ACRYLAMIDE BASED HYDROGELS FOR CONTINUOUS WEAR CONTACT LENSES

by

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SUMMARY

The primary aim of this research has been the development of a hydrogel polymer having a suitable balance of properties to meet the requirements of a continuous wear contact lens material. This has been achieved by making a number of chemical modifications to a simple acrylamide based copolymer in order to produce a material of appropriate water content, oxygen permeability, mechanical strength and long term dimensional stability whilst not encouraging the accumulation of surface deposits. In order to synthesise such a material, a study of the effect on hydrogel properties of a number of variables including the interaction between functional groups within the polymer network, the cross-link density and the conditions of polymerisation has been undertaken. In addition to this a number of potential methods for producing a hydrogel surface having a reduced tendency for spoilation by protein deposition will be outlined, together with details of lens manufacture, toxicological testing and wearing trials that have been carried out prior to the material becoming commercially available.

Key Phrases

Oxygen Permeability Requirement
Hydrophilicity Series of Monomers
Interchain Hydrogen Bonding
Polymer-residual Monomer Complex Formation
Surface Protein Adsorption

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I wish to record my sincere appreciation of the moral support given by my mother and my brother Alan throughout this project.

Finally, but by no means least, I must thank Mrs Joy Wood who has typed this thesis.

This thesis is dedicated to the
memory of my Father

> *'He that hath seen it hath more reason to believe it than he that hath not '*
>
> *Robert Boyle*
> *'The Sceptical Chemist' 1680*

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CHAPTER VI EFFECTS OF POLYMERISATION CONDITIONS ON THE PROPERTIES OF HYDROGELS RELEVANT TO THE PRODUCTION OF A LATHE-CUT CONTINUOUS WEAR CONTACT LENS

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CHAPTER I

INTRODUCTION AND BACKGROUND TO THE DEVELOPMENT OF CONTACT LENS MATERIALS

I.i GENERAL INTRODUCTION

This course of research has been concerned with the development of a continuous wear contact lens material using acrylamide based hydrogel copolymers. In order to synthesise an appropriate material it is obviously essential that the biocompatibility of the lens with the cornea should meet with the requirements for a long term biomedical implant. It is therefore not only necessary to outline the optical functions of a contact lens, but also review the chemical and structural aspects of the cornea which are relevant to the problems of extended contact lens wear.

In order to obtain a clearer insight into the problems associated with tailoring the properties of polymers to meet the optimal design characteristics of a contact lens, the historical development of materials used for daily wear contact lenses will be traced. The advantage of tissue compatibility offered by hydrogel copolymers will be stressed and details of various hydrogel contact lens materials that are currently commercially available will also be outlined. As a large number of hydrogels are utilised as daily wear contact lenses the commercial viability of the introduction of a continuous wear contact lens material using an acrylamide based copolymer must also be discussed.

The final part of this chapter will be devoted to a summary of the characteristics required of a continuous wear contact lens material and the development of acrylamide based hydrogels made during this research to obtain a marketable product which is currently undergoing clinical assessment.

I.ii FUNCTION OF A CONTACT LENS

The primary application of a contact lens is to correct defects in vision caused by irregularities in the shape of an individual's eyeball which prevent an image focussing clearly on the retina, yet remain invisible and comfortable in situ.[1] Amongst the main complaints that contact lenses are used to remedy is myopia (short sightedness) in which light from an object focusses in front of the retina due to the focal length of the eye being too short since the eye-ball is too long. The two other major defects are presbyopia (long sightedness), which is due to a short eye-ball causing the object image to fall beyond the retina, and astigmatism in which images focus on the retina but in different planes due to widely differing curvatures of the cornea.

I.iii THE CORNEA

Structure

The cornea is a most important optical component of the eye since it is the major refractive surface of the eye structure. It is a transparent structure consisting of five layers, namely the epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium, as shown in figure Ia.[2] Bowman's membrane and Descemet's membrane are generally thought of as modified extensions of the stroma and endothelium respectively. Thus the corneal structure is sometimes thought of in a simplified form as consisting of only three layers, epithelium, stroma and endothelium.

The epithelium consists of five or six layers of cells of three types. The superficial layer is comprised of large flattened surface cells, whereas the next three layers become polyhedral shaped and then merge to form a single layer of columnar basal cells. The epithelium approximately comprises the outermost 10 per cent of the total corneal thickness being typically 0.04 mm thick and is capable of rapid regeneration after injury.

Bowman's membrane is considered as being a single superficial condensed layer of the stroma, being clear and uniform and between 10 and 13 microns in thickness. Despite being comprised of irregularly arranged collagen fibres which impart resistance to injury and infection, Bowman's membrane is not regenerable when damaged. It is therefore essential that the membrane remains intact although a certain amount of damage to the surrounding epithelium may be tolerated.

The stroma is about 0.45 mm in thickness, approximately 90 per cent of that of the cornea as a whole, and is comprised of two structural elements, namely cells and lamellae. The lamellae are of collagen fibrils, approximately 300 Å in diameter, which lie parallel to the surface and to each other, being embedded in a mucoid matrix of water, proteins and mucopolysaccharides. This springy structure keeps the lamellae apart preventing their compression, and also allows for the transference of substances through the tissue ensuring sufficient nutrition.[2,3,4] Cells, being the second structural element of the stroma, lie in the interlamellar spaces of the structure. The structure of the stroma is used in the explanation of corneal transparency, which is vital for its maintenance as an optical medium. The lattice theory, which is now the most widely accepted of several pertaining to corneal transparency, was put forward by Maurice[5] proposing that the perfectly regular arrangement of collagen fibrils causes them to behave as a series of diffraction gratings. Hence any light scattering arising from differences in refractive indices between the collagen fibrils and the mucoid matrix is eliminated.

Descemet's membrane is a strong structureless layer, five to ten microns in thickness, which is secreted by the endothelium and has resistance to elastic tissue strains. The corneal structure is completed by the endothelium which consists of a single layer of flat hexagonal cells approximately five microns high and 18 to 20 microns wide.[6]

I.iv CORNEAL METABOLISM AND OXYGEN TRANSPORT

Corneal clarity is generally maintained by the energy supplied from the metabolism of glucose in the presence of oxygen. This energy is utilised for the transport of water away from the cornea, causing it to remain in a partially hydrated or deturgescent state. In the absence of oxygen, glucose will break down to lactic acid in increasing amounts which will not provide sufficient energy for the maintenance of deturgesence and hence water will accumulate in the stroma, giving rise to a swelling of the mucoid matrix.[7] This will cause a disruption of the spatial regularity of the collagen fibrils to take place resulting in an increase in corneal opacity and thickness. The symptom of this defect, known as corneal edema, is the formation of multicoloured haloes surrounding a point source of light.

It is known that oxygen, necessary for glucose metabolism, is acquired directly from the atmosphere and carried to the cornea by four recognised routes.[8] It is now accepted that of primarial importance in the transport of oxygen is the pre-corneal tear film which contains dissolved air and oxygenates the cornea by a bathing process during the blink cycle. The three other pathways that enable oxygen transportation are via the limbal blood vessels, the aqueous humour and the blood of the conjunctival vessels. During sleep oxygen to maintain the normal corneal metabolism is provided by the capillaries of the palprebal conjunctiva.

I.v CHEMISTRY AND FUNCTIONS OF THE PRE-CORNEAL TEAR FILM[8-11]

The composition of the pre-corneal tear film shows only slight differences from that of blood plasma, being slightly more dilute (98.2 per cent water) and having a far lower protein content (0.6 per cent). The residual dissolved solid material of the tear film is comprised of mucopolysaccharides, lipids, glucose and inorganic salts such as sodium and potassium chloride. The osmotic pressure of tears is about the same as that for blood plasma, being isotonic with a 0.9 per cent saline solution and having a pH value of approximately 7.4 to 7.5.

One of the more important functions of the pre-corneal tear fluid, apart from supplying oxygen for the metabolism of the cornea, is its lubricating effect which allows the eyelid to remove any proteinaceous debris by sweeping across the cornea. The tear fluid is also responsible for the control of bacterial secretions from the cornea, as lysozyme, which is a constituent of tears, acts as a bacteriocide by dissolving the bacterial membrane. The importance of this process will be made more apparent when the problems of lens spoilation due to proteinaceous deposits are discussed in Chapter VII.

I.vi HISTORICAL DEVELOPMENT OF CONTACT LENS MATERIALS

Although the actual concept of a contact lens may be traced back to Leonardo da Vinci almost 500 years ago,[18] it was not until 1887 that the first example of lenses being fitted to a human eye can be found. All early lenses were individually ground from glass and it was not until the 1940's that poly(methyl methacrylate) began to gain favour as a contact lens material, first in scleral form and finally as corneal lenses in 1948.[14]

The choice of poly(methyl methacrylate) as the thermoplastic to supercede glass was somewhat empirically based upon its properties of toughness, physiological inactivity and ease of processability.[15] The rigidity and impermeability to oxygen of this polymer make it necessary for contact lenses fabricated from this material to be worn on a daily wear basis and to be removed prior to sleep. In view of these disadvantages poly(methyl methacrylate) is known as a hard contact lens material and must be fitted in such a way as to promote the flow of oxygen to the cornea, by rocking on a pre-corneal layer of tear fluid which transports dissolved oxygen via a pumping motion.[16,17]

This problem has encouraged the development of rigid thermoplastics such as poly(4-methyl pent-1-ene) and cellulose acetate butyrate having a far greater oxygen permeability than that of poly(methyl methacrylate). These materials have failed to replace poly(methyl methacrylate) as the most widely used hard contact lens material due to other complications arising from their structures.[18] The surface characteristics of poly(methyl methacrylate) are such that a coherent layer of tear fluid may be sustained upon the lens giving rise to a greater degree of physiological compatibility than that of poly(4-methyl pent-1-ene) which is not wettable by tear fluid unless subjected to a specific surface treatment. This problem does not arise with certain varieties of cellulose acetate butyrate but, due to the dimensional instability of this material, difficulties arise in obtaining correctly fitted lenses.[19]

The rigidity of all these hard lens materials leads to erosion of the epithelial cells of the cornea over a period of time. Although the corneal epithelium is capable of rapid regeneration, prolonged irritation by a rigid hard lens material may lead to permanent damage to Bowman's membrane. This possibility often leads to certain patients having to resort to spectacle wear after having been fitted with hard lenses.

This drawback has led to the development of polymers for potential soft contact lens materials having a far greater degree of comfort. Two types of polymers that have been widely investigated as potential soft contact lens materials are synthetic elastomers, of which the most studied example is silicone rubber, and hydrogels, such as poly(2-hydroxy ethyl methacrylate). Table IA shows a comparison of the mechanical properties of these materials with those of poly(methyl methacrylate) and the cornea itself.[20] It would seem from Table IA that silicone rubber, being stronger yet softer than the cornea, might prove to be a better soft contact lens material. The mechanical properties of silicone rubbers and also hydrogels are of course governed by their network structures and cross-link densities. A more complete account of the effect of these variables on the properties of hydrogels will be given in Chapters III and V.

