023
111	0.00

Where 0 represents the units of the HEMA monomer in the copolymer, and 1 represents the units of the NVP monomer within the copolymer

Table 4.212: Calculated Triad Distributions from Statistical Analysis

Triad Sequences	Bernoullian ($P_0 = 0.87$)*	First-order-Markov ($P_{01} = 0.13$, $P_{10} = 0.85$)†
000	0.659	0.643
001/100	0.197	0.192
101	0.015	0.014
010	0.098	0.094
110/011	0.029	0.033
111	0.002	0.003

* Where P_0 is the transitional probability, which in Bernoullian Statistics represents the probability of finding a "0-unit" within the copolymer. Thus corresponding to the mole fraction of "0-units" observed for the copolymer.

† Where P_{01} and P_{10} are transitional probabilities, which in Markovian Statistics give the probability of adding a "1-unit" onto a chain with a "0-unit" radical at its end, and the probability of adding a "0-unit" onto a chain with a "1-unit" radical at its end, respectively. Thus in a first-order Markov system the transition probabilities depend upon the outcome of the immediately preceding event.

From the above data we may calculate the number-average sequence lengths for each individual monomer unit, as described in section 4.11, and shown below in Table 4.213 :

Table 4.213: Comparison of Number-Average Sequence Lengths

Number-Average Sequence Lengths							
Observed		Calculated				Computer Simulation	
^{13}C NMR		Bernoullian		1st order Markov			
HEMA	NVP	HEMA	NVP	HEMA	NVP	HEMA	NVP
6.52	1.00	6.69	1.00	6.54	1.00	6.49	1.00

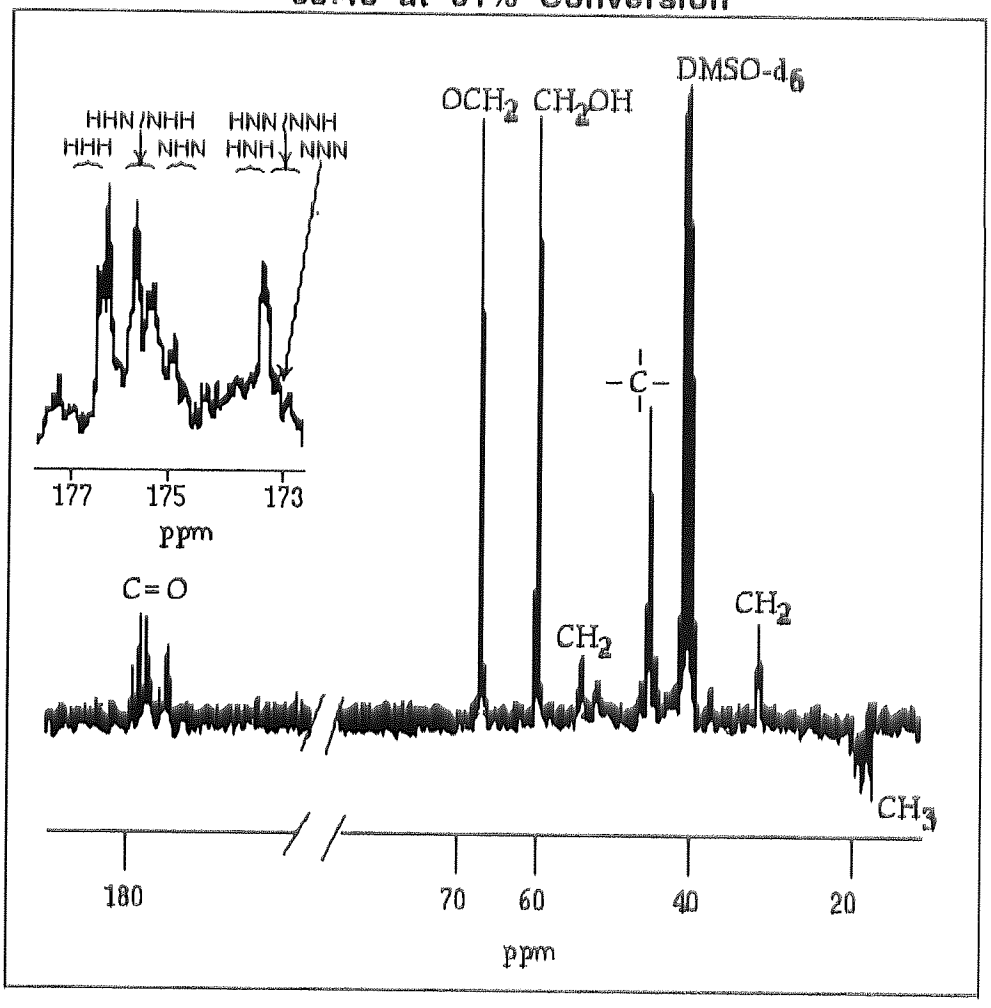
Table 4.214, below gives a comparison of compositions of the above copolymer, determined through ^{13}C NMR analysis, elemental analysis and computer simulation data, at 37% conversion :

Table 4.214 Comparison of Copolymer Compositions at 37% Conversion

Composition(Mole %)					
^{13}C NMR		Elemental Analysis		Computer Simulation	
HEMA	NVP	HEMA	NVP	HEMA	NVP
86.70	13.30	86.61	13.39	86.89	13.11

4.212 A HEMA : NVP :: 60:40 Copolymer sampled at 61% Conversion

Figure 4.212: ^{13}C NMR Spectrum of a HEMA:NVP Copolymer :: 60:40 at 61% Conversion



Where 'H' represents a HEMA monomer unit and 'N' represents a NVP monomer unit in the copolymer.

Analysis of the above HEMA : NVP :: 60:40 copolymer ^{13}C NMR spectra, by methods described earlier in section 4.1, lead to the following comonomer triad fractions, shown in Table 4.215:

Table 4.215: Observed Triad Distributions for a HEMA : NVP :: 60:40 Copolymer sampled at 61% Conversion

Triad Sequences	Observed Fraction
000	0.499
001/100	0.235
101	0.060
010	0.144
110/011	0.047
111	0.016

Where 0 represents the units of the HEMA monomer in the copolymer, and 1 represents the units of the NVP monomer within the copolymer.

Table 4.216: Calculated Triad Distributions from Statistical Analysis

Triad Sequences	Bernoullian ($P_0 = 0.78$)	First-order-Markov ($P_{01} = 0.25, P_{10} = 0.72$)
000	0.475	0.405
001/100	0.268	0.270
101	0.038	0.045
010	0.134	0.130
110/011	0.076	0.101
111	0.011	0.021

From the data above we may calculate the number-average sequence lengths for each individual monomer unit, as described in section 4.11, and shown below in Table 4.217 :

Table 4.217: Comparison of Number-Average Sequence Lengths

Number-Average Sequence Lengths							
Observed		Calculated				Computer	
^{13}C NMR		Bernoullian		1st order Markov		Simulation	
HEMA	NVP	HEMA	NVP	HEMA	NVP	HEMA	NVP
3.62	1.00	3.55	1.00	2.92	1.00	3.31	1.00

Table 4.218, below gives a comparison of compositions of the above copolymer, determined through ^{13}C NMR analysis, elemental analysis and computer simulation data, at 61% conversion :

Table 4.218: Comparison of Copolymer Compositions at 61% Conversion

Composition(Mole %)					
^{13}C NMR		Elemental Analysis		Computer Simulation	
HEMA	NVP	HEMA	NVP	HEMA	NVP
79.30	20.70	78.48	21.52	81.99	18.01

4.22 Analysis of a MMA : NVP :: 60 : 40 copolymer

From the reactivity ratios (MMA = 4.04, NVP = 0.01), it can be seen that the MMA radical much prefers to add to its own monomer against adding the NVP monomer. The NVP radical prefers to cross-propagate by adding to the MMA monomer, rather than adding its own monomer. Also we have a 3:2 ratio of MMA : NVP in the initial feed. We would expect this to lead to a copolymer with large blocks of MMA monomer units interspersed with the occasional NVP monomer unit. Thus the MMA monomer would be used-up through the early period of the polymerisation and a large block of the remaining NVP monomer units would be added at the end.

This copolymer is very similar to the HEMA : NVP copolymer analysed in section 4.21. Although here the MMA radical has a slightly lower tendency to self-propagate compared with the HEMA radical in the previous copolymer, and the NVP radical is seen to have a slightly lower tendency to cross-propagate than in the copolymer studied in the previous section. Consequently we would expect to see this in the sequence distributions and in the number-average

sequence lengths, if compared at a similar % conversion. If we look at the computer simulation of this copolymer, as shown in figure 4.22, with this initial composition ratio, we see a quite reasonable approximation of what we predicted:

Figure 4.22 : Computer simulated sequence distribution of a copolymer of MMA : NVP :: 60 : 40.

60 Mole % of Monomer A, MMA

40 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer MMA is represented by O and NVP is represented by X :

XOOXOOOOXOOOOOOOXOOXOOXOOXOOOOOOXOXOOOOOOXOOOOOXOOOOOOOO
OOOXOOOOOOOOOOOOOOOOXOXOOOOOOOOOOOOOOOXOOOOOOXOXOOOOXOOO
OOXOOOOOOXOXOOOOOOOOOOOXOOOXOOOOOOOOXOOXOXOXOOOXOOOOOXOO
OOOXOOOOOOOXOOOXOOOOOOOOOOOOOOOXOXOXOOOOXOOXOOOOOOOOXOOO
OOXOOOOOOOXOXOOOOOOOOOXOOOOOOOOOXOOOOOOOOOOOOOOOOOOOOO
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OOOXOOOOOOOOXOXOOOXOOOOOOOOXOOXOOOOXOOOOOOXOOOOOOXOXOXOOO
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The simulated copolymer contains 1200 MMA units and 800 NVP units.

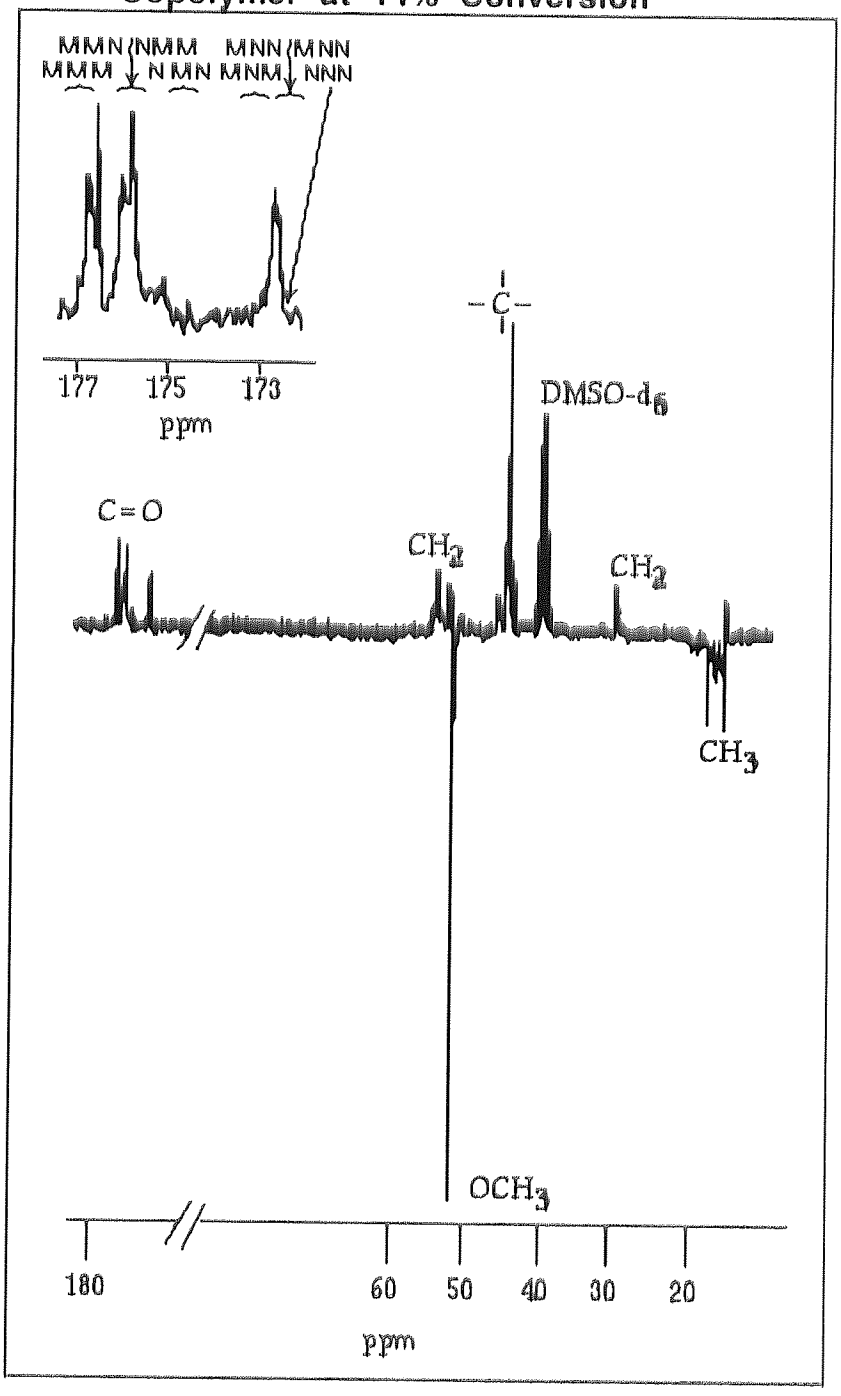
Table 4.22 : Sequence lengths seen in the simulated sequence distribution of figure 4.22.

Sequence Distributions:

Length	MMA	NVP
1	116	327
2	65	7
3	34	0
4	34	0
5	17	0
6	15	0
7	15	0
8	7	0
9	7	0
10	11	0
11	2	0
12	2	0
15	3	0
16	2	0
18	1	0
19	2	0
28	1	0
459	0	1

4.221 A MMA : NVP :: 60:40 Copolymer sampled at 14% Conversion :

Figure 4.221: ^{13}C NMR Spectrum of a MMA:NVP :: 60:40 Copolymer at 14% Conversion



Where 'M' represents a MMA monomer unit and 'N' represents a NVP monomer unit in the copolymer.

Analysis of the above MMA : NVP :: 60:40 copolymer ^{13}C NMR spectra, by methods described earlier in section 4.1, lead to the following comonomer triad fractions, shown in Table 4.221:

Table 4.221: Observed Triad Distributions for a MMA : NVP :: 60:40 Copolymer sampled at 14% Conversion

Triad Sequences	Observed Fraction
000	0.645
001/100	0.197
101	0.017
010	0.093
110/011	0.048
111	0.00

Where 0 represents the units of the MMA monomer in the copolymer, and 1 represents the units of the NVP monomer within the copolymer.

Table 4.222: Calculated Triad Distributions from Statistical Analysis

Triad Sequences	Bernoullian ($P_0 = 0.86$)	First-order-Markov ($P_{01} = 0.14, P_{10} = 0.84$)
000	0.636	0.621
001/100	0.207	0.202
101	0.017	0.016
010	0.104	0.096
110/011	0.034	0.038
111	0.003	0.004

From the above data we may calculate the number-average sequence lengths for each individual monomer unit, as described in section 4.11, and shown below in Table 4.223 :

Table 4.223: Comparison of Number-Average Sequence Lengths

Number-Average Sequence Lengths							
Observed		Calculated				Computer Simulation	
^{13}C NMR		Bernoullian		1st order Markov			
MMA	NVP	MMA	NVP	MMA	NVP	MMA	NVP
6.17	1.00	6.12	1.00	6.00	1.00	5.64	1.00

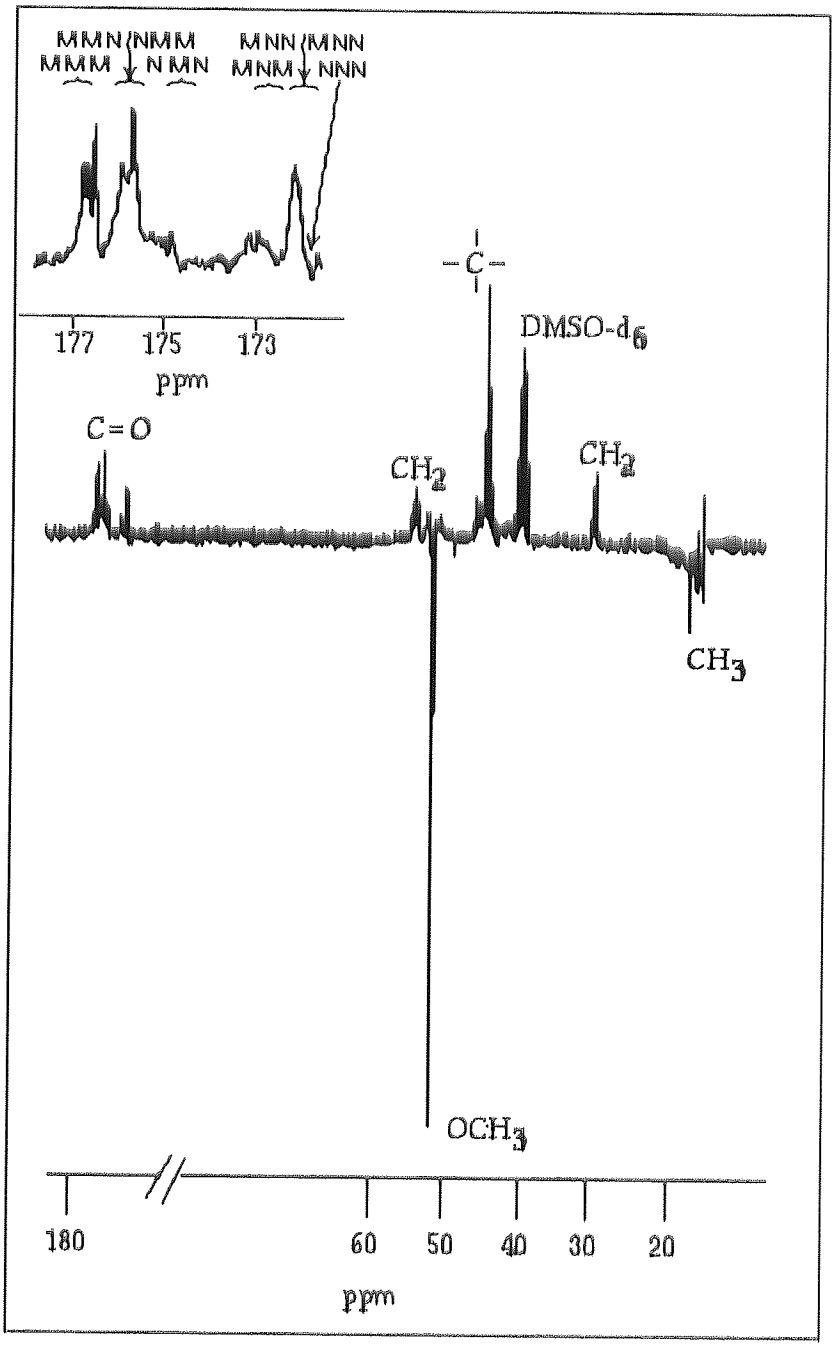
Table 4.224, below gives a comparison of compositions of the above copolymer, determined through ^{13}C NMR analysis, elemental analysis and computer simulation data, at 14% conversion :

Table 4.224: Comparison of Copolymer Compositions at 14% Conversion

Composition(Mole %)					
^{13}C NMR		Elemental Analysis		Computer Simulation	
MMA	NVP	MMA	NVP	MMA	NVP
85.90	14.10	85.55	14.45	84.65	15.35

4.222 A MMA : NVP :: 60:40 Copolymer sampled at 50% Conversion :

Figure 4.222: ^{13}C NMR Spectrum of a MMA:NVP :: 60:40 Copolymer at 50% Conversion



Where 'M' represents a MMA monomer unit and 'N' represents a NVP monomer unit in the copolymer.

Analysis of the above MMA : NVP :: 60:40 copolymer ^{13}C NMR spectra, by methods described earlier in section 4.1, lead to the following comonomer triad fractions, shown in Table 4.225:

Table 4.225: Observed Triad Distributions for a MMA : NVP :: 60:40 Copolymer sampled at 50% Conversion

Triad Sequences	Observed Fraction
000	0.469
001/100	0.284
101	0.033
010	0.154
110/011	0.044
111	0.014

Where 0 represents the units of the MMA monomer in the copolymer, and 1 represents the units of the NVP monomer within the copolymer.

Table 4.226: Calculated Triad Distributions from Statistical Analysis

Triad Sequences	Bernoullian ($P_0 = 0.77$)	First-order-Markov ($P_{01} = 0.22, P_{10} = 0.74$)
000	0.457	0.450
001/100	0.272	0.254
101	0.041	0.036
010	0.136	0.120
110/011	0.081	0.085
111	0.012	0.015

From the data above we may calculate the number-average sequence lengths for each individual monomer unit, as described in section 4.11, and shown below in Table 4.227 :

Table 4.227: Comparison of Number-Average Sequence Lengths

Number-Average Sequence Lengths							
Observed		Calculated				Computer Simulation	
^{13}C NMR		Bernoullian		1st order Markov			
MMA	NVP	MMA	NVP	MMA	NVP	MMA	NVP
3.73	1.00	3.35	1.00	3.36	1.00	4.19	1.00

Table 4.228, below gives a comparison of compositions of the above copolymer, determined through ^{13}C NMR analysis, elemental analysis and computer simulation data, at 50% conversion :

Table 4.228: Comparison of Copolymer Compositions at 50% Conversion

Composition(Mole %)					
^{13}C NMR		Elemental Analysis		Computer Simulation	
MMA	NVP	MMA	NVP	MMA	NVP
78.80	21.20	77.31	22.69	80.90	19.10

4.23 Analysis of a HEMA : NVP :: 20 : 80 copolymer

It is apparent from section 4.21 that HEMA and NVP, when present in relatively equal quantities, will produce a relatively poor sequence distribution of monomer units in the final copolymer(i.e., long, extended sequences of individual monomer units). This is simply a consequence of their reactivity ratios(HEMA = 4.841, NVP = 0.001), and as a result we see that the HEMA radical much prefers to add to its own monomer against adding the NVP monomer. The NVP radical prefers to cross-propagate by adding to the HEMA monomer, rather than adding its own monomer, which produces the poor sequence distribution seen in figure 4.21. In this section we will analyse a HEMA:NVP::20:80 copolymer, the greatly increased NVP content should, according to the computer simulation of the sequence distribution shown in figure 4.23, produce a copolymer with a small ratio of HEMA:NVP units(around 1:2) up to about 40% conversion. Thus in effect we will have produced a copolymer with a relatively good sequence distribution(i.e., short, regular sequences of individual monomer units). This will provide a good opportunity to study the accuracy of the computer simulation program, when

the copolymer synthesized has a relatively good sequence distribution. This situation is quite different from the four previously examined in sections 4.211, 4.212, 4.221 and 4.222, although the monomers involved are the same or similar, the sequence distributions produced shown in figures 4.21 and 4.22 are all relatively poor in contrast to the sequence distribution seen in figure 4.23, up to about 40% conversion.

Figure 4.23 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 20 : 80.

20 Mole % of Monomer A, HEMA

80 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :

```
OXOOOXOOOOXOOOXOOXOOOXOXOOOOXOOOOXOXOOOOOOOOOOXOOXOXOXOOXO
XOXOXOXOOOOXOOXOXOXOXOXOXOOXOXOOOOOXOOOOOOOOOOXOXOXOOOOOOOO
XOXOXOOOXOOOXOXOXOXOOOXOOXOXOOOXOOOXOOOOOOOOXOXOOXOOOXOXOX
OOOOXOOOOXOXOXOOXOOOOXOXOOOOXOXOOOXOOXOOOXOXOOOOXOOOOXOXO
XOXOXOXOXOOOXOXOXOXOOXOOXOXOOXOOOXOXOOOXOOXOXOXXOOXOOXOXOX
OXOOOXOXOXOOOXOOXOXOXOOXOXOXOOXOXOOOOXOOOXOXOOOOOOOXOOOXOO
XOXOXOXOOXOOOXOOXOOOOOOOOOXOXOXOXOOXOXOOXOOOXOOXOOXOXOOOOX
OXOOXOXOXOOXOXOXOOOOXOOXOXOOOOXOOOXOXOXOXOXOXOXOXOXOOXOXOX
OOOXOXOOXOXOOXOXOXOXOXOOXOOXOOXOXOOOXOOXOOXOOXOXOXOXOOXOX
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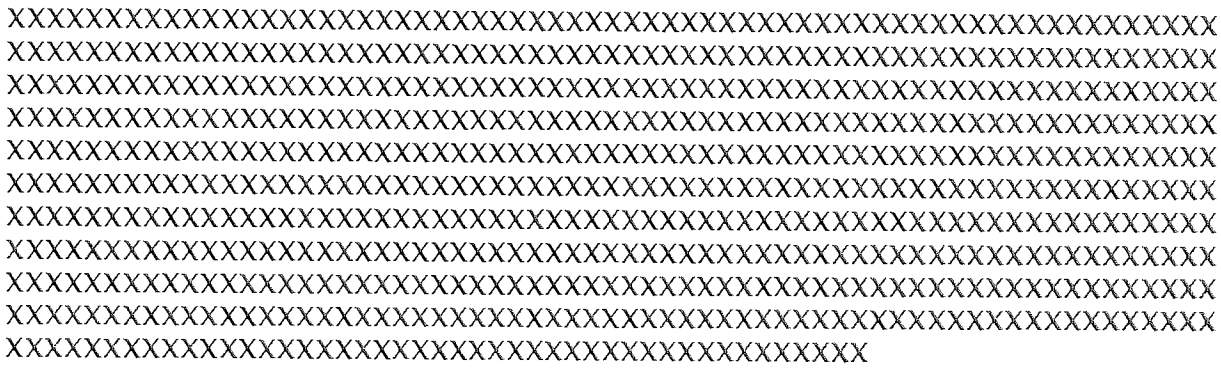


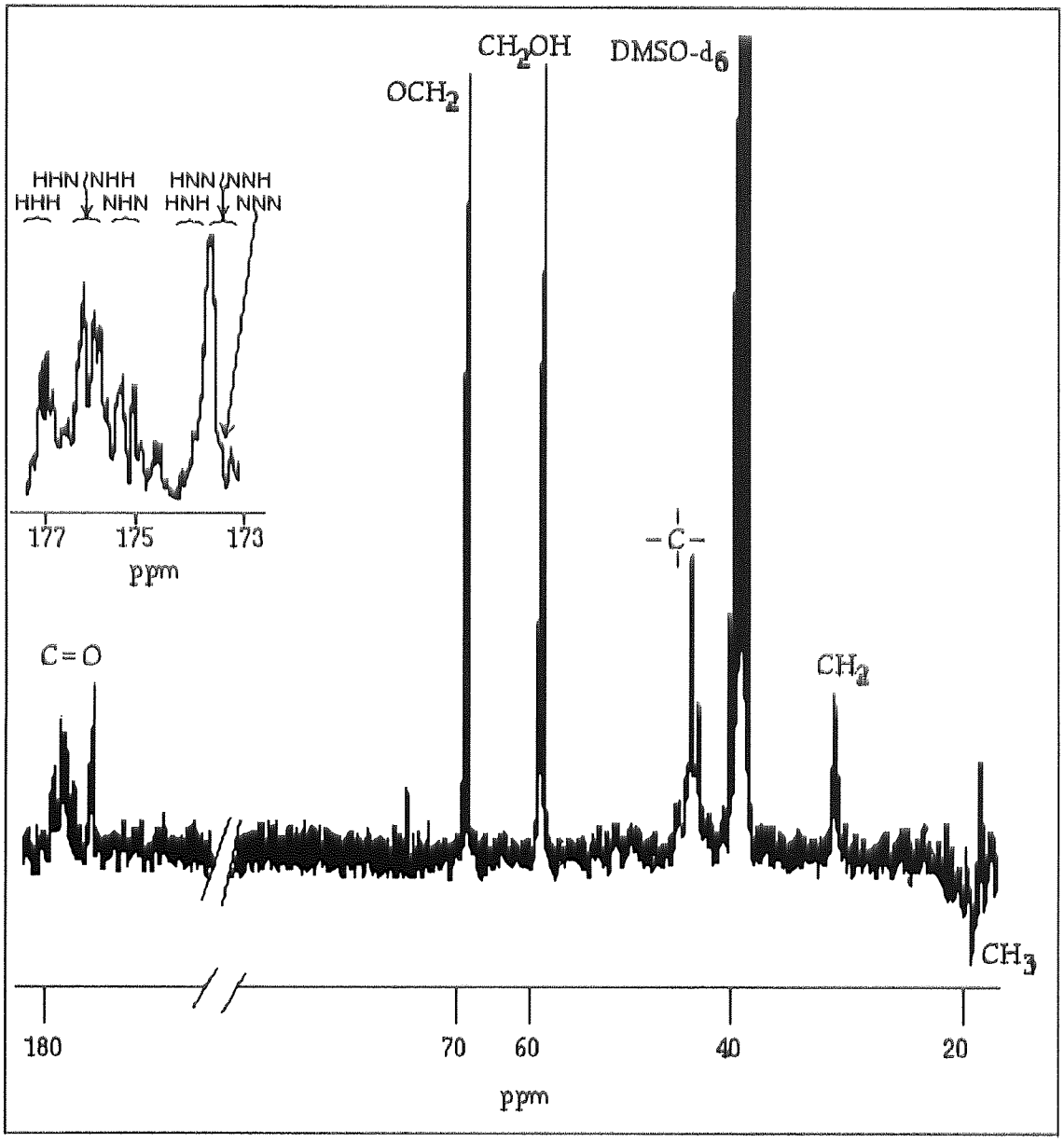
The simulated copolymer contains 400 HEMA units and 1600 NVP units.

Table 4.23 : Sequence lengths seen in the simulated sequence distribution of figure 4.23.

Sequence Distributions:

Length	HEMA	NVP
1	138	221
2	43	3
3	23	0
4	14	0
5	1	0
6	1	0
7	2	0
8	1	0
9	2	0
1373	0	1

Figure 4.231: ^{13}C NMR Spectrum of a HEMA:NVP :: 20:80 Copolymer at 27% Conversion



Where 'H' represents a HEMA monomer unit and 'N' represents a NVP monomer unit in the copolymer.

Analysis of the above HEMA : NVP :: 20:80 copolymer ^{13}C NMR spectrum, by methods described earlier in section 4.1, leads to the determination of the comonomer triad fractions, shown below:

Table 4.231 and table 4.232, below, show the observed and calculated comonomer triad fractions, respectively. Table 4.233 gives a comparison of the number-average sequence lengths for each individual monomer unit, whilst table 4.234 compares the compositions of the copolymer calculated from ^{13}C NMR analysis, elemental analysis and computer simulation data, at 27% conversion.

Table 4.231: Observed Triad Distributions for a HEMA : NVP :: 20:80 Copolymer sampled at 27% Conversion.

Triad Sequences	Observed Fraction
000	0.218
001/100	0.312
101	0.110
010	0.149
110/011	0.202
111	0.009

Where 0 represents the units of the HEMA monomer in the copolymer, and 1 represents the units of the NVP monomer within the copolymer.

Table 4.232: Calculated Triad Distributions from Statistical Analysis

Triad Sequences	Bernoullian ($P_0 = 0.64$)	First-order-Markov ($P_{01} = 0.36$, $P_{10} = 0.62$)
000	0.262	0.254
001/100	0.295	0.286
101	0.083	0.080
010	0.147	0.138
110/011	0.166	0.169
111	0.047	0.052

From the above data we may calculate the number-average sequence lengths for each individual monomer unit, as described in section 4.11, and shown below in Table 4.233 :

Table 4.233: Comparison of Number-Average Sequence Lengths

Number-Average Sequence Lengths							
Observed		Calculated				Computer Simulation	
^{13}C NMR		Bernoullian		1st order Markov			
HEMA	NVP	HEMA	NVP	HEMA	NVP	HEMA	NVP
1.67	1.00	1.78	1.00	1.72	1.00	1.88	1.00

Table 4.234, below gives a comparison of compositions of the above copolymer, determined through ^{13}C NMR analysis, elemental analysis and computer simulation data, at 27% conversion :

Table 4.234: Comparison of Copolymer Compositions at 27% Conversion

Composition(Mole %)					
^{13}C NMR		Elemental Analysis		Computer Simulation	
HEMA	NVP	HEMA	NVP	HEMA	NVP
64.00	36.00	64.42	35.58	65.74	34.26

4.3 Summary

It can be seen from section 4.2, that the computer simulation program based on the Monte-Carlo method is reasonably accurate in predicting the overall sequence distribution, of individual monomer units, which would be observed upon polymerisation. This is apparent in tables 4.213, 4.217, 4.223, 4.227 & 4.233, which show a good correlation between the observed number-average sequence lengths (from ^{13}C NMR analysis) and the predicted number-average sequence lengths from the computer simulation program. There is a slight deviation at higher conversions in comparison with the computer predicted number-average sequence lengths. This deviation in the terminal model at higher conversions has been noted by other workers[59]. But the deviation observed here is not significant enough to prevent one from gaining a reasonably good impression of the sequence distribution of individual monomer units in the synthesized polymer. Also, tables 4.214, 4.218, 4.224, 4.228

& 4.234 show a reasonably good correlation between the observed copolymer compositions (from ^{13}C NMR and Elemental analysis), at the various conversions, and the predicted copolymer compositions from the computer simulation program. The data from both statistical analyses, Bernoullian and First-order Markov, does not reconcile well with the observed data for triad fractions. This may possibly be due to the fact that the polymerisation systems being studied do not follow these statistical profiles and may follow higher order Markovian statistics, or the differences may be due to errors in the assignment of peaks which may be compounded when the triad fractions of different tacticities are added (as illustrated in figure 4.1) to give the overall comonomer triad fractions shown in the above tables.

In summary we may state that the computer simulation programs produce sufficiently accurate simulations of the sequence distribution of individual monomer units that would be seen upon polymerisation, to warrant their use in designing polymers with controlled sequence distributions.

CHAPTER FIVE

A PROCEDURE FOR THE DESIGN OF POLYMERS WITH CONTROLLED SEQUENCE DISTRIBUTIONS

5.0 A Procedure for the Design of Polymers with Controlled Sequence Distributions

It is apparent, from chapter 3, that the main factors which govern the sequence distribution of a polymer are, the concentration of the monomers and their reactivity ratios. Since the concentrations are easily varied this is usually not a problem in helping to achieve a certain sequence distribution. But the reactivity ratios are not easily varied. In fact they are specific for a particular pair of monomers, since they are inherently dependent on the chemical functionality of the monomers concerned. Thus we cannot easily alter this, as the main reason a particular monomer is chosen is for its chemical properties. In this chapter we will expound a procedure which will enable us to manipulate the way monomers, with their reactivity ratios, are used in order to produce a relatively good sequence distribution (short, regular sequences of individual monomer units) in the final polymer.

5.1 Reactivity Ratios and Sequence Distributions

Let us consider how reactivity ratios affect the sequence distributions seen in the polymerized polymer. The monomer reactivity ratios r_1 and r_2 are the ratios of the rate constants for a radical adding to its own monomer to that of its addition to another. It is a measure of preference for its own kind of monomer to that of another. If $r_1>1$, the radical $M_1^{\bullet}$ on the growing end of the chain prefers to add M_1. If $r_1<1$, the radical $M_1^{\bullet}$ prefers to add M_2. These relationships also apply to r_2 with respect to radical $M_2^{\bullet}$. Table 5.0, overleaf, gives examples of some common monomer reactivity ratios[93-98] :

Table 5.0 : Some Monomer Reactivity Ratios

Monomer 1	r_1	Monomer 2	r_2	Reference
HEMA	0.810	MMA	0.192	99
HEMA	0.65	STY	0.57	100
HEMA	4.841	NVP	0.001	101
HEMA	4.126	NNDMA	0.238	Q-e*
NNDMA	0.410	MMA	1.650	102
NVP	0.01	MMA	4.04	103

* calculated from the Q-e scheme, see section 3.3.

Several important insights regarding our understanding of how free radical copolymerisation reactivity ratios affect the sequence distributions seen in the polymerized copolymer, emerge from considering the four special cases of the reactivity ratios seen, for the Terminal Model, in section 3.21. We may illustrate and examine these special cases by the following examples:

(i) When $r_1 \approx r_2 \approx 1$. We may illustrate this case by considering the following example of HEMA : AOEMA :: 50 : 50(where AOEMA = Acetoxy Ethyl methacrylate), with $r_1 = 1.020$ and $r_2 = 0.990$, respectively. Figure 5.1, below, shows the computer simulated sequence distribution for this copolymer. Table 5.1 shows the sequence lengths seen in figure 5.1 :

Figure 5.1 : Computer simulated sequence distribution of a HEMA : AOEMA :: 50 : 50 copolymer.

50 Mole % of Monomer A, HEMA

50 Mole % of Monomer B, AOEMA

r(AB) = 1.020 r(BA) = 0.990

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, AOEMA is represented by X :

OXXXOXOXOOXXOXXOOOOOOOOXOOXOXXOXXXXXOXXXOOOXOXXXXOXOOOXOOO
OOOXXOOOOXOXXOXOOXOXOXOXOOOOXXXXXOXXOOXOXOOOXOXXOXOOOXXOOO
XXOXXOXXOOXXOXOXOOXOXXXOXXOXOXXOXOXOXXXXXOXXOXOXXXOOOXXXXO
XOOOOXOXXXOOOXXXXXXOOXXOXXOXOXXOXOXXXXXXXOOXOXXOOOOXXOXXXXO
XOXOOXOOOXXXOOXXXXXXXXOOXXOOXOXOXXOXOXOXXXXXOXXXXOXOXXXXOXO
OXOXOOOOXXXOOXOOXOXOOOOOXOOXOXOOXOXOXXXOOOOOXXXXXXOXOOOXXX
OXXOXXXOXXXXOOOOXOXOOXOOXOXOOOXXXOOXXOOOXOOOXXOXXOXOXOXXOO
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XOOXXOXOOXOOOXOOXOXOXOXOXXXOXXOOOOXOOOXOXXOXOXXOOXOXXOXXXX
XXXOOOXXOOOOOOOXXXXXOXOXOOXXOXXOXXOOXOXXOXXOOXOOXOOXOOOOOO
OOXOOOOOXXXOXXOXOXXXXXOOOOOXOXOXXOOOOXXXOXXOXXOXXXOXXXOOOXX
OOXXXOXOXXXXXXXOOOXOOOOOOOOXXXOXOOOOOXOOOXXXXXXXXOOOOOXOOX
OOXOXOXOOOXOOOOOOXXXXXOOXOXXOXOXXOOXOOXXXOXOXOXXXOOXOXXXXO
OOOXOXXXOXOXOXOOXOXOXOOOXXOXOOOXXOXXXXXOOXXOOXXXXOOXOOOOXOOO
XOXXXXOXOXOXOOXOOOOOOOXOOOOOOOOXXXOOXOXXOXOXOXOOXXOXOOXXOOXXO
OOXOOOOXXOXOOXXXX

The simulated copolymer contains 1000 HEMA units and 1000 AOEMA units.

Table 5.1 : Sequence lengths seen in the simulated sequence distribution of figure 5.1.

Sequence Distributions:

Length	HEMA	AOEMA
1	258	256
2	139	142
3	52	53
4	25	27
5	18	14
6	3	10
7	5	3
8	2	1
9	3	0
10	1	0
11	0	1
12	1	0
23	0	1

Here, we may firstly note that we have what is known as 'Ideal Copolymerisation'. This is a special case of free radical polymerisation that arises when $r_1 \times r_2 = 1$ (i.e., when both active centres show the same preference for addition of one of the monomers), see chapter 3. Under these conditions, $r_2 = \frac{1}{r_1}$, and the relative rates of incorporation of the two monomers into the copolymer are independent of the identity of the unit at the end of the propagating chain. The term ideal copolymerisation was coined[6] historically to show the analogy between the variations in the copolymer composition as a function of the comonomer feed compositions for different values of r_1, and the variations seen in the vapour-liquid equilibria in ideal mixtures. It does not in any sense imply a desirable type of copolymerisation.

In our present example we also have $r_1 \approx r_2 \approx 1$, where the two monomers show equal reactivities toward both propagating species. Here the copolymer

composition is the same as the comonomer feed with a random placement of the two monomers along the copolymer chain. This behaviour is referred to as random or Bernoullian. As would be expected we see a large number of individual monomer sequence lengths. The overall sequence distribution is reasonably good, but contains too many long individual monomer sequence lengths to be classified as a really good sequence distribution.

(ii) When $r_1 \approx r_2 \approx 0$. We may illustrate this case by considering the following example of STY : MALAN :: 50 : 50(where STY = Styrene and MALAN = Maleic Anhydride), with $r_1 = 0.040$ and $r_2 = 0.001$, respectively. Figure 5.2, below, shows the computer simulated sequence distribution for this copolymer. Table 5.2 shows the sequence lengths seen in figure 5.2 :

Figure 5.2 : Computer simulated sequence distribution of a STY : MALAN :: 50 : 50 copolymer.

50 Mole % of Monomer A, STY

50 Mole % of Monomer B, MALAN

r(AB) = 0.040 r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer STY is represented by O, MALAN is represented by X :

XOXOOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOOOXOXOXOXOOXOXOXOXOXOXO
XOXOXOXOOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOOXOXOXO
XOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXO
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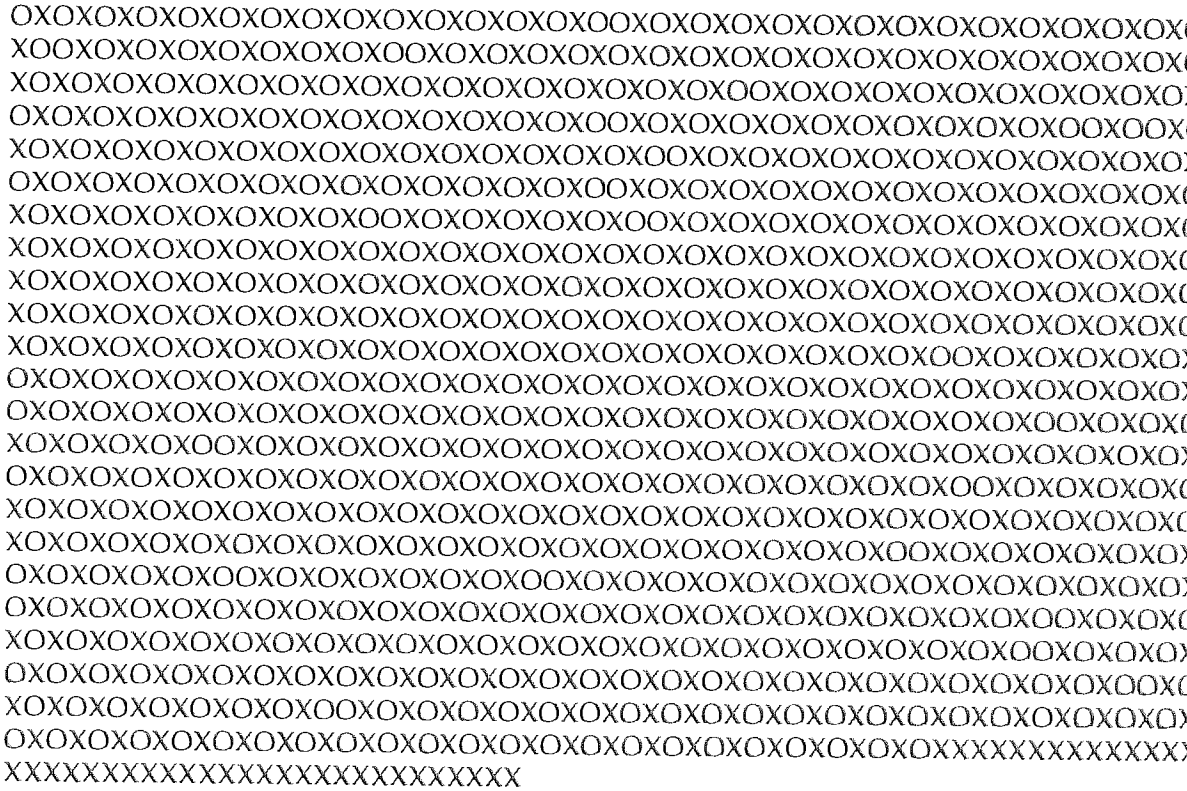


The simulated copolymer contains 1000 STY units and 1000 MALAN units.

Table 5.2 : Sequence lengths seen in the simulated sequence distribution of figure 5.2.

Sequence Distributions:

Length	STY	MALAN
1	920	959
2	37	0
3	2	0
41	0	1

Here the two monomers enter into the copolymer in equimolar amounts in a non random, alternating arrangement along the copolymer chain. This tendency towards alternation increases as $r_1 \times r_2 \rightarrow 0$, and perfect alternation will occur when $r_1 \times r_2 = 0$. From the above simulation in figure 5.1, we see that

the overall sequence distribution is very good, except for the small residue of Maleic Anhydride at the end of the polymerisation.

(iii) When $r_1>1$ & $r_2<1$. We may illustrate this case by considering the following example of AN : DEFM :: 50 : 50(where An = Acrylonitrile and DEFM = Diethyl Fumarate), with $r_1 = 10.0$ and $r_2 = 0.10$, respectively. Figure 5.3, below, shows the computer simulated sequence distribution for this copolymer. Table 5.3 shows the sequence lengths seen in figure 5.3 :

Figure 5.3 : Computer simulated sequence distribution of a AN : DEFM :: 50 : 50 copolymer.

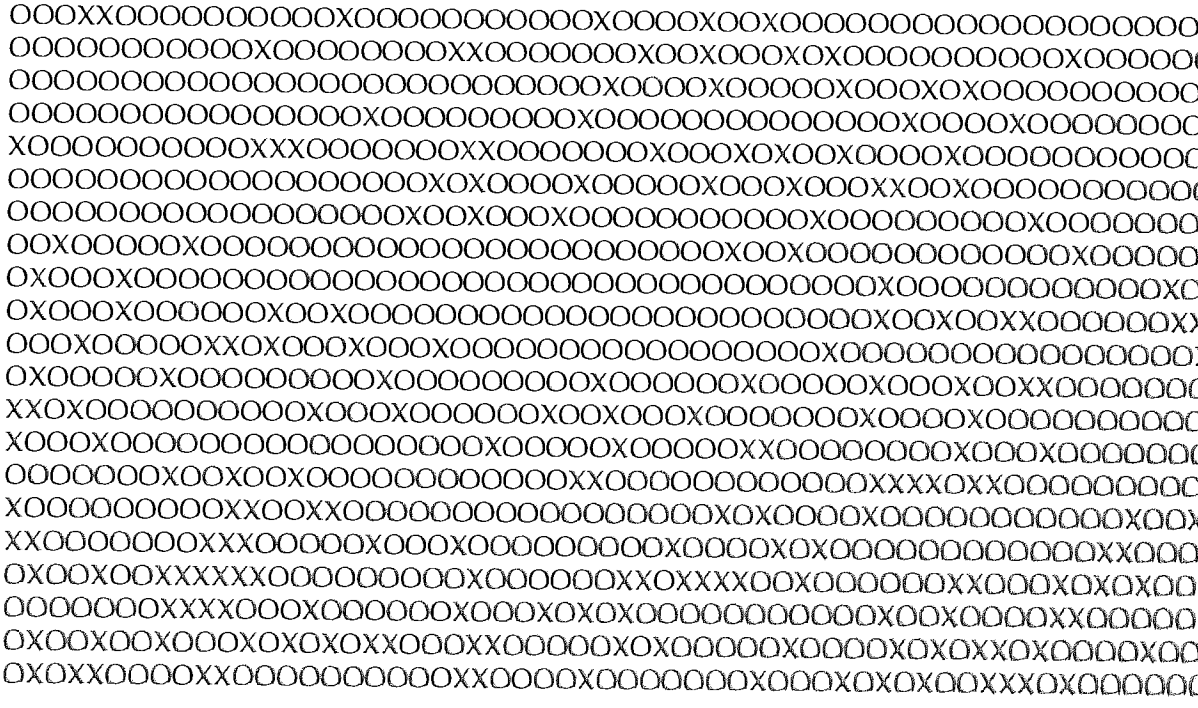
50 Mole % of Monomer A, AN

50 Mole % of Monomer B, DEFM

r(AB) = 10.0 r(BA) = 0.10

Polymerized to 100% Conversion

In the simulated terpolymer AN is represented by O, DEFM is represented by X :



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The simulated copolymer contains 1000 AN units and 1000 DEFM units.

Table 5.3 : Sequence lengths seen in the simulated sequence distribution of figure 5.3

Sequence Distributions:

Length	AN	DEFM
1	39	130
2	30	29
3	26	7
4	14	5
5	11	0
6	10	2
7	7	1
8	3	1
9	10	0
10	6	0
11	4	0
12	5	2
14	2	0
16	1	0
17	3	1
24	2	0
26	1	0
29	1	0
30	1	0
33	1	0
34	1	0
703	0	1

Here, again, we may note that $r_1 \times r_2 = 1$, therefore we have the situation of ideal copolymerisation. But here the sequence distribution is totally different to that seen in figure 5.1. This is because the reactivity ratios of the two monomers are quite different, and consequently one of the monomers is more reactive than the other towards both propagating species. This leads to the monomer with the higher reactivity ratio being used up much earlier in the reaction, consequently leaving behind a large residue of the lesser reactive monomer. This will subsequently come in at the end as a large block.

Overall the sequence distribution seen is very poor (generally a large number of long individual monomer sequence lengths). The problem in these situations, as exemplified by the simulated sequence distribution in figure 5.3, is that it becomes progressively more difficult to produce copolymers containing appreciable amounts of both monomers as the difference in the reactivity ratios of the two monomers increases. Unfortunately, this situation tends to arise most frequently in free-radical copolymerisations.

(iv) When $r_1 < 1$ & $r_2 < 1$. We may illustrate this case by considering the following example of MMA : NVPY :: 50 : 50(where NVPY = N-vinyl Pyridine), with $r_1 = 0.40$ and $r_2 = 0.86$, respectively. Figure 5.4, below, shows the computer simulated sequence distribution for this copolymer. Table 5.4 shows the sequence lengths seen in figure 5.4 :

Figure 5.4 : Computer simulated sequence distribution of a MMA : NVPY :: 50 : 50 copolymer.

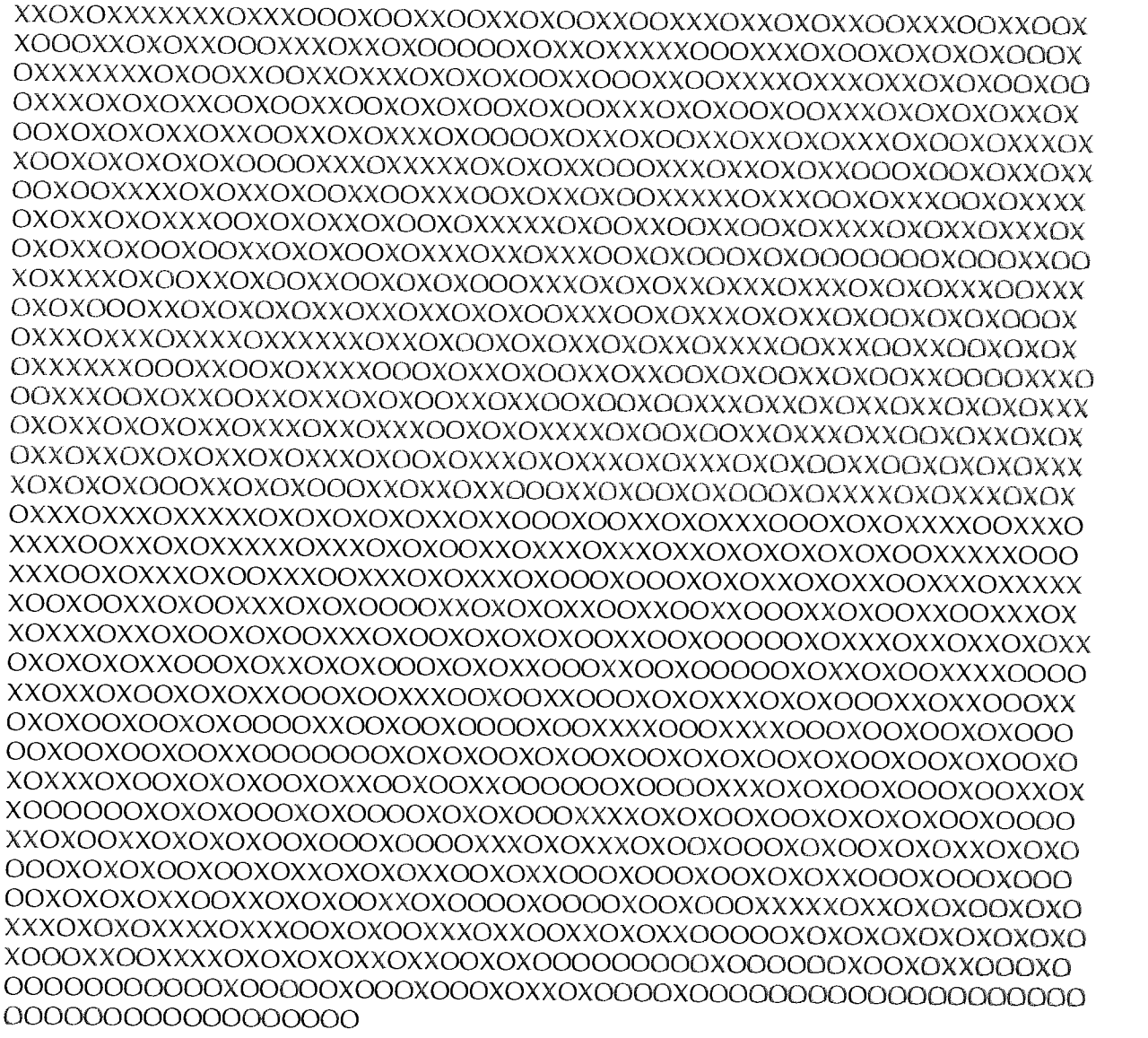
50 Mole % of Monomer A, MMA

50 Mole % of Monomer B, NVPY

r(AB) = 1.020 r(BA) = 0.990

Polymerized to 100% Conversion

In the simulated terpolymer MMA is represented by O, NVPY is represented by X :



The simulated copolymer contains 1000 MMA units and 1000 NVPY units.

Table 5.4: Sequence lengths seen in the simulated sequence distribution of figure 5.4.

Sequence Distributions:

Length	MMA	NVPY
1	374	353
2	145	143
3	50	71
4	15	19
5	7	8
6	3	3
7	2	2
9	1	0
12	1	0
38	1	0

Here $r_1 \times r_2 < 1$, thus we are moving away from the ideal type of behaviour, and there is an increasing tendency towards alternation. Both monomers prefer cross-propagation but to differing degrees. In the simulated sequence distribution, shown in figure 5.4, we have a small residue of the slightly less reactive MMA at the end. The overall the sequence distribution seen is reasonably good, but it does contain some long individual monomer sequence lengths, which prevent this sequence distribution from becoming a really good one.

5.2 Designing Polymers with Improved Sequence Distributions

In section 5.2, we saw the influence of monomer reactivity ratios on the sequence distribution of the synthesized polymer, with concentrations held equal. Figures 5.1-5.4 illustrate that the shortest individual monomer sequences

seen are when both r_1 and r_2 tend towards zero, i.e., when $r_1 \approx r_2 \approx 0$. This is followed by figure 5.1, where both r_1 and r_2 tend towards one, i.e., $r_1 \approx r_2 \approx 1$ and figure 5.4 where $r_1 < 1$ and $r_2 < 1$, here the difference between the reactivity ratios becomes very important. A large difference between the reactivity ratios will result in a faster rate of consumption of one monomer with respect to the other monomer. This will manifest itself in the sequence distributions seen. We will tend to see a poor sequence distribution with long, extended individual monomer sequences, and a large block of the residual lesser reactive monomer coming in at the end of the polymerisation. This exemplified by figure 5.3. Infuriatingly, this latter example tends to be more representative of real situations, than any of the other three cases. Thus normally the monomers selected for their biological and/or physical properties, which are required in the synthesized biomaterial for a particular biological environment, tend to produce, upon polymerisation, a very poor sequence distribution. This may be seen in the contact lens formulations given in chapter 3.

Utilising the information gained from figures 5.1-5.4, we can develop the necessary approach for designing polymers with controlled sequence distributions. We may illustrate this hypothetically by attempting to modify the very poor sequence distribution seen in figure 5.3. We will simulate the sequence distribution seen upon the polymerisation of the two monomers, in figure 5.3, in the presence of a third monomer to produce a terpolymer with a much improved sequence distribution. It can be seen from figure 5.3 that there are two main problems here, firstly we must try to reduce the range of monomer sequence lengths seen from 1 to 34, to a much narrower range with overall shorter monomer sequence lengths; and, secondly we must try to reduce the large block of 703 monomer units of residual diethyl fumarate

(DEFM), that is present at the end of the polymerisation. Bearing in mind the sequence distributions seen in figures 5.1-5.4, we see that there are two possible criteria for choosing the third monomer: firstly the third monomer chosen may be such that it has low reactivity ratios with both monomers and *vice versa*, such that we have a tendency towards alternation, i.e., $r_{13} < 0$, $r_{23} < 0$, $r_{31} < 0$, $r_{32} < 0$, and $r_{13} \approx r_{31} \approx 0$ and $r_{23} \approx r_{32} \approx 0$(where r_{31} and r_{32} represents the reactivity ratios of the third monomer with respect to monomers one and two). In our present situation with the two monomers being acrylonitrile (AN) and DEFM (in figure 5.3), we may choose the third monomer as styrene (STY). The simulated sequence distribution seen upon the polymerisation of these three monomers is shown below in figure 5.5:

Figure 5.5 : Computer simulated sequence distribution of a AN : DEFM : STY :: 33 : 33 : 34 terpolymer.

33 Mole % of Monomer A, AN

33 Mole % of Monomer B, DEFM

34 Mole % of Monomer C, STY

r(AB) = 10 r(AC) = 0.15 r(BA) = 0.100

r(BC) = 0.394 r(CA) = 0.330 r(CB) = 0.110

Polymerized to 100% Conversion

In the simulated terpolymer AN is represented by O, DEFM is represented by X and STY is represented by ©:

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The simulated terpolymer contains 660 AN units, 660 DEFM units and 680 STY units.

Table 5.5 : Sequence lengths seen in the simulated sequence distribution of figure 5.5.

Sequence Distributions:

Length	AN	DEFM	STY
1	475	459	574
2	64	47	41
3	15	7	8
4	3	2	0
78	0	1	0

The sequence distribution seen above in figure 5.5 is a vast improvement upon that seen in figure 5.3. We have a small residue of DEFM, but this is negligible compared to the large residue seen in figure 5.3.

The second criterion for choosing the third monomer would again involve the third monomer to have low reactivity ratios with the least reactive monomer, here DEFM, i.e., $r_{23} < 0$, $r_{32} < 0$, and $r_{23} \approx r_{32} \approx 0$, thus again giving us a tendency towards alternation between these two monomers. We see from figure 5.3, that to improve the simulated sequence distribution, this tendency towards alternation between the chosen third monomer and the least reactive monomer is an important and necessary factor, in both criteria, because it will lead to the break up of the large residual block of the least reactive monomer, seen at the end of the polymerisation. In this criterion the third monomer would show a similar reactivity towards the most reactive monomer(here, Acrylonitrile, AN), as does the least reactive monomer (here, Diethyl fumarate, DEFM). The affect of this third monomer would be to preferentially copolymerize with the least reactive monomer, with respect to the most reactive monomer. In such a situation a monomer that has reactivity ratios that reflect the above mentioned behaviour, may be Vinyl chloride (it is known that Vinyl chloride, VC, is a gas at room temperature, it is used here purely to illustrate the above described approach). The simulated sequence distribution seen upon the polymerisation of these three monomers is shown below in figure 5.6:

Figure 5.6 : Computer simulated sequence distribution of a AN : DEFM : VC :: 33 : 33 : 34 terpolymer.

33 Mole % of Monomer A, AN

33 Mole % of Monomer B, DEFM

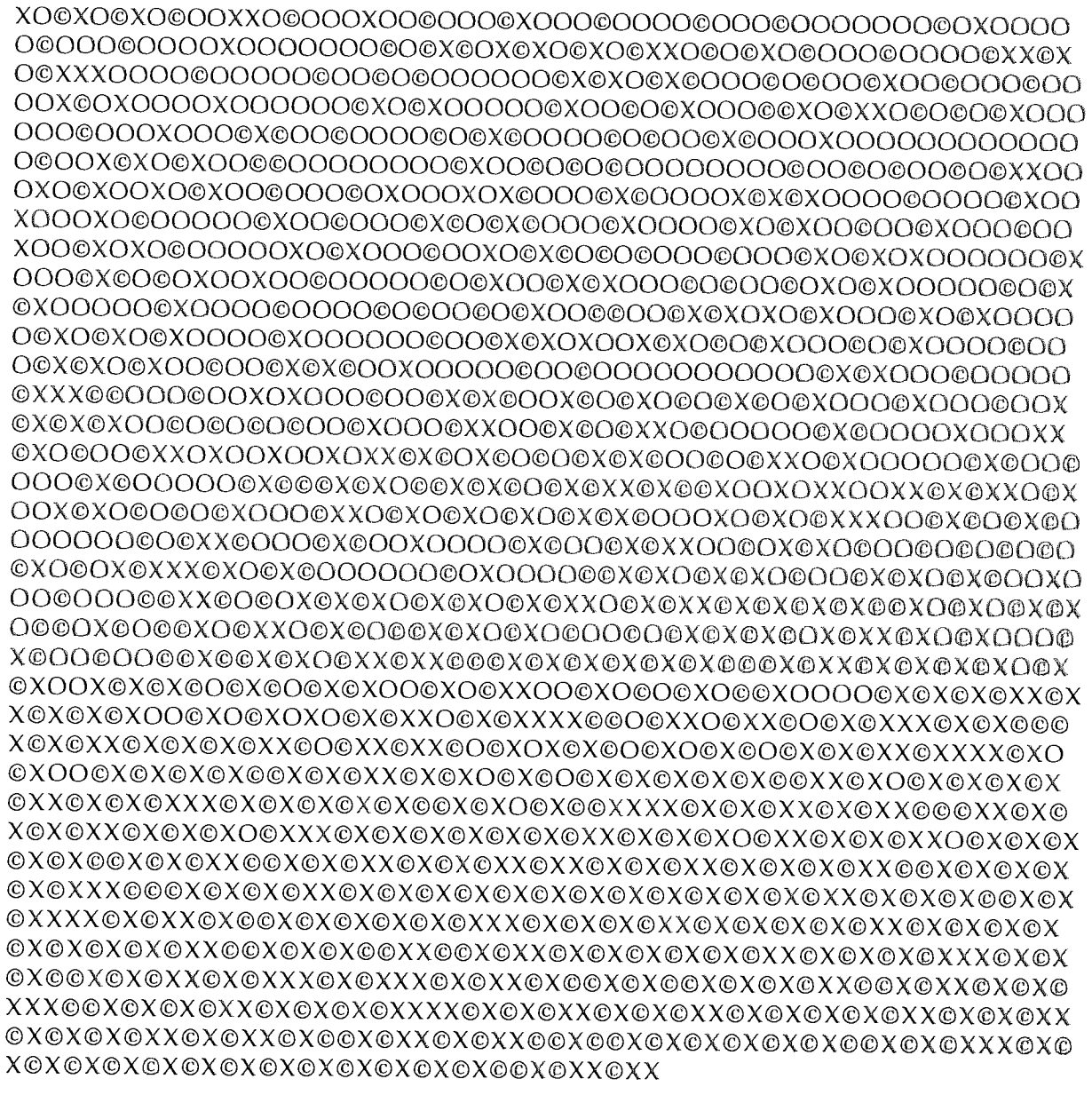
34 Mole % of Monomer B, VC

r(AB) = 10 r(AC) = 2.55 r(BA) = 0.100

r(BC) = 0.300 r(CA) = 0.070 r(CB) = 0.130

Polymerized to 100% Conversion

In the simulated terpolymer AN is represented by O, DEFM is represented by X and VC is represented by O:



The simulated copolymer contains 660 AN units, 660 DEFM units and 680 VC units.

Table 5.6 : Sequence lengths seen in the simulated sequence distribution of figure 5.6.

Sequence Distributions:

Length	AN	DEFM	VC
1	157	444	586
2	65	77	38
3	42	14	6
4	20	5	0
5	14	0	0
6	6	0	0
7	3	0	0
8	2	0	0
11	1	0	0
13	1	0	0

Here in figure 5.6 we again see a vast improvement upon the sequence distribution seen in figure 5.3. It can be seen, in figure 5.6, that we have eliminated the large residual block of DEFM present in the simulated sequence distribution seen in figure 5.3, the largest individual monomer sequence length here is of thirteen units. There is a difference in the distribution of the three monomer units throughout the simulated sequence distributions seen in figures 5.5 and 5.6. In figure 5.5 we can see that the three monomer units are fairly homogeneously distributed throughout the simulated sequence distribution. In contrast, in figure 5.6, we see that the most reactive monomer is consumed in the first 60% of the overall conversion, and we are left with a near enough alternating copolymer of the remaining two monomer units. This still overall produces a terpolymer with a fairly good sequence distribution, and in contrast to figure 5.5 there is no residual block of any monomer unit at the end of the polymerisation. Thus both approaches produce polymers with relatively good sequence distributions, although the first criterion produces the most homogeneous distribution of individual monomer units.

5.3 Summary

The examples given in this chapter serve to illustrate the basic patterns seen in the sequence distributions of polymers with various extremes of reactivity ratios. Also, an approach has been described whereby the judicious introduction of another monomer, may be utilised to improve a bad or relatively poor sequence distribution, into one that is relatively quite good. This same process will be used in chapter 6 to design biopolymers, containing predominantly hydrophilic monomers, with relatively good sequence distributions of individual monomer units.

CHAPTER SIX

CELL ADHESION STUDIES ON POLYMERS WITH CONTROLLED SEQUENCE DISTRIBUTIONS

6.0 Cell Adhesion Studies on Polymers with Controlled Sequence Distributions

The design of biologically responsive polymers with controlled sequence distributions requires: first and foremost a thorough understanding of the factors which control the sequence distributions seen upon polymerisation to form the polymer; and, secondly with this information we can then incorporate certain monomers into the polymerisation reaction, to form polymers with controlled sequence distributions, whilst being endowed with biologically responsive properties.

From the previous chapter, it can be seen that the main factors which govern the sequence distribution of a polymer are, the concentration of the monomers and their reactivity ratios. Since the concentrations are easily varied this is usually not a problem in helping to achieve a certain sequence distribution. But the reactivity ratios are not easily varied. In fact they are specific for a particular pair of monomers, since they are inherently dependent on the chemical functionality of the monomers concerned. Thus we cannot easily alter this, as the main reason a particular monomer is chosen is for its chemical properties. In chapter 5, we have illustrated an approach in which the judicious introduction of a third monomer may be used to produce an enhanced sequence distribution, for a pair of monomers, which would normally on polymerisation produce a very poor sequence distribution(long, extended sequences of individual monomer units).

The reason why reactivity ratios are such a problem in designing polymers with controlled sequence distributions, lies firstly in their fundamental

definition, i.e. they are specific for a particular pair of monomers; and secondly, when one starts to define the required properties of the synthesized polymer we inevitably start to limit ourselves to the range of monomers (and consequently the range of reactivity ratios available) that may be used to produce the required polymer. For example, if we wanted to design a new biomaterial, which must firstly have a high water content, therefore requiring hydrophilic monomers; secondly if the surface is to be charged then this may be achieved through the use of monomers that contain ionisable groups or monomers containing permanent charges, such as the zwitterionic monomers. Although it is necessary to take into account these factors when designing the new biomaterial. They inadvertently set limitations on the range of reactivity ratios available, through the limited number of monomers that will contain the desired properties.

In this chapter we will be concerned with the design of biomaterials consisting predominantly of hydrophilic monomers, thereby having high equilibrium water contents, polymerised and cross-linked as a membrane (by the procedure described in section 2.22). These membranes will also contain a certain amount of monomers with specific biomimetic/biologically responsive functional groups. Above all, these materials will be designed with a good sequence distribution as the prime criterion.

As previously mentioned, the size of the hydrophobic and hydrophilic domains, illustrated by the various sequence lengths, tends to affect the susceptibility of the surface of these materials to serum proteins. The larger these individual domains are, the more likely it is that the surface will be prone to protein adhesion. Hydrophobic domains tend to be more susceptible

to deposition of cell adhesion proteins, and hence the larger these domains are the more likely it is that they will deposit cell adhesion proteins, such as vitronectin and fibronectin. This consequently leads to greater amounts of cell adhesion. Since it is known that, generally cells will only adhere to surfaces likely to deposit proteins. Thus cell adhesion studies may be used to assess the level of biocompatibility or biotolerance of these materials in order to ascertain their potential use as biomaterials.

6.1 Cell Adhesion Analysis on Membranes Polymerized to 100% Conversion

In this section we will firstly consider the affect of a single type of polar group, e.g., the hydroxyl group of HEMA or the nitrogenous groups of NVP and NVI, in combination with relatively hydrophobic monomers, e.g., MMA, EMA and STY, upon cell adhesion with respect to the sequence distribution of individual monomer units in the synthesized polymeric membrane. We will subsequently investigate the affect of different cross-linkers upon cell adhesion and how this relates to the sequence distribution of individual monomer units in the cross-linked membrane. Finally we will consider the affect of cell adhesion on high Equilibrium Water Content (EWC) membranes which have relatively good sequence distributions, whilst containing various functional/biomimetic monomer units. The % cell adhesion was calculated relative to tissue culture plastic (TCP), which was arbitrarily chosen as being 100% cell adhesive. The last column in all of the following column charts depicts the % cell adhesion and EWC for polyHEMA, which is known to be relatively non-adhesive to cells.

6.11 HEMA/MMA/EMA Membranes

Figure 6.11 shows the % cell adhesion and % EWC for membranes of HEMA/MMA/EMA with the compositions as shown in table 6.11.

Figure 6.11 : HEMA/MMA/EMA Membranes

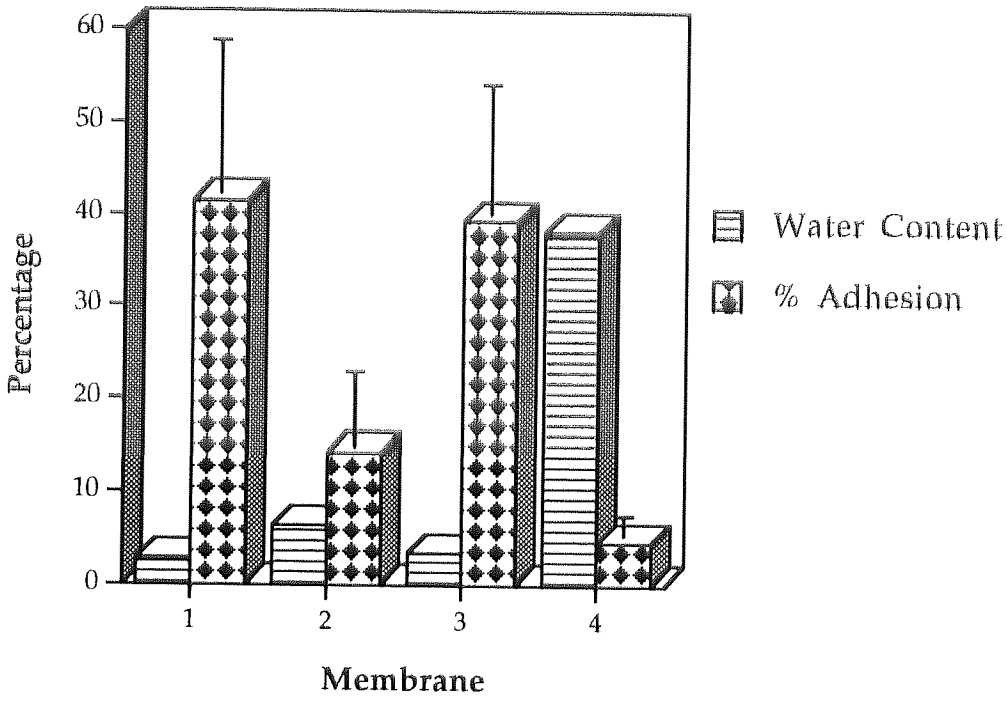


Table 6.11 : Data for Figure 6.11

No.	Composition	% Water Content	% Cell Adhesion
1	HEMA:MMA:EMA 33:33:34	2.8	41.5
2	HEMA:MMA:EMA 40:30:30	6.3	14.2
3	HEMA:MMA:EMA 30:40:30	3.3	39.3
4,9,13	PolyHEMA	38.0	4.5
17,21	25,30,35		

In figure 6.11 we see that, generally, as the EWC increases, the % cell adhesion decreases. In terms of sequence distribution, from figures 6.12 to 6.14, we see that membrane No. 1 has a relatively poor sequence distribution compared to membranes 2 and 3, which both have similar and relatively good sequence distributions. Thus here it appears that cell adhesion is governed mainly by the EWC, although it is interesting to see a membrane, such as No. 2, with such a low EWC (only 6.3%) having a relatively low amount of cell adhesion, yet containing highly polar monomers.

Figure 6.12 : Computer simulated sequence distribution of a HEMA : MMA : EMA :: 33 : 33 : 34 terpolymer.

33 Mole % of Monomer A, HEMA

33 Mole % of Monomer B, MMA

34 Mole % of Monomer C, EMA

r(AB) = 0.81 r(AC) = 1.882 r(BA) = 0.192

r(BC) = 0.936 r(CA) = 0.388 r(CB) = 1.013

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and EMA is represented by © :

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The simulated terpolymer contains 660 HEMA units, 660 MMA units and 680 EMA units.

Table 6.12 : Sequence lengths seen in the simulated sequence distribution of figure 6.12.

Sequence Distributions:

Length	HEMA	MMA	EMA
1	343	414	218
2	96	85	84
3	25	13	33
4	10	6	28
5	2	0	4
6	0	1	2
7	0	1	1
11	0	0	1
16	0	0	1
17	0	0	1

Figure 6.13 : Computer simulated sequence distribution of a HEMA : MMA : EMA :: 40 : 30 : 30 terpolymer.

40 Mole % of Monomer A, HEMA

30 Mole % of Monomer B, MMA

30 Mole % of Monomer C, EMA

r(AB) = 0.81 r(AC) = 1.882 r(BA) = 0.192

r(BC) = 0.936 r(CA) = 0.388 r(CB) = 1.013

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and EMA is represented by © :

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The simulated terpolymer contains 800 HEMA units, 600 MMA units and 600 EMA units.

Table 6.13 : Sequence lengths seen in the simulated sequence distribution of figure 6.13.

Sequence Distributions:

Length	HEMA	MMA	EMA
1	345	418	245
2	115	65	80
3	42	16	24
4	17	1	9
5	2	0	6
6	1	0	6
7	1	0	3
8	1	0	0

Figure 6.14 : Computer simulated sequence distribution of a HEMA : MMA : EMA :: 30 : 40 : 30 terpolymer.

30 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, MMA

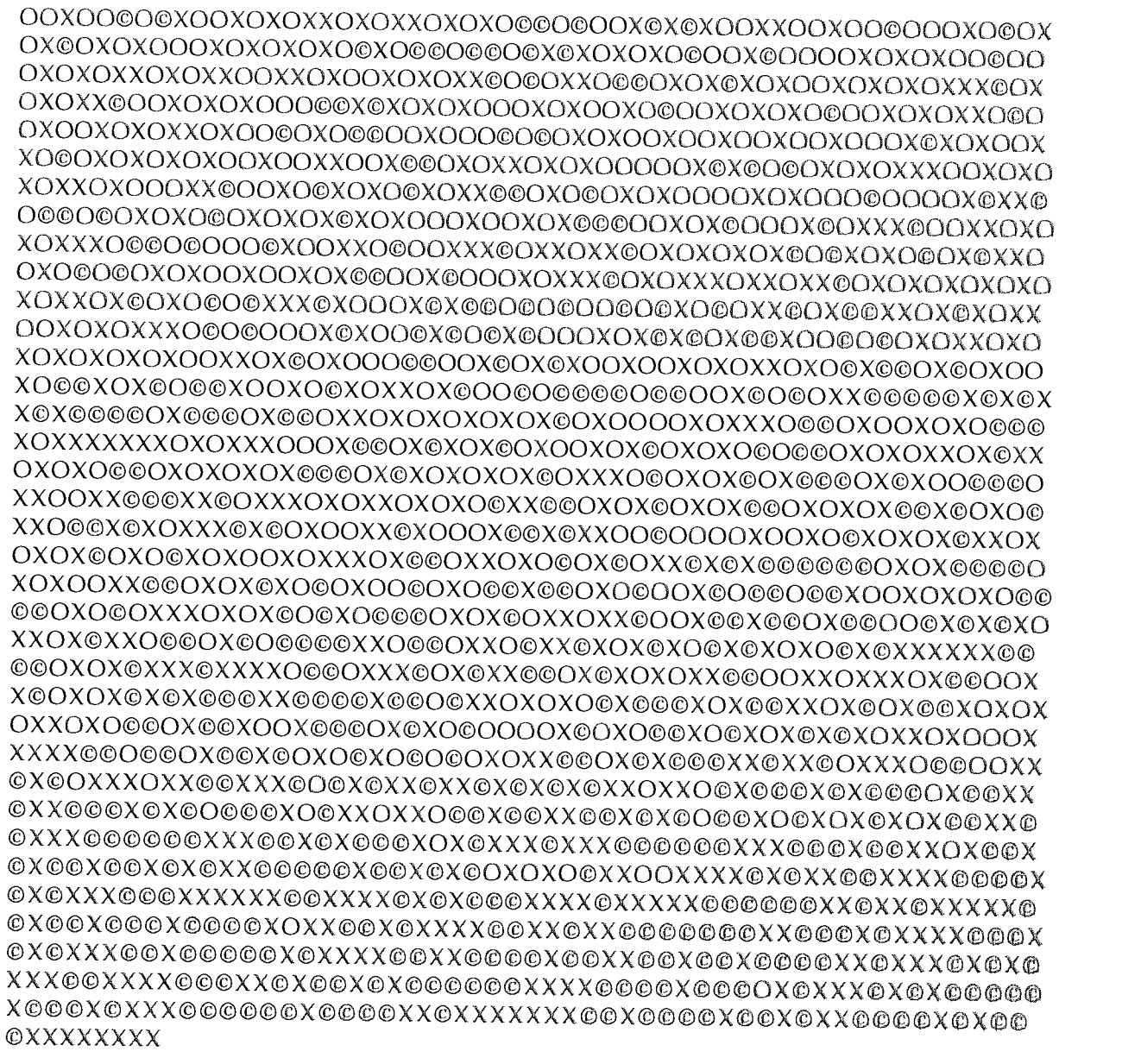
30 Mole % of Monomer C, EMA

r(AB) = 0.81 r(AC) = 1.882 r(BA) = 0.192

r(BC) = 0.936 r(CA) = 0.388 r(CB) = 1.013

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and EMA is represented by © :



The simulated terpolymer contains 600 HEMA units, 800 MMA units and 600 EMA units.

Table 6.14 : Sequence lengths seen in the simulated sequence distribution of figure 6.14.

Sequence Distributions:

Length	HEMA	MMA	EMA
1	371	418	228
2	70	97	84
3	20	33	27
4	6	10	15
5	1	3	4
6	0	2	6
7	0	2	1
8	0	1	0

From the above figures we can see that all these membranes are relatively adhesive to cells. But we see that the least adhesive membrane is the one that has the highest EWC and the shortest sequence lengths, that is membrane No. 2 represented by figure 6.13. The shorter sequences of hydrophobic and hydrophilic domains at the surface of these membranes reduces the amount of interaction that can occur with serum proteins, thus reducing the possibility of significant deposition of these proteins, which is usually followed by lower amounts of cell adhesion. This probably explains the reason why membrane No. 2 produces the lowest amount of cell adhesion.

6.12 HEMA/MMA/STY Membranes

Figure 6.15, below, shows the % cell adhesion and % EWC for membranes of HEMA/MMA/EMA with the compositions as shown in table 6.15.

Figure 6.15 : HEMA/MMA/STY Membranes

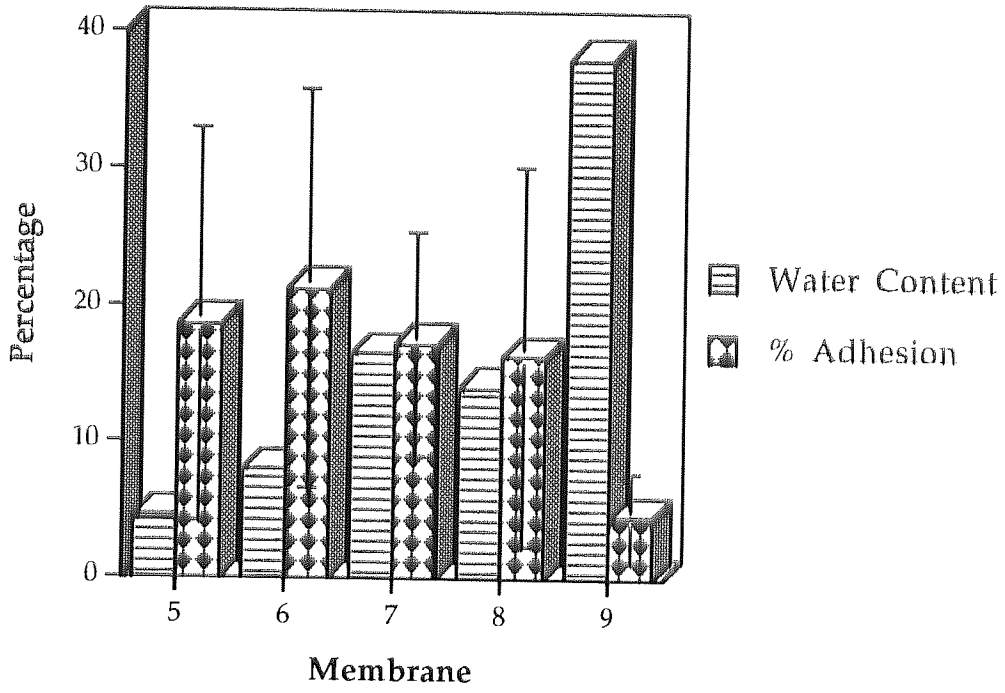


Table 6.15 : Data for Figure 6.15

No.	Composition	% Water Content	% Cell Adhesion
5	HEMA:MMA:STY 33:34:33	4.5	18.6
6	HEMA:MMA:STY 50:25:25	7.9	21.2
7	HEMA:MMA:STY 60:10:30	16.5	17.2
8	HEMA:MMA:STY 60:30:10	14.0	16.3

In figure 6.15 we see that there is no real correlation between the EWC and % cell adhesion for this set of membranes. But from figures 6.16 to 6.19 we see that

there is some correlation with the sequence distribution of the monomer units. It can be seen that an increase in the EWC from 4.5% to 7.9%, for membranes 5 and 6, actually produces slightly more cell adhesion for the membrane containing the higher EWC. In contrast from figures 6.16 and 6.17 (also tables 6.16 and 6.17) we see that membrane No. 5 has a slightly better sequence distribution when compared to membrane No. 6. Comparing membranes 7 and 8, we again see that the membrane with the slightly higher EWC (No. 7) produces slightly more cell adhesion. But from the simulated sequence distributions shown in figures 6.18 and 6.19, we see that membrane No. 7 which produces slightly more cell adhesion and yet has a higher EWC, has a relatively poor sequence distribution when compared to membrane No. 8. In comparison with membrane No. 9, which represents PolyHEMA, we see that this series of membranes are significantly more cell adhesive than PolyHEMA. In this series of membranes it appears that the sequence distribution of the individual monomer units within the polymer does have some affect upon the subsequent cell adhesiveness of the polymers.

Figure 6.16 : Computer simulated sequence distribution of a HEMA : MMA : STY :: 33 : 34 : 33 terpolymer.

33 Mole % of Monomer A, HEMA

34 Mole % of Monomer B, MMA

33 Mole % of Monomer C, STY

r(AB) = 0.81 r(AC) = 1.65 r(BA) = 0.192

r(BC) = 0.418 r(CA) = 0.500 r(CB) = 0.49

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and STY is represented by © :

The simulated terpolymer contains 660 HEMA units, 680 MMA units and 660 STY units.

Table 6.16 : Sequence lengths seen in the simulated sequence distribution of figure 6.16.

Sequence Distributions:

Length	HEMA	MMA	STY
1	369	532	339
2	71	57	84
3	22	6	32
4	9	4	4
5	7	0	2
6	2	0	2
9	0	0	1
10	0	0	1

Figure 6.17 : Computer simulated sequence distribution of a HEMA : MMA : STY :: 50 : 25 : 25 terpolymer.

50 Mole % of Monomer A, HEMA

25 Mole % of Monomer B, MMA

25 Mole % of Monomer C, STY

r(AB) = 0.81 r(AC) = 1.65 r(BA) = 0.192

r(BC) = 0.418 r(CA) = 0.500 r(CB) = 0.49

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and STY is represented by © :

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The simulated terpolymer contains 1000 HEMA units, 500 MMA units and 500 STY units.

Table 6.17 : Sequence lengths seen in the simulated sequence distribution of figure 6.17.

Sequence Distributions:

Length	HEMA	MMA	STY
1	300	424	276
2	136	32	71
3	55	4	17
4	30	4	17
5	11	0	1
6	9	0	0
7	1	0	0
8	1	0	0
9	1	0	0
10	1	0	1

Figure 6.18 : Computer simulated sequence distribution of a HEMA : MMA : STY :: 60 : 10 : 30 terpolymer.

60 Mole % of Monomer A, HEMA

10 Mole % of Monomer B, MMA

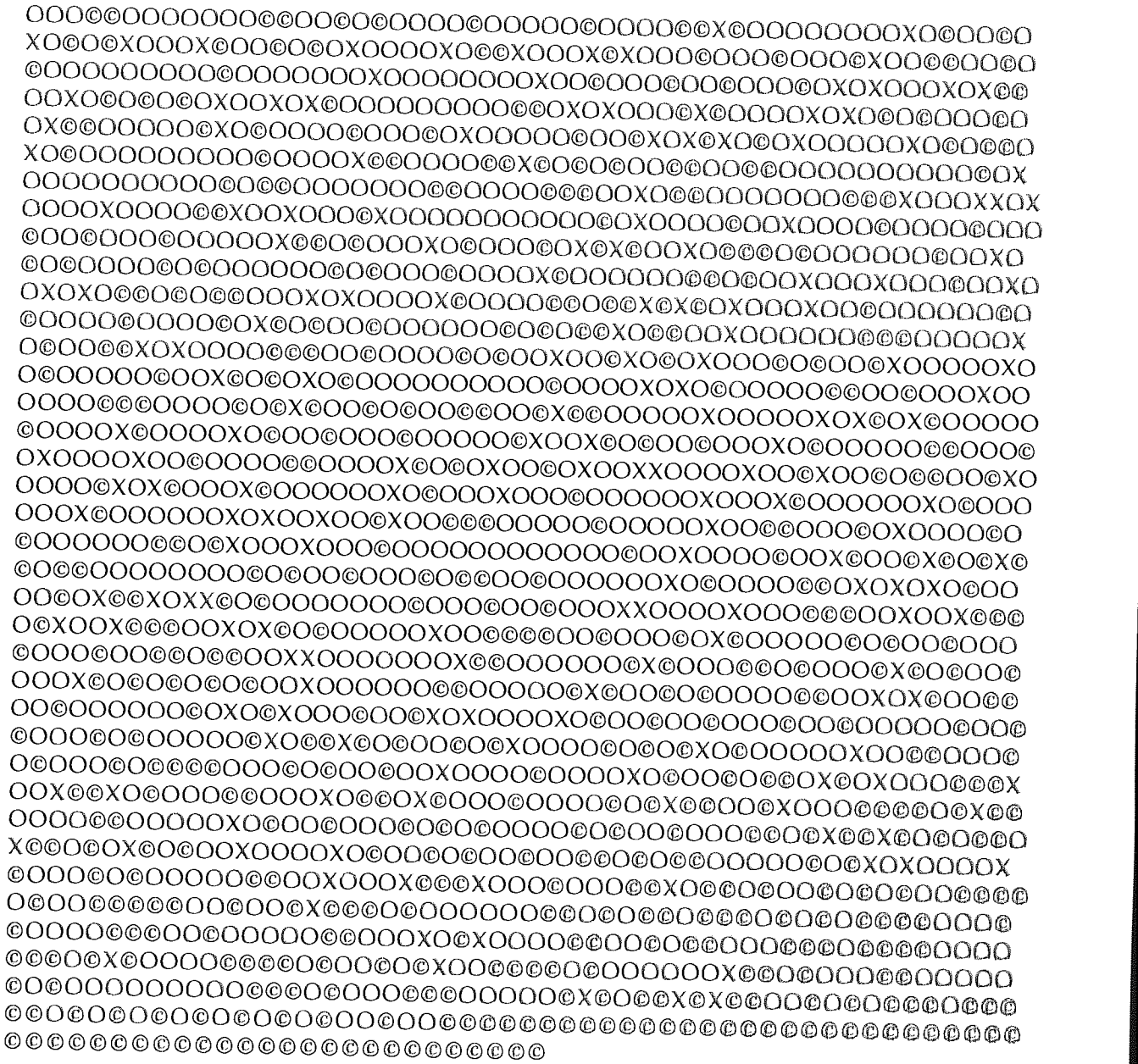
30 Mole % of Monomer C, STY

r(AB) = 0.81 r(AC) = 1.65 r(BA) = 0.192

r(BC) = 0.418 r(CA) = 0.500 r(CB) = 0.49

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and STY is represented by © :



The simulated terpolymer contains 1200 HEMA units, 200 MMA units and 600 STY units.

Table 6.18 : Sequence lengths seen in the simulated sequence distribution of figure 6.18.

Sequence Distributions:

Length	HEMA	MMA	STY
1	191	190	293
2	101	5	75
3	67	0	20
4	48	0	8
5	29	0	2
6	19	0	0
7	6	0	0
8	3	0	0
9	4	0	0
10	3	0	0
11	1	0	0
12	1	0	0
55	0	0	1

Figure 6.19 : Computer simulated sequence distribution of a HEMA : MMA : STY :: 60 : 30 : 10 terpolymer.

60 Mole % of Monomer A, HEMA

30 Mole % of Monomer B, MMA

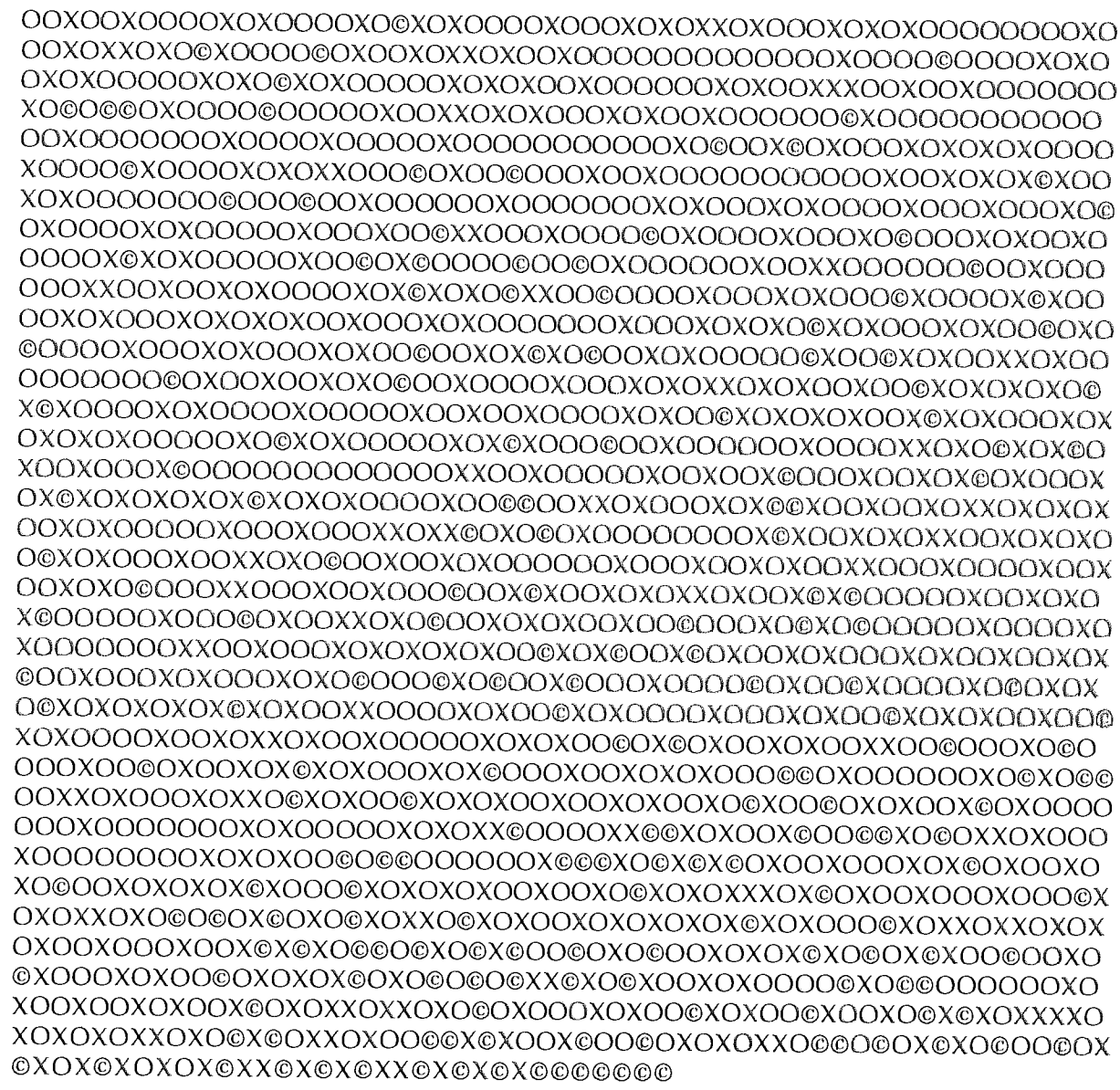
10 Mole % of Monomer C, STY

r(AB) = 0.81 r(AC) = 1.65 r(BA) = 0.192

r(BC) = 0.418 r(CA) = 0.500 r(CB) = 0.49

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, MMA is represented by X and STY is represented by © :



The simulated terpolymer contains 1200 HEMA units, 600 MMA units and 200 STY units.

Table 6.19 : Sequence lengths seen in the simulated sequence distribution of figure 6.19.

Sequence Distributions:

Length	HEMA	MMA	STY
1	303	502	166
2	130	44	12
3	61	2	1
4	37	1	0
5	18	0	0
6	11	0	0
7	8	0	1
8	3	0	0
9	1	0	0
11	2	0	0
13	3	0	0

The above figures again illustrate the relationship between the size of the sequence lengths seen and the amount of cell adhesion that occurs. We note that membranes No. 5 and No. 8, although here not having the highest EWC's, do display the shortest average sequence lengths, thus providing the smallest possible domains for interaction with serum proteins, which probably results in the proteins not adhering in very major quantities thus producing reasonable but not excessive levels of cell adhesion. It may be noted that these membranes are generally more adhesive than polyHEMA.