The main drawback to the use of silicone rubber and other synthetic elastomers as soft contact lense materials is that, like poly(4-methyl pent-1-ene), a surface treatment is required to render the material wettable by tear fluid. This problem does not arise with hydrogel polymers as they possess hydrophilic polar groups which gives rise to the absorption of water into a three dimensional gel network structure, producing a wettable surface.

Since the earliest patent by Wichterle[21] on the application of poly(2-hydroxy ethyl methacrylate) as a contact lens material in 1961,

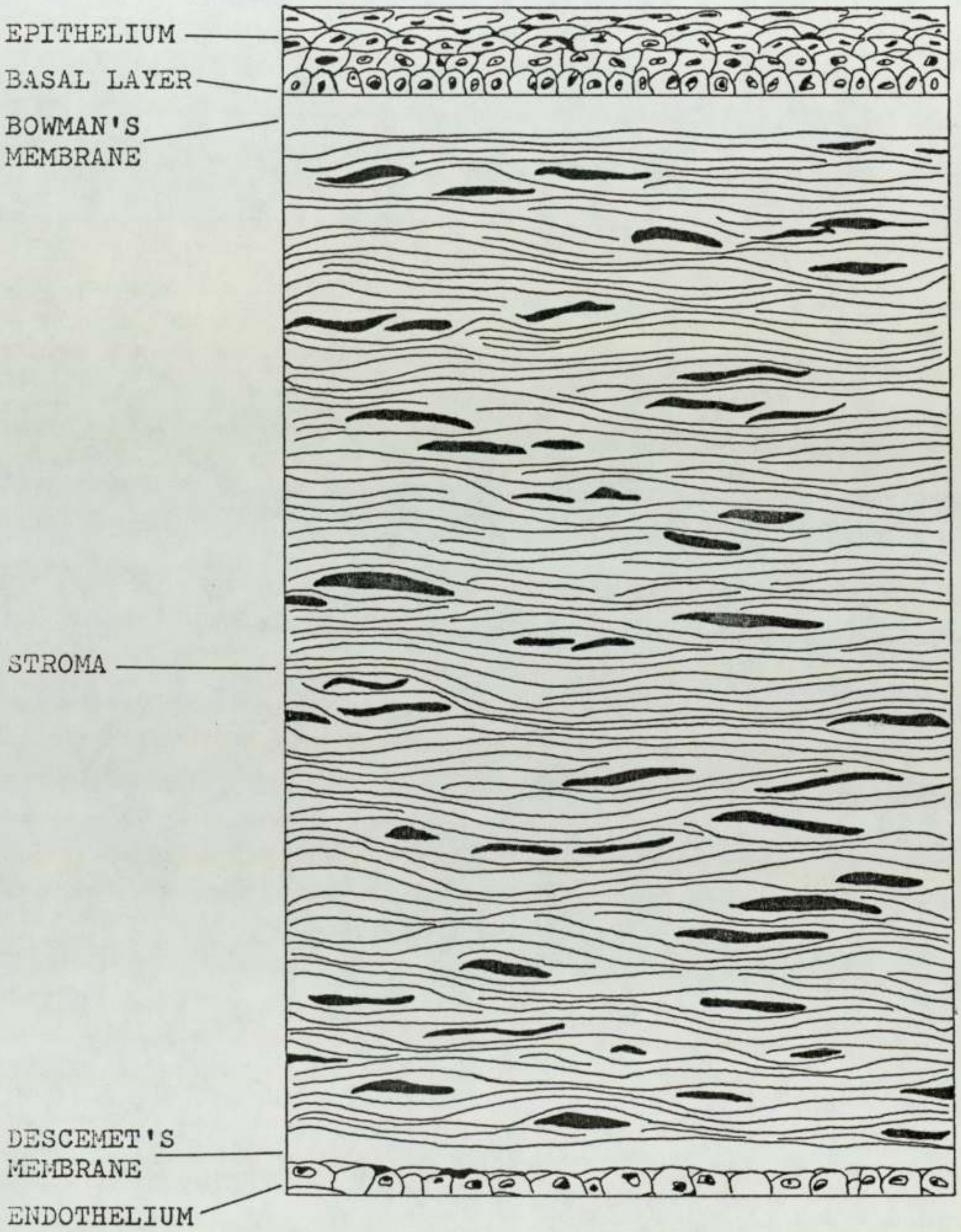


FIGURE 1 Sectional View of the Cornea

TABLE IA

MECHANICAL PROPERTIES OF POTENTIAL CONTACT LENS MATERIALS COMPARED TO THAT OF THE CORNEA

Material	Modulus of Rigidity (Nm^{-2})	Tensile Strength (Nm^{-2})	Tear Strength (kg/mm)
Cornea	1×10^7	5×10^6	1.5
Poly(Methyl methacrylate)	1×10^9	5×10^7	Strong, but brittle
Poly (2-hydroxy ethyl methacrylate)	0.5×10^7	5×10^5	1×10^{-2}
Silicone rubber	0.8×10^7	1×10^7	2.0

TABLE IB

HIGH WATER CONTENT HYDROGELS MARKETED AS CONTACT LENS MATERIALS

Name of Product	Manufacturer	Composition of lens material	% water content	Reference
Duragel	Cooper-Vision Optics	Amido-Amino copolymer	73.5	30, 31
Flexol	Burton Parsons	HEMA, AMA, MAA	72	32, 33
Hydrocon	Kontur Kontact Lens	HEMA, P-NVP	56	34
Permalens	Cooper-Vision Optics	NVP, HEMA, MAA	72	35
SP-77	Contact Lens Manufacturing	Undisclosed	77	-
Theraflex	Union Optics	NVP, MMA, GMA	60	36, 37, 38
Yumecon	Tokyo Contact Lens Research	Undisclosed	70	39

a vast number of claims have been filed citing numerous hydrogel compositions and methods of preparation. An extensive review of the patent literature related to the use of hydrogels as contact lens materials has recently been compiled by Pedley, Skelly and Tighe.[22] A large number of soft contact lens materials based on poly(2-hydroxy ethyl methacrylate) and having a water content of approximately 40 per cent are marketed by various business concerns throughout the world. In addition to these, a number of hydrogel contact lens materials with water contents less than 40 per cent are also manufactured by copolymerising 2-hydroxy ethyl methacrylate with monomers of reduced hydrophilicity. Of even greater interest however are those soft contact lenses manufactured from high water content hydrogel polymers which offer suitable compatibility for extended periods of wear. A summary of some of these materials that are currently marketed is illustrated in Table IB.[22] The much improved comfort and tissue compatibility offered by these materials encourages the prospect of contact lens wear on a prolonged basis.

I.vii COMMERCIAL VIABILITY OF CONTINUOUS WEAR CONTACT LENSES

The past decade has seen a definite upsurgence in the popularity of contact lenses, although it is expected that spectacles will remain for some time as the major optical appliance for the correction of refractive defects in vision. The growth in the numbers of contact lens wearers from the innovation of plastic lens materials in 1948 has been initially slow, as is illustrated by the fact that in 1972 the ratio of spectacle to contact lens wearers was approximately 33 to 1. The reasons attributed to the slow initial growth in comparison to the more rapid expansion in the middle seventies are multifold, but amongst the more important factors are the adverse effects of the lens on the cornea. Hydrophobic or 'hard' contact lenses give rise to discomfort and visual inactivity whereas contamination or fracture during day to day handling of hydrophilic or 'soft' contact lenses may occur.

A continuous wear lens material would go some way to overcoming these problems in that if it is to undergo prolonged contact with the cornea, it should have a high degree of tissue compatability and hence minimise discomfort. Since the lens is to be worn continually the risk of bacterial contamination, rupture and loss due to handling will be greatly reduced.

In the opinion of many, the overriding deterent to any prospective contact lens wearer is the high cost of the lenses. 'Soft' lenses may retail from about £80 up to £120 or higher, it is important to note however that approximately two-thirds of the cost goes to the optician who fits the lenses.

The upturn in the numbers of contact wearers can, in the majority of cases, be put down to convenience and cosmetic reasons. It is hardly surprising therefore, that women and sportsplayers are the main groups to which contact lens wear has appeal, especially as it is well publicised that leading figures of television (eg Linda Carter) and the sportsworld (eg Geoff Boycott) wear contact lenses, promoting a more glamourous image for the product.

Here again the introduction of a continuous wear contact lens material would be shown to have a definite marketable potential by enhancing the image of contact lenses as a more attractive and convenient alternative to spectacles. One of the least conducive aspects of contact lens wear is removal and placing the lenses into a wetting solution prior to sleep, in a similar manner to soaking false dentures.

Continuous wear lenses would therefore eliminate this aspect and hence have a decided advantage over daily wear lenses in the promotion of a glamourous image.

I.viii REQUIREMENTS FOR A CONTINUOUS WEAR LENS MATERIAL

Any plastic material to be used in a biomedical application is subject to requirements that are both precise and severe. The following characteristics have been suggested[23] as appropriate for a material that is to be in extended contact with living tissue:-

1) It may be obtained in a reproducible manner.
2) It should be fabricated into the required form without undergoing degradation or any other change that may adversely affect its intended function.
3) It must possess the chemical, physical and mechanical properties necessary for the desired application.
4) It may be sterilised (by heat or chemical means) without alteration of the desired properties or dimensions.
5) The material should exhibit inertness in the appropriate biological environment.
6) It is essential that the material has toxicological inactivity in the relevant biological environment.

The restrictions placed upon a material that may be suitable for continuous wear contact lenses are even more acute.[24] An ideal contact lens has been defined as one having the following five functional criteria:-

a) comfort and safety
b) visual acuity
c) ease of wearing

d) dimensional and optical stability

e) simple care procedure.