6.13 NVP/MMA/NVI Membranes

Figure 6.20, below, shows the % cell adhesion and % EWC for membranes of NVP/MMA/NVI with the compositions as shown in table 6.20.

Figure 6.20 : NVP/MMA/NVI Membranes

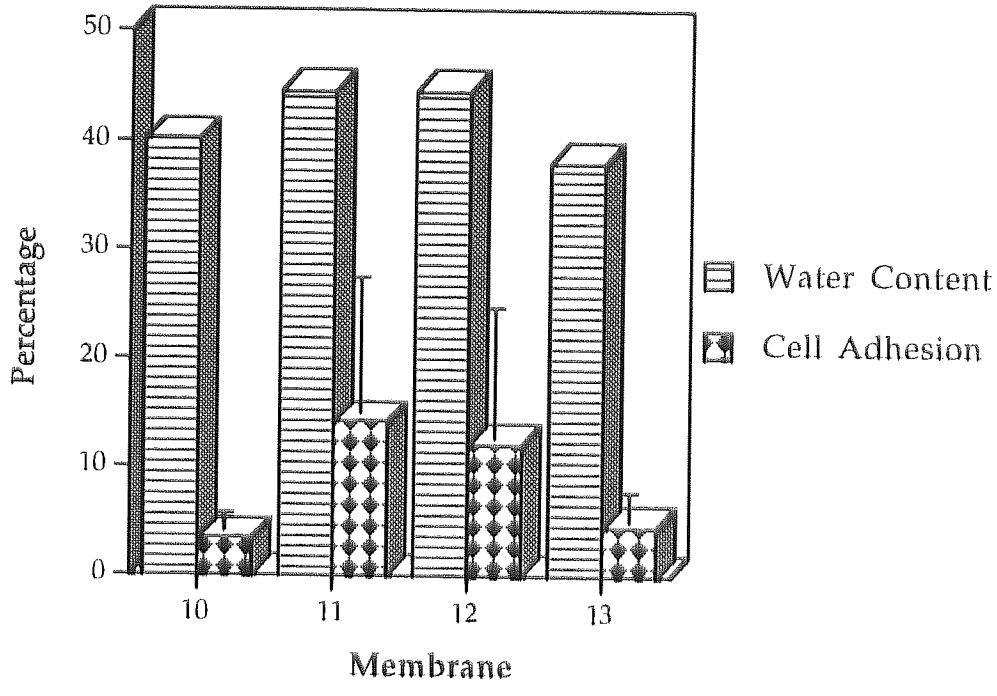


Table 6.20 : Data for Figure 6.20

No.	Composition	% Water Content	% Cell Adhesion
10	NVP:MMA:NVI 33:33:34	40.2	3.4
11	NVP:MMA:NVI 30:40:30	44.5	14.2
12	NVP:MMA:NVI 20:35:45	44.5	12.0

From figure 6.20 we see that there is no real correlation between the EWC and the % cell adhesion. In fact the membrane with the lowest EWC has the lowest % cell adhesion. From figures 6.21 to 6.23 we see that all of these membranes

containing nitrogenous groups have relatively poor sequence distributions. The membrane with the worst sequence distribution (No. 10) has the lowest % cell adhesion. This is an anomalous situation since this particular membrane also has the lowest EWC. In comparing membranes No. 11 and No. 12 we see that their EWC are equal but membrane No. 12 produces slightly less cell adhesion. This is in spite of containing a much higher % of NVI which is positively charged in an aqueous environment and since cells generally have an overall negative charge it would be expected that membrane No. 12 would deposit more cells than membrane No. 11. From considering figures 6.22 and 6.23, which illustrate the simulated sequence distributions of these membranes, we see that membrane No. 12 has a slightly better sequence distribution relative to membrane No. 11. Therefore, it appears that in these latter two membranes the relative sequence distribution has been the differentiating factor in the % cell adhesion that occurs on these membranes. It is interesting to note here that previously it has been found that polymers containing NVP tend to be fairly adhesive to cells up to 60% EWC after which they produce generally non-adhesive (to cells) materials. We see in membrane No. 10 a material that produces a relatively low amount of cell adhesion with an EWC of only 40.2%. Figure 6.24 will demonstrate this general trend found for NVP copolymers.

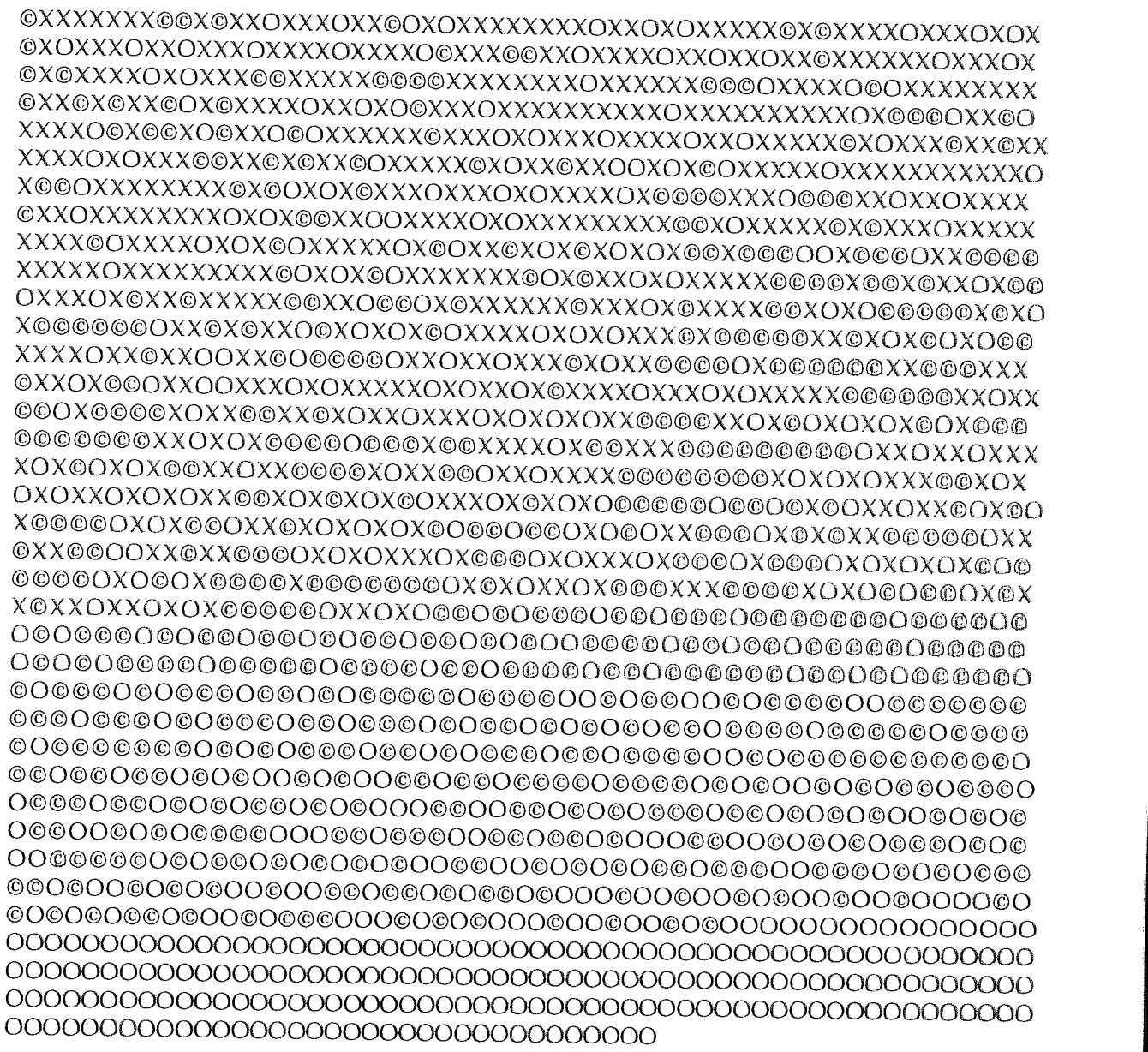
Figure 6.21 : Computer simulated sequence distribution of a NVP : MMA : NVI :: 33 : 33 : 34 terpolymer.

33 Mole % of Monomer A, NVP
33 Mole % of Monomer B, MMA
34 Mole % of Monomer C, NVI

r(AB) = 0.01	r(AC) = 0.174	r(BA) = 4.04
r(BC) = 4.603	r(CA) = 2.368	r(CB) = 0.67

Polymerized to 100% Conversion

In the simulated terpolymer NVP is represented by O, MMA is represented by X and NVI is represented by © :



The simulated terpolymer contains 660 NVP units, 660 MMA units and 680 NVI units.

Table 6.21 : Sequence lengths seen in the simulated sequence distribution of figure 6.21.

Sequence Distributions:

Length	NVP	MMA	NVI
1	354	144	177
2	34	72	71
3	6	30	31
4	1	20	25
5	0	12	15
6	0	5	4
7	0	2	3
8	0	5	1
9	0	3	1
10	0	2	2
11	0	1	1
216	1	0	0

Figure 6.22 : Computer simulated sequence distribution of a NVP : MMA : NVI :: 30 : 40 : 30 terpolymer.

30 Mole % of Monomer A, NVP

40 Mole % of Monomer B, MMA

30 Mole % of Monomer C, NVI

r(AB) = 0.01 r(AC) = 0.174 r(BA) = 4.04

r(BC) = 4.603 r(CA) = 2.368 r(CB) = 0.67

Polymerized to 100% Conversion

In the simulated terpolymer NVP is represented by O, MMA is represented by X and NVI is represented by © :

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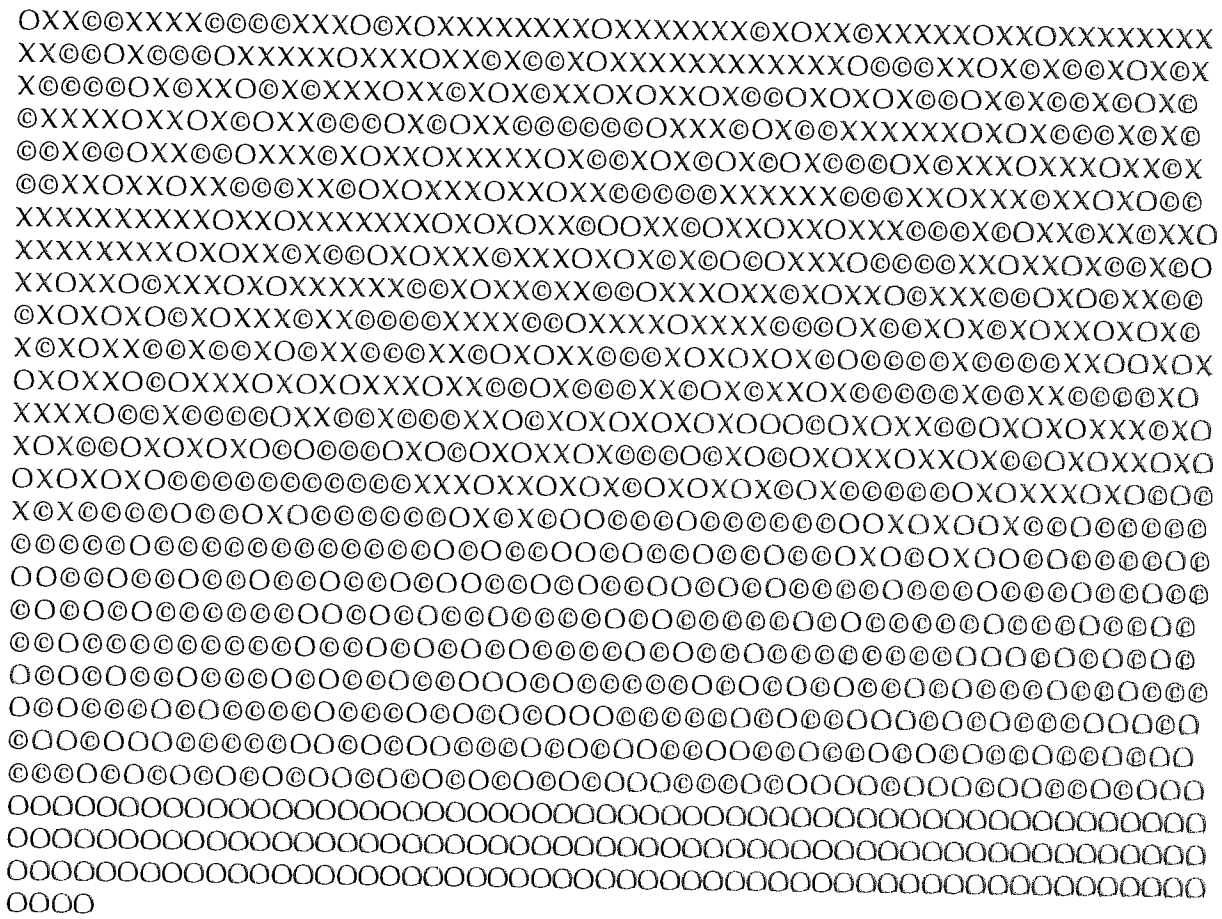

The simulated terpolymer contains 600 NVP units, 800 MMA units and 600 NVI units.

Table 6.22 : Sequence lengths seen in the simulated sequence distribution of figure 6.22.

Sequence Distributions:

Length	NVP	MMA	NVI
1	355	174	156
2	21	78	72
3	9	40	39
4	1	21	16
5	0	7	9
6	0	10	4
7	0	7	0
8	0	3	1
9	0	3	1
10	0	2	1

11	0	0	1
12	0	3	1
15	0	1	0
172	1	0	0

Figure 6.23 : Computer simulated sequence distribution of a NVP : MMA : NVI :: 20 : 35 : 45 terpolymer.

20 Mole % of Monomer A, NVP

35 Mole % of Monomer B, MMA

45 Mole % of Monomer C, NVI

r(AB) = 0.01 r(AC) = 0.174 r(BA) = 4.04

r(BC) = 4.603 r(CA) = 2.368 r(CB) = 0.67

Polymerized to 100% Conversion

In the simulated terpolymer NVP is represented by O, MMA is represented by X and NVI is represented by © :

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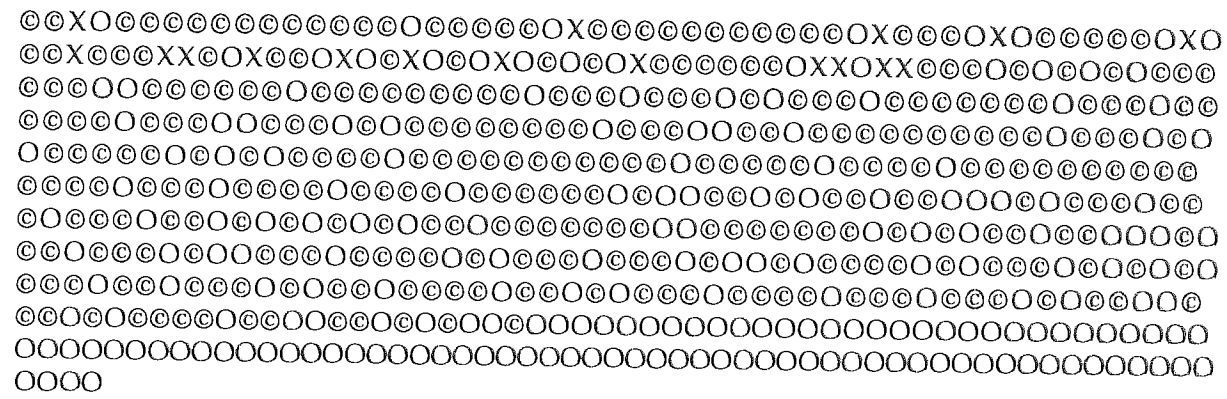


The simulated terpolymer contains 400 NVP units, 700 MMA units and 900 NVI units.

Table 6.23 : Sequence lengths seen in the simulated sequence distribution of figure 6.23.

Sequence Distributions:

Length	NVP	MMA	NVI
1	277	145	127
2	14	77	70
3	2	42	58
4	0	20	27
5	0	9	15
6	0	6	14
7	0	3	5
8	0	2	5
9	0	2	3
10	0	1	3
11	0	1	2
12	0	2	2
14	0	1	1
89	1	0	0

In the above figures we observe that all the membranes have relatively poor sequence distributions, i.e., produce relatively long sequence lengths. This coupled with the presence of a positively charged monomer (NVI), would suggest that we should observe a high degree of interaction of the surfaces of

these membranes with serum proteins, thus resulting in relatively large amounts of cell adhesion. But we have an anomalous situation here in that we observe only relatively moderate amounts of cell adhesion, and further we see that membrane No. 10, represented in figure 6.21, produces very little cell adhesion and yet has a moderate EWC.

6.14 HEMA/NVP Membranes

Figure 6.24, below, shows the % cell adhesion and % EWC for membranes of HEMA/NVP with the compositions as shown in table 6.24.

Figure 6.24 : HEMA/NVP Membranes

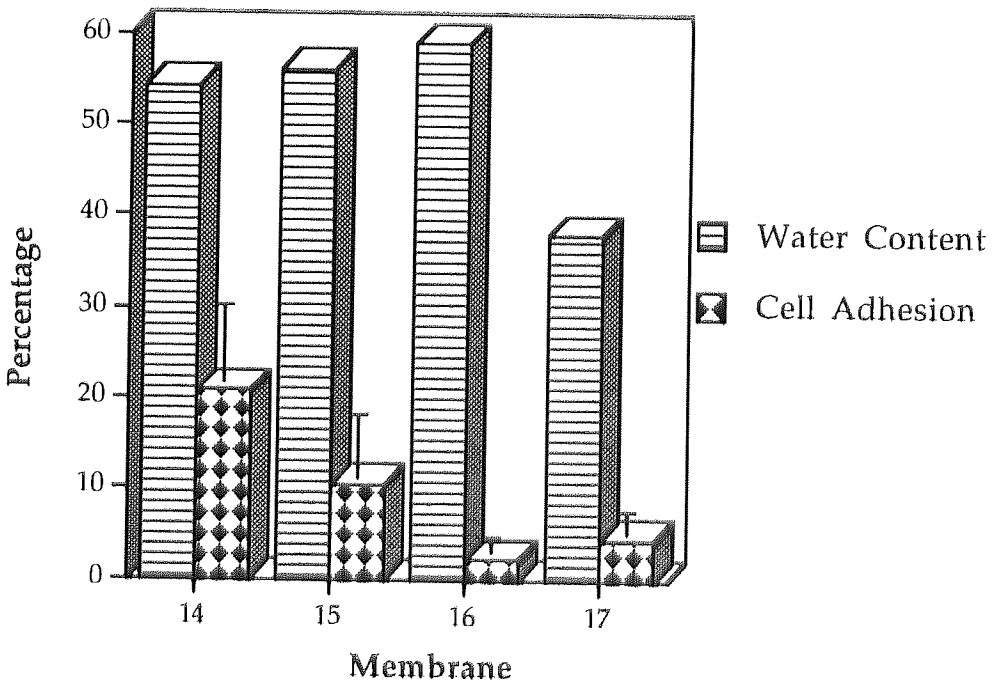


Table 6.24 : Data for Figure 6.24

No.	Composition	% Water Content	% Cell Adhesion
14	HEMA:NVP 60:40	54.3	20.9
15	HEMA:NVP 55:45	56.1	10.5
16	HEMA:NVP 50:50	58.9	2.3

Work previously done in these laboratories has demonstrated the affect of EWC on the cell adhesive properties of HEMA/NVP membranes[11]. It has been demonstrated that as the EWC approaches 60% the cell adhesiveness of these type of materials decreases rapidly, and such materials with over 60% EWC are essentially non-adhesive to cells. Figure 6.24 adequately illustrates this point, and from figures 6.25 to 6.27 which show the simulated sequence distributions of these membranes, we see that these membranes generally have poor sequence distributions of individual monomer units. In this situation the non-adhesive affect seems to be governed primarily by the EWC of these materials.

Figure 6.25 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 60 : 40.

60 Mole % of Monomer A, HEMA

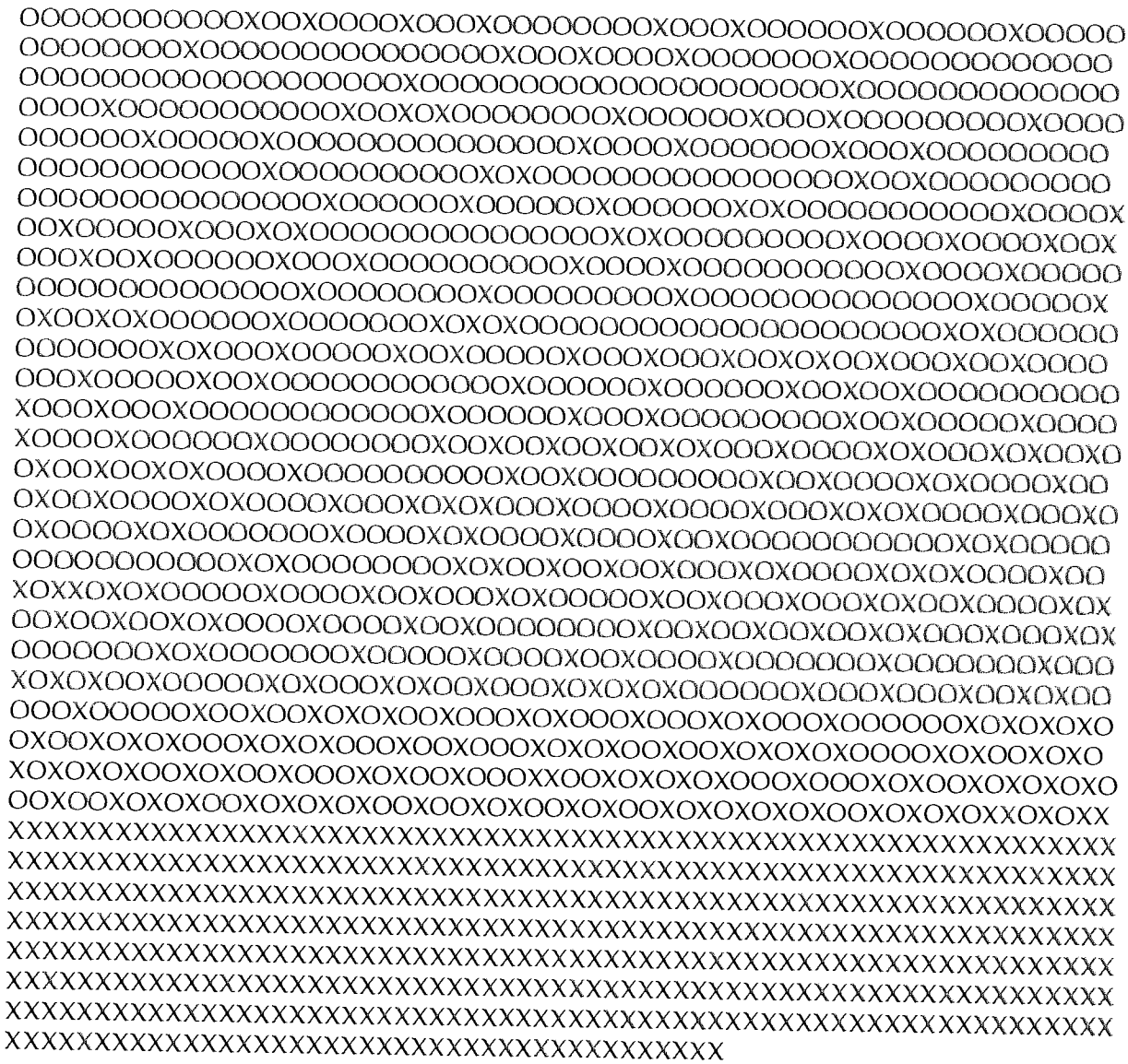
40 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :



The simulated copolymer contains 1200 HEMA units and 800 NVP units.

Table 6.25 : Sequence lengths seen in the simulated sequence distribution of figure 6.25.

Sequence Distributions:

Length	HEMA	NVP
1	95	310
2	68	3
3	45	0
4	32	0
5	13	0
6	14	0
7	9	0
8	6	0
9	5	0
10	5	0
11	5	0
12	2	0
13	2	0
14	1	0
15	3	0
16	2	0
17	1	0
19	1	0
21	3	0
24	1	0
32	1	0
484	0	1

Figure 6.26 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 55 : 45.

55 Mole % of Monomer A, HEMA

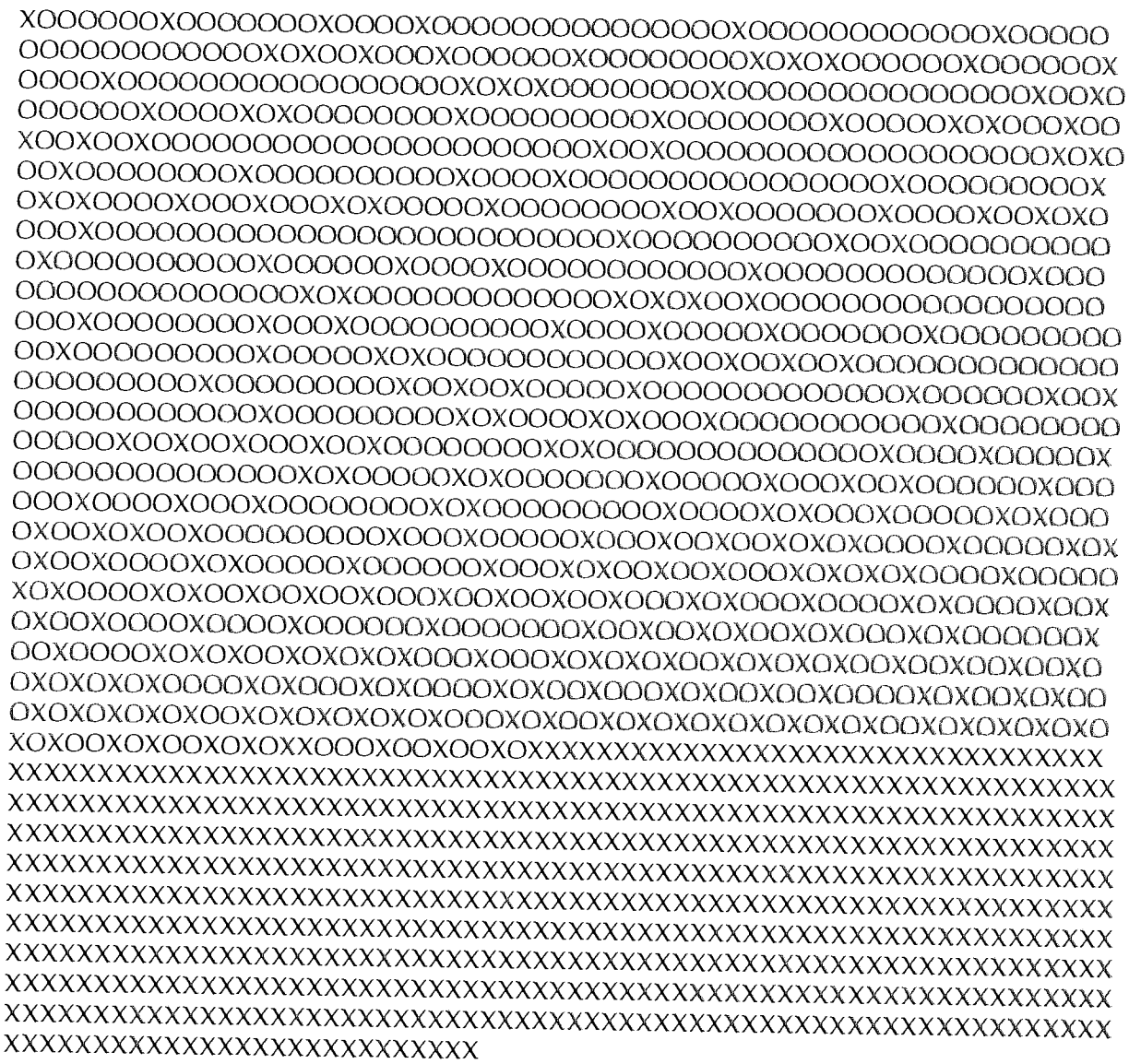
45 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :



The simulated copolymer contains 1100 HEMA units and 900 NVP units.

Table 6.26 : Sequence lengths seen in the simulated sequence distribution of figure 6.26.

Sequence Distributions:

Length	HEMA	NVP
1	89	271
2	57	1
3	26	0
4	26	0
5	13	0
6	11	0
7	6	0
8	9	0
9	7	0
10	4	0
11	3	0
12	4	0
13	4	0
14	2	0
15	2	0
16	1	0
17	1	0
19	1	0
20	1	0
22	2	0
26	1	0
627	0	1

Figure 6.27 : Computer simulated sequence distribution of a copolymer of HEMA : NVP :: 50 : 50.

50 Mole % of Monomer A, HEMA

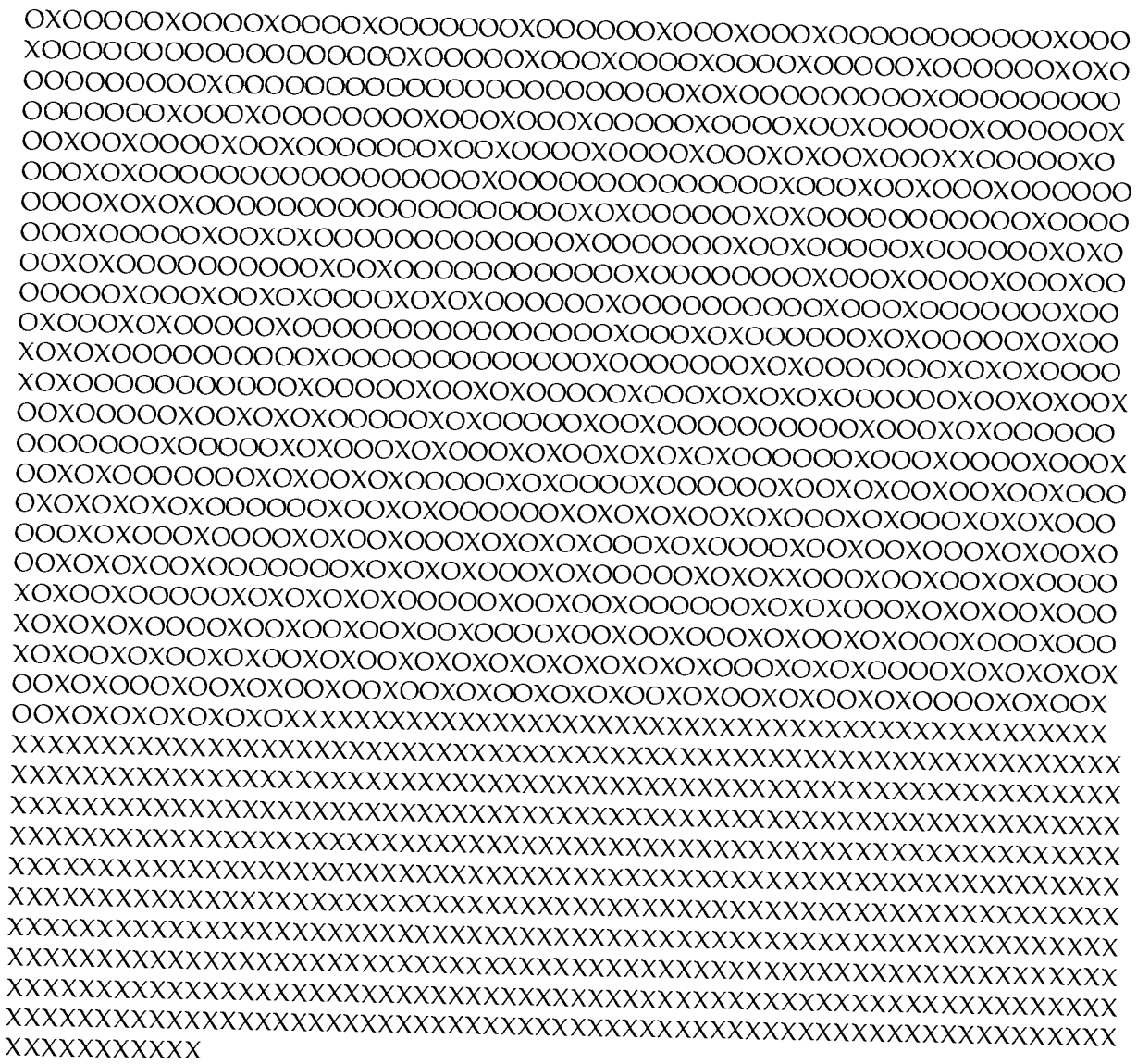
50 Mole % of Monomer B, NVP

r(AB) = 4.841

r(BA) = 0.001

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and NVP is represented by X :



The simulated copolymer contains 1000 HEMA units and 1000 NVP units.

Table 6.27 : Sequence lengths seen in the simulated sequence distribution of figure 6.27.

Sequence Distributions

Length	HEMA	NVP
1	120	308
2	60	2
3	42	0
4	22	0
5	20	0
6	14	0
7	10	0
8	2	0
9	1	0
10	6	0
11	3	0
12	1	0
13	3	0
14	1	0
16	2	0
17	1	0
18	1	0
19	1	0
23	1	0
688	0	1

From the above figures we observe that all the membranes produce relatively long average sequence lengths. Thus here the relatively low amounts of cell adhesion seen, can only be accounted for by changes in the EWC of these membranes.

6.15 HEMA/NVP/Cross-linker Membranes

Figure 6.28, below, shows the % cell adhesion and % EWC for membranes of HEMA/NVP/Cross-linker with the compositions as shown in table 6.28.

Figure 6.28 : HEMA/NVP/Cross-linker Membranes

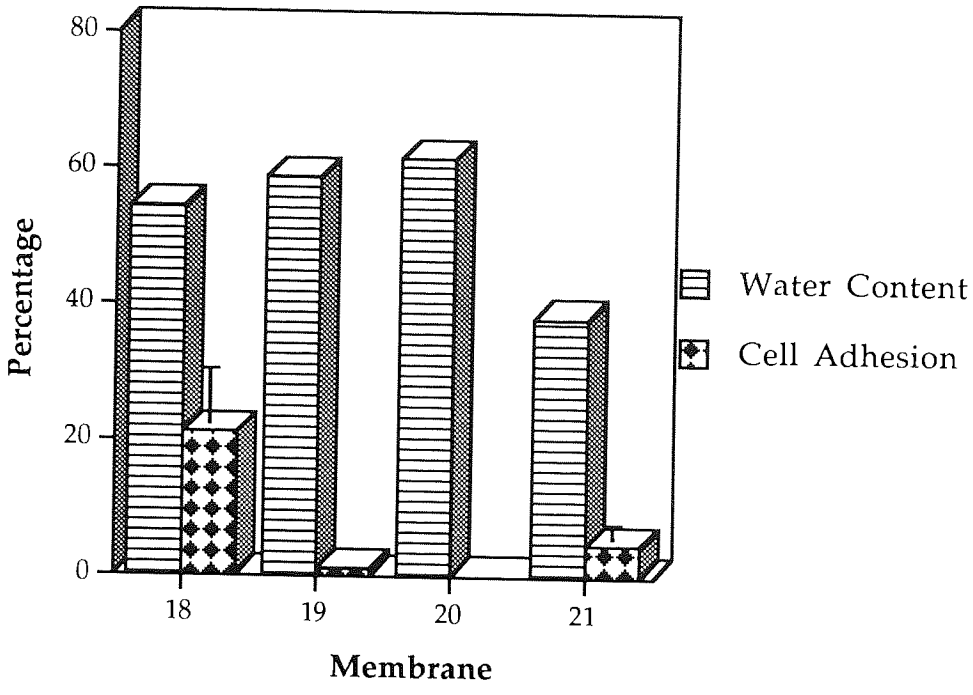


Table 6.28 : Data for Figure 6.28

No.	Composition	% Water Content	% Cell Adhesion
18	HEMA:NVP:EGDMA 59:40:1	54.3	20.9
19	HEMA:NVP:DATDAM 59:40:1	61.4	0
20	HEMA:NVP:TAC 59:40:1	58.5	1.0

From figure 6.28 we see a dramatic decrease in the % cell adhesion with different cross-linkers. The overall pattern is similar to that seen in the previous series of membranes, i.e., as the HEMA/NVP copolymers approach an EWC of 60% we see a rapid decrease in the amount of cell adhesion that occurs

on these materials. From figures 6.29 to 6.34, which show the simulated sequence distributions of these membranes, we see that EGDMA is the most reactive out of the three cross-linkers being studied. Thus it can be seen in figures 6.29 and 6.30, EGDMA tends to come in quite early on in the conversion with respect to the bulk amount of NVP. DATDAM, as seen in figures 6.31 and 6.32, is in contrast fairly unreactive and tends to remain towards the end of the reaction where it can seen that it has some affect upon the residual block of NVP. This breaking up of some of the residual block of the NVP present towards the end of the reaction probably accounts for the increased EWC seen for this membrane relative to the other two membranes. Thereby we produce a material with an EWC greater than 60%, and as seen in figure 6.28 this membrane is virtually non-adhesive to cells. TAC seems to be of an intermediate reactivity compared to EGDMA and DATDAM, in that the first bond tends to react fairly early on in the reaction but the second bond tends to exhibit a much reduced reactivity and appears to have some affect upon the residual NVP block seen at the end of the reaction (please see figures 6.33 and 6.34). This affect is not as pronounced as that seen for DATDAM and this is reflected in the slightly lower EWC seen for this membrane. But as can be seen in figure 6.28 this increased EWC is sufficient to still produce a material that is fairly non-adhesive to cells, even when compared to PolyHEMA (membrane N0. 21).

Figure 6.29 : Computer simulated sequence distribution of a HEMA : NVP : EGDMA :: 59 : 40 : 1 terpolymer.(Showing only the addition of the 1st bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

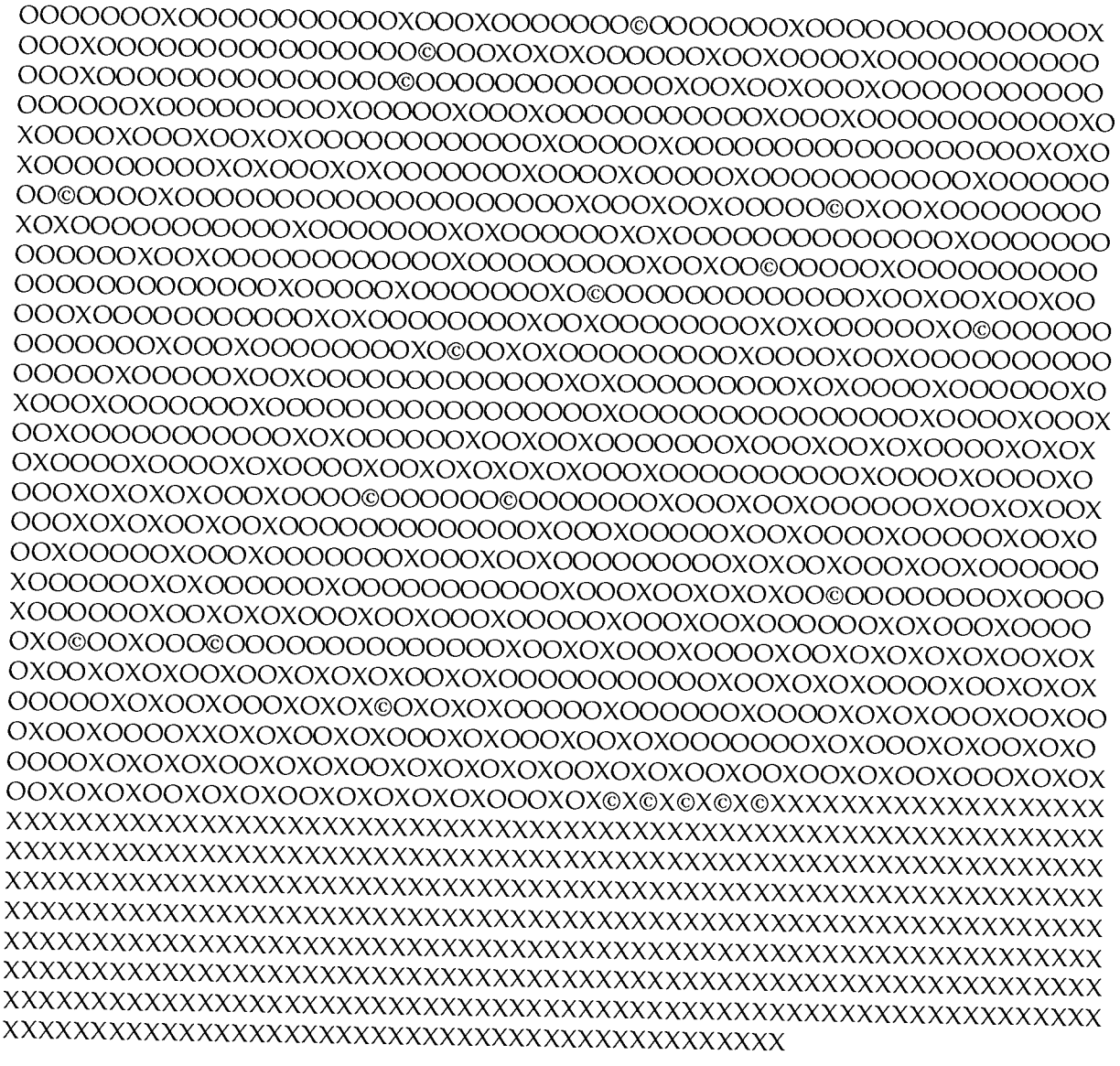
1 Mole % of Monomer C, EGDMA

r(AB) = 4.841 r(AC) = 1.882 r(BA) = 0.001

r(BC) = 0.006 r(CA) = 0.388 r(CB) = 6.37

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and EGDMA is represented by © :



The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 EGDMA units.

Table 6.29 : Sequence lengths seen in the simulated sequence distribution of figure 6.29.

Sequence Distributions:

Length	HEMA	NVP	EGDMA
1	101	293	20
2	62	1	0
3	37	0	0
4	21	0	0
5	16	0	0
6	13	0	0
7	11	0	0
8	6	0	0
9	6	0	0
10	1	0	0
11	9	0	0
12	2	0	0
13	6	0	0
14	4	0	0
15	3	0	0
16	1	0	0
17	2	0	0
18	1	0	0
20	1	0	0
23	1	0	0
505	0	1	0

Figure 6.30 : Computer simulated sequence distribution of a HEMA : NVP : EGDMA :: 59 : 40 : 1 terpolymer.(2nd bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

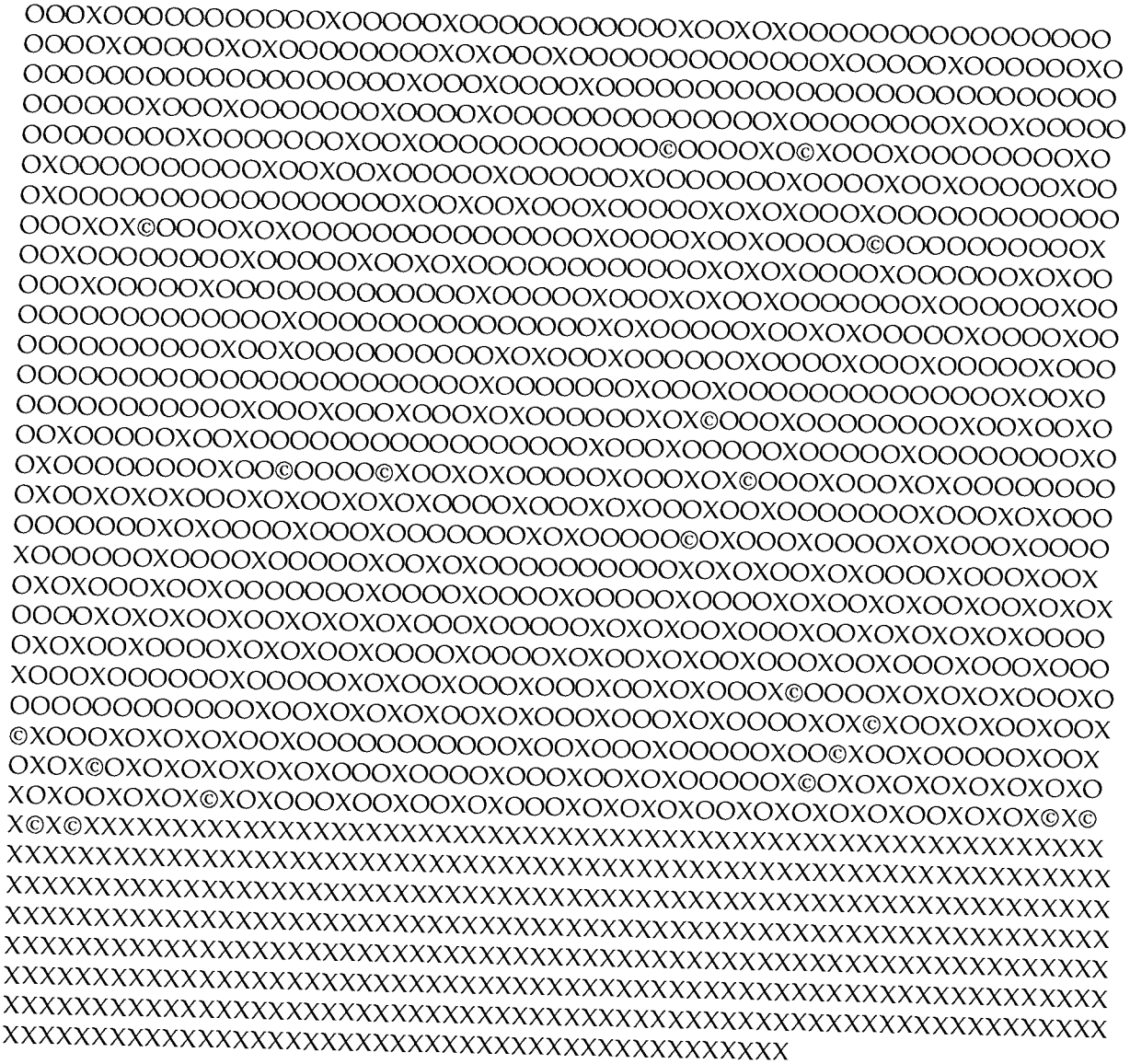
1 Mole % of Monomer C, EGDMA

r(AB) = 4.841 r(AC) = 2.834 r(BA) = 0.001

r(BC) = 0.002 r(CA) = 0.023 r(CB) = 0.099

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and EGDMA is represented by © :



The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 EGDMA units.

Table 6.30 : Sequence lengths seen in the simulated sequence distribution of figure 6.30.

Sequence Distributions:

Length	HEMA	NVP	EGDMA
1	104	319	20
2	59	0	0
3	49	0	0
4	26	0	0

5	27	0	0
6	8	0	0
7	8	0	0
8	7	0	0
9	1	0	0
10	5	0	0
11	3	0	0
12	4	0	0
13	4	0	0
14	2	0	0
15	4	0	0
17	2	0	0
20	2	0	0
26	1	0	0
32	1	0	0
481	0	1	0

Figure 6.31 : Computer simulated sequence distribution of a HEMA : NVP : DATDAM :: 59 : 40 : 1 terpolymer.(1st bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

1 Mole % of Monomer C, DATDAM

r(AB) = 4.841 r(AC) = 9.67 r(BA) = 0.001

r(BC) = 0.150 r(CA) = 0.065 r(CB) = 4.912

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and DATDAM is represented by © :

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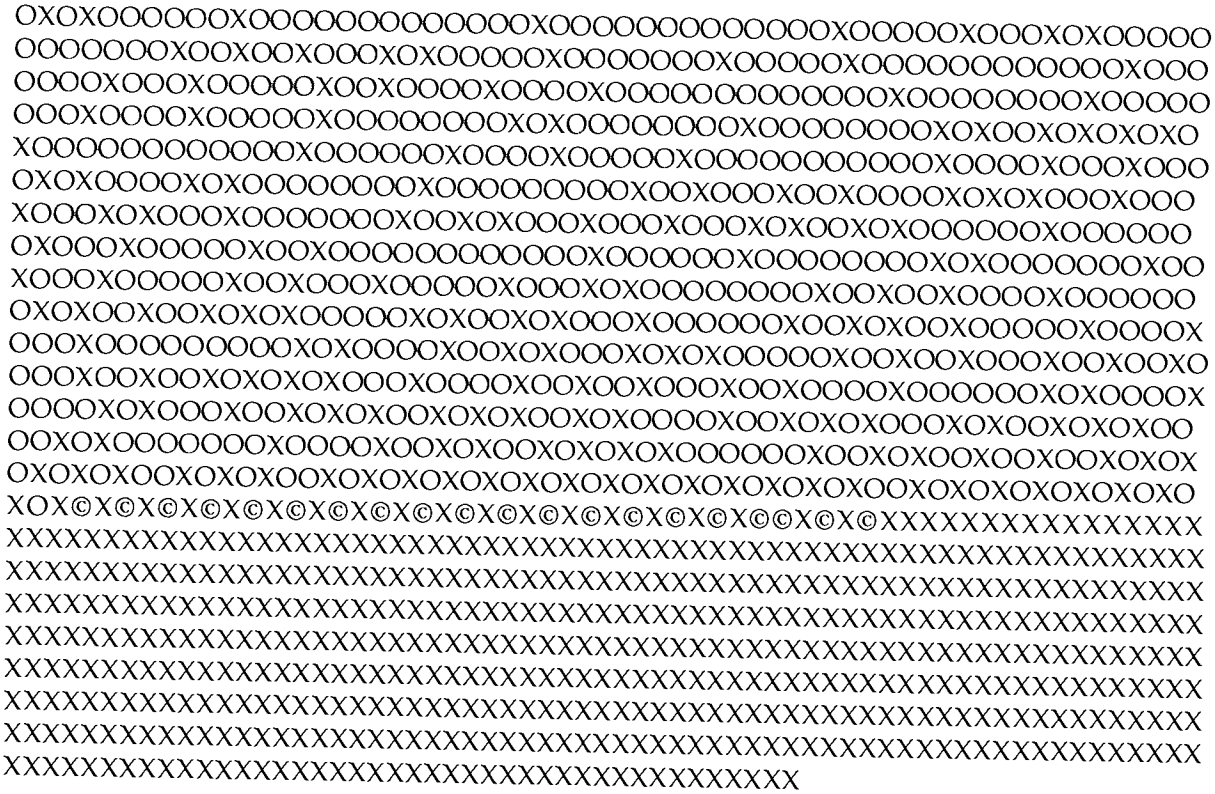

The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 DATDAM units.

Table 6.31 : Sequence lengths seen in the simulated sequence distribution of figure 6.31.

Sequence Distributions:

Length	HEMA	NVP	DATDAM
1	84	301	18
2	52	0	1
3	34	0	0
4	24	0	0
5	17	0	0
6	14	0	0
7	13	0	0
8	13	0	0

9	6	0	0
10	3	0	0
11	3	0	0
12	5	0	0
13	4	0	0
14	3	0	0
15	1	0	0
16	2	0	0
17	1	0	0
18	1	0	0
25	2	0	0
27	1	0	0
499	0	1	0

Figure 6.32 : Computer simulated sequence distribution of a HEMA : NVP : DATDAM :: 59 : 40 : 1 terpolymer.(2nd bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

1 Mole % of Monomer C, DATDAM

r(AB) = 4.841 r(AC) = 74.747 r(BA) = 0.001

r(BC) = 0.516 r(CA) = 0.013 r(CB) = 0.447

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and DATDAM is represented by © :

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The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 DATDAM units.

Table 6.32 : Sequence lengths seen in the simulated sequence distribution of figure 6.32.

Sequence Distributions:

Length	HEMA	NVP	DATDAM
1	97	297	20
2	42	1	0
3	39	0	0
4	14	0	0
5	23	0	0
6	9	0	0
7	6	0	0
8	7	0	0
9	6	0	0
10	6	0	0
11	5	0	0
12	5	0	0
13	5	0	0
14	3	0	0

15	4	0	0
16	1	0	0
17	1	0	0
23	1	0	0
24	1	0	0
25	2	0	0
33	1	0	0
501	0	1	0

Figure 6.33 : Computer simulated sequence distribution of a HEMA : NVP : TAC :: 59 : 40 : 1 terpolymer.(1st bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.841 r(AC) = 4.266 r(BA) = 0.001

r(BC) = 0.001 r(CA) = 0.001 r(CB) = 0.001

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and TAC is represented by © :

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The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 TAC units.

Table 6.33 : Sequence lengths seen in the simulated sequence distribution of figure 6.33.

Sequence Distributions:

Length	HEMA	NVP	TAC
1	101	303	20
2	50	1	0
3	48	0	0
4	15	0	0
5	17	0	0
6	13	0	0
7	12	0	0
8	8	0	0
9	3	0	0
10	7	0	0
11	4	0	0
12	5	0	0
13	2	0	0
18	4	0	0
19	2	0	0
21	1	0	0

22	1	0	0
24	1	0	0
26	1	0	0
34	1	0	0
495	0	1	0

Figure 6.34 : Computer simulated sequence distribution of a HEMA : NVP : TAC :: 59 : 40 : 1 terpolymer.(2nd bond)

59 Mole % of Monomer A, HEMA

40 Mole % of Monomer B, NVP

1 Mole % of Monomer C, TAC

r(AB) = 4.841 r(AC) = 47.78 r(BA) = 0.001

r(BC) = 0.264 r(CA) = 0.020 r(CB) = 0.547

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NVP is represented by X and TAC is represented by © :

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The simulated terpolymer contains 1180 HEMA units, 800 NVP units and 20 TAC units.

Table 6.34 : Sequence lengths seen in the simulated sequence distribution of figure 6.34.

Sequence Distributions:

Length	HEMA	NVP	TAC
1	84	30	18
2	52	3	1
3	34	0	0
4	33	0	0
5	23	0	0
6	12	0	0
7	12	0	0
8	12	0	0
9	5	0	0
10	6	0	0
11	8	0	0
13	2	0	0
14	1	0	0
15	2	0	0
17	1	0	0
18	2	0	0
23	1	0	0
24	1	0	0
28	1	0	0
490	0	1	0

From the above figures we observe how the sequence distribution of the main monomer units can have a significant affect upon the distribution of the cross-linker. In the above figures we see that the main monomers have quite different reactivity ratios, this is reflected in the varying simulated sequence distribution of monomer units with conversion. Thus here the distribution of the cross-linker will be significantly affected according to its reactivity, in relation to the reactivities of the main constituent monomers. The observed results indicate that the cell adhesion characteristics of these membranes are governed predominantly by the EWC.

6.16 NVP/NVI/SPE Membranes

Figure 6.35, below, shows the % cell adhesion and % EWC for membranes of NVP/NVI/SPE with the compositions as shown in table 6.35.

Figure 6.35 : NVP/NVI/SPE Membranes

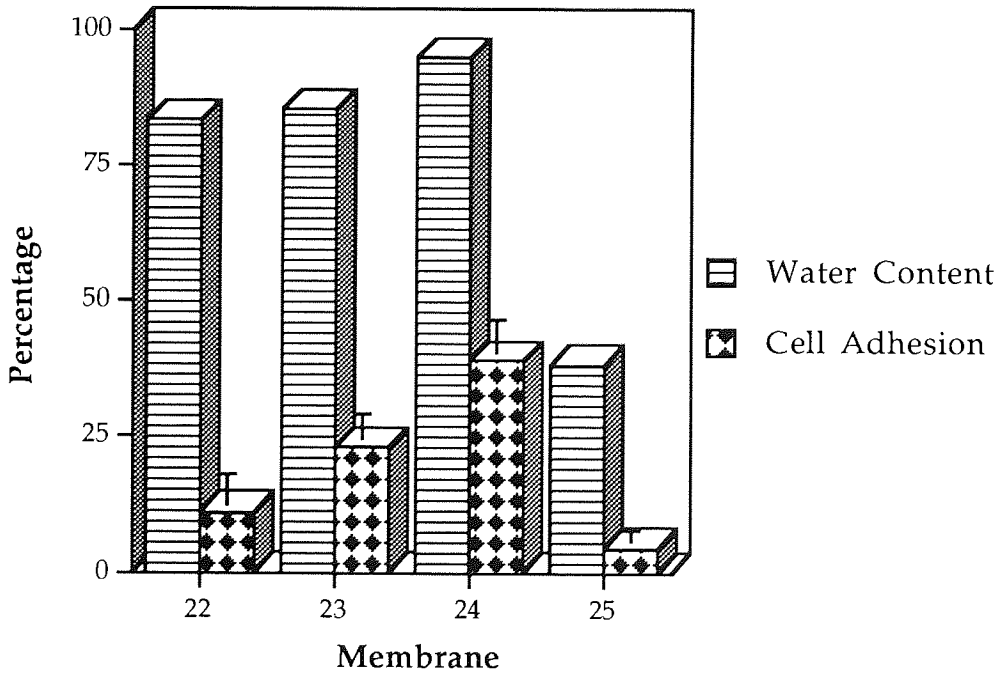


Table 6.35 : Data for Figure 6.35

No.	Composition	% Water Content	% Cell Adhesion
22	NVP:NVI:SPE 40:35:25	83.3	11.0
23	NVP:NVI:SPE 40:40:20	85.2	22.7
24	NVP:NVI 50:50	94.9	38.7

From figure 6.35 we see that as the EWC rises the % cell adhesion also rises. This is an anomalous situation. But it may be explained, as mentioned earlier, by the fact that as we move along the series, from membrane No. 22 to No. 24, we have an increasing amount of positive charge in the membrane courtesy of the increasing content of NVI. This may be looked at in reverse (membrane 24 to 22) where an increasing amount of SPE, a zwitterionic monomer, reduces cell adhesion despite a fall in the EWC. Considering figures 6.36 to 6.38 and tables 6.36 to 6.38, we see that the best sequence distribution seen is that for membrane No. 22 and the worst is that for membrane No. 24. This follows the pattern of increasing cell adhesion as the sequence distribution worsens. All of the simulated sequence distributions seen possess a slight residual block of a particular monomer, which possibly accounts for the fact that none of the above mentioned membranes are highly non-adhesive to cells when compared to PolyHEMA, membrane No. 25.

Figure 6.36 : Computer simulated sequence distribution of a NVP : NVI : SPE :: 40 : 35 : 25 terpolymer.

40 Mole % of Monomer A, NVP

35 Mole % of Monomer B, NVI

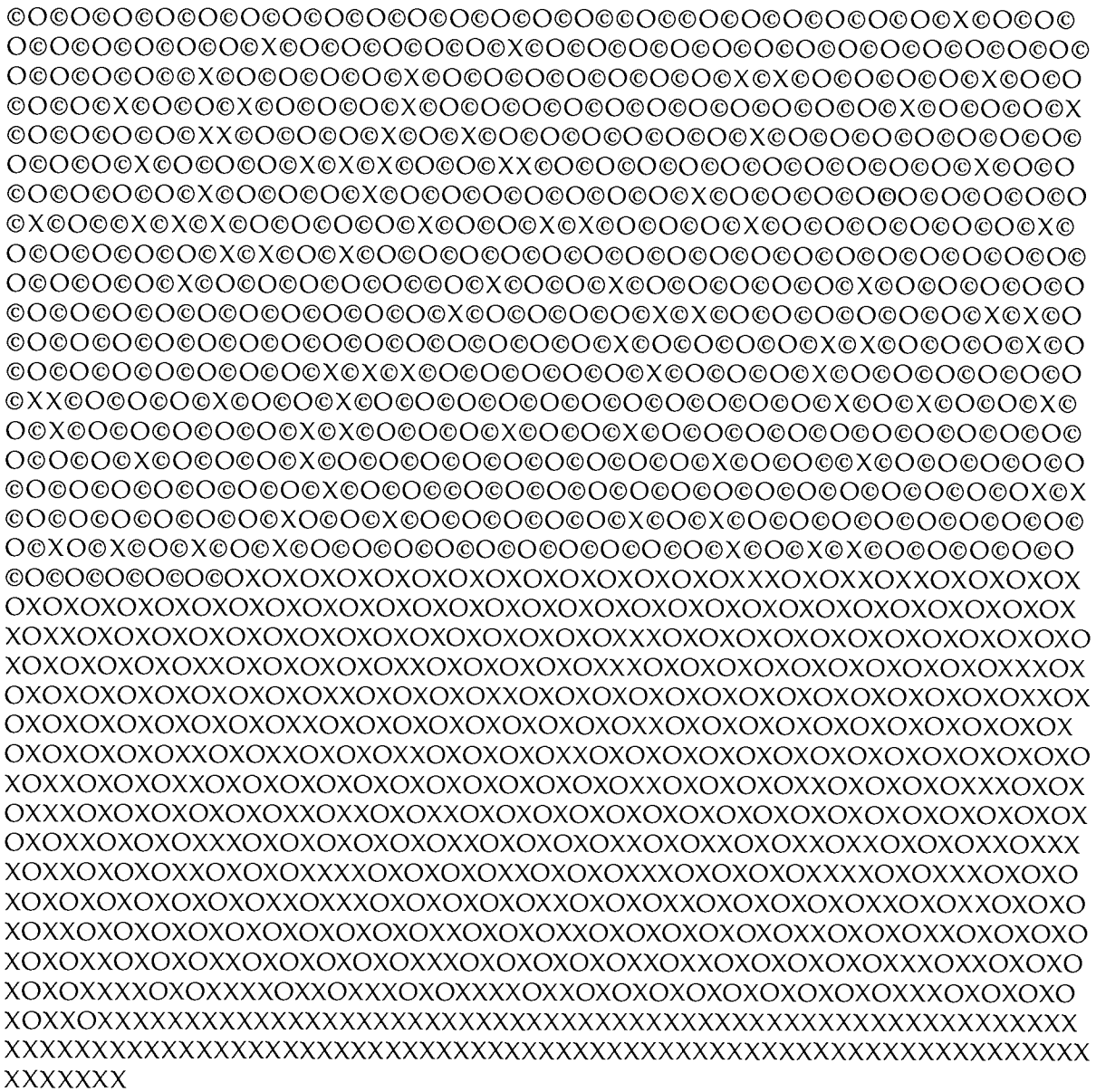
25 Mole % of Monomer C, SPE

r(AB) = 0.174 r(AC) = 0.0001 r(BA) = 2.368

r(BC) = 0.013 r(CA) = 0.052 r(CB) = 0.214

Polymerized to 100% Conversion

In the simulated terpolymer NVP is represented by O, NVI is represented by X and SPE is represented by © :



The simulated terpolymer contains 800 NVP units, 700 NVI units and 500 SPE units.

Table 6.36 : Sequence lengths seen in the simulated sequence distribution of figure 6.36

Sequence Distributions:

Length	NVP	NVI	SPE
1	800	401	486
2	0	53	7
3	0	14	0
4	0	6	0
127	0	1	0

Figure 6.37 : Computer simulated sequence distribution of a NVP : NVI : SPE :: 40 : 40 : 20 terpolymer.

40 Mole % of Monomer A, NVP

40 Mole % of Monomer B, NVI

20 Mole % of Monomer C, SPE

r(AB) = 0.174 r(AC) = 0.0001 r(BA) = 2.368

r(BC) = 0.013 r(CA) = 0.052 r(CB) = 0.214

Polymerized to 100% Conversion

In the simulated terpolymer NVP is represented by O, NVI is represented by X and SPE is represented by © :

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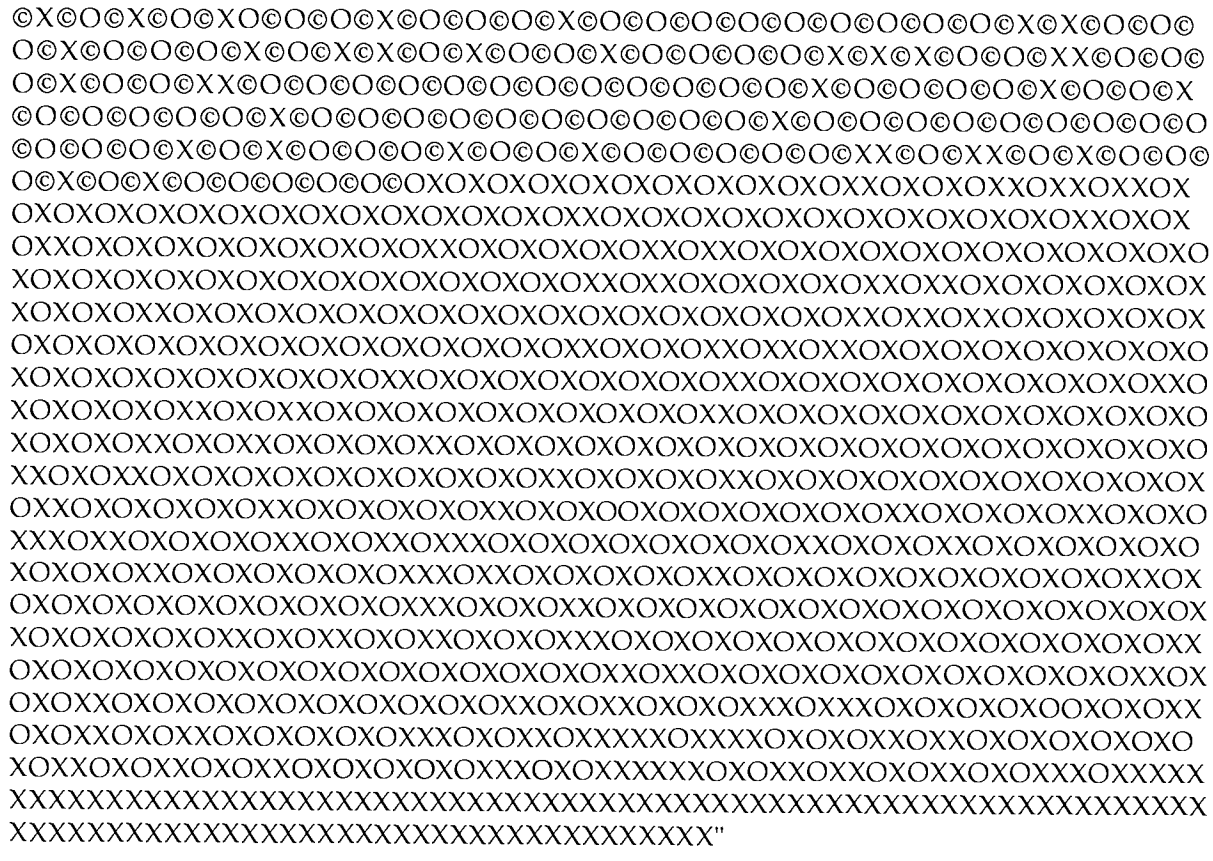

The simulated terpolymer contains 800 NVP units, 800 NVI units and 400 SPE units.

Table 6.37 : Sequence lengths seen in the simulated sequence distribution of figure 6.37.

Sequence Distributions:

Lengths	NVP	NVI	SPE
1	796	494	388
2	2	78	6
3	0	10	0
4	0	1	0
5	0	1	0
6	0	1	0
105	0	1	0

Figure 6.38 : Computer simulated sequence distribution of a copolymer of NVP : NVI :: 50 : 50.

50 Mole % of Monomer A, NVP

50 Mole % of Monomer B, NVI

r(AB) = 0.174

r(BA) = 2.368

Polymerized to 100% Conversion

In the simulated copolymer NVP is represented by O and NVI is represented by X :

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The simulated copolymer contains 1000 NVP units and 1000 NVI units.

Table 6.38 : Sequence lengths seen in the simulated sequence distribution of figure 6.38.

Sequence Distributions:

Length	NVP	NVI
1	302	211
2	72	95
3	26	54
4	18	27
5	6	20
6	3	8
7	3	13
8	0	2
9	3	3
10	1	2
12	0	1
13	2	0
15	0	1
272	1	0

The figures above show that all the membranes have some residual monomer coming in at the end of the reaction, as a block. We also observe that as the EWC rises the amount of cell adhesion also rises. In these membranes we see that the amount of cell adhesion that occurs on the surface of these materials is predominantly determined by the quantity of the positively charged monomer, NVI. Ignoring the large residual block at the end of the simulated sequence distributions, we note that the average sequence lengths are quite short, but the presence of the positively charged NVI significantly increases the degree of interaction of these surfaces with the serum proteins, which will subsequently lead to greater cell adhesion.

6.17 (HEMA/HEA&/EOEMA)&(NNDMA&/NVP) Membranes

Considering the simulated sequence distributions shown in chapter 3, we observe that most contact lens compositions are based predominantly, about 60% on a hydroxyalkyl methacrylate and 40% on a nitrogenous monomer such as NVP or NNDMA, or *vice versa*. The resulting sequence distributions seen were all very poor because of the large difference between the reactivity ratios of the monomers concerned. In this and the following section we will be concerned with trying to substitute or replace part of the composition of one type of monomer with others containing similar types of chemical groups, e.g., HEMA may be replaced by 2-hydroxyethyl acrylate (HEA) and NVP may be fully or partly replaced by NNDMA. This would be done utilising the approaches suggested in chapter 5 thereby creating the possibility of producing membranes with relatively good sequence distributions and hopefully low cell adhesion characteristics. Figure 6.39, below, shows the % cell adhesion and % EWC for membranes of (HEMA/HEA&EOEMA)&(NNDMA&/NVP) with the compositions as shown in table 6.39.

Figure 6.39 : (HEMA/HEA&/EOEMA)&(NNDMA&/NVP) Membranes

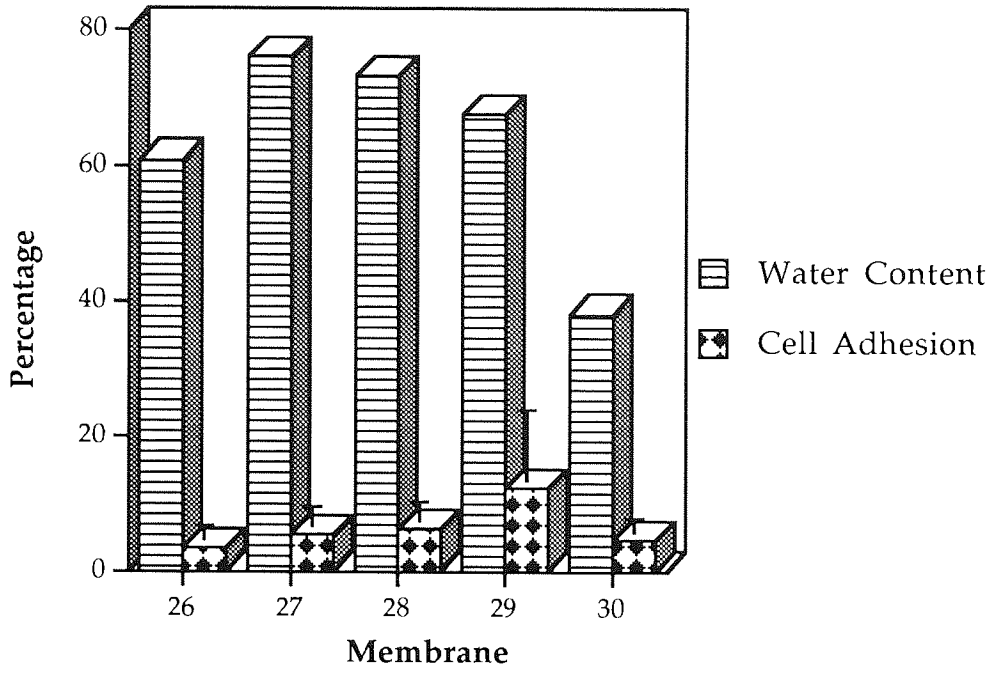

Table 6.39 : Data for Figure 6.39

No.	Composition	% Water Content	% Cell Adhesion
26	HEMA:NNDMA:NVP 62:27:11	60.8	3.3
27	HEA:NNDMA:NVP 62:27:11	75.8	5.4
28	HEA:EOEMA:NNDMA 50:12:38	73.1	6.1
29	HEA:EOEMA:NVP 50:12:38	67.4	12.3

From figure 6.39 we see that there is little correlation between EWC and % cell adhesion. From figures 6.40 to 6.43 and tables 6.40 to 6.43 we again see no real correlation between sequence distribution and % cell adhesion. Generally though, the membranes all have relatively good sequence distributions except membrane No. 26 which has a slightly extended sequence distribution, and they all have relatively high EWC's. Thus as shown in figure 6.39 they are all relatively non-adhesive to cells.

Figure 6.40 : Computer simulated sequence distribution of a HEMA : NNDMA : NVP :: 62 : 27 : 11 terpolymer.

62 Mole % of Monomer A, HEMA

27 Mole % of Monomer B, NNDMA

11 Mole % of Monomer C, NVP

r(AB) = 4.124 r(AC) = 4.841 r(BA) = 0.238

r(BC) = 6.635 r(CA) = 0.001 r(CB) = 0.023

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NNDMA is represented by X and NVP is represented by © :

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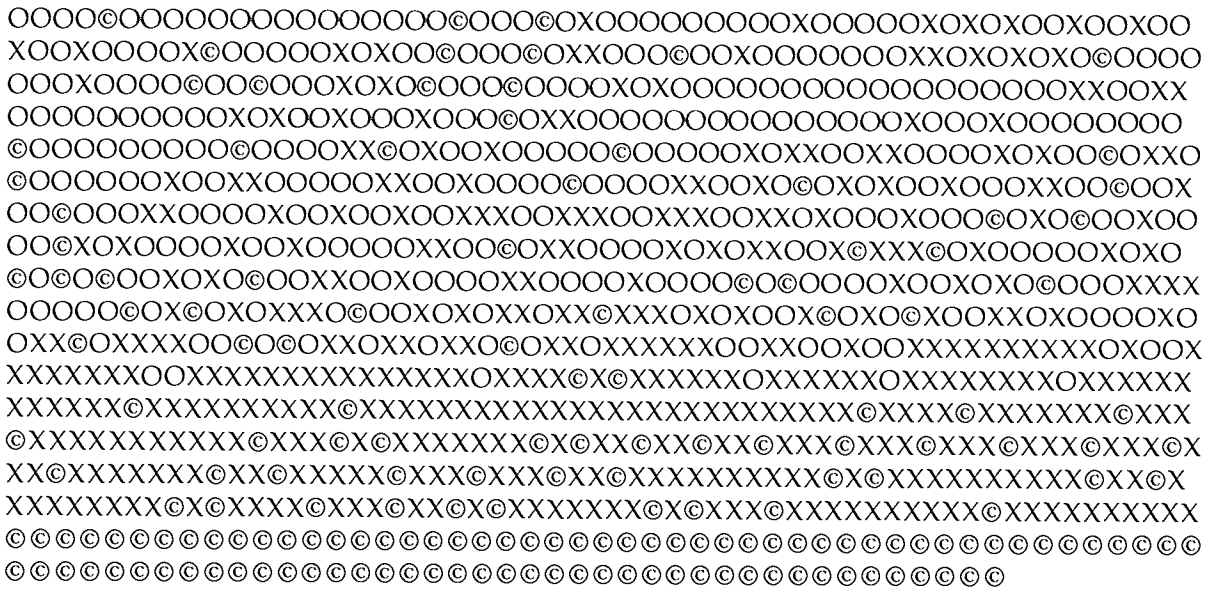

The simulated terpolymer contains 1240 HEMA units, 540 NNDMA units and 220 NVP units.

Table 6.40 : Sequence lengths seen in the simulated sequence distribution of figure 6.40.

Sequence Distributions:

Length	HEMA	NNDMA	NVP
1	87	172	130
2	59	47	0
3	26	18	0
4	32	5	0
5	20	1	0
6	12	3	0
7	10	4	0
8	6	2	0
9	13	1	0
10	5	6	0
11	5	1	0
12	2	1	0
13	3	0	0
15	3	1	0
16	2	0	0

17	3	0	0
18	1	0	0
19	1	0	0
20	2	0	0
24	1	0	0
25	1	0	0
26	0	1	0
90	0	0	1

Figure 6.41 : Computer simulated sequence distribution of a HEA : NNDMA : NVP :: 62 : 27 : 11 terpolymer.

62 Mole % of Monomer A, HEA

27 Mole % of Monomer B, NNDMA

11 Mole % of Monomer C, NVP

r(AB) = 0.316 r(AC) = 0.363 r(BA) = 0.598

r(BC) = 6.635 r(CA) = 0.002 r(CB) = 0.023

Polymerized to 100% Conversion

In the simulated terpolymer HEA is represented by O, NNDMA is represented by X and NVP is represented by © :

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The simulated terpolymer contains 1240 HEA units, 540 NNDMA units and 220 NVP units.

Table 6.41 : Sequence lengths seen in the simulated sequence distribution of figure 6.41.

Sequence Distributions:

Length	HEA	NNDMA	NVP
1	380	381	220
2	160	56	0
3	61	11	0
4	28	1	0
5	17	2	0
6	6	0	0
7	1	0	0
8	2	0	0
9	3	0	0
74	1	0	0

Figure 6.42 : Computer simulated sequence distribution of a HEA : EOEMA : NNDMA :: 50 : 12 : 38 terpolymer.

50 Mole % of Monomer A, HEA

12 Mole % of Monomer B, EOEMA

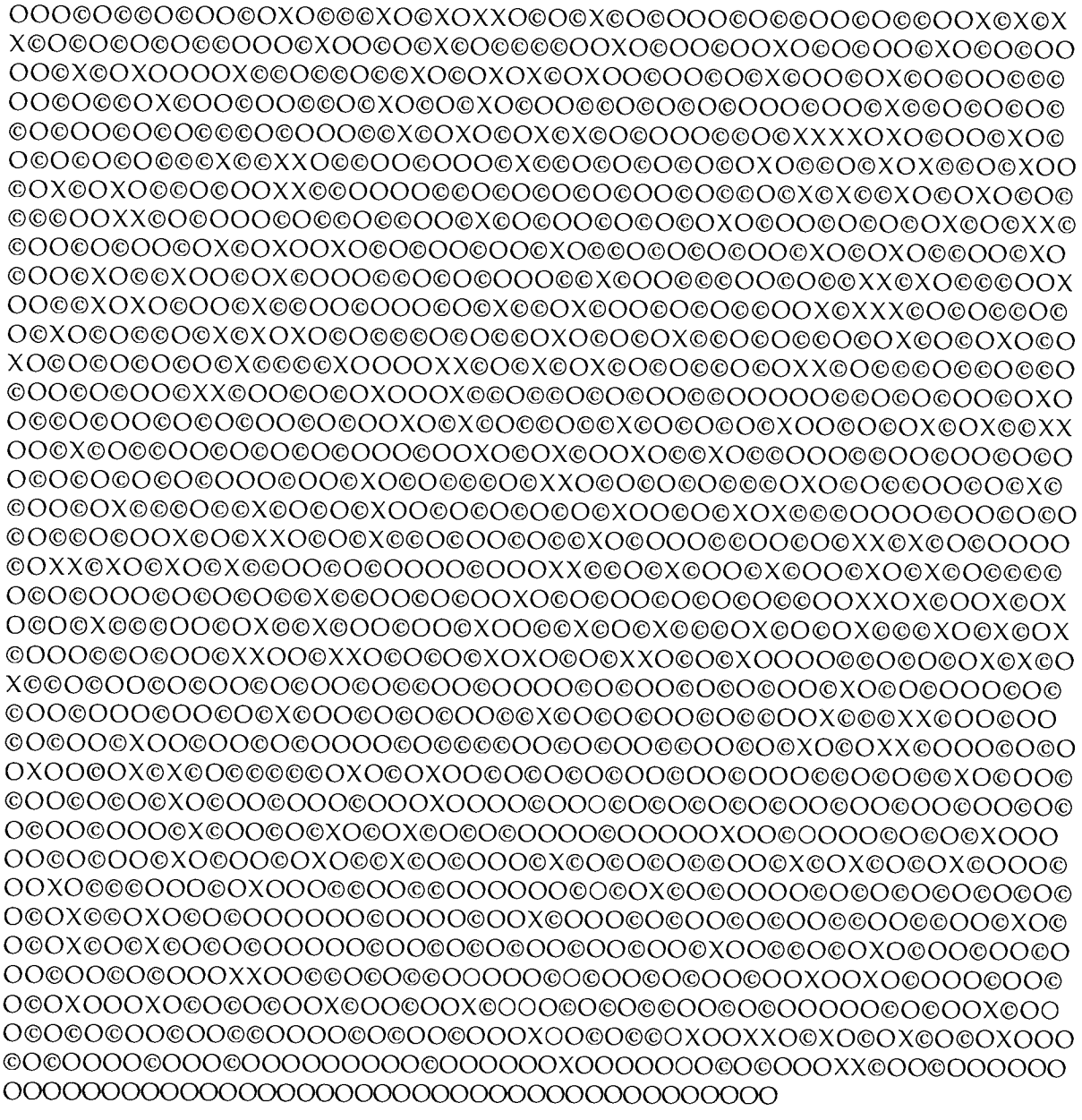
38 Mole % of Monomer C, NNDMA

r(AB) = 0.478 r(AC) = 0.316 r(BA) = 1.596

r(BC) = 0.988 r(CA) = 0.598 r(CB) = 0.559

Polymerized to 100% Conversion

In the simulated terpolymer HEA is represented by O, EOEMA is represented by X and NNDMA is represented by © :



The simulated terpolymer contains 1000 HEA units, 240 EOEMA units and 760 NNDMA units.

Table 6.42 : Sequence lengths seen in the simulated sequence distribution of figure 6.42.

Sequence Distributions:

Length	HEA	EOEMA	NNDMA
1	388	183	494
2	154	25	95
3	42	1	17
4	17	1	5
5	6	0	1
6	3	0	0
7	1	0	0
9	1	0	0
46	1	0	0

Figure 6.43 : Computer simulated sequence distribution of a HEA : EOEMA : NVP :: 50 : 12 : 38 terpolymer.

50 Mole % of Monomer A, HEA

12 Mole % of Monomer B, EOEMA

38 Mole % of Monomer C, NVP

r(AB) = 0.478 r(AC) = 0.363 r(BA) = 1.596

r(BC) = 2.300 r(CA) = 0.002 r(CB) = 0.004

Polymerized to 100% Conversion

In the simulated terpolymer HEA is represented by O, EOEMA is represented by X and NVP is represented by © :

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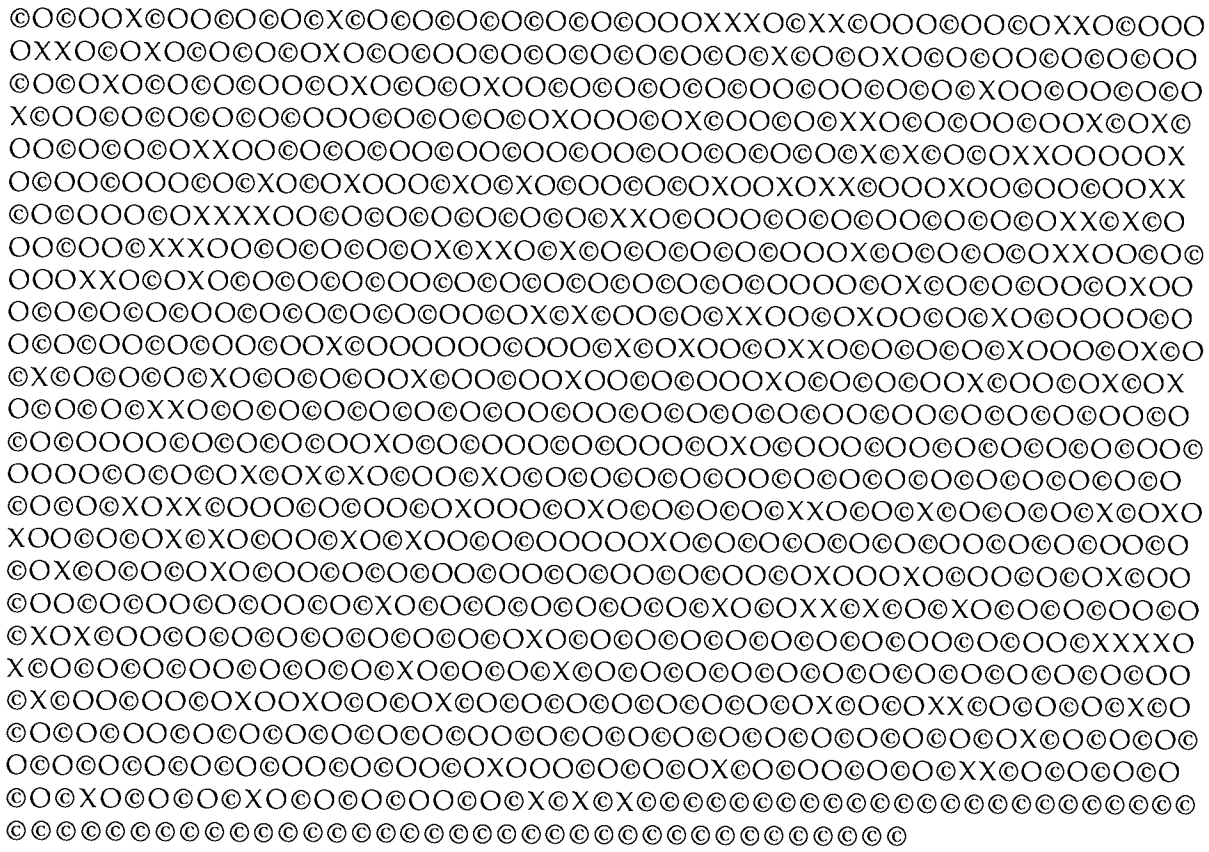


The simulated terpolymer contains 1000 HEA units, 240 EOEMA units and 760 NVP units.

Table 6.43 : Sequence lengths seen in the simulated sequence distribution of figure 6.43.

Sequence Distributions:

Length	HEA	EOEMA	NVP
1	550	151	697
2	144	36	1
3	32	3	0
4	10	2	0
5	4	0	0
6	1	0	0
61	0	0	1

The figures above show that all the membranes have a slight residual block of monomer units at the end of the reaction. In spite of this, these membranes tend to generally produce relatively non-adhesive surfaces to cells. The average sequence lengths, excluding the residual block, vary quite a bit. And there seems to be little correlation between the average sequence lengths and percentage cell adhesion.

6.18 HEA:EOEMA:PEG:NNDMA:NVP/NVI:SPE/ITA Membranes

As shown in the previous section we have managed to synthesize membranes which contain a high EWC whilst having relatively good sequence distributions which has together resulted in them being relatively non-adhesive to cells. In this section we will take this a little bit further by trying to produce membranes whose structures are more biomimetic, by including the relevant functional-group containing monomers, e.g., by including PEG, which contains pendant ethylene oxide chains, we may try to mimic the pendant carbohydrate chains found on the surface of living membranes. Many biological surfaces/molecules also contain some degree of charge, we may try to mimic this behaviour by including monomers that either contain a permanent charge such as Itaconic acid (ITA) or the zwitterionic monomer SPE, or we may include monomers which in an aqueous environment become charged such as NVI. Figure 6.44, below, shows the % cell adhesion and % EWC for membranes of HEA:EOEMA:PEG:NNDMA:NVP/NVI:SPE/ITA with the compositions as shown in table 6.44.

Figure 6.44: HEA:EOEMA:PEG:NNDMA:NVP/NVI:SPE/ITA Membranes

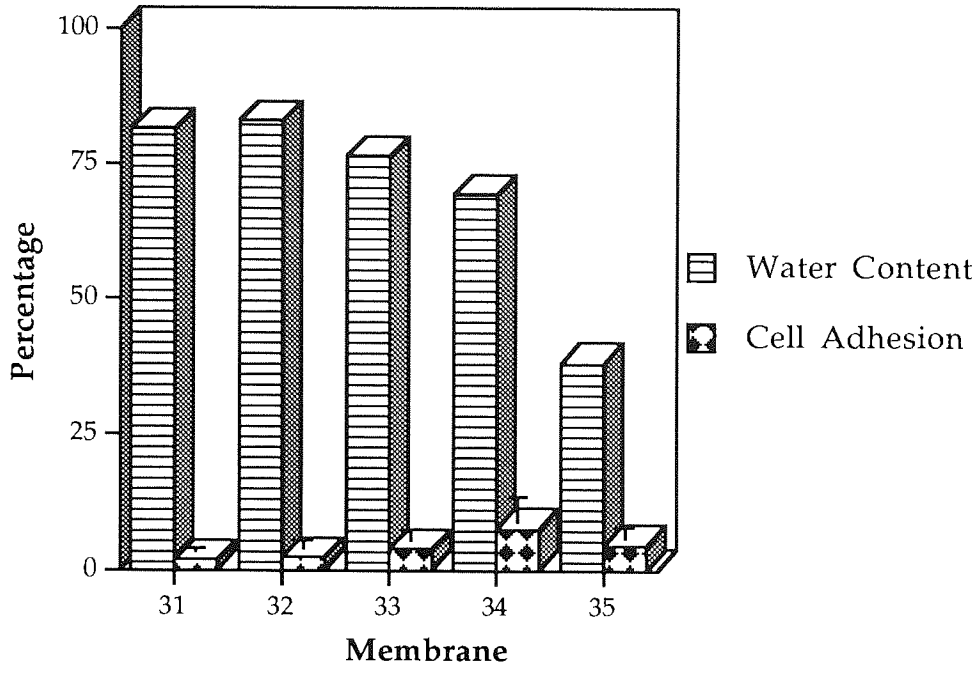


Table 6.44 : Data for Figure 6.44

No.	Composition	% Water Content	% Cell Adhesion
31	HEA:EOEMA:PEG:NNDMA:NVP:SPE 25:12:25:27:9:2	81.4	1.7
32	HEA:EOEMA:PEG:NNDMA:NVI:SPE 25:12:25:27:9:2	82.7	2.2
33	HEA:EOEMA:PEG:NNDMA:NVP:ITA 25:12:25:27:9:2	76.2	3.6
34	HEA:EOEMA:PEG:NNDMA:NVP:ITA 25:12:22:27:9:5	69.4	7.5

From figure 6.44 above we see that there is no real correlation between equilibrium water content and % cell adhesion. Since the computer simulation program can only simulate the sequence distribution of three components at any one time, then no single computer simulated sequence distribution can adequately describe the sequence distribution of individual monomer units that would be seen upon the polymerisation of the above membranes. Figures 6.45 to 6.48 may be used as a reasonable guide to the expected sequence distribution, in conjunction with figures 6.49 to 6.55, which illustrate the inter-relationship between the various components of the above membranes, shown here as copolymer simulations. What may be deduced from figure 6.44 and figures 6.45 to 6.55, is that all the above synthesized membranes, containing biomimetic monomer units, produce highly hydrophilic membranes which display relatively good sequence distributions of individual monomer units, are quite good in terms of preventing cell adhesion.

Figure 6.45 : Computer simulated sequence distribution of a HEA : EOEMA : NNDMA :: 61 : 12 : 27 terpolymer.

61 Mole % of Monomer A, HEA

12 Mole % of Monomer B, EOEMA

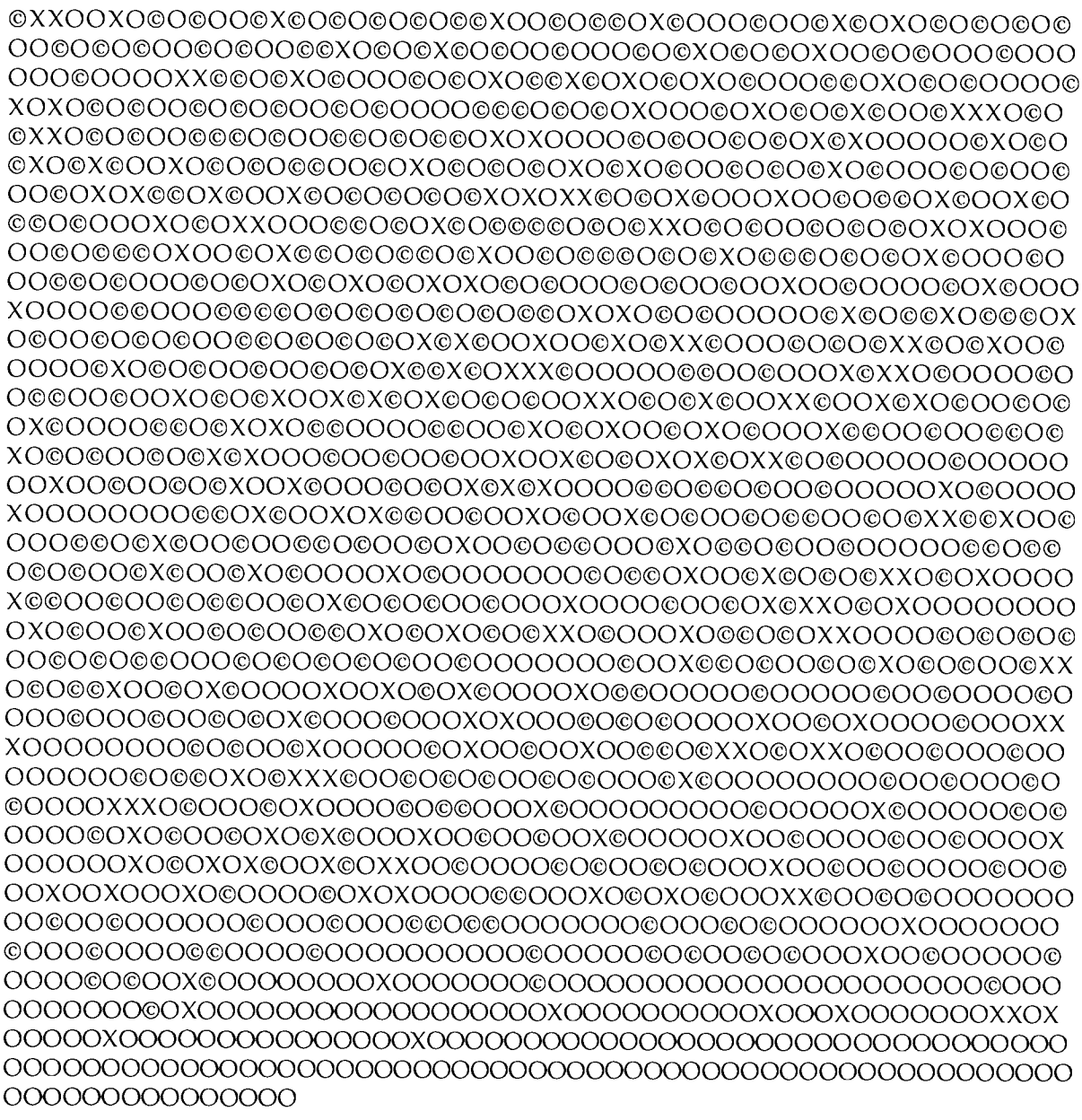
27 Mole % of Monomer C, NNDMA

r(AB) = 0.478 r(AC) = 0.316 r(BA) = 1.596

r(BC) = 0.988 r(CA) = 0.598 r(CB) = 0.559

Polymerized to 100% Conversion

In the simulated terpolymer HEA is represented by O, EOEMA is represented by X and NNDMA is represented by © :



The simulated terpolymer contains 1220 HEA units, 240 EOEMA units and 540 NNDMA units.

Table 6.45 : Sequence lengths seen in the simulated sequence distribution of figure 6.45.

Sequence Distributions:

Length	HEA	EOEMA	NNDMA
1	229	179	402
2	119	23	56
3	48	5	6
4	34	0	2
5	15	0	0
6	4	0	0
7	7	0	0
8	5	0	0
9	3	0	0
10	3	0	0
15	1	0	0
18	1	0	0
22	1	0	0
103	1	0	0

Figure 6.46 : Computer simulated sequence distribution of a PEG : EOEMA : NNDMA :: 61 : 12 : 27 terpolymer.

61 Mole % of Monomer A, PEG

12 Mole % of Monomer B, EOEMA

27 Mole % of Monomer C, NNDMA

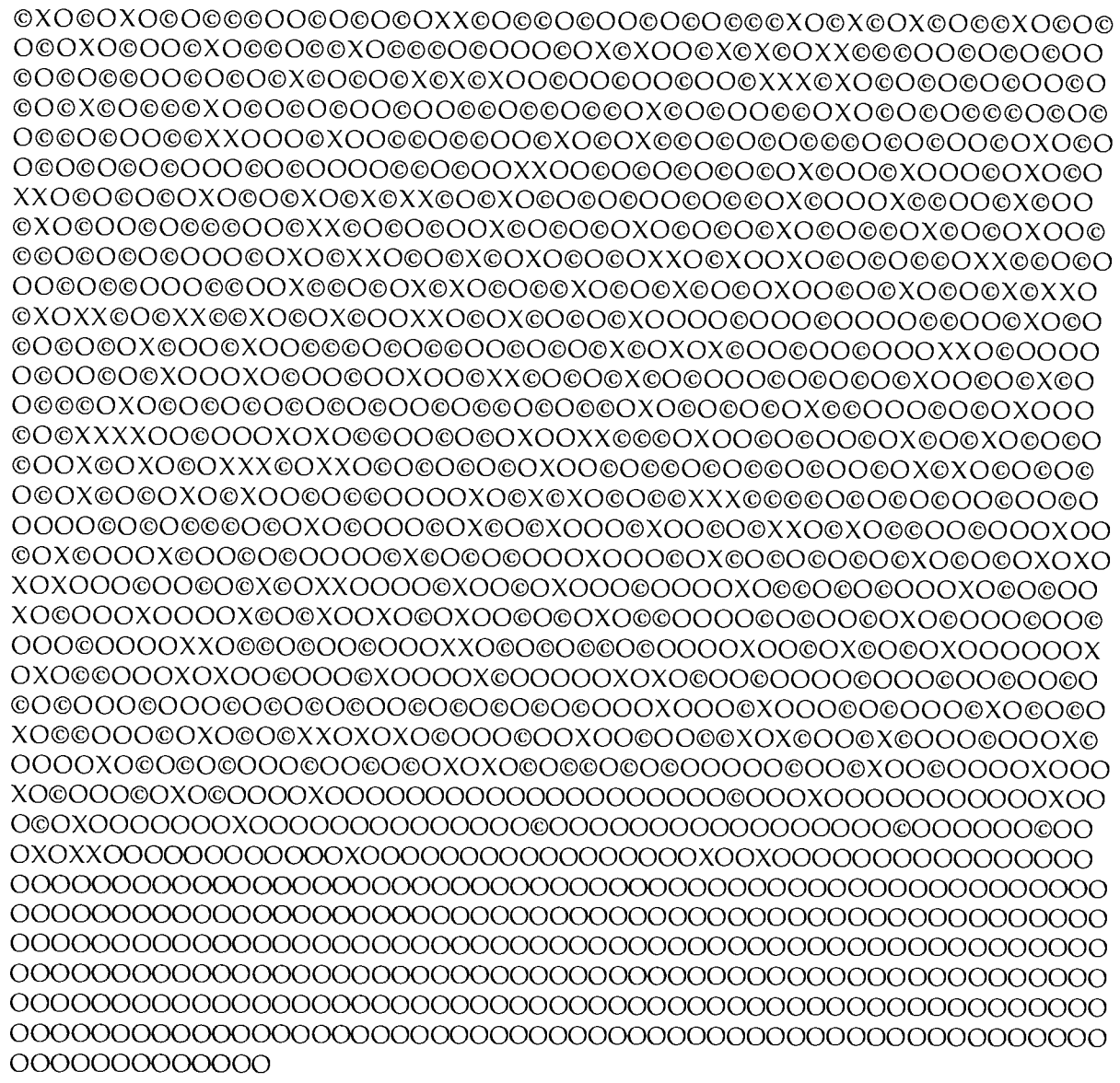
r(AB) = 0.213 r(AC) = 0.118 r(BA) = 2.665

r(BC) = 0.988 r(CA) = 0.836 r(CB) = 0.559

Polymerized to 100% Conversion

In the simulated terpolymer PEG is represented by O, EOEMA is represented by X and NNDMA is represented by © :

O©©O©O©©©O©O©OXO©©©OXOXO©XO©O©©O©O©O©XO©OO©XO©XO©OO©O
X©X©O©O©OOO©©O©OO©©©O©X©OXO©OO©X©OXO©©X©XXX©O©O©O©XO©



The simulated terpolymer contains 1220 PEG units, 240 EOEMA units and 540 NNDMA units.

Table 6.46 : Sequence lengths seen in the simulated sequence distribution of figure 6.46.

Sequence Distributions:

Length	PEG	EOEMA	NNDMA
1	347	176	390
2	88	24	49
3	48	4	16

4	16	1	1
5	4	0	0
6	2	0	0
7	1	0	0
11	1	0	0
12	1	0	0
14	1	0	0
17	2	0	0
20	1	0	0
359	1	0	0

Figure 6.47 : Computer simulated sequence distribution of a HEA : EOEMA : NNDMA :: 59 : 14 : 27 terpolymer.

59 Mole % of Monomer A, HEA

14 Mole % of Monomer B, EOEMA

27 Mole % of Monomer C, NNDMA

r(AB) = 0.478 r(AC) = 0.316 r(BA) = 1.596

r(BC) = 0.988 r(CA) = 0.598 r(CB) = 0.559

Polymerized to 100% Conversion

In the simulated terpolymer HEA is represented by O, EOEMA is represented by X and NNDMA is represented by © :

X©©©O©XOO©©XO©OOXOXOOXX©O©OO©O©XOOXO©O©OO©O©OOO©X©O©O©
O©©©O©O©©OOX©OOOOO©O©O©OXOX©OO©OOOOO©X©O©O©O©XX©O©OO©O
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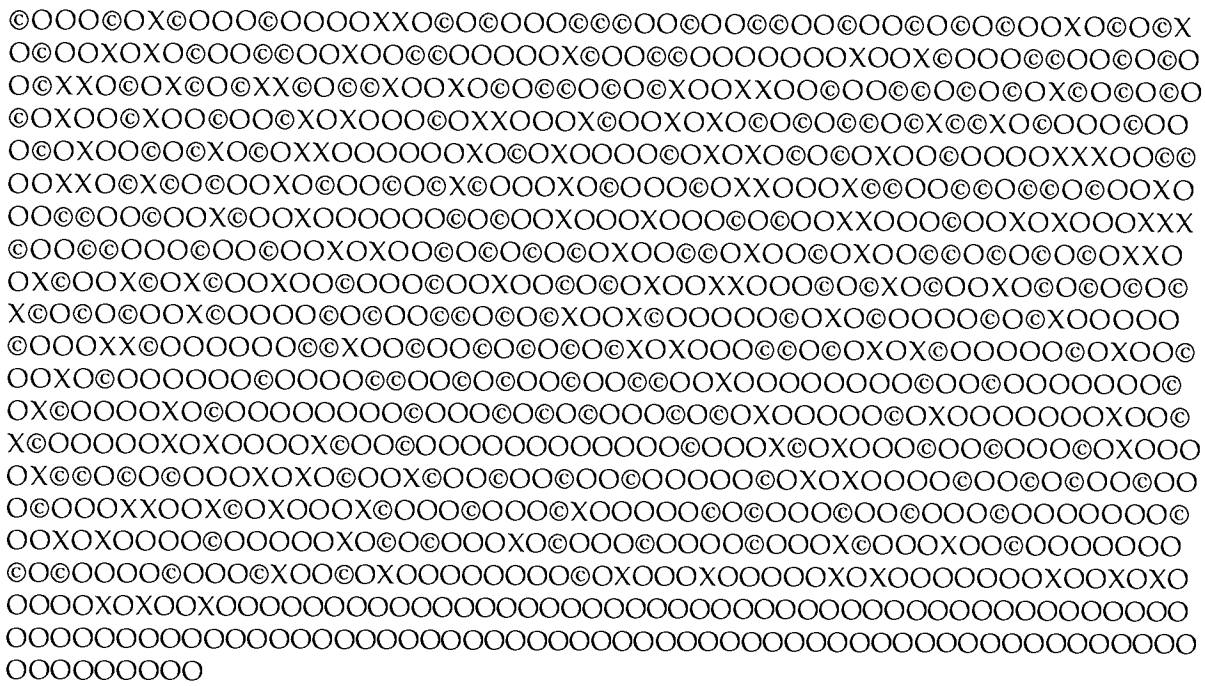


The simulated terpolymer contains 1180 HEA units, 280 EOEMA units and 540 NNDMA units.

Table 6.47 : Sequence lengths seen in the simulated sequence distribution of figure 6.47.

Sequence Distributions:

Length	HEA	EOEMA	NNDMA
1	288	203	393
2	136	28	55
3	71	7	11
4	27	0	1
5	14	0	0
6	7	0	0
7	6	0	0
8	3	0	0
12	1	0	0
109	1	0	0

Figure 6.48 : Computer simulated sequence distribution of a PEG : EOEMA : NNDMA :: 59 : 14 : 27 terpolymer.

59 Mole % of Monomer A, PEG

14 Mole % of Monomer B, EOEMA

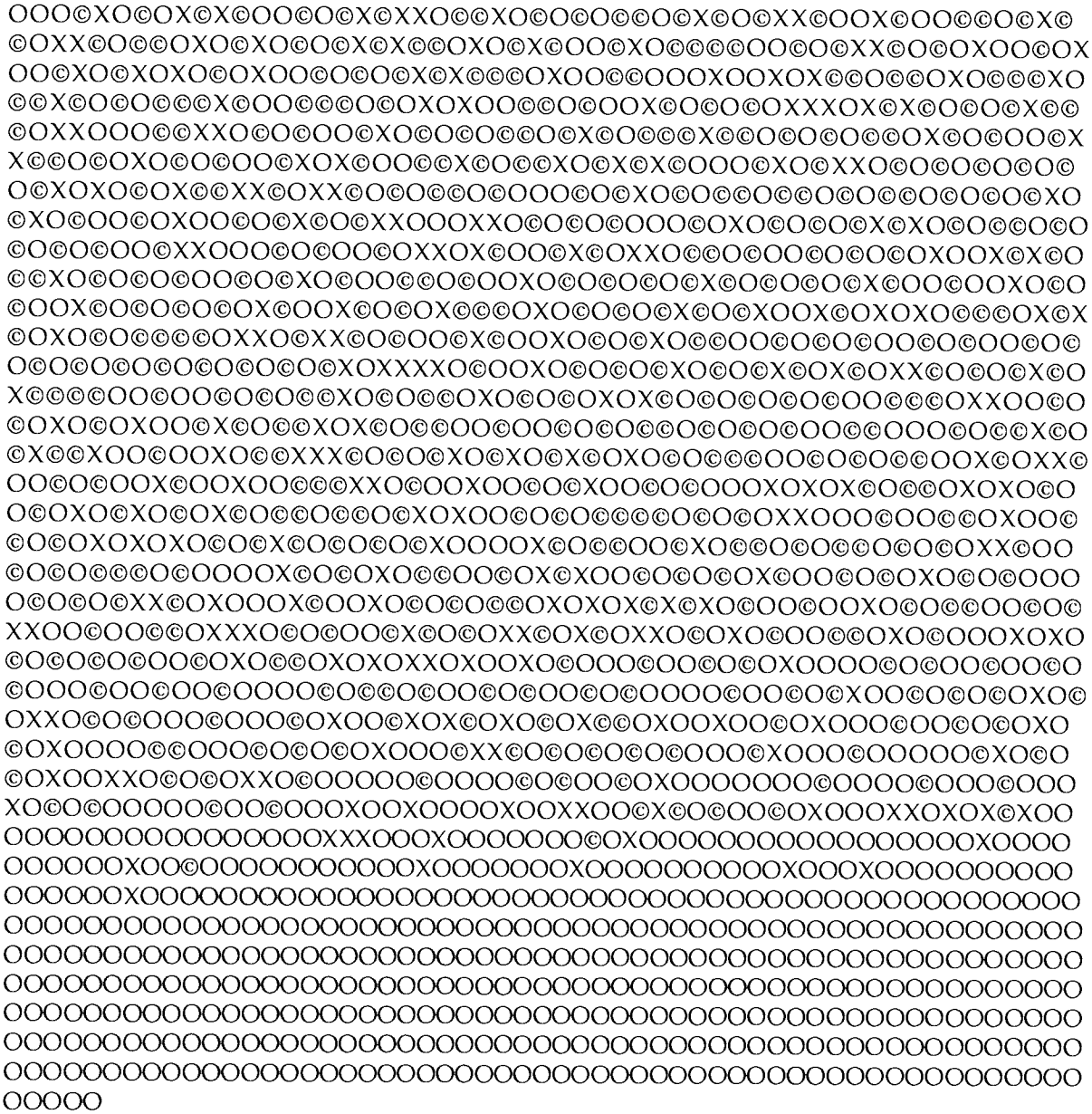
27 Mole % of Monomer C, NNDMA

r(AB) = 0.213 r(AC) = 0.118 r(BA) = 2.665

r(BC) = 0.988 r(CA) = 0.836 r(CB) = 0.559

Polymerized to 100% Conversion

In the simulated terpolymer PEG is represented by O, EOEMA is represented by X and NNDMA is represented by © :



The simulated terpolymer contains 1180 PEG units, 280 EOEMA units and 540 NNDMA units.

Table 6.48 : Sequence lengths seen in the simulated sequence distribution of figure 6.48

Sequence Distributions:

Length	PEG	EOEMA	NNDMA
1	361	196	378
2	97	34	55
3	28	4	12
4	10	1	4
5	3	0	0
7	3	0	0
10	2	0	0
11	1	0	0
16	1	0	0
17	1	0	0
18	1	0	0
383	1	0	0

Figure 6.49 : Computer simulated sequence distribution of a copolymer of HEA : PEG :: 50 : 50.

50 Mole % of Monomer A, HEA

50 Mole % of Monomer B, PEG

r(AB) = 1.881

r(BA) = 0.504

Polymerized to 100% Conversion

In the simulated copolymer HEA is represented by O and PEG is represented by X :

XOOXXXXOOOOOXOOOXOOOXOXOOOOOXXXXXXOXOOXXXOXOXOOOXOXOXXOOOO
OOOOXOOXOXXOOXXOOXXXOOOOOOOXXOXOOOXOOOXXXXXXXOOOXXXOOOOOOX
XOXOXOOOOXOOXOOXOOOXOXXOOXXOOOOOXXOXOXXXOXXOXOOOOOXXOOOOXO
XOOXOXOXOOOOXOOOXOOOOOXXOOOXOOOOOOOXXOXOXOOXOXOXOXOXXOXOX
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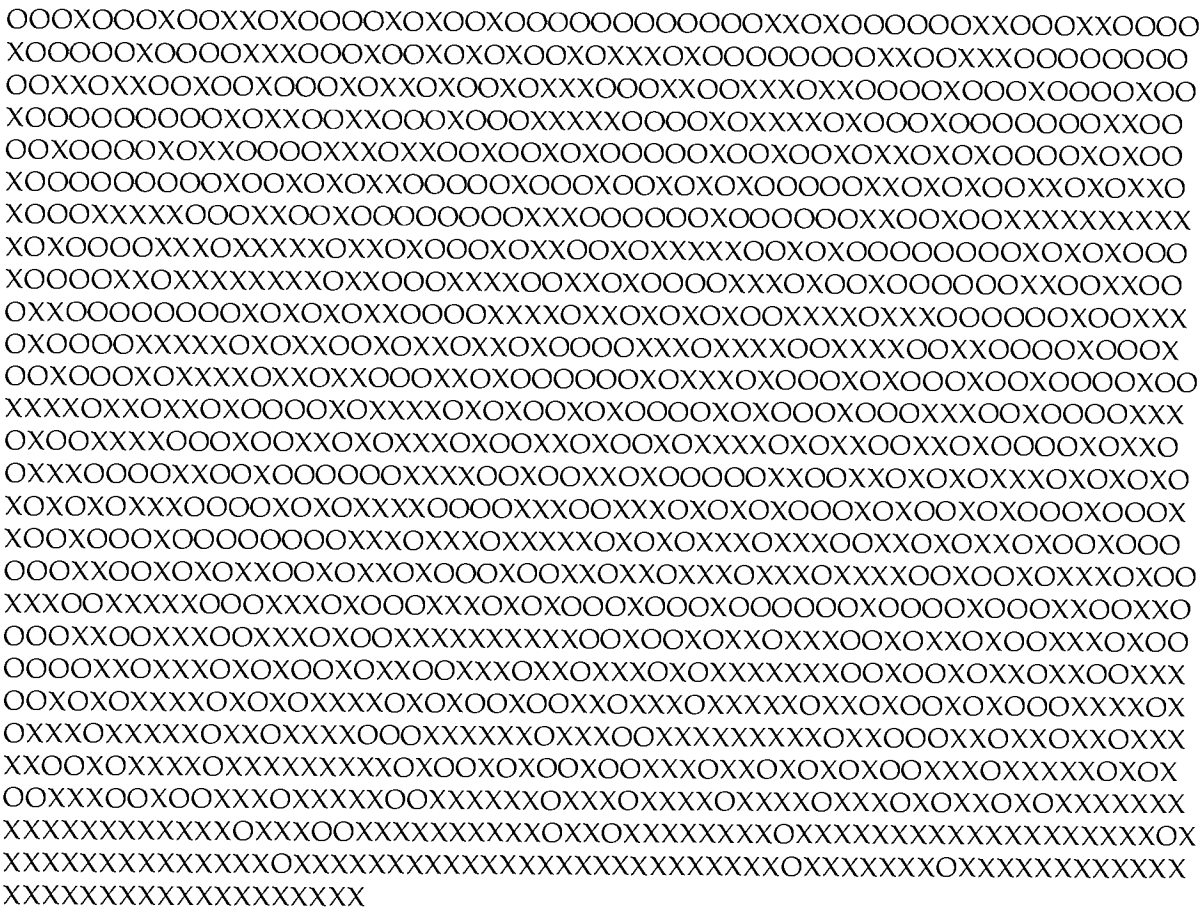
OXOXOOOOXXOXXXOXXOOOOOXXOXXOOXOOXXXXOXOXXOOXOOOOOOXXXOOXXO
XOOOOXOOOXOOOXOOOXXXXOOOOXOXOOXOXOXXOOXOXOOOXOOXOOOXOXOOX



The simulated copolymer contains 1000 HEA units and 1000 PEG units.

Table 6.49 : Sequence lengths seen in the simulated sequence distribution of figure 6.49

Sequence Distributions:

Length	HEA	PEG
1	235	255
2	106	102
3	53	57
4	33	24
5	12	12
6	14	3
7	3	3

8	6	2
9	3	2
10	1	2
11	0	1
12	1	0
15	0	1
19	0	2
26	0	1
31	0	1

Figure 6.50 : Computer simulated sequence distribution of a copolymer of NNDMA : PEG :: 50 : 50.

50 Mole % of Monomer A, NNDMA

50 Mole % of Monomer B, PEG

r(AB) = 0.810

r(BA) = 0.192

Polymerized to 100% Conversion

In the simulated copolymer NNDMA is represented by O and PEG is represented by X :

XOOXXOXOXOOXOXOXOXOOOOOXOXOXOXOXOOXOOOXOXOXOOOOXOOOXOOOOO
XOXOOXOOOOXOXOOXOXOOXOOOOOOOXOXOOOOOOXOOXOOXOXOXOOOOXOOOX
OOOXXOOOOOOOXOOXOXOXOXOXOXOXXOXOXOXOXOXOOOXOOXOOXOXOXXOOXO
OXOOXOXOXOOXOOXOXOXOXOXOOXXOXOOOXOXOXOXOXOOOXOXOXOXOOXOOOO
OOOOXOOOOXOXOXOOOXOOOXOOXOOXOOXXOOXOOOOOXXOXOOXOXOXOXXOXX
OOOOXOXOOXOOXOXOXOOOOXOOXOOOXOOXOOXOOOOOOXOOOXOXOOXOXOOOX
OOOXXOOOXOOXOXOOXXOXXOOXXOXXOXOXOXOXOOXOOXOXOXOOXOOOOOOXOO
OOXOXOXOXOOOOXOXOXOOXOXOOOXOOOOXOXOOOXOOXOXOXOOOOOXXOOOXXOXO
XOXOOOXXOOXOOOXOXOXOOXOXOOXOXOXOXXOXXOXOXXOXOXOOOXOXOXOXOX
OXOXXOXOXOOOOXOXOOXOXXXXXOOXOXXOOXXOXOXOOXOXXOOXOXOOXOXOXXO
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OXOOOOXOOXOOXOXOOOXOXXXOXOOOOOOXOXOOXOXOXOXXOOXOOXOOOOOOX
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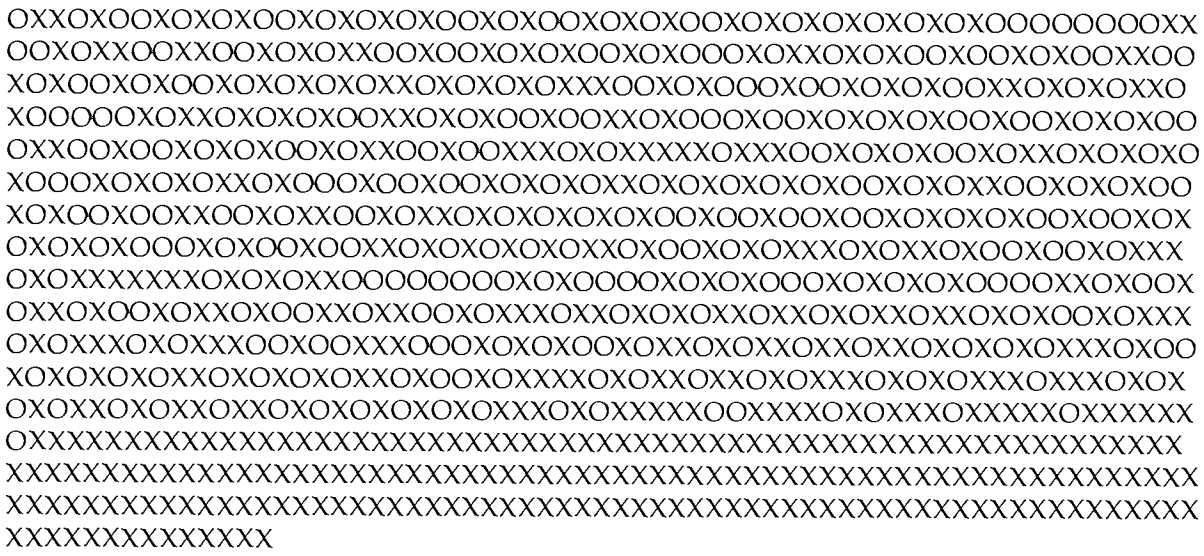

The simulated copolymer contains 1000 NNDMA units and 1000 PEG units.

Table 6.50 : Sequence lengths seen in the simulated sequence distribution of figure 6.50.

Sequence Distributions:

Length	NNDMA	PEG
1	402	510
2	158	91
3	40	22
4	13	2
5	6	4
6	7	1
7	2	1
8	3	0
201	0	1

Figure 6.51 : Computer simulated sequence distribution of a copolymer of EOEMA : PEG :: 50 : 50.

50 Mole % of Monomer A, EOEMA

50 Mole % of Monomer B, PEG

r(AB) = 2.665

r(BA) = 0.213

Polymerized to 100% Conversion

In the simulated copolymer EOEMA is represented by O and PEG is represented by X :

OOOOOXOOXXOOOOOXOOOOOOOXOXOXXXOOOOOXOXOOOXXOOOXOOOOOXXOXO
OOXOOXOXOOOOXOXXOOOOOOOOOOOOOOXXOXOOOOOOOXOOOOOOOOOXOOXO
XOXOOXXOOOOOOOOOXOOOOOXOOXXOOOOOOOOOOOOOXXOOOXOOOOOOOOX
OXOOOOOXOOXOXOXXOXOXXOOOXOXOOOOXOOOXOOOXXOOOOOXXOOOOOXOXO
OXOOXOXOOOXOOOXXOOOOOXOOOOXOOOOOOOXOOOOOOOXOOXOOOOOXXOX
OOOOOXOOOOXOXOXOXXOOOXOOOOOOOXOOOOOXOOOXXOOOXOOOXOXOOOOOX
XOXOXOOXOOXOXOXXOXXOOOOOXOOOXOOOOOOOOXOOOOXOOOXOXXOOOOOOO
OXXOOOOOOOOOOXXOXOOOOXOOXXOOOXOOOOXOOXOOOOOOOXOXOXOOXOOXO
OOOOXOXOXXXXOOOOXOOOXOOOOXXOOOOOXOOOOOOOOOOOOXOOOXXOXOXOO
OOOOOXOOXOOXOXOOOOXXXOOOOOXOOOOXXOOOOXOOOXOOOOOOXOOOOXOO
OXOOOOOOOXXXXXXOOXOOXOXOOOOXXXOOOOOOOOXOOOOOOOOOOOXOOOXOXX
OOOOXOXOOOOOOOOOOOXXOXOOXOXXOOOXOOOOXOOOOOOOOOXOOXOXOOOOX
OOOXOXOXXOOOXOOXXOXOXOOXOXXXXXXOOOXXXOOOXXXOOOXOOOOOOXOOOO
OXOOXOOOOXOXOXOOOXXOXOOOXXOOXOOOOOXOOOOOOOXOOOOOOOXXXOOOO
OXXOOOOXOXOXXOOOOOOXOXOOOOOOOOOOOOXOXOOXXXOOOOOOOXOOOOXO
OOXOXOXOXOOXOOOXXXOXXOOOOOXOXOOOOOXOOOOXOXOOOOXOOOOOOXOX
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The simulated copolymer contains 1000 EOEMA units and 1000 PEG units.

Table 6.51 : Sequence lengths seen in the simulated sequence distribution of figure 6.51.

Sequence Distributions:

Length	EOEMA	PEG
1	181	251
2	77	87
3	56	29
4	28	16
5	25	6
6	7	3
7	10	0
8	5	3
9	3	1
10	3	1
12	2	0
13	1	0
14	1	0
23	0	1
310	0	1

Figure 6.52 : Computer simulated sequence distribution of a copolymer of NVP : PEG :: 50 : 50.

50 Mole % of Monomer A, NVP

50 Mole % of Monomer B, PEG

r(AB) = 0.002

r(BA) = 0.099

Polymerized to 100% Conversion

In the simulated copolymer NVP is represented by O and PEG is represented by X:

XOXXOXOXOXOXOXOXOXOXOXOXOXOXXOXXXOXOXOXOXOXOXOXOXXOXOXOXOXO
XOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXXOXOXOXOXOXOXOXOXOXOX
OXOXOXXOXXXOXXOXOXOXOXOXOXOXOXXOXXXOXOXOXOXOXOXOXOXOXOXXOXOXOX
OXOXOXXOXOXOXOXOXOXOXOXOXXOXOXOXOXOXOXOXOOXOXOXOXOXOXOXOXOXO
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OOOOOOOOOO

The simulated copolymer contains 1000 NVP units and 1000 PEG units.

Table 6.52: Sequence lengths seen in the simulated sequence distribution of figure 6.52.

Sequence Distributions:

Length	NVP	PEG
1	902	817
2	4	87
3	0	3
90	1	0

Figure 6.53 : Computer simulated sequence distribution of a copolymer of NVI : PEG :: 50 : 50.

50 Mole % of Monomer A, NVI

50 Mole % of Monomer B, PEG

r(AB) = 0.089

r(BA) = 0.26

Polymerized to 100% Conversion

In the simulated copolymer NVI is represented by O and PEG is represented by X :

XOXOXOXOXOXOXOXOXOOXOXOXOXOXOOXXXOXXXOXOXOXOXOOXOXOXOXXOXXO
XOXXOXOXOXOXOXOXOOOXOXOXOXXOXOXXOXOXOXOXOXOXOOXOXOXOXXOXOXX
OXXOXOXOXOXOXOXOXOXOXOXXXOXOXXXOXOXOXXOXXOXOXXOXOXOXXOXXXOXO
OXOXOXOXOXOOXOXOXOXOXOXOXOXXXOXOXXOXOXOXOXOXOOXOXOXOXOXOXO
XOXOXOXXXXOXOXOXOOXOXOXOXOXOXXXOXOXXXOOXXOXOOXOXXXOXXOXOXOXO
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OXOXXOXOXOXXOXOXOXOXOXOXOXXXOXOXOXOOOXXOXOXOXOXOXOXOXOXOXXO
XXOXOXXXOXOXOXOOOXOXOOXOXXOXOXOOXOXOXXXOXOXXOXXOXXOXOXOXOXX
XOXOXOXOXOXXOOXOXOXOXOOXOXXXOXOXXXOXXOXOXOXOXXXOXOXOXOXXXOXOOXO
XOXOXOXOXOXOXOXOXOXOXOXOOXOXOXOXXXOXOXOXOOXXOXXXOXOXOOOXOO
OXOXOXOXOXOXOXXOXOXOXOOXOXOXOXOXOXOXOXOXXXOXOXOXOXOXOXXXOXXOX
OXXOXOOXXOXXXOXOXOXOXOXXOXOXOXOXOXOXOXOXOXOOXOOXOOXXXOXOXOOOXO
XOXOXXXOXOXOXOXXXOXXXOXOXOXOXXXOXOXXXOXOXOXOXOXOXOOXOXOXOXOOXOXO
XOOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOOXO
XOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXXXOXOXOXOXOXOXOXXXOXOXXXOXOXOXOXO
XOOXOXOOXOXOXOXOOXXXOOXOXOXOXOOXOXOXOXOXOXOXOXOXOXXXOXOXOXOX
OXOXOOXXOXOXOOXXOXOOXXOXOXOXOXXXOXOXOXOXOOXOOOXOXOXOXOXOXOX
OXOXOOXOXXXOXOXXXOXOXOOOXXOXOXOXOOOXOXOXOXOOXOXOXOXOXOXOXOOO
XOXOXOXOXOXOXOXOXXXOXOXOXOXOXOOXOXOXOXOXOXOOXOXOXOOXOOXOXOX
OOXOXOOXOXOXOXOXOXOXOXOXOXOXOXXXOXOXOXOXOXOXOXXXOOXOXOXOXOXOOX
OXXOXOXOXOXOOOXOXOOXOXOXOOXOXOXOOOXOXOXOOXOXOXOOOOOOOOOOOO
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
OOOOOOOOOOOOO

The simulated copolymer contains 1000 NVI units and 1000 PEG units.

Table 6.53 : Sequence lengths seen in the simulated sequence distribution of figure 6.53.

Sequence Distributions:

Length	NVI	PEG
1	732	680
2	72	110
3	15	23
4	0	4
5	0	3
79	1	0

Figure 6.54 : Computer simulated sequence distribution of a copolymer of SPE : PEG :: 50 : 50.

50 Mole % of Monomer A, SPE

50 Mole % of Monomer B, PEG

r(AB) = 2.09

r(BA) = 0.379

Polymerized to 100% Conversion
In the simulated copolymer SPE is represented by O and PEG is represented by X:

OOOOOOXOOOXXXOOXOOOOXXOOXXOXXOOOOOOOOOOOOXXOXXOXOXOOOOXXOOO
OOOOOOXXOXOXOOXOOOXOOXOXXOOOOOOOXXXOOOOOOOXOOOXXOXXOOOOXO
OXXOOOOOXXOXOOOOOXXXXXOXOXOOOOOOXXXOXOOOXXXOOOXOXOOXOXOOOOX
OOOOOXOXOOOOXOOXXOOOOOOOOOXOOXOOOXOXOXOXOXOOXXOXOOOOOXOOO
OXOOOOOOOOOOXOOOOXOXXOOXOOXOXOXXXOOXXOXXOOOOOOOOOXXXOOO
OOOXXXOOOOOXOOXXOXOXOXOOOOOOOOXXOOXOOXXOOXXOOXXOXOOOOOOOX
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OXXOOXOOXOOOOOOOOOOOOOOOOXOOXOOXOXOXOXOXOOOOOOOOOXOXXXOO
OOOXXXXOOOOXXOXXOOOXOXOXOOOOXOOXOXOXOOXOOOXOOXOOOXOOOOXOX
OXOXOXXOOOOOOOOXOOXXXOXOOXXOOXOOOOXOXOOOOOOOXOXOOXOOOOOO
OOOOOOOOOOOXOOXOXOXXOXOXOOOXXXOOOOOXOOOXOOOOOOXOOXXOXXOOO
XXOXXOOOOXXOOOXXOOOOXOOXOOXOOXOOXOXXOOOOOOOXXOOOXOOOXOOXX
XXOXXOOXOOOOXXOOOXXOXOOXOOOOOOOOOXOXXXOXXOXOOXXXOOOOOOOO
XXOXOOOXXXXOOXOOXXOOXOXOOXOXOOXXXOXOXXOOOXOOXOOOXXOOOOOXXX
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OXOOOXOOOOOOOOXOXXOOXOOOOOOXOOOOXOXXOOOXOXOOOXOXOXOOOXOXX
OOOOOOXOXOXOOOOXXXOOXOXOOOOXXOOOXXXOXOOXOOXXOOXXOXOOOOOX
XOOXXXOOOOOOXOXOXOXOOOOXXOOOOOOXXXXOOXXOXOXOXOOOOOXXXXXXOO
XXXXXOOOOOOOXXXOXOXXXXOXOXOOXXXOOOXXOXOXOXOOOOOOXXXXXOXXOOO
OOXOOOOXOXOXOXOOXXOXOXOOXOXOXXXXXOXXXXXXXOXXXXXXOXXOOOOOOOX
OXOXOXXXOOOOXXOXOXOOOOOOOXXXXXOXXOXXOOXXXXOXXXOOOOXXOXXXOXX
XOXOOXXOXXXOOXOXXXOXXOOXOOXOXXXXOXOXXXXXXOOOXXOXOOXOXXOOXXO
XOOXXOOOOXXOXXXOXXOOXOXOOXXOXOXXOXOXXOOXXXOOXOXOOOXOOXOXOO
OXOXOOXXOXOXXOXOXXXOXXOOOXXXXXXXXOXXOOXXOOXOXXOOOOOOXXXXOXX
OXXXOXOXOOXOOOXOXOXOOXOOOXOXOXOOXXXXXOXOXXXXOXXOXOXXXOXXOOXXO
XXXXOOXXOOOOOXXXXXXXOXXXOXOXOXXXOOXXOOOXXXXXXOOXOXOXXOOOOXO
XOOOXXOXXXXXXXXXXOXXXXOOOOXXXOOXXXXOXOXXXOOXXXOXOXXXOXXOXOXXO
XXXOXXOOXOOXOOXOXOOOXXXOXXOXXXOXXOOOOOOXXXXOOOOXXOXXXXXOXOX
XXOXXOXOXXXXXXXOOXXXXOOXXXOXXXXXXOXXXXXOXOOXOXXXXXXXOXXOXXXX
XXOXXXXOOOXOXXXOOOXOXXXXXXXOOOXXXXXXXXXXXXXXXXXXXOXXXXXXXXXXX
XXXXXOXXXXXOXOXOXXXXXOXXOXXXXXXXXOXXXXXOXOXOXXOXXOOXXXOXXXXO
OOXXXXOXXXXXXXXXXOXXOXXOXXOXXOXXXXXXXXXXXXXOXXXXXXOXXOOXOXXOXX
XXXXOXOXXXXOXXOXXXOXXXXXXOXXXXXXXOXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXX

The simulated copolymer contains 1000 SPE units and 1000 PEG units.

Table 6.54 : Sequence lengths seen in the simulated sequence distribution of figure 6.54.

Sequence Distributions:

Length	SPE	PEG
1	227	234
2	98	113
3	42	44
4	25	17
5	15	11
6	12	9
7	9	6
8	4	2
9	6	0
10	1	2
11	1	0
12	0	1
17	2	1
18	0	1
106	0	1

Figure 6.55 : Computer simulated sequence distribution of a copolymer of ITA : PEG :: 50 : 50.

50 Mole % of Monomer A, ITA

50 Mole % of Monomer B, PEG

r(AB) = 2.896

r(BA) = 0.333

Polymerized to 100% Conversion

In the simulated copolymer ITA is represented by O and PEG is represented by X :

XOOOOXOOOOOXXOOOOOOOOOOOXOOOOOOOOXOOXOOOXOXOXOOOOOOOXOXO
OOOXOOOXOXXOOOOOOXOOOOOOXOOOOOOOOOOOXOOOOOXXOOOOOOOOOXOO
OOOXOOXOXXOOOOXXOOOOOOOOXOXXOOOXOOOXXOOXOOOOOXOOOOXOOOXOX
OOXOOOOXXOOOXOOXOOOOOXOOOOOOXOOOXXOXXOXOOXXOXOOXOOOOOOXXO
OOOXOXOOOOXXOOOXOOOOXOOXOOXOOXOOOOOXXXOOOOXXXOOXXOOOOOXOO
OOOOXOOOXXXOXOOXXOOOXXOOXOOOXOXXOOOXOOOOOOOOXXXOOXOXXOXXO
OOXOOXOOOOOOXOXOOOXOOXXOOOOOXOOOXXOOXXOOOOOOOXOOOOOOOXOO
OOXXOXOOOXOOOXOOXOXOOOXXOOXXXOOOOOOOXOOOOOOXOOOOOOOOXOXOO
OOOOOXOXOOOXXOOOOOXOOOXOOXXOXOOXOOXXOOOOOOXOOXXOOXOOOOOXX
OXOOXOOOXXOOOOOOOOXXOOOXOOOXXOOOOOOXOOOOXXOOOOXOXXOXXO

XOOOOXXOOOXOOOOOXXOOOOOXOOXOOOOXOOOXOOOOOXXXXOXXXOXOXOOXOO
OOOXOXOOOOOOOOXOOXOOOOXXOXOXOOXXXOOOXOOOOOOXOOXOOOXOOXOXO
OXOOOOOOOXOOXOXXXOOOXXXXOOOOOXOXOOXXOXOXOOOXOXXOXXOOOOOXO
OOXXOOOOOXXXOOOXXOOXOOXXXOXOOOXXOOOOOOXXXOOOXOOOOXXXXXOXOX
OOOOOOXOOOOOOOXOOOXOOOXOOOXXXOOOXOOXXXOOXOXOOOXXXOOOXXOOO
XOOOOXXOXXXXXOXOOOXOOXOOOOXOXOXXOOXOOOOOXXXOOOOOOOOXOOOOO
OXXOXXOOOOOOOXXOOOXXXXXOOXOOOXOOOXXOXOOOOXOOXOOOOXXOXXOOOX
OOXOOOOOXOOXOOOOXOOOOXXOXOOOOXXOOOXXOXXOOXXOXOXOOXXOXXXOXX
OOOXXOOOXXOOXOXOOOXXXOXXOOOOOOXOOOOXOOXXOXXXOXOXXXOOOXXOXX
OOOXXXOXXXOOXOXOXXXXOOOXXOXOXXXXOOOOOXOXOXOOOXOXOOOOOXOOOO
XOXOOXXXOXXOXOOXXXXXOOXOXXXOXXOXOOOXOOOXXXXOXOXXXOOOXXOXXXO
OXOOOXOXXOXOXXXOXXXOXOOXXOXOOXOOXXOXOXXXOXXXXXOOXOXOOXXXXXOX
OOOOXOOOOOXXOXOXXXOOOXOOOOXXXOOOOOOOXXOOXOOOOOXXXXXOXXOXOX
XXOOOXXXXOOXOXXXXOOXXXXXXOXOOXOOXOOOXXXOXOXOOOXXOOXOXOOXXXX
XOOXXOOXOXOXXOOXOOXOXXOXOOXXXOOXXXOXXOXOOOXXOOOXXOOXXXOXOO
OXOOOXOXXXOXXOXXXXXXXXOXXXOXXXXXXOXOXXXOOOOOOOOXXXOOXOXXOOXX
OOXXOXOXXXXXOXOOXXXXOXXOOOXXXXOOXXOXXXXXXOXXXXOOOXXOOXXXXXOX
XOOOXXXOXOXXXXXXOXXOXOXXOOOXXOXOXXXOOXOOOXXXXXXXXXXXXOXXXOXO
OXXOOXOXXOXXXXXXXXXXXOOXOOXOXXXXXOOOXOXXXXOXXXXXXXXOOXXXXX
OOXOXXXXXXXXXXXXXOXXOOXXXOXXXXXXXOXXOXXXXXXXXXXXXXXOXXXXXXX
XOXXXXOXOXXXXXXXXXXOXXXXXXXXXOXXXXXOXXXXXXXXXXXXXXXXXXXXXXX
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XXXXXXXXXXXXXX

The simulated copolymer contains 1000 ITA units and 1000 PEG units.

Table 6.55 : Sequence lengths seen in the simulated sequence distribution of figure 6.55.

Sequence Distributions:

Length	ITA	PEG
1	148	209
2	86	99
3	71	42
4	27	12
5	23	13
6	13	4
7	10	1
8	7	2
9	2	1
10	0	2
11	2	1
12	0	1
13	0	1
14	0	1
228	0	1

From the terpolymer simulations (shown in figures 6.45 to 6.48) and the copolymer simulations (shown in figures 6.49 to 6.55), we may deduce that the average sequence lengths of these highly hydrophilic membranes, would be quite short. This, as the results illustrate, would prevent significant interactions from occurring, between the serum proteins and the surfaces of these membranes. This will subsequently result in lowering the amount of cell adhesion that occurs at these surfaces. The fact that these membranes also contain biomimetic monomers will serve to enhance the biotolerance of these materials, as noted by the much reduced amount of cell adhesion that occurs at the surface of these materials.

6.2 Cell Adhesion Analysis on Spin-coated polymers at various Conversions

In this section we will consider more directly how the sequence distribution observed at various stages of conversion of linear polymers synthesized by solution polymerisation, by the method described in chapter 2, affect the % cell adhesion on spin-coated films of these polymers.

6.21 HEMA/NVP Polymers

Figure 6.56, below, shows the % cell adhesion and % EWC for polymers of HEMA/NVP with the compositions as shown in table 6.56.

Figure 6.56 : HEMA/NVP polymers

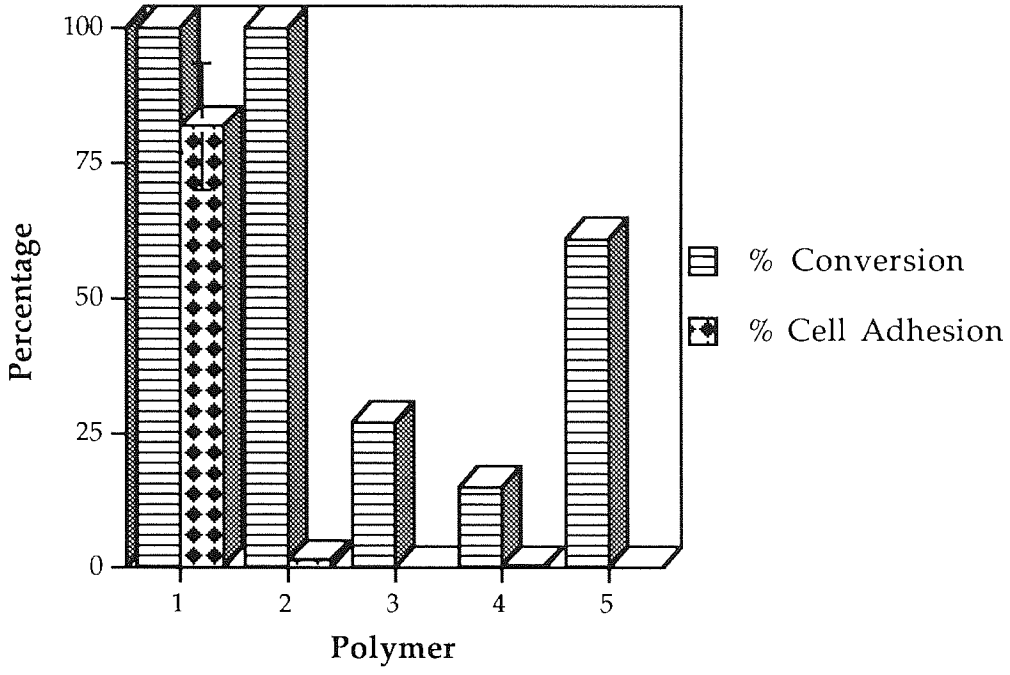


Table 6.56 : Data for Figure 6.56

No.	Polymer/ Copolymer	Mole % in Polymer (Mole % in Feed)	Percent Conversion	% Cell-Adhesion
1	PolyNVP	100	100	87.4
2,9	PolyHEMA	100	100	1.3
3	HEMA:NVP	64.42:35.58 (20:80)	27	0
4	HEMA:NVP	86.16:13.84 (60:40)	15	0.25
5	HEMA:NVP	78.21.52 (60:40)	61	0

From figure 6.56 we see that as the % conversion rises the % cell adhesion decreases. From the simulated sequence distributions shown in figures 4.22 and 4.23 and the analysis of number-average sequence lengths presented in section 4.2 chapter 4, we observe that increasing conversion, for these systems, results in an overall decrease in the individual number-average sequence lengths which results in an improvement in the sequence distribution seen at higher conversions in comparison to that seen at lower conversions. This change observed in the sequence distribution with increasing conversion is characteristic of a copolymerisation where the two monomers have quite different reactivity ratios. Thus, here it appears that as the sequence distribution improves the amount of cell adhesion decreases.

6.22 MMA/NVP Polymers

Figure 6.57, below, shows the % cell adhesion and % EWC for polymers of MMA/NVP with the compositions as shown in table 6.57.

Figure 6.57 : MMA/NVP polymers

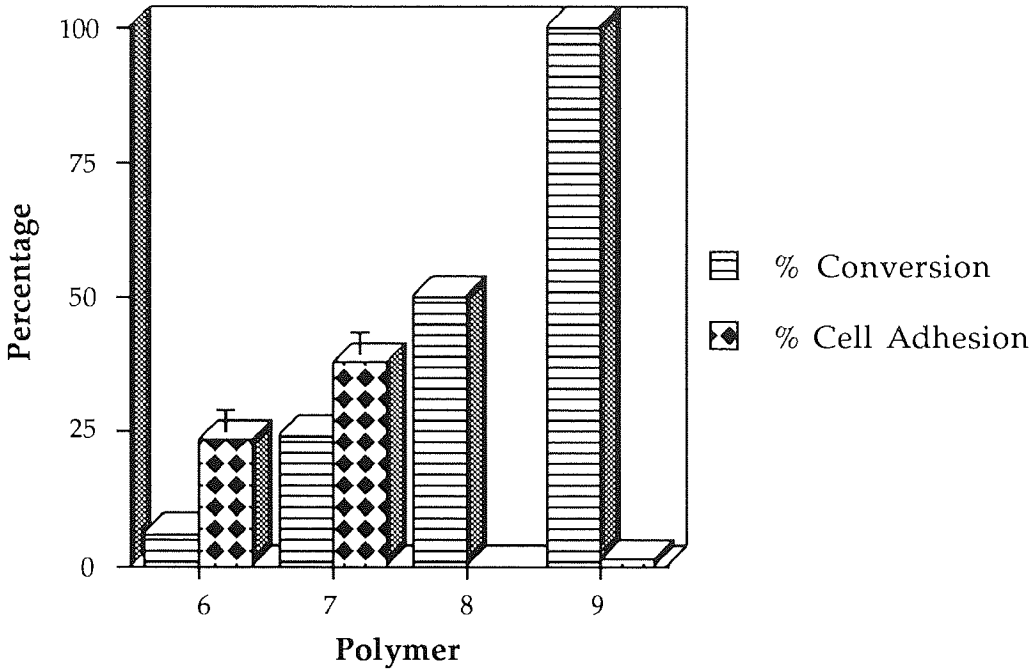


Table 6.57 : Data for Figure 6.57

No.	Polymer/ Copolymer	Mole % in Polymer (Mole % in Feed)	Percent Conversion	% Cell-Adhesion
6	MMA:NVP	86.21:13.79 (60:40)	6	23.4
7	MMA:NVP	82.44:17.56 (60:40)	24	37.9
8	MMA:NVP	77.31:22.69 (60:40)	50	0

From figure 6.57 we see that as the % conversion rises the % cell adhesion decreases. Except for polymers 6 and 7, but here if we consider the % compositions shown in table 6.57, and the simulated sequence distribution

shown in figures 4.22 (chapter 4) we see that there is very little real difference between the sequence distributions seen for these two samples at the two conversions mentioned above. Where as with a significant increase in the conversion (and subsequent increase of NVP in the copolymer), we see a much improved sequence distribution, as shown in figure 4.22 and the accompanying analysis of number-average sequence lengths presented in section 4.2 chapter 4, we again observe that increasing conversion, for these systems, results in an overall decrease in the individual number-average sequence lengths which is reflected in an improvement in the observed sequence distribution at higher conversions in comparison to that at lower conversions. This change observed in the sequence distribution with increasing conversion is characteristic of a copolymerisation where the two monomers have quite different reactivity ratios. Thus, here it appears that as the sequence distribution improves the amount of cell adhesion decreases.

6.23 HEMA/MMA Polymers

Figure 6.58, below, shows the % cell adhesion and % EWC for polymers of HEMA/MMA with the compositions as shown in table 6.58.

Figure 6.58 : HEMA/MMA polymers

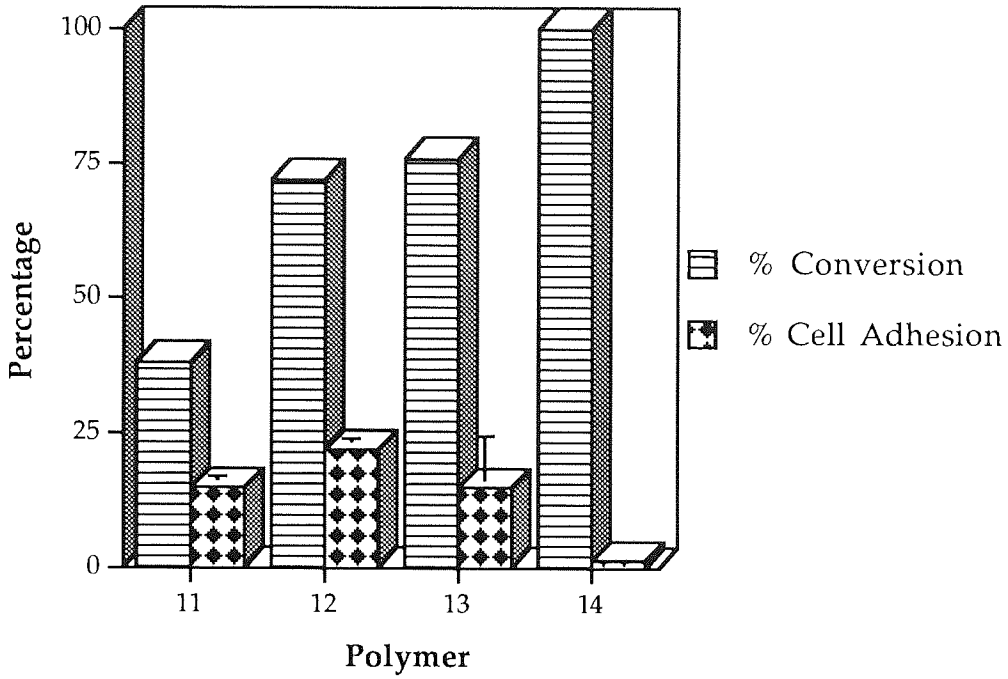


Table 6.58 : Data for Figure 6.58

No.	Polymer/ Copolymer	Mole % in Feed	Percent Conversion	% Cell-Adhesion
10	HEMA:MMA	50:50	38	14.7
11	HEMA:MMA	50:50	72	21.7
12	HEMA:MMA	50:50	76	14.7

From figure 6.58 we see that there is no real correlation between % conversion and % cell adhesion. This probably reflects the fact that monomers with similar reactivity ratios do not show a significant change in the sequence distribution seen with increasing conversion. This is illustrated, below, in figure 6.59 and table 6.59, which show the simulated sequence distribution of individual monomer units that would be seen upon copolymerisation. From the previous two examples we see that an increase in the conversion results in a decrease in the % cell adhesion, simply because an increase in the conversion of those two systems results in an improved sequence distribution courtesy of a reduction in the individual number-average sequence lengths of the two monomers concerned. This does not occur in this system and we would not therefore expect to see a subsequent reduction in % cell adhesion with increasing conversion, this is observed clearly in figure 6.23.

Figure 6.59 : Computer simulated sequence distribution of a copolymer of HEMA : MMA :: 50 : 50.

50 Mole % of Monomer A, HEMA

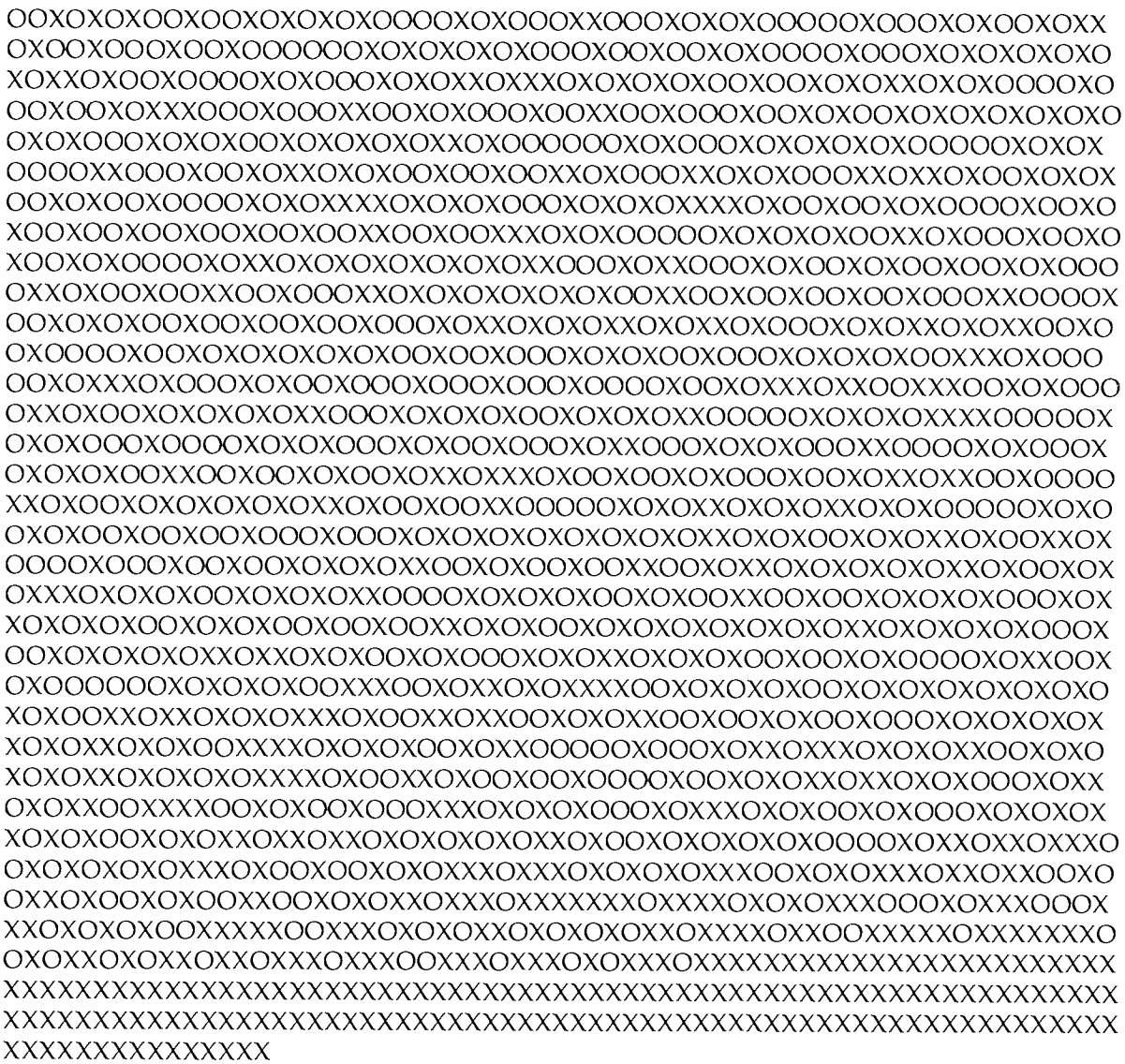
50 Mole % of Monomer B, MMA

r(AB) = 0.810

r(BA) = 0.192

Polymerized to 100% Conversion

In the simulated copolymer HEMA is represented by O and MMA is represented by X :



The simulated copolymer contains 1000 HEMA units and 1000 MMA units.

Table 6.59 : Sequence lengths seen in the simulated sequence distribution of figure 6.24

Sequence Distributions:

Length	HEMA	MMA
1	402	495
2	146	95

3	53	30
4	21	9
5	9	2
6	3	0
7	0	2
165	0	1

6.3 Summary

It is apparent in this chapter that the sequence distribution of the individual monomer units within the synthesized polymer does have some affect upon the subsequent cell adhesion characteristics of the material. This affect seems more pronounced at moderate equilibrium water contents (EWC), although at higher EWC's the reduction in % cell adhesion is reflected in an underlying trend of improving sequence distributions of the individual monomer units within the polymer. Also it is observed, in section 6.15, that the sequence distribution provides an ideal method of understanding how the improvement seen in the macro property, e.g., the EWC and the subsequent improvement in resistance to cell adhesion, with the introduction of different monomer units is reflected in the change of the basic sequence distribution of the individual monomer units. It is also observed that the sequence distribution alone is not sufficient to predict the cell adhesion characteristics of the synthesized materials. Noticeably, monomers with strong individual chemical functionalities such as being permanently charged may produce effects which over-ride those predicted from the micro-structure analysis of the synthesized material.

Thus in general a relatively good sequence distribution tends to offer better resistance to cell adhesion. This is simply because, by having a relatively good

sequence distribution, we avoid the formation of large hydrophobic blocks, thus we will reduce the amount of protein adsorption. This is important as it will consequently reduce the amount of cell adhesion that occurs, at the surface of these materials, since cell adhesion depends upon the primary adsorption of cell adhesion proteins, such as vitronectin and fibronectin.

CHAPTER SEVEN

CONCLUDING DISCUSSION

7.0 Concluding Discussion

In recent years biomaterial scientists have discovered to their detriment that the large selection of materials currently being used in biological environments, most of which were designed for commodity or engineering applications, have many shortcomings. Some of the most basic problems arise from the fact that these materials have tended to be relatively hydrophobic. In contrast biological environments, for example the human body, tend to be based on aqueous systems. Additionally, currently used materials have generally been chosen because of ease of fabrication, rather than because they may duplicate the behaviour of a particular natural tissue in its normal environment. Thus, usually these materials are structurally fairly simple and functionally inert, compared to the living structurally complex and highly responsive natural material they will be replacing. This tends to result in biocompatibility problems which are initiated by the dynamic interface conversion processes. This marks the onset of the spoilation processes and may result in the synthetic tissue being ultimately rejected.

Many factors are known to affect this biocompatibility or biotolerance of the synthetic material. One aspect which has been the basis of the study presented in this thesis is the sequence distribution of the individual monomer units in relation to the non-specific adsorption of proteins with the subsequent adhesion of cells at the surface of these materials. By studying naturally occurring polymers, for example proteins, we may observe that the molecular architecture of these materials is composed of hydrophilic, hydrophobic and charged units arranged in short, regular sequences. Existing biomaterials, even when hydrophilic, such as hydrogels, do not attempt to make use of these

principles. At Aston it has been noted that polymers with short, regular sequences of individual monomer units tend to be less susceptible to non-specific protein adhesion in contrast to polymers with long, extended sequences of individual monomer units.

Since it is known that, generally, cells will only adhere to surfaces that deposit proteins. We may utilise this information by using cell adhesion studies as a biological probe, to ascertain the susceptibility of the surface, of a prospective biomaterial, to non-specific protein adhesion. And, thus we may gain an indication to the biocompatibility or biotolerance of this material. This is a very important consideration since many hydrophilic materials are used in diverse biological applications, for example in liver support systems, synthetic cartilage, soft tissue prostheses, etc. This has been the ultimate aim of this study to synthesize biologically responsive materials which are based upon a relatively good sequence distribution of the individual monomer units. Whilst also having low cell adhesion characteristics. Thus in effect trying to mimic naturally occurring materials.

The ability to model the sequence distribution of free-radical polymers and therefore to design and synthesize polymers which mimic the behaviour of function of biological systems is of great importance. The examples given by the computer simulated sequence distributions of the various generic contact lens materials e.g., Etafilcon-A, Surfilcon-A, etc., clearly demonstrate the power of this technique in giving us a visual representation of the individual monomer units within the sequence distribution. Contact lens materials were chosen to demonstrate this computer simulation technique because, of biomaterials, their

compositions are amongst the most systematically regulated, they are hydrophilic and also they provide a wide range of compositions for analysis.

It is well known that the quantity and distribution of a cross-linker in polymeric materials has profound affects upon the subsequent properties of these materials. Comparing relatively simple copolymeric materials such as Etafilcon-A and Surfilcon-A, we observe how different cross-linkers, even when present at only 1% concentration, can be significantly differently distributed throughout the simulated sequence distributions of these materials. This will in due course affect the macro-properties (e.g., EWC, tensile strength etc.,) of these materials. We may illustrate this situation by perusing the data shown in section 6.15 of chapter 6. Here a set of HEMA/NVP membranes were synthesized with different cross-linkers. Each membrane contained only one type of cross-linker present at one mole percent. The difference in the EWC's and percentage cell adhesion properties is reflected in the differing sequence distributions observed for these membranes with the various cross-linkers.

Now reverting back to our original situation, where we were considering the different simulated sequence distributions seen for the contact lens materials Etafilcon-A and Surfilcon-A, with different cross-linkers. The question that arises is why the different cross-linkers may produce such different affects in these contact lens materials. The answer lies in the reactivity ratios of the pairs of monomers that constitute these copolymeric materials. Considering Etafilcon-A, we see that the two monomers of this copolymeric material have relatively similar reactivity ratios. Therefore, as shown by the simulated sequence distribution, we have one monomer relatively well dispersed in the other, to produce a relatively consistent sequence distribution from the start of

the reaction to 100% conversion. Although, the vastly different concentrations of the two monomers precludes the possibility of producing a relatively good sequence distribution (short, regular sequences of individual monomer units). Thus, here, we may note that the distribution of different cross-linkers at 1% concentration, in such a sequence distribution of monomer units, is likely to be fairly uniform throughout the copolymer. For example EGDMA which, of the cross-linkers used, has the most similar reactivity ratios to the main constituent monomers is found to be fairly uniformly distributed throughout the simulated sequence distribution of this material (see figures 3.21 & 3.22).

In contrast, if we consider Surfilcon-A, we see that the two monomers of this copolymeric material have vastly different reactivity ratios. This is reflected in the simulated sequence distributions seen in figures 3.27-3.32, in chapter 3. Here we see that in the initial part of the polymerisation the more reactive monomer is consumed in preference to the lesser reactive monomer. This is reflected in the simulated sequence distribution, where we see large blocks of the more reactive monomer interspersed with isolated units of the lesser reactive monomer. As the reaction continues we gradually exhaust our supply of the more reactive monomer, and at approximately 60% conversion we produce a large residual block of the lesser reactive monomer. Not only is this a relatively poor sequence distribution (long, extended sequences of individual monomer units), but the changes in the sequence distribution from the start of the polymerisation to 100% conversion are quite distinct. Thus, here, we may note that the distribution of different cross-linkers, even at 1% concentration, in such a sequence distribution of monomer units, is likely to be quite diverse for each type of cross-linker. Thus for example EGDMA, which is more reactive than NVP, is found to be predominantly consumed by 50% conversion. In

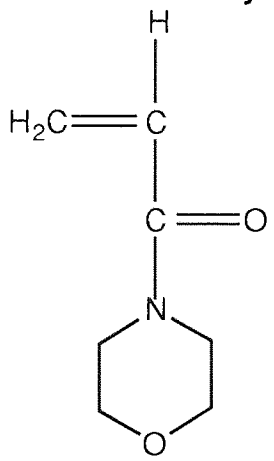
contrast both DATDAM and TAC display a similar reactivity towards NVP, and both of these cross-linkers are similar or slightly more reactive towards MMA than NVP. This results in these latter two cross-linkers being more uniformly distributed throughout the simulated sequence distribution seen for Surfilcon-A, in contrast to EGDMA (see figures 3.27-3.32). Consequently we would expect to see some variation in the macro-properties of this material with different cross-linkers. This type of material is exemplified in the aforementioned membranes analysed in section 6.15 of chapter 6, which do show noticeable differences in the macro-properties with different cross-linkers. These differences in the macro-properties, are reflected in the simulated sequence distributions of these membranes with the different cross-linkers. This effect is more pronounced in HEMA/NVP copolymers, since HEMA $\approx$ MMA, but HEMA does not contribute to the rigidity of the backbone. Therefore the modulus is for NVP/HEMA than NVP/MMA copolymeric materials, and thus is even more dependent upon a really good network of cross-links for good mechanical properties.

The preceding discourse serves to emphasize the importance of reactivity ratios in determining the simulated sequence distribution that would be seen upon the polymerisation of a set of monomer units. The basic reactivity ratio data has become increasingly available since copolymerisation theory was first developed, but the difficulty in visualising and thus interpreting the data, in terms of its affect upon the subsequent reaction between the monomer units concerned, has resulted in its lack of accessibility. Also we note that historically polymerisation studies have been concerned with purists aspects, that is studies based on low conversion and low concentration polymers. In stark contrast, biomaterials tend to consist of materials at high conversion and high

concentration, and there has been little drive for the analysis of such materials from polymer science. A few key trends in the reactivity ratios have been noted, as mentioned in chapter 3,. With the development of this simulation technique, we may justifiably say that, not only have we put flesh onto the proverbial bones but we have provided a complete functional attire.

This work is also seen as a tool for new monomer synthesis because, from the Q-e scheme we have an ability to predict the reactivity of target monomers and to select appropriate polymerisable stems for functional groups of interest. We may illustrate this principle by considering NVP, which is very hydrophilic but unfortunately it has a quite low reactivity. Looking for similar monomers we find Acrylamide (AM) which has almost the same type of functional groups as NVP, it is very hydrophilic and more reactive than NVP, but it is readily hydrolysed, thus here we have a problem with stability. Attachment of methyl groups to the amide nitrogen of AM produces N,N-dimethyl acrylamide (NNDMA), this is much less prone to hydrolysis than AM. This is also fairly hydrophilic and still is more reactive than NVP. Unfortunately the problem with NNDMA is that the methyl groups on the nitrogen are susceptible to chain transfer reactions, during polymerisation. Thus it is suggestive that we would like to have the AM type stem for the new monomer, but to improve the stability we probably need to have the nitrogen of the amide group as part of a ring, possibly even a heterocyclic ring containing another electro-negative atom such as oxygen. This may lead to a further improvement in the hydrophilicity of this new monomer. This process of logical reasoning led to the synthesis, by colleagues in this research group[104], of a potentially valuable monomer N-acryloyl morpholine (NACM), whose structure is shown below:

Figure 7.1: Structure of N-Acryloyl morpholine



N-Acryloyl morpholine

This monomer has only recently become available on a large scale at a price comparable to other hydrophilic monomers through a Japanese chemical company. Its Q-e data is as follows, Q = 0.39, and e = 0.08. A sample of reactivity ratios, calculated using the Q-e scheme, with some common hydrophilic monomers are given in table 7.1 below:

7.1 Table of Reactivity Ratios with N-acryloyl morpholine

Monomer 1	r_1	Monomer 2	r_2
HEMA	3.799	NACM	0.211
MMA	1.759	NACM	0.512
NNDMA	0.798	NACM	0.407
NVP	0.014	NACM	3.868
NVI	0.168	NACM	3.336
SPE	0.226	NACM	0.280

The increased reactivity of NACM compared to NVP can be illustrated by running a computer simulation of the sequence distribution of the contact lens

material Tetrafilcon-A. We already have the simulated sequence distribution for this material, in figure 3.41, by replacing NVP in this formulation with NACM, we may see if there is any improvement upon the simulated sequence distribution, shown in figure 3.41.

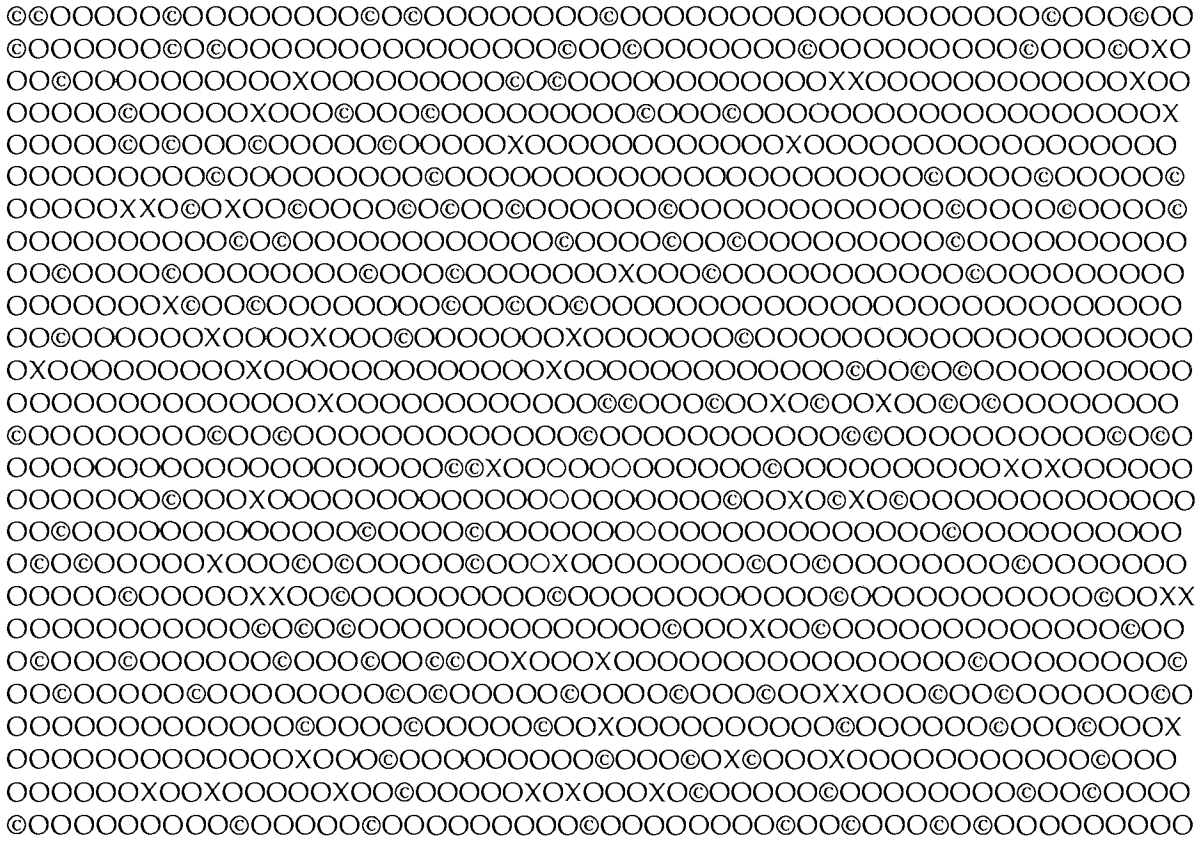
Figure 7.2 : Computer simulated sequence distribution of pseudo Tetrafilcon-A contact lens formulation, containing NACM in place of NVP.

80 Mole % of Monomer A, HEMA
10 Mole % of Monomer B, NACM
10 Mole % of Monomer C, MMA

r(AB) = 3.799 r(AC) = 0.810 r(BA) = 0.211
r(BC) = 0.512 r(CA) = 0.192 r(CB) = 1.759

Polymerized to 100% Conversion

In the simulated terpolymer HEMA is represented by O, NACM is represented by X and MMA is represented by © :



The simulated terpolymer contains 1600 HEMA units, 200 NACM units and 200 MMA units.

Table 7.2 : Sequence lengths seen in the simulated sequence distribution of figure 7.2.

Sequence Distributions:

Length	HEMA	NACM	MMA
1	59	107	188
2	51	7	6
3	46	0	0
4	18	2	0
5	26	1	0
6	13	1	0
7	6	0	0
8	18	1	0
9	14	0	0
10	5	0	0
11	6	0	0
12	10	0	0
13	10	0	0
14	3	0	0
15	2	0	0
16	3	0	0
19	2	0	0
21	4	0	0
22	1	0	0
24	1	0	0
26	1	0	0
29	1	0	0
52	0	1	0

Looking at figure 7.2 and table 7.2 we do see some improvement upon the sequence distribution shown in figure 3.41, there is a reduction in the total number of sequence lengths seen and we have a much smaller block of residual monomer at the end of the reaction.

Extensive use of these computer simulation programs can only be made once their validity has been determined. Two main parameters were assessed here, the composition and the number average-sequence lengths of the individual monomer units. This was carried out through the analysis of linear polymers synthesized by free-radical solution polymerisation. The composition data gained from elemental analysis and ^{13}C NMR was compared with that given by the computer simulated sequence distribution. Number-average sequence lengths for individual monomer units were determined by ^{13}C NMR analysis and compared with those calculated from the computer simulated sequence distribution. As shown in chapter four of this thesis, both parameters from the computer simulated sequence distribution compared quite closely with those determined experimentally. Although the analysis has been carried out on linear polymers at high conversions, we must remember that the computer simulation programs produce a sequence distribution of monomer units from 0% to 100% conversion. But the good correlation between the predicted and observed results, at these relatively high conversions, suggests that we may confidently base the future synthesis of polymeric membrane materials, synthesized to 100% conversion, on the predictions of the sequence distribution that would be seen when a set of monomers were to be polymerised, produced by the computer simulation programs.

In chapter five we presented an approach which allows one to manipulate the use of monomers, with their reactivity ratios, in such a manner to enable us to design polymers with controlled sequence distributions. This is particularly useful where the monomers in a certain formulation, have very different reactivity ratios. One must not under-estimate the value of such approaches, since the ability to simulate the sequence distribution of monomers upon polymerisation, is in itself not conduce to producing polymers with relatively short, regular sequences of individual monomer units, which would mimic the molecular architecture of naturally occurring materials. Thus we realise the importance of such procedures in aiding the development of materials more akin to naturally tissues.

Chapter six describes how cell adhesion studies have been used as a biological probe in investigating the surface biocompatibility or biotolerance of polymeric membranes containing controlled sequence distributions of individual monomer units. Before we look at the conclusions that can be drawn from the results of chapter six, a brief but critical review of the mechanism of deposition of proteins would be highly beneficial. Studies with fibrinogen have shown that cell adhesion will only occur on surfaces which will first deposit fibrinogen, and only when the conformation of fibrinogen is altered in some way. Fibrinogen deposited on a surface which has previously been coated with denatured albumin does not promote cell adhesion. Comparing the conformations of fibrinogen on this surface and on surfaces where fibrinogen is adsorbed directly onto the native polymer, we find that the conformations are vastly different. On this latter surface it was found that the α-helical structure of fibrinogen, which controls the way that the protein coils up into its globular form, was totally destroyed and what was seen, was a sheet like

structure of fibrinogen over the polymer surface, i.e., adsorption of fibrinogen onto this polymer surface has resulted in the denaturation of the protein. In contrast the polymer surface which was previously coated with denatured albumin, produced little change in the subsequently adsorbed fibrinogen, which was found to exist almost exclusively in its α-helical globular form. This surface did not promote cell adhesion. Work with albumin, has also shown that the protein undergoes various degrees of conformational change when adsorbed on different surfaces[17]. The greatest conformational change appears to occur on hydrophobic surfaces, but hydrophilic surfaces do cause some conformational changes and this is affected by the time of adsorption onto the surface. The greater time the protein spends on the surface the greater the conformational change produced in it. It seems that interactions between hydrophobic surfaces and the protein are much stronger than interactions between hydrophilic surfaces and the protein. Consequently greater conformational change is produced when proteins are adsorbed onto hydrophobic surfaces, than hydrophilic surfaces. This greater conformational change is more likely to cause the protein to be denatured. The interaction with hydrophilic surfaces is such that it is likely the protein could adsorb reversibly and since it spends a small amount of time on the surface, it is less likely to be significantly altered conformationally. It must be noted that here, as mentioned earlier, surfaces that undergo primary albumin adsorption tend not to promote cell adhesion. Similar experiments carried out using fibrinogen, produced closely related results. It was observed that the greatest conformational change in fibrinogen was produced when adsorbed onto hydrophobic surfaces compared to hydrophilic surfaces. Research on the size of islands or surface domains on the polymer surface, has shown that the total amount of cell adhesion that occurs on these polymer surfaces is directly proportional to the

size of these surface domains[19]. The size of surface domains necessary to illicit a cell adhesion response varies with the shape of the domains. Since protein adhesion must occur before cell adhesion can occur on these surfaces, it suggests that there are two possible reasons for this relationship of cell adhesion being proportional to the size of surface domains. Firstly, if the surface domains are so small then insufficient interaction may occur between the surface and any adsorbed proteins, this will result in very little change in the conformation of the adsorbed proteins, such that any binding sites for cell adhesion may not be exposed; secondly, if the surface domains are widely spaced, then even if we have protein adsorbed in the right conformation for a cell to form an attachment to it, the distance between these cell attachments, related to the distance between the surface domains, will be such that stable binding focal points cannot be formed between the cell and the polymer surface. Poly(HEMA) is known to be resistant to non-specific protein adsorption, it seems to be a logical place to start with when developing new biomaterials. Various biomaterials are required to cope with the different properties needed for different biological environments. Thus to improve the properties of poly(HEMA) it is necessary to copolymerize HEMA with other monomers. Studies have shown that the alteration of the poly(HEMA) surface through the introduction of another monomer by 1 ppm, removes its immunity to fibronectin adsorption(another serum protein)[12]. Thus it appears that once we start to add or combine different monomers to polyHEMA, we need to consider the sequence distributions that would be seen upon polymerization of the monomers. Since it is evident that the smaller the sequence lengths of the individual monomer units, the less chance the adsorbed protein has to interact with these surface domains, therefore it is less likely to undergo great conformational changes, which might result in it not

exposing the necessary binding sequences that a cell requires for it to form an attachment to the surface. Therefore controlled sequence distributions of individual monomer units appear to be important in preventing non-specific protein adsorption and consequently reducing the number of cells that will adhere to the surface. The results of chapter six confirm this, and suggest that the sequence distribution of individual monomer units does have some affect upon the subsequent cell adhesive properties of these materials. This is a very important result since any future development of prospective biomaterials, must be accomplished with this result borne in mind. When considering other substances that may be deposited on these polymer surfaces a similarly systematic approach to that applied to protein deposition may be used. For example another large group of substances often found deposited on polymer surfaces are the lipids. Lipids occur in nature in a wide variety of forms, they may be saturated, unsaturated, may contain numerous functional etc., but their over-riding characteristic is that they tend to be hydrophobic. It is this characteristic which will determine their interaction with polymer surfaces. Polymer surfaces containing hydrophobic groups or regions will illicit the strongest interactions with lipids, whilst regions containing hydrophilic groups will illicit much weaker interactions with lipids. Here again a controlled sequence distribution of monomer units in the polymer, will ensure that any regions of hydrophobocity are relatively diverse, thereby reducing the total interactions with lipids and thus minimising the amount of lipids that will be deposited on the polymer surface.

7.1 Recommendations for Further Work

(1) To modify the computer simulation program such that the output is more readily interpretable, that is instead of having basic symbols representing the monomer units we may have, say, the abbreviated forms of their names. This would allow a much easier interpretation of the simulated sequence distribution.

(2) To incorporate a data base into the computer program, perhaps in the form of a two or three dimensional array. This would hold a store of reactivity ratios for a variety of monomers, which the program can be asked to access to run simulated sequence distributions.

(3) To investigate thoroughly the affect of a single type of functional group of varying sequence lengths, amongst a background of polyHEMA or polySTY, both of which are known to be relatively non-adhesive to cells as homopolymers.

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REFERENCES

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APPENDIX ONE

MATERIALS SYNTHESIZED

MATERIALS SYNTHESIZED

Solution polymerized linear polymers :

Monomers	Feed Ratio (mol %)
HEMA : MMA	50 : 50
HEMA : NVP	20 : 80
HEMA : NVP	60 : 40
MMA : NVP	60 : 40
HEMA	100
MMA	100
NVP	100

Cross-linked membranes :

All membranes contain 1% EGDMA cross-linker, except where another is mentioned.

Hydrogel No.	MONOMERS (mol %)					
	HEMA	MMA	EMA	STY	NVP	NVI
1	100	-	-	-	-	-
2	33	33	34	-	-	-
3	40	30	30	-	-	-
4	30	40	30	-	-	-
5	33	34	-	33	-	-
6	50	25	-	25	-	-
7	60	10	-	30	-	-
8	60	30	-	10	-	-
9	-	33	-	-	33	34
10	-	40	-	-	30	30
11	-	35	-	-	20	45

Hydrogel No.	MONOMERS (mol %)				
	HEMA	NVP	EGDMA	DATDAM	TAC
12	60	40	-	-	-
13	55	45	-	-	-
14	50	50	-	-	-
15	59	40	1	-	-
16	59	40	-	1	-
17	59	40	-	-	1

Hydr-gel	MONOMERS (mol %)								
	HEMA	NVP	NVI	SPE	NNDMA	HEA	EOEMA	PEG	ITA
18	-	40	35	25	-	-	-	-	-
19	-	40	40	20	-	-	-	-	-
20	-	50	50	-	-	-	-	-	-
21	62	11	-	-	27	-	-	-	-
22	-	11	-	-	27	62	-	-	-
23	-	-	-	-	38	50	12	-	-
24	-	38	-	-	-	50	12	-	-
25	-	9	-	2	27	25	12	25	-
26	-	-	9	2	27	25	12	25	-
27	-	9	-	-	27	25	12	25	2
28	-	9	-	-	27	25	12	22	5

APPENDIX TWO

COPOL PROGRAM LISTING

Copol 1