Since a continuous wear lens may be considered as an extension of the cornea any material used for this application should possess three properties of major importance in addition to the most fundamental characteristic of having optical clarity. The cornea is avascular and acquires oxygen directly from the atmosphere in order to respire in an undisturbed manner, it is therefore essential that the material is permeable to gases such as oxygen or carbon dioxide. The minimum oxygen tension required to maintain normal corneal clarity and respiration has been estimated as 12-18 mm Hg[25] and from this it is believed that a continuous wear contact lens should have an oxygen permeability coefficient not less than 200 cm^3 mm cm^{-2} sec^{-1} $cmHg^{-1}$, approximately two-thirds that of the stroma.[26] In addition to direct permeation through the lens oxygen may also be transported to the cornea via an air saturated reservoir of tear fluid which lies between the lens and the eye. It is therefore necessary for the contact lens material to have a surface that is hydrophilic in order that the lachrymal fluid may wet the lens sufficiently for a continuous tear film to be maintained on the lens. However the surface properties of the material should not encourage the accumulation of proteinaceous debris on the lens which may lead to loss of optical clarity.[18] Finally the material should possess the strength required to resist the deforming force of the eyelid during the blink cycle, yet be easily elastically deformable and rapidly recoverable in order to minimise mechanical pressure on the eye and avoid visual instability.[20]

The concept of a continuous wear contact lens as an extension of the cornea is even more difficult to achieve as a practical reality in that the cornea is comprised of several structural elements which govern its properties. The bulk properties are generally governed by the stroma whereas the epithelium is responsible for the characteristics of the corneal surface; the different compositions of these component layers add to the complexity of the balance of properties that should be approached by any polymeric continuous wear material. Some of the more relevant features of the cornea that would be desirable for any plastic continuous wear lens are summarised in Table IC.[15]

I.ix DEVELOPMENT OF A POTENTIAL CONTINUOUS WEAR MATERIAL

From the requirements outlined in the previous section it is hardly surprising that no known homopolymer satisfactorily mimics sufficient of those properties desirable for an intended continuous wear material. However the excellent soft tissue compatability shown by swollen hydrogel polymers encourages the belief that they are the correct class of materials for this application. It has been found[12] that the 'dissolved' oxygen permeability of hydrogels increases exponentially with increasing water content (W) according to the following expression:-

$$Pd = 24 \times 10^{-10} e^{0.0443W} \qquad (I.1)$$

Where Pd is the dissolved oxygen permeability coefficient in cm^{3} (S.T.P.) mm cm^{-2} s^{-1} cm^{-1} Hg and is related to the oxygen flux (F) by the equation I.2

$$F = \frac{Pd}{L} \times \Delta p \qquad \text{(L = lens thickness)} \qquad (I.2)$$

It has been concluded from this information that in the case where no tear fluid transports oxygen behind the lens a hydrogel suitable as a continuous wear material should have an equilibrium water content of not less than 65 per cent and preferably greater than 70 per cent.

TABLE IC[15]

PROPERTIES OF THE CORNEA TO BE APPROACHED BY AN EXTENDED WEAR CONTACT LENS MATERIAL

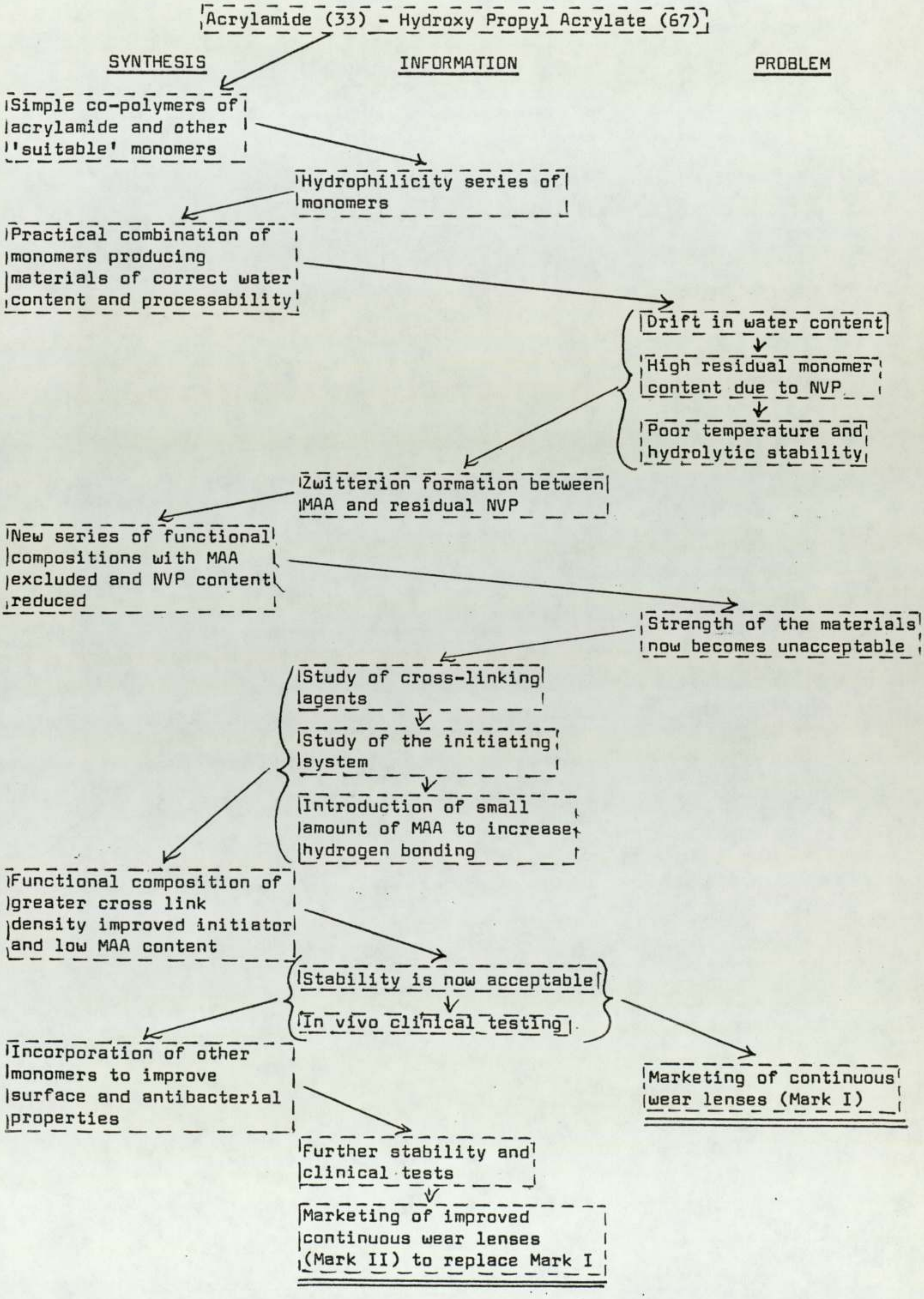
Water Content	~81% (17% free, 65% bound)
Critical Surface Tension	~35 dynes cm^{-1}
Refractive Index	1.37
Mechanical Properties	Linear viscoelastic material at low stress modulus of rigidity $\sim 1.3 \times 10^{8}$ dynes cm^{-2}
Oxygen Permeability	$\sim 300 \times 10^{-10}\ cm^{3}\ mm\ cm^{-2}\ S^{1}\ cm^{-1}\ Hg$
Oxygen Consumption	$3.5 - 7 \times 10^{6}\ \ell\ cm^{-2}\ h^{-1}$
Minimum Oxygen Tension for corneal clarity	12 - 18 mm Hg
Normal Oxygen Tension in tear fluid	155 mm Hg (open eye) 55 mm Hg (closed eye)

At such high water contents the strength of the majority of hydrogels falls far below that required for use as a contact lens and therefore a hydrophilic co-polymer consisting of monomers that are capable of hydrogen bonding has been suggested as being appropriate for this application.[28] Amides are known to exhibit strong hydrogen bonding characteristics and acrylamide, in particular, will form plurimolecular aggregates both with itself and with certain solvents. Thus a hydrogel co-polymer containing acrylamide, or a derivative thereof, would in theory at least seem to go some way toward satisfying some of the desired requirements. This view is strongly reinforced by the fact that the co-polymer acrylamide (33 mole %) - hydroxy propyl acrylate (67 mole %) has been found suitable to produce lenses for extended wear over a 14-day period[29]; in addition to this the lenses have been found to be sterilisable by autoclaving without displaying evidence of degradation.

I.x SCOPE AND OBJECTIVES OF THE PRESENT WORK

The aims of this project are to examine the stability of hydrogen-bonded hydrogels whilst developing a co-polymer suitable as a continuous wear material from the simple acrylamide-hydroxy propyl acrylate polymer having optimized properties. The development of a marketable continuous wear lens within the scope of this project is set out in Table ID in which the developments made from the original acrylamide-hydroxy propyl acrylate material may be seen quite clearly.

TABLE ID DEVELOPMENT OF A CONTINUOUS WEAR LENS MATERIAL



CHAPTER TWO

CHAPTER II

SYNTHESIS AND EXPERIMENTAL TECHNIQUES

II.1 INTRODUCTION

This chapter is concerned with the synthesis of hydrogel co-polymers and the methods employed for monitoring some of the properties of fundamental importance in the design of a continuous wear lens material.

II.2i REAGENTS

Monomers

The liquid monomers used during the course of this research are shown in Table II.A.

TABLE II.A

Monomer	Abbreviation	Molecular Wt	Supplier
Hydroxy ethyl methyacrylate	HEMA	130	BDH
Hydroxy propyl acrylate	HPA	130	BASF
Methyl methacrylate	MMA	100	BDH
Acrylic acid	AA	72	Koch-Light
Methacrylic acid	MAA	86	Koch-Light
Styrene	St	104	Koch-Light
N-vinyl pyrrolidone	NVP	111	Koch-Light

Each was purified by a conventional reduced pressure distillation, carried out under a stream of nitrogen gas in the presence of an inhibitor such as hydroquinone.

The purity of these monomers was checked by gas liquid chromatography using a Pye series 104 model 23/34 gas chromatograph fitted with a silicon gum SE30 column and a flame ionisation detector. Each purified monomer was stored in a refrigerator until required.

Acrylamide and those of its derivatives used in this research are solids at room temperature and are listed in Table II.B.

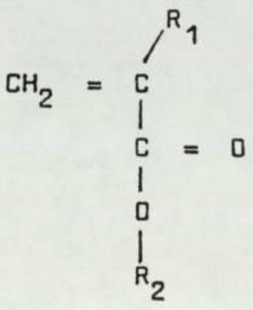
TABLE II.B

Monomer	Abbreviation	Molecular Wt	Supplier
Acrylamide	ACM	72	Koch-Light
Methacrylamide	MACM	85	Aldrich
Diacetone-acrylamide	DAACM	169	Polysciences
N-Hydroxy methylacrylamide	HMACM	101	BDH

These monomers were used as provided by the manufacturers without further purification.

Chemical Structures of Monomers

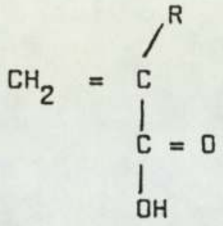
FIGURE IIa



1) HEMA ($R_1 = CH_3$, $R_2 = CH_2\text{-}CH_2\text{-}OH$)

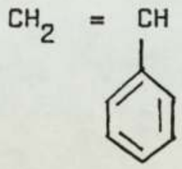
2) HPA ($R_1 = H$, $R_2 = CH_2\text{-}\underset{\overset{|}{OH}}{CH}\text{-}CH_3$)

3) MMA ($R_1 = CH_3$, $R_2 = CH_3$)

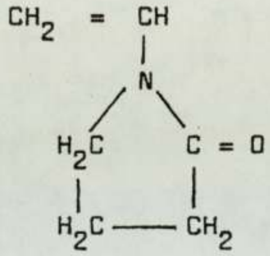


4) AA (R = H)

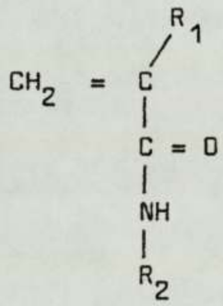
5) MAA ($R = CH_3$)



6) St

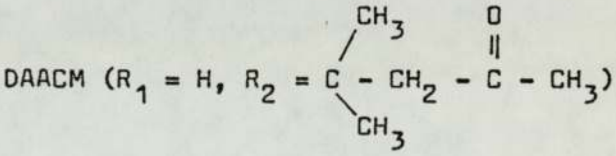


7) NVP



8) ACM ($R_1 = H$, $R_2 = H$)

9) MACM ($R_1 = CH_3$, $R_2 = H$)

10) 

DAACM ($R_1 = H$, $R_2 = C(CH_3)_2 - CH_2 - C(=O) - CH_3$)

11) HMACM ($R_1 = H$, $R_2 = CH_2OH$)

II.2ii CROSS-LINKING AGENTS

The following reagents shown in table II.C were employed as cross-linking agents during this research.