```
10    REM COPOLYMER-by the Monte Carlo method
20    REM S.J.MOSS modified by P.H.Corkhill
30    REM Chemical Engineering and Applied Chemistry
40    REM Aston University, Birmingham, B4 7ET, ENGLAND
100   REM *** MAIN PROGRAM ***
110   GOSUB 500
120   GOSUB 1000
130   GOSUB 1500
140   GOSUB 1800
150   GOSUB 2000
160   GOSUB 3000
170   GOTO 4000
200   STOP
500   REM *** INITIALISE ***
510   INCA=0:INCB=0
530   TA=0:TB=0:SUM=0
540   NA=0:NB=0
550   SA=0:SB=0:AMAX=0:BMAX=0
560   CLS:PRINT"PLEASE WAIT INITIALISING ARRAYS"
570   FOR I=1 TO 200
580   NA(I)=0:NB(I)=0:NEXT I
590   PRON=0: COMP=0
600   RETURN
1000  REM *** ENTER DATA ***
1010  CLS:PRINT :PRINT"Input name of monomer 1";
1020  INPUT M1$
1030  PRINT :PRINT"Input name of monomer 2";
1040  INPUT M2$
1050  PRINT :PRINT"Enter the reactivity ratios"
1060  PRINT :PRINT"r1";
1070  INPUT R1$:R1=VAL(R1$)
1080  PRINT :PRINT"r2";
1090  INPUT R2$:R2=VAL(R2$)
1100  PRINT :PRINT"Enter theoretical mole percentage of";M1$;"
      in the polymer";
1110  INPUT PA$:PA=VAL(PA$)
1120  IF PA>=0 AND PA<=100 THEN 1141
1130  1100  PRINT :PRINT"MOLE PERCENTAGE MUST BE BETWEEN 0 AND
      100: PLEASE RE-ENTER ";
1140  GOTO 1110
1141  COMP=0:PRINT :PRINT "Polymerise to 100% conversion ?"
1142  A$=INKEY$
```