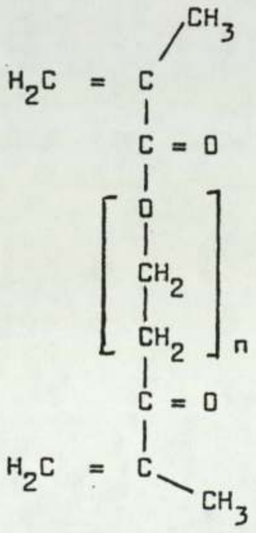
TABLE II.C

Cross-linking agent	Abbreviation	Physical State	Supplier
Ethylene glycol dimethacrylate	EDMA	Liquid	BDH
Poly ethylene oxide (Av Mol wt = 400) dimethacrylate	PEO(400) DMA	Liquid	Polysciences
Polyethylene oxide (Av Mol wt = 200) dimethacrylate	PEO(200) DMA	Liquid	Polysciences
Divinyl benzene	DVB	Liquid	BDH
Methylene bis acrylamide	MBACM	Solid	Cambrian
Dihydroxy ethylene bis acrylamide	DHEBACM	Solid	Laboratory Preparation
1,1,1 Trimethoxylol propane trimethacrylate	TMPTM	Liquid	Polysciences

All cross-linking agents were used as supplied without further purification, although a more detailed discussion of the problems arising from impurities present in cross-linking agents will be given in Chapter V.

Chemical Structures of Cross-Linking Agents

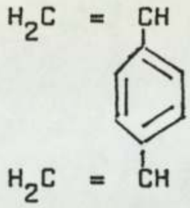
FIGURE IIb



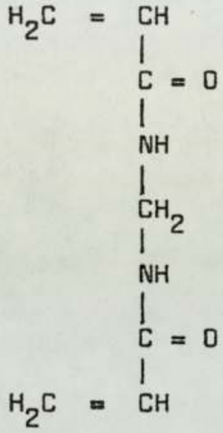
a) EDMA (n = 1)

b) PEO(400) DMA (n = 8 or 9)

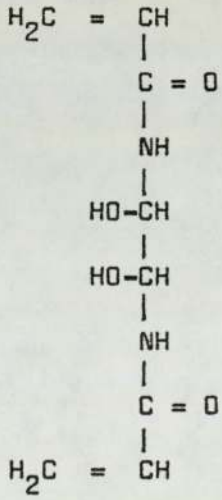
c) PEO(200) DMA (n = 4 or 5)



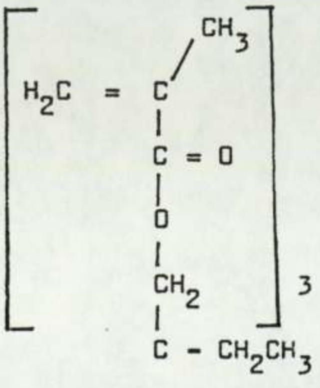
d) DVB



e) MBACM



f) DHEBACM



g) TMPTM

II.2iii INITIATORS

Various free radical initiators were used during this project and are as listed in Table II.D.

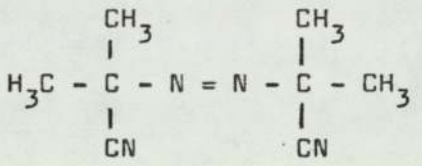
TABLE II.D

Initiator	Abbreviation	Physical State	Supplier
Azo bis iso butyronitrile	AZBN	Solid	BDH
Methyl ethyl ketone peroxide	MEKP	Liquid	Laporte
Tertiary butyl peroctoate	TBPO	Liquid	Laporte
Di-tertiary butyl cyclohexyl propane dicarbonate	DTBCPDC	Liquid	Laporte
Trimethyl cyclohexyl per ketal	TMCPK	Liquid	Laporte
Tertiary butyl perisononoate	TBIPN	Liquid	Laporte

All reagents were used as supplied by the manufacturer without further purification and were stored in a refrigerator prior to use.

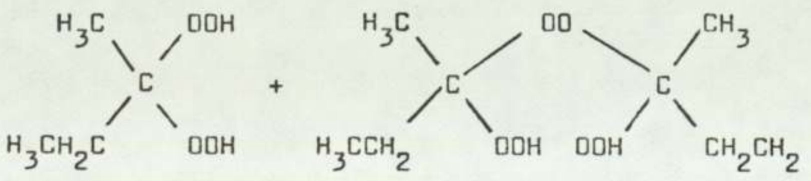
Chemical Structures of Initiators

FIGURE IIc



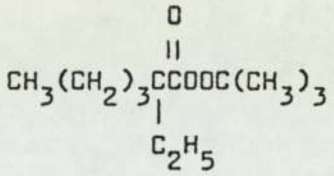
$$H_3C-\overset{\overset{CH_3}{|}}{\underset{\underset{CN}{|}}{C}}-N=N-\overset{\overset{CH_3}{|}}{\underset{\underset{CN}{|}}{C}}-CH_3$$

i) AZBN



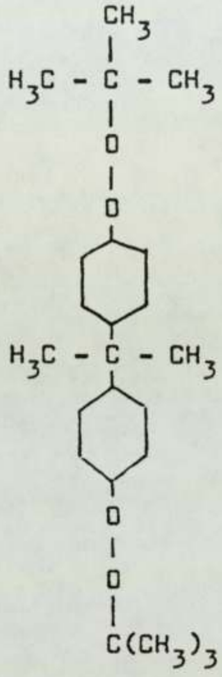
ii) MEKP
(supplied as a
mixture of
peroxide structures)

+ other structures

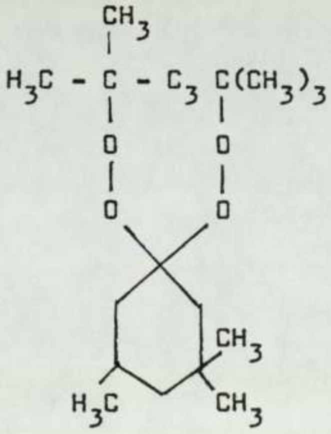


$$CH_3(CH_2)_3\underset{\underset{C_2H_5}{|}}{C}\overset{\overset{O}{\|}}{C}OOC(CH_3)_3$$

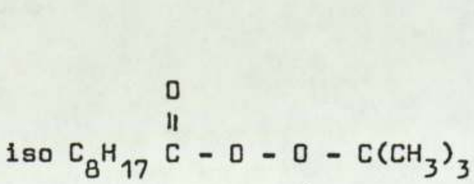
iii) TBPO



iv) DTBCPDC



v) TMCPK



$$iso\ C_8H_{17}\overset{\overset{O}{\|}}{C}-O-O-C(CH_3)_3$$

vi) TBPIN

The use of fluorinated and other monomeric compounds to produce surface modified hydrogel materials will be described in some detail in Chapter VII, together with the relevant synthetic methods employed.

II.3i METHODS OF POLYMERISATION

All the co-polymers produced were prepared by bulk polymerisation in rod or membrane form. The simpler co-polymers were prepared as membranes in order to facilitate the measurement of physical properties, whereas those polymers that were considered as viable continuous wear lens materials were made in rod form allowing lenses to be lathe cut for clinical assessment.

II.3ii PREPARATION OF RODS

Rods were prepared by the co-polymerisation of a suitable mixture of constituent monomers with a cross-linking agent in the presence of a free radical initiator. The polymerisation was carried out in a sealed polyethylene tube in order to facilitate the removal of the polymerised rod.[27]

In certain formulations the liquid monomer content proved insufficient to dissolve the solid acrylamide derivative constituent; this was usually remedied by the addition of small amounts of water to the reaction mixture to dissolve the remaining solid material.

A typical example is the co-polymerisation of a monomer mixture consisting of acrylamide N-vinyl pyrrolidone, hydroxy propyl acrylate and styrene in molar ratios of 40:40:10:10, together with ethylene glycol dimethacrylate (1.0% by wt) and methyl ethyl ketone peroxide (1.0%). After a homogeneous solution had been attained, either by warming or the addition of water the mixture was poured into a polythene tube (150 mm x 12.5 mm) sealed at one end. After flushing the mixture with nitrogen, the tube was sealed with a rubber bung of appropriate size covered with a thin polyethylene film and secured with adhesive tape. The polymerisation was carried out in a water bath at 40°C for a week, then at 60°C for 3 days and finally in an oven at 80°C for 2 hours before removing the rod by cutting open the polyethylene tube.

II.3iii PREPARATION OF MEMBRANES

Copolymer membranes were produced by bulk polymerisation of a monomer mixture in a suitable glass mould. The mould generally consisted of two glass plates (15 x 10 cm), each covered by a sheet of melinex (polyethylene terephthalate) as a mould release agent, being placed together with a polyethylene gasket (0.2 mm in thickness) separating the melinex sheets. Spring clips were used to hold the mould together, leaving sufficient space for the injection of the monomer mixture into the mould cavity. This is illustrated diagramatically in Figure II.d. As an illustration, a monomer mixture of acrylamide and hydroxy propyl acrylate in a molar ratio of 33 to 67, with ethylene glycol dimethacrylate (1.0% by wt) and azo bis isobutyronitrile (0.1% by wt) was prepared as a homogeneous solution. After purging with nitrogen, the solution was injected into the mould cavity formed by the polyethylene gasket by a syringe and polymerised in an oven at 65°C for 3 days followed by a postcure at 90°C for 2 hours to ensure a complete co-polymerisation. On removal of the spring clips, the mould was opened and almost without exception the co-polymer membrane was found to separate easily from the melinex sheet. On those few occasions when mould release presented a problem, the melinex sheet with the polymer membrane adhering to it were hydrated in distilled water until the hydrated membrane could be separated.