```
1143 IF A$= "N" OR A$= "n" THEN 1150
1144 IF A$= "Y" OR A$= "y" THEN 1146
1146 COMP=1
1150 CLS:PRINT :PRINT M1$: PRINT "REACTIVITY ratio =";R1:PRINT
     PA;"Mole %"
1160 PRINT :PRINT M2$: PRINT "REACTIVITY ratio =";R2:PRINT
     (100-PA);"Mole %"
1162 IF COMP=0 THEN 1170
1165 PRINT :PRINT"Polymerise to 100% conversion"
1170 PRINT :PRINT "Is this correct ?"
1180 A$=INKEY$: IF A$="Y" OR A$="y" THEN 1210
1190 IF A$="N" OR A$="n" THEN 1200
1195 GOTO 1180
1200 PRINT :PRINT "PLEASE RE-ENTER DATA":FOR I = 1 TO 500:
     NEXT I: GOTO 1000
1210 RETURN
1500 REM *** CALCULATE FEED RATIO ***
1510 INCA=INT(20*PA):INCB=2000-INCA
1515 IF INCA=0 OR INCB=0 THEN RETURN
1530 COUNT=0
1540 MR= INCA/INCB
1560 P1= R1*MR : P2=R2/MR
1570 RETURN
1800 REM *** OUTPUT DATA TO PRINTER ? ***
1810 CLS:PRINT :PRINT "Would you like a hard copy ?"
1820 A$=INKEY$: IF A$="Y" OR A$="y" THEN 1850
1830 IF A$="N" OR A$="n" THEN RETURN
1840 GOTO 1820
1850 PRON=1
1860 LPRINT :PRINT M1$:LPRINT "Reactivity ratio =" ;R1LPRINT
     PA;"Mole %"
1870 LPRINT :PRINT M2$:LPRINT "Reactivity ratio =" ;R2LPRINT
     (100-PA);"Mole %"
1872 IF COMP=0 THEN 1880
1875 LPRINT :LPRINT "POLYMERISED TO 100% CONVERSION"
1880 LPRINT:RETURN
200  REM *** CALCULATION AND PRINTOUT ***
2020 IF PRON <> 1 THEN 2040
2030 LPRINT:LPRINT "In the simulated copolymer ";M1$;" is
     represented by and .";M2$;" is represented by X" :LPRINT
     :PRINT:GOTO 2050
2040 CLS:PRINT:PRINT "In the simulated copolymer ";M1$;" is
     represented by and .";M2$;" is represented by X" :PRINT
     :PRINT
```