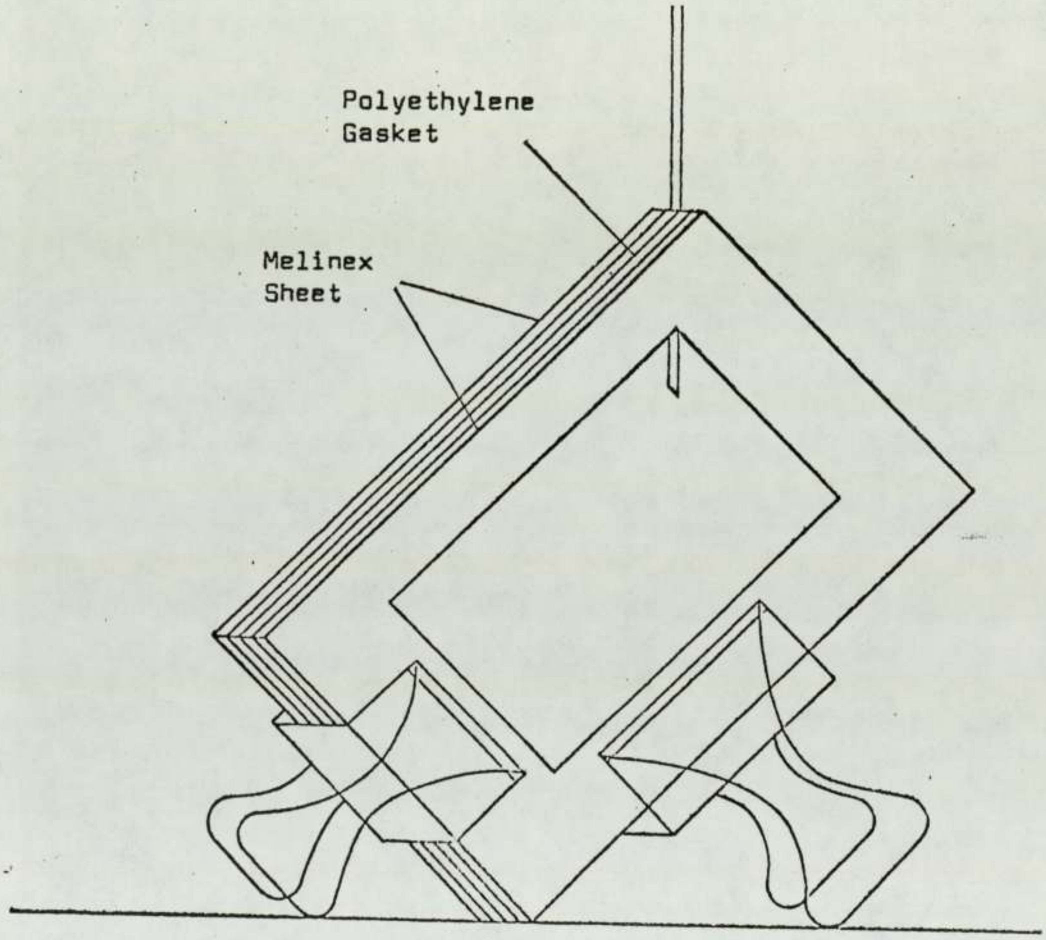


Figure II.d

II.4 PROPERTIES OF HYDROGELS

II.4i EXPERIMENTAL DETERMINATION OF EQUILIBRIUM WATER CONTENT AND SOLUBLE RESIDUALS

The equilibrium water content (EWC) of a hydrogel may be defined as the ratio of the weight of water contained in the hydrogel to the weight of the hydrogel at equilibrium hydration expressed as a percentage. The weight of water in the hydrogel is obtained by subtracting the weight of a polymer sample dehydrated to constant weight from the weight of the gel at equilibrium hydration, hence the equilibrium water content may be expressed in terms of the following equation:-[41]

$$\%\ \text{EWC} = \frac{\text{Weight of water (Ww)}}{\text{Weight of gel (Wg)}} \times 100$$

$$= \frac{\text{Wt of hydrated sample} - \text{Wt of dehydrated sample}}{\text{Wt of dehydrated sample}} \times 100$$

$$= \frac{Wg - Wp}{Wg} \times 100 \qquad \text{(II.1)}$$

where Wp = Weight of dehydrated polymer.

In the case of the more simple co-polymers that were prepared in the form of membranes, the equilibrium water content was measured by cutting samples from a membrane that had been hydrated in distilled water for a time sufficient to ensure the attainment of equilibrium (typically a month). The samples were cut from the hydrated sheet with a cork borer (size 7) and transferred to a previously weighed sample bottle after having any surface water carefully removed by filter paper. After weighing, the sample was dehydrated under vacuum at 60°C until constant weight was attained whereupon the EWC was calculated according to equation II.1

For those complex polymers that were prepared in rod form, the measurement of equilibrium water content was performed on samples of thin discs (1.0 to 2.0 mm in thickness) cut from the rod and polished on sandpaper to remove any debris on the disc. The weight of the polished disc was found by weighing in a pre-weighed sample bottle and then, by hydrating in distilled water until equilibrium was attained and dehydrating under vacuum, the equilibrium water content was calculated in the same way as that for the membranes. In addition to the equilibrium water content, a measure of any residual material in the co-polymer that is extractable may be gained by expressing the difference in the initial and dehydrated weights as a percentage of the initial weight. This may be expressed in the form of equation II.2

$$\% \text{ Residuals} = \frac{\text{Initial wt of polymer} - \text{Dehydrated wt of polymer}}{\text{Initial wt of polymer (Wi)}} \times 100$$

$$= \frac{Wi - Wp}{Wi} \times 100 \qquad \text{(II.2)}$$

Only in the case of those co-polymers prepared in rod form was the calculation of the residuals possible since the membranes proved too difficult to cut prior to hydration. It should be remembered that this technique gives no information of the nature of the extractable residuals ie whether they consist of residual monomer, low molecular weight oligomers or the products of polymer degradation etc.

II.4ii DETERMINATION OF THE DEFORMATIONAL PROPERTIES OF HYDROGEL POLYMERS

In order to correlate the behaviour of a hydrogel material as a contact lens, a knowledge of its resistance to the deforming force imposed by the eyelid during the blink cycle is necessary. The deformational behaviour of some of the hydrogel copolymers synthesised during this research has therefore been studied using a pneumatic microindentation apparatus developed by Monk and Wright for testing surface coatings.[42] A full description of the apparatus, the modifications necessary for using the instrument with hydrogels and how the results are interpreted in relation to the applicability of a polymer as a contact lens material has been given by Ng.[40]

The mathematical treatment by which the results obtained using this microindentation technique may be used to gain a measure of the mechanical strength of a hydrogel copolymer will be outlined in detail in Chapter III. In addition to this the pneumatic microindentor may be used to obtain a measure of the compression modulus of a hydrogel and thereby be used to calculate the cross-link density of the material. A full description of the method employed and an outline of the mathematical approximations to be made will be given in Chapter V.

II.4iii DETERMINATION OF HYDROGEL DENSITIES

In order to calculate the cross-link density of a hydrogel network a knowledge of the swelling ratio of the polymer is required. This may be calculated by measuring the density of a hydrogel polymer in both the swollen and dehydrated state. The measurement of densities has therefore been carried out using a Davenport density gradient column. Once more a description of the instrument together with details of its calibration have been given by Ng.[40] The mathematical process by which the density determinations may be used in conjunction with microindentation results to calculate cross-link densities is also outlined in Chapter V.

II.4iv OTHER TECHNIQUES

In addition to those experimental methods already described, a number of other workers within this research group have used a number of other techniques to measure the properties of hydrogel copolymers synthesised during this research project.

Barnes[43] has calculated the polar and dispersive components of the surface energy of hydrogel copolymers containing fluorinated substituents. The method employed has involved the measurement of the contact angles made on a hydrogel surface by a number of liquids, each having different polar and dispersive components. The complete mathematical treatment by which the calculation of the surface energy of a hydrogel may be carried out from the measurement of various contact angles is outside the scope of this thesis and has therefore been omitted.

In a few selected cases it has been necessary to carry out determinations of the proportions of 'free' and 'bound' water within the hydrogel network by differential scanning calorimetry. The use of this experimental technique for determining the nature of the water content of a hydrogel has recently been described by Pedley and Tighe.[44]

Work has also commenced upon the determination of the extent of proteinaceous deposition of albumin and fibrinogen upon the surfaces of hydrogels. The amount of protein laid down on a hydrogel surface has been calculated using radioactive labelled species[45] of both proteins in contact with materials synthesised during this research. Again a detailed discussion of the apparatus used and the mathematical formulae employed lie outside the scope of this thesis.

CHAPTER THREE

CHAPTER III

STRUCTURE-PROPERTY RELATIONSHIPS OF HYDROGEL POLYMERS RELEVANT TO THE DESIGN OF A CONTINUOUS WEAR CONTACT LENS MATERIAL

III.1 INTRODUCTION

In any attempted design of a hydrogel polymer as a continuous wear contact lens material, it should be remembered that the most important single property of these polymers is the water content. Indeed the water content of hydrogels may be thought of as a means of characterising these polymers, by giving an insight into the bulk hydrophilicity of the constituent monomers. A hydrophilicity series of monomers may in principle be deduced by an observation of the water contents of various hydrogel copolymers, synthesised by the combination of monomers of differing hydrophilicities. This hierarchy may then be used to facilitate the selection of monomers for inclusion in a copolymer composition that will have the appropriate properties for a continuous wear contact lens material.

This chapter is therefore concerned with the effects of varying the chemical structures of hydrogel copolymers in relation to the resulting water contents. In addition to an outline of the most relevant features of the relationships between hydrogel structures and water contents, a discussion of the actual validity of a hydrophilicity series of monomers will be undertaken. The use of such a series in the design of a continuous wear contact lens material will also be questioned, in the light of the results obtained for hydrogels prepared from certain co-monomer formulations. In order to present a more complete discussion, the relevant results of previous workers will be included with those obtained during the course of this research.

As the main field of study in this research was centred upon acrylamide based hydrogels, this chapter also includes a study of the copolymers and terpolymers of acrylamide in comparison with those of other unsaturated amide monomers. This comparison will not be restricted to a discussion of the water contents of these hydrogels, but an assessment of various copolymers in terms of their deformational properties, as studied by using the Monk and Wright pneumatic micro-indentor, will also be given. The elastic and rigidity moduli of various hydrogels were determined in addition to a few dehydrated samples by the Hertzian equation.[46] In certain cases departure from the behaviour predicted by the Hertzian equation was found to occur. The consequences of this in relation to the means of comparing their elastic and rigidity moduli with those polymers obeying the equation will be discussed.

III.2 ESTABLISHMENT OF A HYDROPHILICITY SERIES OF MONOMERS

The first hydrogel to attain any significance as a contact lens material was poly(2-hydroxy ethyl methacrylate) crosslinked with a small amount of ethylene glycol dimethacrylate.[47] The properties of this polymer however, do not meet with the requirements for a continuous wear contact lens, as outlined in Chapter I. Studies have therefore been undertaken to investigate the many interesting features of the relationships between structure and the water contents of various hydrogel copolymers.