```
2050 WSUM = 1 + MR: W1 = MR/WSUM :W2 = 1/WSUM
2060 X = WSUM * RND (7)
2070 RAD$ = "X" THEN 2280
2110 IF INCA<=0 AND COMP=1 THEN 2220
2120 REM *** REACTIONS OF MONOMER 1 ***
2130 X1= (1+P1) * RND (TIMER)
2135 IF INCB<=0 AND COMP=1 THEN 2150
2140 IF X1<1 THEN 2220
2150 NA=NA+1:SA=SA+1:INCA=INCA-1:COUNT=COUNT + 1
2160 IF PRON<>1 THEN 2180
2170 LPRINT".";:GOTO 2190
2180 PRINT ".";
2190 IF COUNT = 100 AND COMP=1 THEN GOSUB 1515
2200 NEXT I
2210 GOTO 2340
2215 REM *** CHANGE MONOMER 1 TO MONOMER 2 ***
2220 RAD$="X":NB=NB+1:SB=SB+1: NA(SA)=NA(SA)+1:SA=0:INCB=INCB-
     1:COUNT=COUNT+1
2230 IF PRON<>1 THEN 2250
2240 LPRINT "X";:GOTO 2260
2250 PRINT "X"
2260 IF COUNT = 100 AND COMP=1 THEN GOSUB 1515
2270 GOTO 2200
2275 REM *** REACTIONS OR MONOMER 2 ***
2280 IF INCB<=0 AND COMP=1 THEN 2320
2290 X2=(1+P2) * RND(TIMER)
2295 IF INCA<=0 AND COMP = 1 THEN 2310
2300 IF X2<1 THEN 2320
2310 NB=NB+1:SB=SB+1:INCB=INCB-1:COUNT=COUNT+1:GOTO 2230
2320 REM *** CHANGE FROM MONOMER 2 TO MONOMER 1 ***
2330 RAD$=".":NA=NA+1:SA=SA+1:NB(SB)=NB(SB)+1:SB=0:INCA=INCA-
     1:COUNT=COUNT+1:GOTO 2160
2340 REM *** COUNT LAST SEQUENCE ***
2350 IF SA=0 THEN 2370
2360 NA(SA)=NA(SA)+1:GOTO 2380
2370 NB(SB)=NB(SB)+1
2380 TA=TA+NA:TB=TB+NB:SUM=TA+TB
2390 IF PRON=1 THEN 2410
2400 PRINT :PRINT"The simulated copolymer contains";TA;M1$;"
     units and";TB;M2$;" units":PRINT INT((TA/2000)*1000)/10;"
     Mole %";M1$ :GOTO 2420
2410 LPRINT :LPRINT"The simulated copolymer contains";TA;M1$;"
     units and";TB;M2$;" units":LPRINT
     INT((TA/2000)*1000)/10;" Mole %";M1$ :GOTO 2420
```

```
2420 RETURN
3000 REM *** SEQUENCE ANALYSIS ***
3010 PRINT :PRINT "PRESS ANY KEY FOR SEQUENCE ANALYSIS"
3020 A$=INKEY$: IF A$="" THEN 3020
3030 CLS:PRINT :PRINT "ANALYSING THE SEQUENCES"
3040  FOR I=1 TO 2000
3050 IF NA(I)>0 THEN AMAX=I
3060 IF NB(I)>0 THEN BMAX=I
3070 NEXT I
3080 LI=BMAX:IF AMAX>BMAX THEN LI=AMAX
3090 IF PRON<>1 THEN 3150
3100 LPRINT :LPRINT "Sequence Distribtuions"
3110 LPRINT :FOR J=1 TO 79:LPRINT "-";:NEXT J
3120 LPRINT :LPRINT "Length",,M1$,,M2$
3130 LPRINT :FOR J=1 TO 79:LPRINT "-";:NEXT J
3140 LPRINT: GOTO 3200
3150 CLS:PRINT :PRINT "Sequence Distributions"
3160 PRINT :FOR J=1 TO 79:PRINT "-";: NEXT J
3170 PRINT :PRINT "Length",,M1$,,M2$
3180 PRINT :FOR J=1 TO 79:PRINT "-";:NEXT J
3190 PRINT
3200 FOR I=1 TO LI
3210 IF NA(I)=0 AND NB(I)=0 THEN 3250
3220 IF PRON<>1 THEN 3240
3230 LPRINT I,,NA(I),,NB(I): GOTO 3250
3240 PRINT I,,NA(I),,NB(I)
3250 NEXT I
3260 RETURN
4000 PRINT :PRINT "ANOTHER RUN ?"
4010 A$=INKEY$:IF A$="" THEN 4010
4020 IF A$="Y" OR A$="y" THEN RUN
4030 IF A$="N" OR A$="n" THEN END
4040 GOTO 4010
```

APPENDIX THREE

POLSIM PROGRAM LISTING

```
DECLARE SUB Polpri ()
DECLARE SUB Fdent ()
DECLARE SUB Hcopy ()
DECLARE SUB PrinC ()
DECLARE SUB PrinA ()
DECLARE SUB PrinB ()
DECLARE SUB Errorhand ()
DECLARE SUB Cfeed ()
DECLARE SUB Cpolinfo ()
DECLARE SUB Ccalc ()
DECLARE SUB Anseq ()
DECLARE SUB Calc ()
DECLARE SUB Cdenter ()
DECLARE SUB Copol ()
DECLARE SUB Polinfo ()
DECLARE SUB Feed ()
DECLARE SUB Denter ()
DECLARE SUB Kbdinput ()
DECLARE SUB Rdisk ()
DECLARE SUB Rpdisk ()
DECLARE SUB Wdisk ()
DECLARE SUB Wpdisk ()
DECLARE SUB Terpol ()
DECLARE SUB Initialize ()
'*********************************************************
DECLARE AND INITIALIZE VARIABLES
'*********************************************************
     COMMON SHARED INCA, INCB, INCC, MR1, MR2, TA, TB, TC,
SUM,           NA, NB, NC, SA
     COMMON SHARED SB, SC, AMAX, BMAX, CMAX, WSUM, PRON, COMP,
          RD, CTPOL, I
     COMMON SHARED P1, P2, P3, P4, P5, P6, PA, PB, PC, RAD$,
          COUNT, RAB, RBA
     COMMON SHARED FileName$, Kbd$, MA$, MB$, MC$,
     DIM SHARED NA(2000), NB(2000), NC(2000), R$(6), R(6)
     DIM SHARED Pol AS STRING
     Pol = STRING$(2000, "*")
     SCREEN 0
     COLOR 15, 0
     R$(1) = "r(AB)": R$(2) = "r(AC)": R$(3) = "r(BA)"
     R$(4) = "r(BC)": R$(5) = "r(CA)": R$(6) = "r(CB)"
     FOR I = 1 TO 6
```

```
            R(I) = 1
        NEXT I
        MR1 = 1: MR2 = 1: RAB = 1: RBA = 1
ON ERROR GOTO Ehand
*********************************************************
MAIN MENU
*********************************************************
DO
        CLS
        PRINT : PRINT, "MAIN MENU": PRINT
        PRINT "(1) Run copolymer simulation"
        PRINT "(2) Run terpolymer simulation"
        PRINT "(3) Save monomer and reactivity ratio data to
disk"
        PRINT "(4) Save simulated polymer to disk"
        PRINT "(5) Load monomer and reactivity ratio data from
             disk"
        PRINT "(6) Load simulated polymer from disk"
        PRINT : PRINT "(7) QUIT"
        PRINT : PRINT "Input your selection"
        Kbd$ = INPUT$(1)
        SELECT CASE Kbd$
             CASE "1"
                  CALL Copol
             CASE "2"
                  CALL Terpol
             CASE "3"
                  CALL Wdisk
             CASE "4"
                  CALL Wpdisk
             CASE "5"
                  CALL Rdisk
             CASE "6"
                  CALL Rpdisk
             CASE "7"
                  EXIT DO
             CASE ELSE
                  BEEP
        END SELECT
LOOP
END
Ehand:
        SELECT CASE ERR
             CASE 25
```

```
                PRINT : PRINT "TURN PRINTER ON THEN PRESS ANY
KEY             TO CONTINUE"
                Pause$ = INPUT$(1)
                RESUME
           CASE 25
                PRINT : PRINT "PRINTER IS OUT OF PAPER: INSERT
                PAPER THEN PRESS ANY KEY TO CONTINUE"
                Pause$ = INPUT$(1)
                RESUME
           CASE 53
                PRINT : PRINT FileName$; "CANNOT BE FOUND:
PLEASE               RE-INPUT FILENAME"
                Pause$ = INPUT$(1)
                CALL Fdent
                RESUME
           CASE 68
                PRINT : PRINT "TURN PRINTER ON THEN PRESS ANY
KEY             TO CONTINUE"
                Pause$ = INPUT$(1)
                RESUME
           CASE ELSE
                ON ERROR GOTO 0
     END SELECT

SUB Anseq
     COLOR 15, 0
     IF SA <> 0 THEN
          NA(SA) = NA(SA) + 1
          ELSE IF SB <> 0 THEN NB(SB) = NB(SB) + 1
          ELSE NC(SC) = NC(SC) + 1
     END IF
     TA = TA  = NA: TB = TB + NB: TC = TC +NC: SUM = TA + TB +
     TC
     IF PRON = 0 THEN GOTO Sp
     IF PRON = 1 THEN OPEN "LPT1:" FOR OUTPUT AS £2
     PRINT £2, : PRINT £2, : PRINT £2, "The simulated
copolymer       contains"; TA; MA$; " units";
     IF CTPOL = 1 THEN PRINT £2, TB; MB$ " units and" ; TC;
MC$;       " units"
     IF CTPOL = 0 THEN PRINT £2, "and"; TB; MB$; " units"
     PRINT £2, INT((TA/2000) * 1000 + .1)/10; " Mole % "; MA$
     PRINT £2, TAB(20); INT((TB/2000) * 1000 + .1)/10; " Mole
%     "; MB$;
```

```
      IF CTPOL = 1 THEN PRINT £2, TAB(40); INT((TC/2000) * 1000
+     .1)/10; " Mole % "; MC$
      CLOSE
      GOTO Es
Sp:
      PRINT : PRINT : PRINT "The simulated copolymer contains";
      TA; MA$; " units";
      IF CTPOL = 1 THEN PRINT TB; MB$; " units and"; TC; MC$; "
      units"
      IF CTPOL = 0 THEN PRINT " and"; TB; MB$; "units"
      PRINT INT((TA/2000) * 1000 + 0.5)/10; " Mole % "; MA$;
      PRINT TAB(20); INT((TB/2000) * 1000 + 0.1)/10; " Mole %";
      MB$;
      IF CTPOL = 1 THEN PRINT TAB(40); INT((TC/2000) * 1000 +
      0.1)/10; "Mole %"; MC$
Es:
      PRINT : PRINT "Press any key for sequence analysis"
      Kbds$ = INPUT$(1)
      CLS : LOCATE 13, 19
      PRINT "ANALYSING SEQUENCES"
      FOR I = 1 TO 2000
            IF NA(I) > 0 THEN AMAX = I
            IF NB(I) > 0 THEN BMAX = I
            IF NC(I) > 0 THEN CMAX = I
      NEXT I
      LI = BMAX
      IF AMAX > BMAX THEN LI = AMAX
      IF CMAX > LI THEN LI = CMAX
      IF PRON = 0 THEN GOTO Scp
      IF PRON = 1 THEN OPEN "LPT1" FOR OUTPUT AS £2
      PRINT £2, : PRINT £2, "Sequence Distributions" : PRINT
£2,
      FOR J = 1 TO 79
            PRINT £2, "-";
      NEXT J
      PRINT £2,
      IF CTPOL = 1 THEN PRINT £2, "Length", , MA$, MB$, MC$
      IF CTPOL = 0 THEN PRINT £2, "Length", , MA$, ,MB$
      FOR J = 1 TO 79
            PRINT £2, "-";
      NEXT J
      PRINT £2
      FOR J =1 TO LI
```

```
            IF NA(J) = 0 AND NB(J) = 0 AND NC(J) = 0 THEN GOTO
Ne
            IF CTPOL = 1 THEN PRINT £2, J, , NA(J), NB(J), NC(J)
            IF CTPOL = 1 THEN PRINT £2, J, , NA(J), , NB(J)
Ne:
      NEXT J
CLOSE
Scp:
      CLS : SCREEN 0
      PRINT : PRINT :Sequence Distributions": PRINT
      FOR J = 1 TO 79
            PRINT "-";
      NEXT J
      IF CTPOL = 1 THEN PRINT "LENGTH", , MA$, MB$, MC$
      IF CTPOL = 0 THEN PRINT "LENGTH", , MA$, , MB$
      FOR J = 1 TO 79
            PRINT "-";
      NEXT J
      PRINT
      FOR J = 1 TO LI
            IF NA(J) = 0 AND NB(J) = 0 AND NC(J) = 0 THEN GOTO
Nex
            IF CTPOL = 1 THEN PRINT J, , NA(J), NB(J), NC(J)
            IF CTPOL = 0 THEN PRINT J, , NA(J), , NB(J)
Nex:
      NEXT J
      PRINT : PRINT "Press any key to continue"
      Kbd$ = INPUT$(1)
END SUB

SUB Calc
      RANDOMIZE (TIMER)
      IF PRON = 1 THEN GOTO Ppri
      PRINT : PRINT "In the simulated copolymer"; MA$; "is
      represented by";
      COLOR 9, 0: PRINT "0";
      COLOR 15, 0: PRINT MB$; " Is represented by";
      COLOR 4, 0: PRINT "X";
      COLOR 15, 0: PRINT "and"; MC$; "Is represented by *"
      PRINT
      GOTO Xsum
Ppri:
```

```
      PRINT £2,: PRINT £2, "In the simulated copolymer"; MA$;
"Is   represented by 0"; MB$; "is represented by X and"; MC$;
"Is   represented by *"
      PRINT £2,
Xsum:
      WSUM = 1 + MR1 + MR2: W1 = 1/WSUM: W2 = (1 + MR1)/WSUM
      X = WSUM * RND(2)
      RAD$ = "0"
      IF X >= W1 THEN RAD$ = "X"
      IF X > W2 THEN RAD$ = "*"
*********************************************************
PROPAGATION STEPS
*********************************************************
      SCREEN 0
      FOR I = 1 TO 2000
            IF RAD$ = "X" THEN GOTO Bmon
            IF RAD$ = "*" THEN GOTO Cmon
            IF INCA <= 0 AND COMP = 1 THEN GOTO AtoB
*********************************************************
REACTIONS OF MONOMER A
*********************************************************
      X1 = (1 + P1 + P2) * RND(3)
      IF INCB <= 0 AND <= 0 AND COMP = 1 THEN GOTO PrA
      IF X1 < (P1 + P2) THEN GOTO AtoB
PrA:
      CALL PrinA
NexI:
      IF COUNT = 100 AND COMP = 1 THEN CALL Feed
      NEXT I
      GOTO Esub
AtoB:
*********************************************************
CHANGE FROM MONOMER A TO MONOMER B
*********************************************************
            IF X1 > P1 THEN GOTO AtoC
            IF INCB <= 0 AND COMP = 1 THEN GOTO Ac:
Ab:
            RAD$ = "X": NA(SA) = NA(SA) + 1: SA = 0
PrB:
      CALL PrinB
            GOTO NexI
AtoC:
*********************************************************
CHANGE FROM MONOMER A TO MONOMER C
```

```
*********************************************************
            IF INCC <= 0 AND COMP = 1 THEN GOTO Ab
Ac:
            RAD$ = "*": NA(SA) = NA(SA) + 1: SA = 0
PrC:
      CALL PrinC
            GOTO NexI
Bmon:
*********************************************************
REACTIONS OF MONOMER B
*********************************************************
            IF INCB <= 0 AND COMP = 1 THEN GOTO BtoA
            X2 = (1 + P3 + P4) * RND(5)
            IF INCA <= 0 AND INCC <= 0 AND COMP = 1 GOTO PrB
            IF X2 < (P3 + P4) THEN GOTO BtoA
            GOTO PrB
BtoA:
*********************************************************
CHANGE FROM MONOMER B TO MONOMER A
*********************************************************
            IF X2 > P3 THEN GOTO BtoC:
            IF INCA <= 0 AND COMP = 1 THEN GOTO Bc
Ba:
            RAD$ = "0": NB(SB) = NB(SB) + 1: SB = 0
            GOTO PrA
BtoC:
*********************************************************
CHANGE FROM MONOMER B TO MONOMER C
*********************************************************
            IF INCC <= 0 AND COMP = 1 THEN GOTO Ba:
Bc:
            RAD$ = "*": NB(SB) = NB(SB) + 1: SB = 0
            GOTO PrC
Cmon:
*********************************************************
REACTIONS OF MONOMER C
*********************************************************
            IF INCC <= 0 AND COMP = 1 THEN GOTO CtoA
            X3 = (1 + P5 + P6) * RND(7)
            IF INCA <= 0 AND INCB <= 0 AND COMP = 1 THEN GOTO
PrC
            IF X3 < (P5 + P6) THEN GOTO CtoA
            GOTO PrC
CtoA:
```

```
*********************************************************
CHANGE FROM MONOMER C TO MONOMER A
*********************************************************
          IF INCA <= 0 AND COMP = 1 THEN GOTO Cb
          IF X3 > P5 THEN GOTO CtoB
Ca:
          RAD$ = "0": NC(SC) = NC(SC) + 1: SC = 0
          GOTO PrA
*********************************************************
CHANGE FROM MONOMER C TO MONOMER B
*********************************************************
CtoB:
          IF INCB <= 0 AND COMP = 1 THEN GOTO Ca
Cb:
          RAD$ = "X": NC(SC) = NC(SC) + 1:SC = 0
          GOTO PrB
Esub:
     IF PRON = 1 THEN CLOSE
END SUB

SUB Ccalc
     RANDOMIZE(TIMER)
     IF PRON = 1 THEN GOTO CPpri
     PRINT : PRINT "In the simulated copolymer"; MA$; "is
     represented by";
     COLOR 9, 0: PRINT "0";
     COLOR 15, 0: PRINT "and"; MB$; "is represented by";
     COLOR 4, 0: PRINT "X"
     PRINT
     GOTO Cxsum
CPpri:
     PRINT £2, : PRINT £2, "In the simulated copolymer"; MA$;
     "is represented by 0 and"; MB$; "is represented by X"
     PRINT $2,
Cxsum:
     WSUM = 1 + MR1: W1 = MR1/WSUM: W2 = 1/WSUM
     X = WSUM * RND(2)
     RAD$ = "0"
     IF X >= MR1 THEN RAD$ = "X"
*********************************************************
PROPAGATION STEPS
*********************************************************
     SCREEN 0
     FOR I = 1 TO 2000
```

```
            IF RAD$ = "X" THEN GOTO CBmon
            IF INCA <= 0 AND COMP = 1 THEN GOTO CAtoB
*************************************************************
REACTIONS OF MONOMER A
*************************************************************
            X1 = (1 + P1) * RND(3)
            IF INCB <= 0 AND COMP = 1 THEN GOTO CPrA
            IF X1 < 1 THEN GOTO CAtoB
CPrA:
      CALL PrinA
CNexI:
            IF COUNT = 100 AND COMP = 1 THEN CALL Cfeed
      NEXT I
      GOTO CEsub
CAtoB:
*************************************************************
CHANGE FROM MONOMER A TO MONOMER B
*************************************************************
            RAD$ = "X": NA(SA) = NA(SA) + 1: SA = 0
CPrB:
      CALL PrinB
            GOTO CNexI
CBmon:
*************************************************************
REACTIONS OF MONOMER B
*************************************************************
            IF INCB <= 0 AND COMP = 1 THEN GOTO CBtoA
            X2 = (1 + P2) * RND(5)
            IF INCA <= 0 AND COMP = 1 THEN GOTO CPrB
            IF X2 < 1 THEN GOTO CBtoA
            GOTO CPrB
CBtoA:
*************************************************************
CHANGE FROM MONOMER B TO MONOMER A
*************************************************************
            RAD$ = "0": NB(SB) = NB(SB) + 1: SB = 0
            GOTO CPrA
CEsub:
      IF PRON = 1 THEN CLOSE
END SUB

SUB Cdenter
      IF RD = 1 THEN GOTO Cprn
Starta:
```

```
      CLS : PRINT "Input the name of monomer A";
      INPUT MA$
      PRINT : PRINT "Input the name of monomer B";
      INPUT MB$
      PRINT : PRINT "Enter the reactivity ratios"
      PRINT : PRINT "r(AB)";
      INPUT RAB$
      RAB = VAL(RAB$)
      PRINT : PRINT "r(BA)";
      INPUT RBA$
      RBA = VAL(RBA$)
Cprn:
      CLS : PRINT : PRINT "Monomer A is"; MA$
      PRINT : PRINT "Monomer B is"; MB$
      PRINT : PRINT "r(AB) ="; RAB, "r(BA) ="; RBA
      PRINT : PRINT "Is this correct (Y/N)"
CALL Kbdinput
      IF Kdb$ = "N" THEN GOTO Starta
Sec2:
      CLS : PRINT "Enter the theoretical mole percentage of";
      MA$; "in the polymer";
Ipaq:
      INPUT PA$: PA = VAL(PA$)
      IF PA >= 0 AND PA <= 0 100 THEN GOTO Sec2A
      BEEP
      PRINT : PRINT "MOLE PERCENTAGE MUST BE BETWEEN 0 AND 100:
      PLEASE RE-ENTER";
      GOTO Ipaq
Sec2A:
      PB = 100 - PA
      CLS : PRINT MA$; PA; "Mole %"
      PRINT : PRINT MB$; PB; "Mole %"
      PRINT : PRINT "Is this correct (Y/N)"
CALL Kbdinput
      IF Kbd$ = "N" THEN GOTO Sec2
      INCA = INT(20 * PA): INCB = 2000 - INCA
      PRINT : PRINT "Polymerize to 100% conversion (Y/N)"
CALL Kbdinput
      IF Kbd$ = "Y" THEN COMP = 1
CALL Hcopy
END SUB

SUB Cfeed
      COUNT = 0
```

```
      IF INCA > 0 AND INCB > 0 THEN MR1 = INCA/INCB
      P1  = MR1 * RAB
      P2 = RBA/MR1
END SUB

SUB Copol
      CALL Initialize
            IF RD = 1 AND CTPOL = 1 THEN RD = 0
            CTPOL = 0
      CALL Cdenter
      CALL Cfeed
      CALL Polinfo
      CALL Ccalc
      CALL Anseq
      RD = 1
      CLOSE
END SUB

SUB Denter
      IF RD = 1 THEN GOTO Ctp
Start:
      CLS : PRINT "Input the name of monomer A";
      INPUT MA$
      PRINT : PRINT "Input the name of monomer B";
      INPUT MB$
      PRINT : PRINT "Input the name of monomer C";
      INPUT MC$
      PRINT : PRINT "Enter the reactivity ratios"
      FOR I = 1 TO 6
            PRINT : PRINT R$(I)
            INPUT RR$
            R(I) = VAL(RR$)
      NEXT I
Ctp:
      CLS : PRINT : PRINT "Monomer A is"; MA$
      PRINT : PRINT "Monomer B is"; MB$
      PRINT : PRINT "Monomer C is"; MC$
      PRINT : PRINT
      FOR I = 1 TO 6
            PRINT R$(I); "="; R(I)
      NEXT I
      PRINT : PRINT "Is this correct (Y/N)"
CALL Kbdinput
IF Kbd$ = "N" THEN GOTO Start
```

```
Sect2:
      CLS : PRINT "Enter the theoretical mole percentage of";
      MA$; "in the polymer";
Ipa:
      INPUT PA$: PA = VAL(PA$)
      IF PA >= 0 AND PA <= 100 THEN GOTO Sect2A
      BEEP
      PRINT : PRINT "MOLE PERCENTAGE MUST BE BETWEEN 0 AND 100:
      PLEASE RE-ENTER";
      GOTO Ipa
Sect2A:
      PRINT : PRINT "Enter the theoretical mole percentage of";
      MB$; "in the polymer";
Ipb:
      INPUT PB$: PB = VAL(PB$)
      IF PB >= 0 AND PB <= 100 - PA THEN GOTO Sect2B
      BEEP
      PRINT : PRINT "MOLE PERCENTAGE MUST BE BETWEEN 0 AND";
100   - PA ": PLEASE RE-ENTER";
      GOTO Ipb
Sect2B:
      PC = 100 - PA - PB
      CLS : PRINT MA$; PA; "Mole %"
      PRINT : PRINT MB$; PB; "Mole %"
      PRINT : PRINT MC$; PC ; "Mole %"
      PRINT : PRINT "Is this correct (Y/N)"
CALL Kbdinput
      IF Kbd$ = "N" THEN GOTO Sect2
      INCA = INT(20 * PA): INCB = INT(20 * PB): INCC = 2000 -
      INCA - INCB
      PRINT : PRINT "Polymerize to 100% conversion (Y/N)"
CALL Kbdinput
      IF Kbd$ = "Y" THEN COMP = 1
CALL Hcopy
      RD = 1
END SUB

SUB Fdent
      CLS : PRINT "Input name of datafile";
Fnam:
      INPUT FileName$
      IF LEN(FileName$) <= 11 THEN GOTO Cdat
      PRINT : PRINT "FILENAME MUST BE LESS THAN 11 CHARACTERS:
      PLEASE RE-ENTER";
```

```
        GOTO Fnam
Cdat:
        IF RIGHT$(FileName$, 4) = ".DAT" THEN GOTO Eofsub
        PRINT : PRINT "FILENAME MUST END WITH .DAT: PLEASE RE-
        ENTER";
        GOTO Fnam
Eofsub:
END SUB

SUB Feed
        COUNT = 0
IF INCA > 0 AND INCB > 0 THEN MR1 = INCB/INCA
IF INCA > 0 AND INCC > 0 THEN MR2 = INCC/INCA
P1 = MR1/R(1)
P2 = MR2/R(2)
P3 = 1/(MR1 * R(3))
P4 = MR2/(MR1 * R(4))
P5 = 1/(MR2 * R(5))
P6 = MR1/(MR2 * R(6))
END SUB

SUB Hcopy
        PRINT : PRINT  "Would you like a hard copy (Y/N)"
CALL Kbdinput
        SELECT CASE Kbd$
                CASE "Y"
                        OPEN "LPT1:" FOR OUTPUT AS £2
                        PRON = 1
                CASE "N"
                        CLS
                        OPEN "SCRN:" FOR OUTPUT AS £2
        END SELECT
END SUB

SUB Initialize
        CLS
        LOCATE 13, 19
        PRINT "PLEASE WAIT-INITIALIZING ARRAYS"
        FOR I = 1 TO 2000
                NA(I) = 0: NB(I) = 0: NC(I) = 0
        NEXT I
        RANDOMIZE(TIMER)
        INCA = 0: INCB = 0: INCC = 0: TA = 0: TB = 0: TC = 0
        SA = 0: SB = 0: SC = 0: AMAX = 0: BMAX = 0: CMAX = 0
```

```
      SUM = 0: NA = 0: NB = 0: NC = 0: PRON = 0: COMP = 0
END SUB

SUB Kbdinput
Begin:
      BEEP
      Kbd$ = INPUT$(1)
      IF Kbd$ = "Y" OR Kbd$ = "y" THEN
            Kbd$ = "Y"
      ELSEIF Kbd$ = "N" OR Kbd$ = "n" THEN
            Kbd$ = "N"
      ELSE GOTO Begin
      END IF
END SUB

SUB Polinfo
      PRINT £2, PA; :Mole % of monomer A,"; MA$
      PRINT £2, : PRINT £2, PB; "Mole % of monomer B,"; MB$
      IF CTPOL = 0 THEN GOTO Cpol
      PRINT £2, : PRINT £2, PC; "Mole % of monomer C,"; MC$
      PRINT £2,
      PRINT £2, R$(1); "="; R(1), R$(2); "="; R(2), R$(3); "=";
      R(3)
      PRINT £2, R$(4); "="; R(4), R$(5); "="; R(5), R$(6); "=";
      R(6)
      PRINT £2
      GOTO Conv
Cpol:
      PRINT £2, : PRINT £2, "r(AB) ="; RAB, "r(BA) ="; RBA
      PRINT £2,
Conv:
      IF COMP = 1 THEN PRINT £2, "POLYMERIZED TO 100%
CONVERSION"
      PRINT £2,
END SUB

SUB Polpri
      IF PRON = 1 THEN GOTO XPpri
      PRINT : PRINT "In the simulated copolymer"; MA$; "is
      represented by";
      COLOR 9, 0: PRINT "0";
      COLOR 15, 0
      IF CTPOL = 0 THEN PRINT "and";
      PRINT MB$; "is represented by";
```

```
      COLOR 4, 0: PRINT "X";
      COLOR 15, 0
      IF CTPOL = 0 THEN PRINT "and"; MC$; "is represented by *"
      IF CTPOL = 0 THEN PRINT
      PRINT
      GOTO Crad
XPpri:
      PRINT £2, : PRINT £2, "In the simulated copolymer"; MA$;
      "is represented by 0";
      IF CTPOL = 0 THEN PRINT £2, "and";
      PRINT £2, MB$; "is represented by X";
      IF CTPOL = 1 THEN PRINT £2, "and"; MC$; "is represented
by    *"
      IF CTPOL = 0 THEN PRINT £2,
      PRINT£2,
Crad:
*********************************************************
PROPAGATION STEPS
*********************************************************
      SCREEN 0
      FOR I = 1 TO 2000
            F = I + 1
            X$ = MID$(Pol, I, 1)
            Y$ = MID$(Pol, F, 1)
            IF X$ = "X" THEN GOTO XBmon
            IF X$ = "*" THEN GOTO XCmon
*********************************************************
REACTIONS OF MONOMER A
*********************************************************
            CALL PrinA
            IF Y$ = "X" THEN GOTO XAtoB
            IF Y$ = "*" THEN GOTO XAtoC
NextI:
      NEXT I
      GOTO Endsub
XAtoB:
*********************************************************
CHANGE FROM MONOMER A TO MONOMER B
*********************************************************
            NA(SA) = NA(SA) + 1: SA = 0
            GOTO NextI
XAtoC:
*********************************************************
CHANGE FROM MONOMER A TO MONOMER C
```

```
*********************************************************
            NA(SA) = NA(SA) + 1: SA = 0
            GOTO NextI
XBmon:
*********************************************************
REACTIONS OF MONOMER B
*********************************************************
            CALL PrinB
            IF Y$ = "0" THEN GOTO XBtoA
            IF Y$ = "*" THEN GOTO XBtoC
            GOTO NextI
XBtoA:
*********************************************************
CHANGE FROM MONOMER B TO MONOMER A
*********************************************************
            NB(SB) = NB(SB) + 1: SB = 0
            GOTO NextI
XBtoC:
*********************************************************
CHANGE FROM MONOMER B TO MONOMER C
*********************************************************
            NB(SB) = NB(SB) + 1: SB = 0
            GOTO NextI
XCmon:
*********************************************************
REACTIONS OF MONOMER C
*********************************************************
            CALL PrinC
            IF Y$ = "0" THEN GOTO XCtoA
            IF Y$ = "X" THEN GOTO XCtoB
            GOTO NextI
XCtoA:
*********************************************************
CHANGE FROM MONOMER C TO MONOMER A
*********************************************************
            NC(SC) = NC(SC) + 1: SC + 0
            GOTO NextI
XCtoB:
*********************************************************
CHANGE FROM MONOMER C TO MONOMER B
*********************************************************
            NC(SC) = NC(SC) + 1: SC = 0
            GOTO NextI
Endsub:
```

```
        IF PRON = 1 THEN CLOSE

END SUB

SUB PrinA
        NA = NA + 1: SA = SA +1: INCA = INCA - 1
        MID$(Pol, I) = "0"
        COUNT = COUNT + 1
        IF PRON = 1 THEN PRINT £2, "0";
        IF PRON = 1 THEN GOTO E
        COLOR 9, 0
        PRINT "0";
E:
END SUB

SUB PrinB
        NB = NB + 1: SB = SB + 1
        INCB = INCB - 1
        COUNT = COUNT + 1
        MID$(Pol, I) = "X";
        IF PRON = 1 THEN PRINT £2, "X"
        IF PRON = 1 THEN GOTO Ens
        COLO4, 0
        PRINT "X";
Ens:
END SUB

SUB PrinC
        NC = NC + 1: SC = SC + 1
        INCC = INCC - 1
        COUNT = COUNT + 1
        MID$(Pol, I) = "*"
        IF PRON = 1 THEN PRINT £2, "*";
        IF PRON = 1 THEN GOTO Ensu
        COLOR 15, 0
        PRINT "*";
Ensu:
END SUB

SUB Rdisk
        CALL Fdent
                OPEN FileName$ FOR INPUT AS £1
                FOR I = 1 TO 6
                        INPUT £1, R(I)
```

```
            NEXT I
            INPUT £1, MA$, MB$, MC$, RAB, RBA, CTPOL
            CLOSE £1
            RD = 1
END SUB

SUB Rpdisk
      CALL Initialize
      CALL Fdent
            OPEN FileName$ FOR INPUT AS £1
            FOR I = 1 TO 6
                  INPUT £1, R(I)
            NEXT I
            INPUT £1, Pol
            INPUT £1, MA$, MB$, MC$, RAB, RBA, CTPOL, PA, PB,
PC,         COMP
            CLOSE £1
            RD = 1
CALL Hcopy
            IF PRON <> 1 THEN GOTO Scrp
            PRINT £2, "DATA FROM"; FileName$: Print £2,
            GOTO Pinf
Scrp:
            CLS
            PRINT "DATA FROM"; FileName$
            PRINT
Pinf:
CALL Polinfo
CALL PolPri
CALL Anseq
            CLOSE
END SUB

SUB Terpol
      CALL Initialize
            IF RD = 1 AND CTPOL = 0 THEN RD = 0
            CTPOL = 1
      CALL Denter
      CALL Feed
      CALL Polinfo
      CALL Calc
      CALL Anseq
      CLOSE
END SUB
```

```
SUB Wdisk
      CALL Fdent
            OPEN FileName$ FOR OUTPUT AS £1
            FOR I = 1 TO 6
                  WRITE £1, R(I)
            NEXT I
            WRITE £1, MA$, MB$, MC$, RAB, RBA, CTPOL
            CLOSE £1
            RD = 1
END SUB

SUB Wpdisk
      CALL Fdent
            OPEN FileName$ FOR OUTPUT AS £1
            FOR I = 1 TO 6
                  WRITE £1, R(I)
            NEXT I
            WRITE £1, Pol
            WRITE £1, MA$, MB$, MC$, RAB, RBA, CTPOL, PA, PB,
PC,         COMP
            CLOSE

END SUB
```