Ng(40) has reported the trends observed in the water contents of hydrogels prepared by copolymerising an hydroxyl substituted unsaturated aliphatic ester with monomers of varying hydrophilic or hydrophobic natures. A selection of results, obtained for copolymers of 2-hydroxy ethyl methacrylate with the hydrophilic monomer N-vinyl pyrrolidone and hydrophobic constituents such as styrene and methyl methacrylate, are shown in Table III.A. These, together with the results for copolymers of 2-hydroxy propyl acrylate and styrene, are portrayed in Graph III.1.

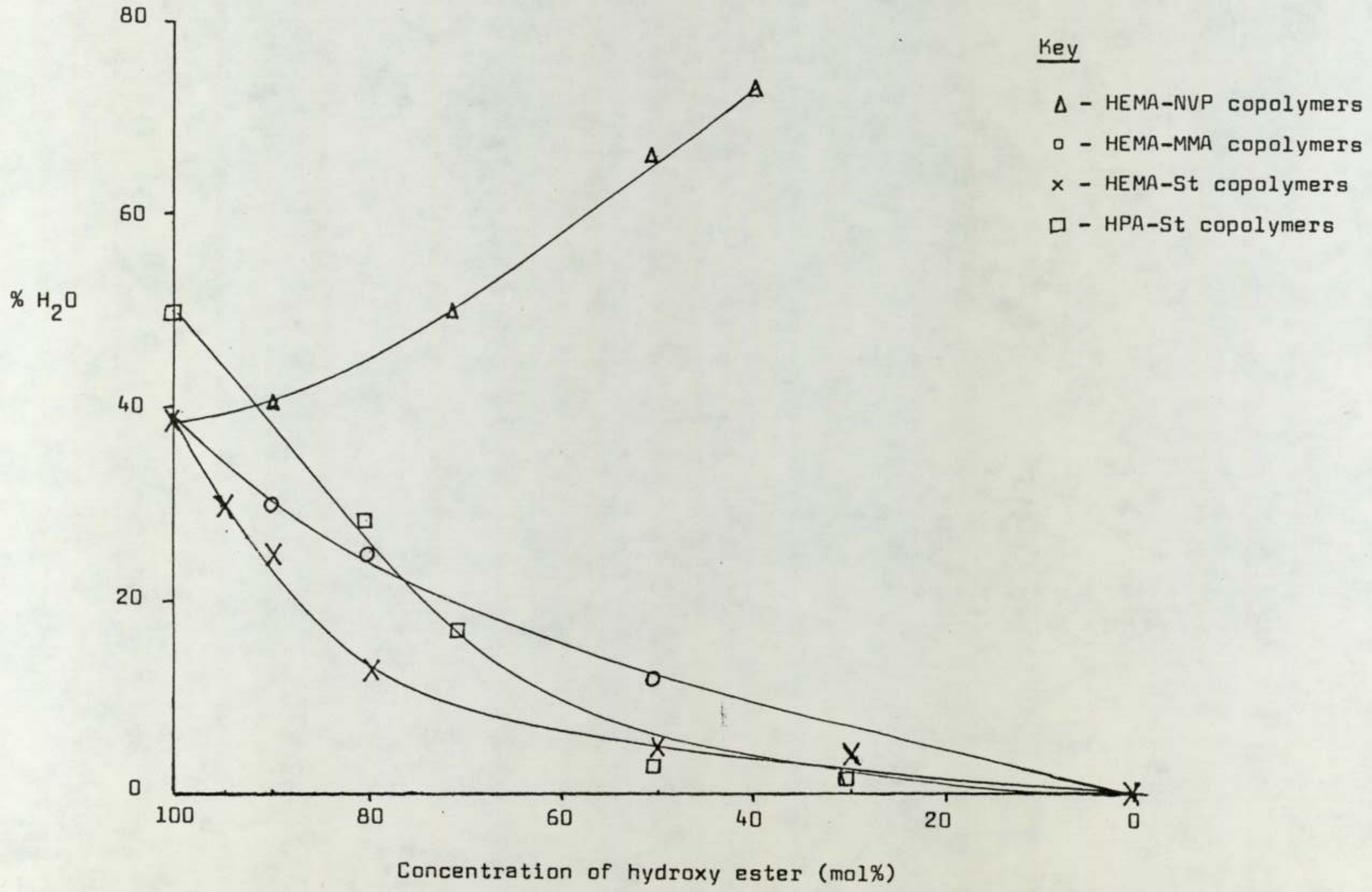
TABLE III.A

WATER CONTENTS OF CO-POLYMERS OF HEMA OR HPA AND A HYDROPHILIC OR HYDROPHOBIC CONSTITUENT

HEMA	St	MMA	NVP	HPA	% Water Content
100					39.0
95	5				29.7
90	10				22.8
80	20				13.1
50	50				5.0
30	70				2.5
90		10			30.9
80		20			25.1
50		50			12.3
90			10		40.6
70			30		49.9
50			50		66.1
40			60		73.2
	20			80	28.5
	30			70	17.2
	50			50	5.9
	70			30	1.4

The results clearly show that the inclusion of increasing numbers of hydrophobic units, such as styrene or methyl methacrylate, into the

GRAPH III.1



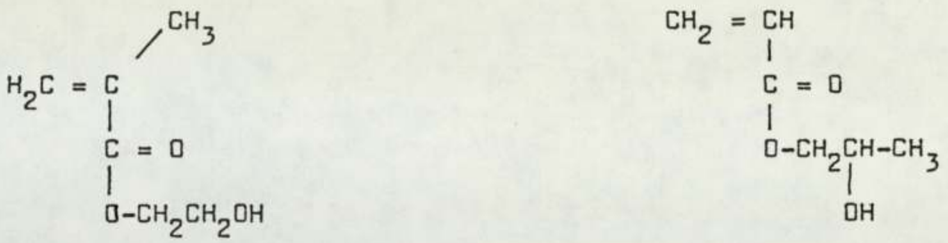
80
60
40
20
0
% H_2O
100
80
60
40
20
0
Concentration of hydroxy ester (mol%)
Key
Δ - HEMA-NVP copolymers
o - HEMA-MMA copolymers
x - HEMA-St copolymers
□ - HPA-St copolymers

copolymer leads to a progressive depression of water content. The results also illustrate the fact that, of the two hydrophobic monomers, styrene has a more pronounced effect. The curve for the 2-hydroxy ethyl methacrylate-styrene copolymers is seen to fall far more dramatically than that for copolymers of 2-hydroxy ethyl methacrylate and methyl methacrylate. This can be attributed to the effect of the bulky phenyl group of styrene attached to the polymer backbone, limiting the accumulation of water within the gel network by steric hindrance. The decrease in water content of copolymers as the proportion of methyl methacrylate constituents is increased, is far less marked in comparison. This is due to the methacrylate side chain having a lesser degree of steric hindrance than that caused by the phenyl group of styrene. In addition the carboxylate group in the ester linkage of the methacrylate side chain confers a degree of polarity that is absent in the phenyl group which also contributes to the fact that styrene is the more hydrophobic monomer.

The efficiency with which styrene reduces the water content of hydrogels is most clearly illustrated by comparing the curves obtained for copolymers of 2-hydroxy ethyl methacrylate-styrene and 2-hydroxypropyl acrylate-styrene. It is seen that 2-hydroxypropyl acrylate is more hydrophilic than its structural isomer 2-hydroxy ethyl methacrylate, but as styrene is added the difference in water contents is reduced and becomes negligible at a 50:50 (mol:mol) composition.

The reason for 2-hydroxy propyl acrylate having a greater hydrophilicity than its structural isomer, may be seen by examining the respective structures in Figure III.a:-

FIGURE III.a



2-hydroxy ethyl methacrylate 2-hydroxy propyl acrylate

The methyl substituent lends greater steric hindrance to water absorption when positioned on the backbone of the hydrogel polymer, as is the case for copolymers of 2-hydroxy ethyl methacrylate. Copolymers of 2-hydroxy propyl acrylate therefore, have higher water contents, since the methyl group is in the side chain and would seem to give rise to a lower steric effect.

The curve observed for copolymers of 2-hydroxy ethyl methacrylate and N-vinyl pyrrolidone, shows that the water content rises as the more hydrophilic constituent, N-vinyl pyrrolidone, is increased. This is as expected, since N-vinyl pyrrolidone has been prepared as a linear homopolymer which is water soluble.

Subsequent studies by Ng[40] on the water contents of terpolymers of 2-hydroxy propyl acrylate, N-vinyl pyrrolidone and styrene are given in Table III.8 and Graph III.2. The results show that the partial replacement of 2-hydroxy propyl acrylate by N-vinyl pyrrolidone also leads to an increase in water content. This tends to indicate that the interaction between the hydrophilic groups of these hydrogels and water molecules is sufficiently strong to prevent hydrogen bonding or dipole-dipole interactions. Hence the hydrophilic sites of these polymers will be almost entirely occupied by water molecules.

GRAPH III.2

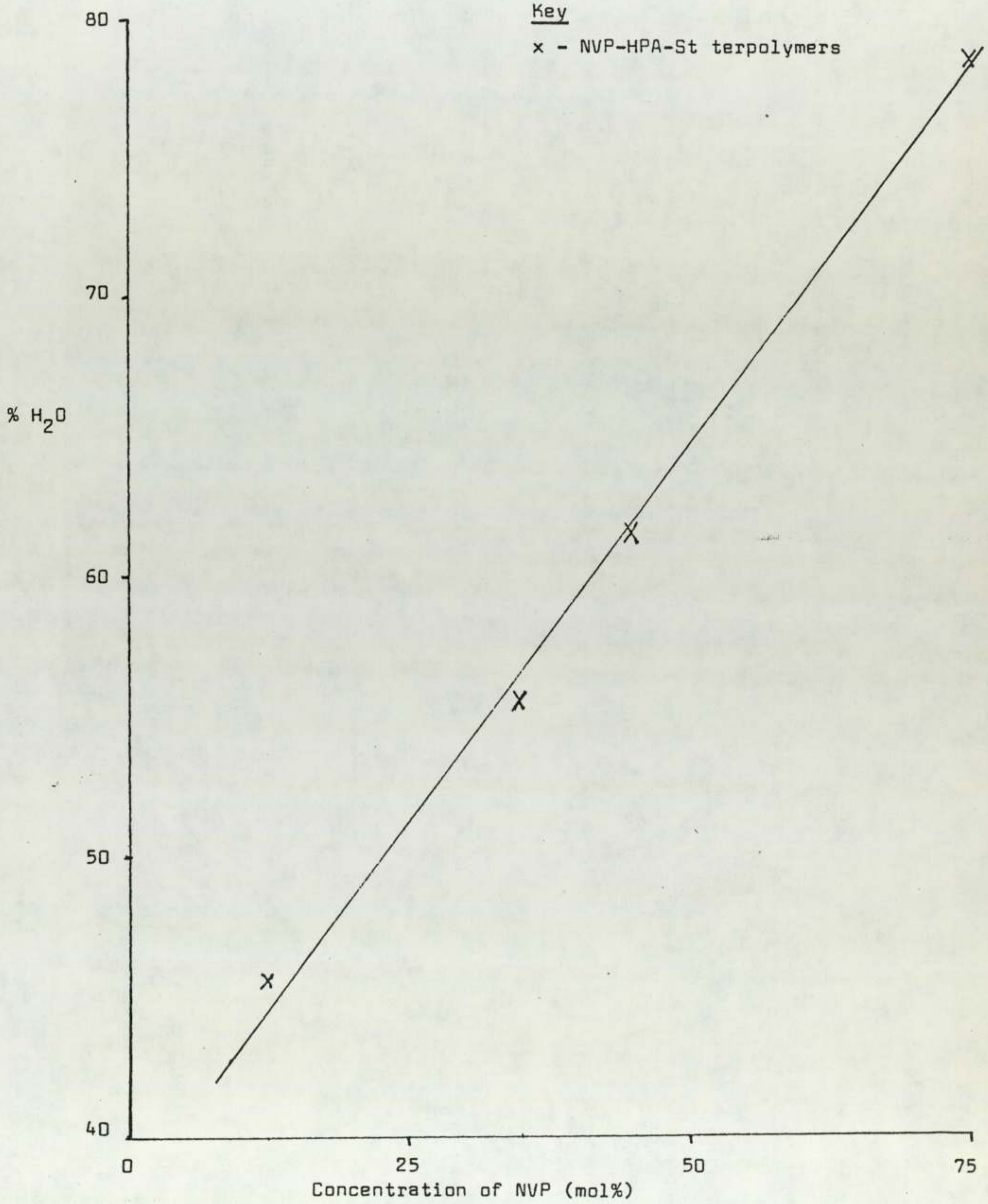

Key
x - NVP-HPA-St terpolymers
80
70
60
50
40
% H_2O
0
25
50
75
Concentration of NVP (mol%)

TABLE III.8

WATER CONTENTS OF TERPOLYMERS OF 2-HYDROXY PROPYL ACRYLATE N-VINYL PYRROLIDONE AND STYRENE

HPA	NVP	St	% Water Content
75	15	10	45.6
55	35	10	55.5
45	45	10	61.6
15	75	10	78.4

From these studies a valid hydrophilicity series of monomers may be drawn up, since none of those considered seem to interact to an extent which will affect the water absorption of these types of hydrogels. The hydrophilicity series for those monomers previously considered in this section is therefore as follows, in order of decreasing hydrophilicity: N-vinyl pyrrolidone > 2-hydroxy propyl acrylate > 2-hydroxy ethyl methacrylate > methyl methacrylate > styrene.

III.3 LIMITATIONS OF AN EXTENDED HYDROPHILICITY SERIES

The extension of the hydrophilicity series of monomers, as outlined in the previous section, to include monomers of a similar hydrophilicity to N-vinyl pyrrolidone, is obviously desirable. Hence, with a view to designing a continuous wear contact lens material, the copolymers of hydrophilic monomers having functional groups capable of conferring strength via internal polymer chain bonding, were studied.

Therefore, the copolymers and terpolymers of unsaturated carboxylic acids and amides have proved to be the focus of attention for a number of recent workers, due to their ability to form strong hydrogen bonds.[48,50]

The most popular examples of these types of monomers that have been studied are methacrylic acid and acrylamide. Acrylic acid, the parent acid of acrylamide, is generally avoided as it tends to form copolymers that behave as polyelectrolytes, giving rise to water contents that may vary with pH.[51,53] While it is therefore unsatisfactory for use in a potential contact lens composition, a number of acrylic acid copolymers have been studied in order to check the trends obtained for the corresponding copolymers of methacrylic acid.

The variance of water content with structure for copolymers of 2-hydroxy ethyl methacrylate with acrylamide and methacrylic acid has been reported by Anderton[54] and Berry[55] respectively. The results of these studies are listed in Table III.C and are depicted in Graph III.3, together with results for methacrylamide copolymers obtained during this research. The trends are most interesting in that the copolymers with acrylamide are seen to behave in an analogous manner to those considered in the previous section. As the more hydrophilic constituent, acrylamide, is increased the water content of the copolymer also rises.

This is also seen to be the trend observed for copolymers containing methacrylamide, although a small initial depression in the water content-copolymer composition profile is apparent. The possible reasons for this will be explored in greater detail at a later point in this chapter, but it should be noted that any depression of water content arising from Van der Waals interactions between methyl substituents attached to the polymer backbone will not be sufficient to explain the results obtained with copolymers containing methacrylic acid.

The water content profile obtained for the corresponding copolymers of methacrylic acid are in direct contrast to those with acrylamide. The water content is seen to fall to a minimum for the 50:50 (mol:mol)

TABLE III.C

WATER CONTENTS OF HEMA BASED COPOLYMERS

HEMA Content (mol %)	ACM Content (mol %)	MACM Content (mol %)	MAA Content (mol %)	% Water Content
100				39.0
75	25			56.0
67	33			59.5
60	40			63.5
55	45			62.5
75		25		36.2
67		33*		39.6
50		50*		47.8
75			25	30.0
50			50	27.5
25			75	40.5
			100	73.5

* Copolymers prepared in the presence of water

composition, indicating the contribution of interchain hydrogen bonding between carboxylic acid groups, as shown in Figure III.b. The hydrogen bonds have the effect of a form of secondary crosslinking which inhibits swelling and restricts the ability of polar hydrophilic groups to cluster water molecules.

Acrylamide, which is itself known to form plurimolecular aggregates in various solvents[56], would be expected to behave in an analogous fashion. Indeed strong hydrogen bonding is a characteristic feature of amides

GRAPH III.3

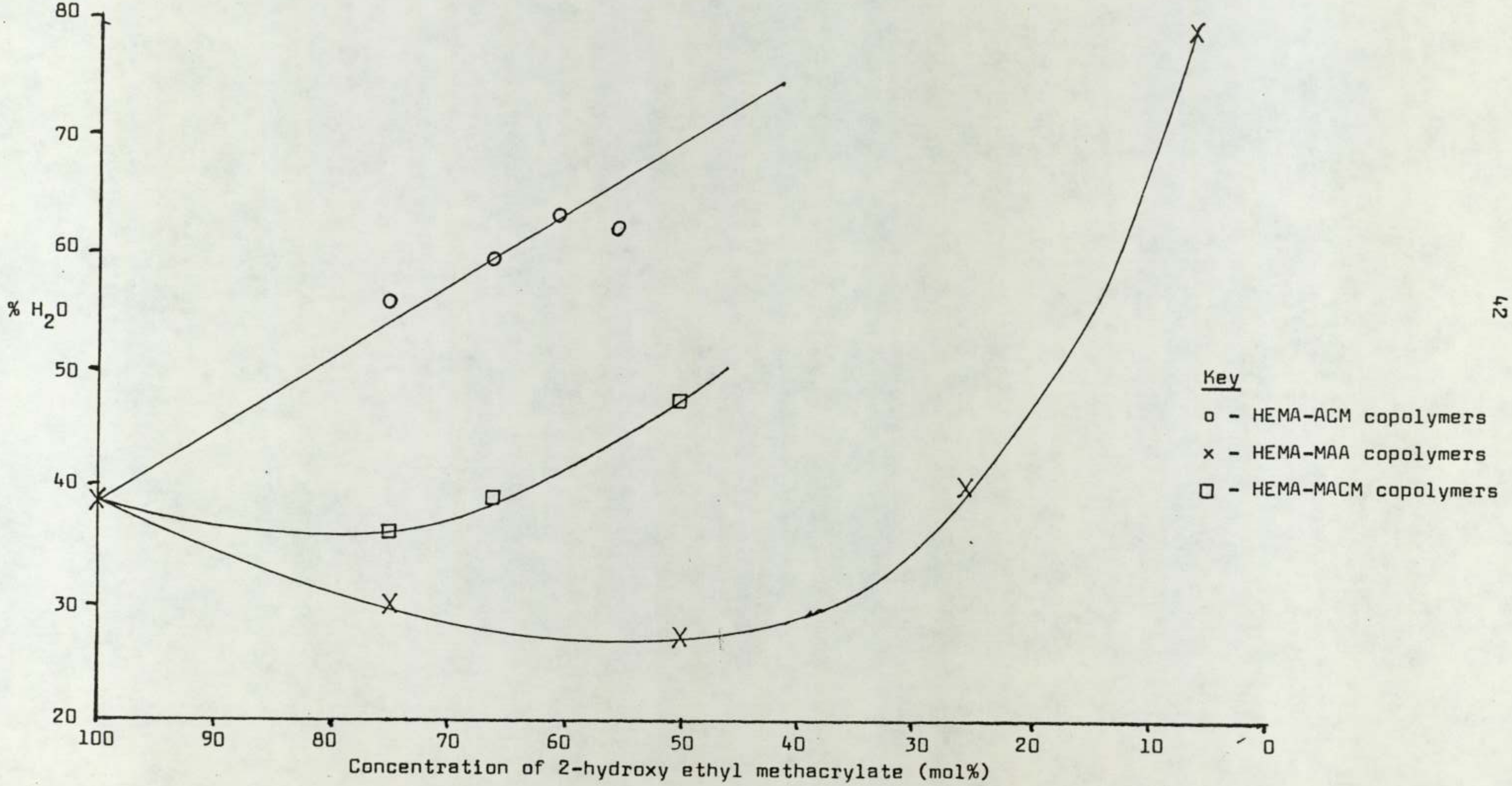
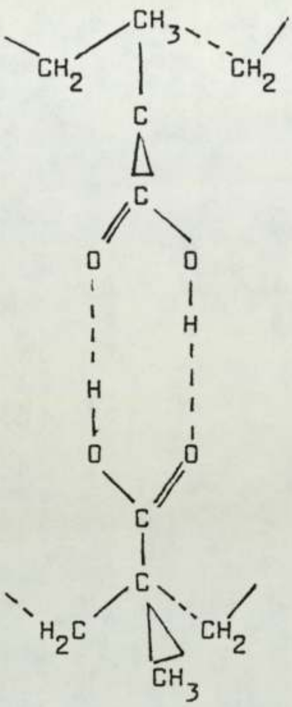

80
70
60
50
40
30
20
% H_2O
100
90
80
70
60
50
40
30
20
10
0
Concentration of 2-hydroxy ethyl methacrylate (mol%)
Key
o - HEMA-ACM copolymers
x - HEMA-MAA copolymers
□ - HEMA-MACM copolymers

FIGURE III.b



Interchain hydrogen bonding between two methacrylic acid units

giving rise to the high boiling points of many of them. As previously stated, however, copolymers of acrylamide and 2-hydroxy ethyl methacrylate do not enter into interchain hydrogen bonding to a significant degree, due to the carbonyl group of acrylamide being shielded.

The behaviour of acrylamide in conjunction with methacrylic acid, in copolymers and terpolymers, is therefore of considerable interest. The results obtained during this research, together with those from recent studies by Pedley[27] and Skelly[57] are listed in Table III.D.

Once more the results indicate that the inclusion of methacrylic acid, itself a hydrophilic monomer, gives rise to strong hydrogen bonding between chains and restricts the water absorption of hydrogels of this type. By considering the simple acrylamide-methacrylic acid copolymers, it is seen that an increase in the acrylamide constituent leads to a slight decrease in water content, from 44% to 40%. This is contrary to the behaviour observed in copolymers of acrylamide and

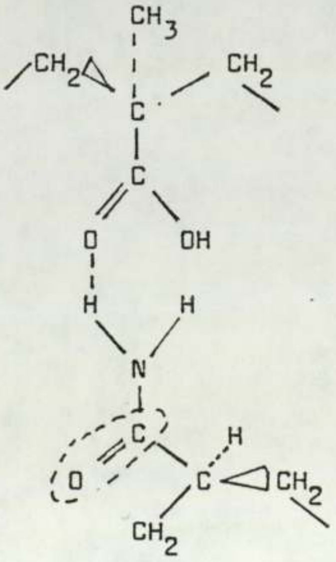
TABLE III.D

WATER CONTENTS OF COPOLYMERS AND TERPOLYMERS OF ACRYLAMIDE

ACM	MAA	HEMA	MMA	St	% Water Content
50	50				40.0
25	75				44.0
25	50	25			27.3
25	25	50			38.5
33	33	33			37.5
30	20	50			44.2
25		50	25		36.5
25		25	50		28.7
25		50		25	27.1

2-hydroxy ethyl methacrylate. The result can be explained however, in terms of the hydrogen bond forming capability of acrylamide with the carbonyl groups of methacrylic acid, as illustrated by Figure III.c :-

FIGURE III.c



Interchain hydrogen bonding between an acrylamide and methacrylic acid unit

The shielded carbonyl group of the acrylamide unit, which limits hydrogen bonding between amide groups, is ringed in Figure III.c.

Hydrogen bonding between amide and carboxylic acid groups also provides an explanation of the results obtained for terpolymers of acrylamide, methacrylic acid and 2-hydroxy ethyl methacrylate. When the molar proportions of acrylamide and methacrylic acid are equal, as in the terpolymer systems ACM 33 mol %, MAA 33 mol %, HEMA 33 mol %, and ACM 25 mol %, MAA 25 mol %, HEMA 50 mol %, water contents of 37.5% and 38.5% respectively are obtained. These are almost identical with that of 40% for the 50:50 (mol:mol) copolymer of acrylamide and methacrylic acid.

When a higher proportion of methacrylic acid units are present, as in the terpolymer ACM 25 mol %, MAA 50 mol %, HEMA 25 mol %, the water content falls to 27.3% because the carboxylic acid groups form more hydrogen bonds and effectively reduce the polymer-water interaction. It may seem curious that this terpolymer has a lower water content than that of the 25:75 (mol:mol) copolymer of acrylamide and methacrylic acid, which has a higher concentration of potential sites for hydrogen bonding. This behaviour is in agreement with that of copolymers of methacrylic acid and 2-hydroxy ethyl methacrylate however. It would appear from Graph III.3 that the hydrogen bonding between methacrylic acid groups achieves its maximum effect at approximately a 50:50 (mol:mol) composition. It is possible therefore, that when the methacrylic acid constituent is sufficiently large for appreciable numbers of blocks of methacrylic acid to be present in the chain, the water-polymer interaction becomes greater and restricts the amount of hydrogen bonding in the gel.

Considering the terpolymer system ACM 30 mol %, MAA 20 mol %, HEMA 50 mol %, it is seen that when a higher number of acrylamide units are present, in comparison with methacrylic acid, a higher water content of 44.2% results. This is due to an increase in the number of acrylamide groups that do not enter into hydrogen bonding with methacrylic acid units, and confer a higher degree of hydrophilicity on the terpolymer.

Comparison of the water contents of the terpolymers ACM 25 mol % MAA 50 mol%, HEMA 25 mol % and ACM 25 mol %, MAA 25 mol %, HEMA 50 mol % with those terpolymers prepared by replacing the methacrylic acid content by methyl methacrylate, shows only a small difference. Therefore the suppression of water content caused by methacrylic acid, in terpolymers of this kind, may be thought of as being equivalent to that of methyl methacrylate. The water content of 27.1% for the terpolymer ACM 25 mol %, HEMA 50 mol%, St 25 mol %, is seen to be almost identical with that for ACM 25 mol %, MAA 50 mol %, HEMA 25 mol %. This seems to indicate that the steric hindrance of styrene is more effective in reducing the water content of these hydrogels than the interchain hydrogen bonding provided by methacrylic acid.

All results for water contents were obtained on the premise that a hydration time of approximately one month would be sufficient for hydrogels to swell to equilibrium and a constant value could therefore be attained. Recent work in these laboratories by Goulding[58] has cast doubt upon this assumption however. These results, obtained during a study of the effect of monomer dilution on the water content of the 50:50 (mol:mol) copolymer of acrylamide and methacrylic acid, are shown in Table III.E. It may be seen from these results that a dramatic difference in water content is found when measurements are made after one and seven months respectively. Chemical analyses, carried out on the hydrogels at these times, indicated that a decrease in the acrylamide

TABLE III.E

EFFECT OF MONOMER DILUTION AND TIME OF HYDRATION ON THE WATER CONTENT AND ACRYLAMIDE CONTENT OF THE 50:50 (mol:mol) ACRYLAMIDE-METHACRYLIC ACID COPOLYMER

Water Added (wt %)	% Water Content (28 days hydration)	% Acrylamide Content (28 days hydration)	% Water Content (30 weeks hydration)	% Acrylamide Content (30 weeks hydration)
0	45.2	36.0	64.2	28.7
2	49.4	38.5	69.0	26.4
5	56.8	39.3	72.4	30.9
7.5	68.5	39.3	84.3	32.6
10	75.3	40.7	86.7	34.3

content of the polymers had also taken place during this period. This may suggest that the acrylamide groups of the copolymer are slowly undergoing hydrolysis to give acrylic acid. This would in turn lead to a relaxation of the hydrogen bonding between acrylamide and methacrylic acid units giving rise to an increase in water content. Another explanation may be that the decrease in acrylamide content of these copolymers is due to low molecular weight polyacrylamide fragments slowly leaching from the gel. This could be totally unrelated to the increase in water content, which can be attributed to a relaxation of hydrogen bonding due to water molecules slowly becoming able to bind to the hydrophilic groups that have undergone interchain hydrogen bonding.

The effect of monomer dilution on the water contents of these hydrogels, found during this study, is also very interesting. The water content is seen to rise from 45.2% to 75.3%, after one month's hydration, when the amount of water added to the comonomer composition is increased from 0 to 10% by weight. This would seem to suggest that the water becomes a partial solvent for the aggregation of acrylamide monomer units prior to polymerisation and acts as a medium to produce blocks of acrylamide in the polymer chain. From Table III.E it is seen that analysis of these hydrogels did indeed show that the acrylamide content became greater as monomer dilution was increased. Not only would this cause an increase in water content by supplying a copolymer with a greater number of hydrophilic units, but since a polymer will be formed with a number of water molecules directly associated with functional groups, a decrease in hydrogen bonding can also be expected.

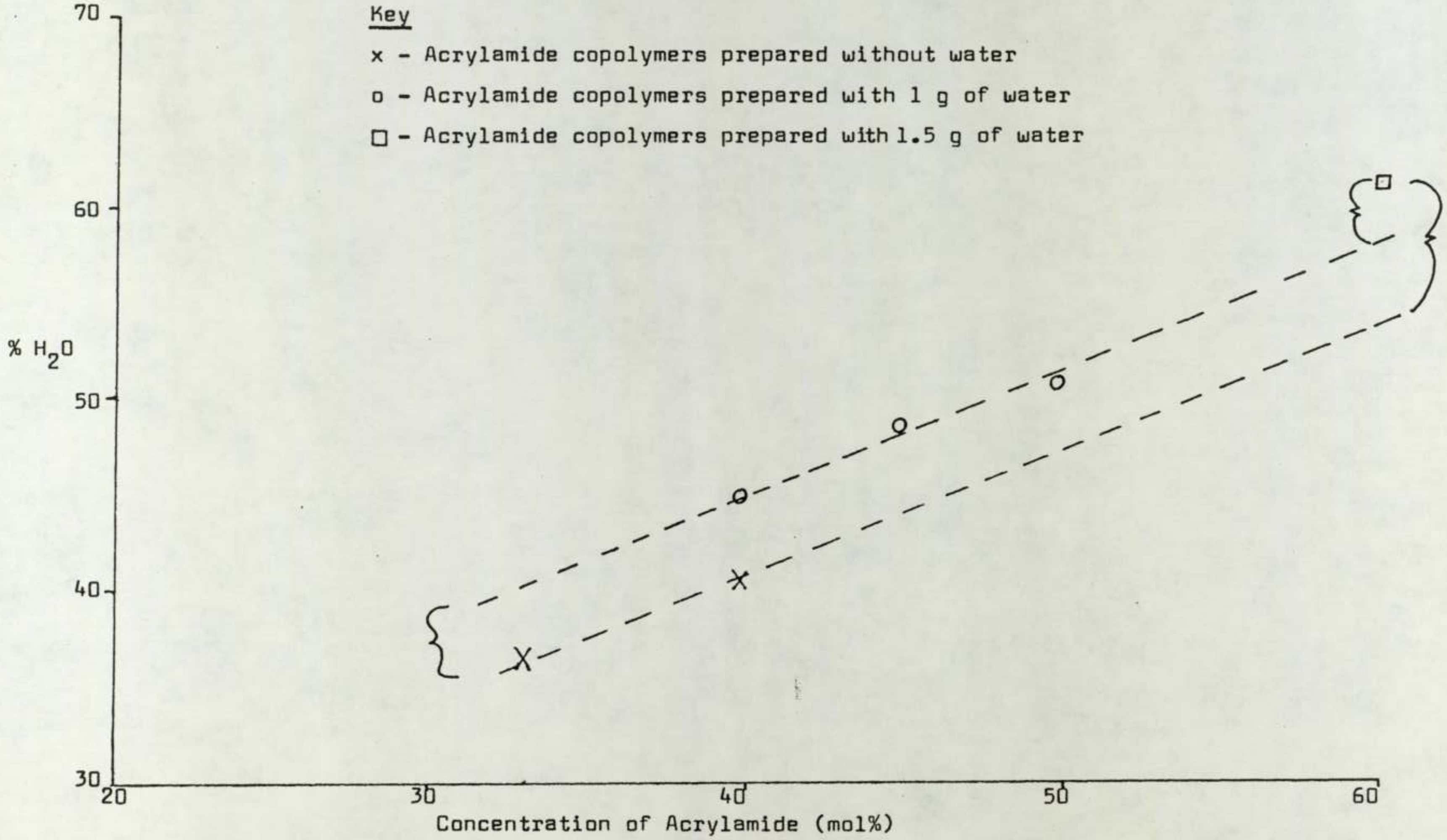
During the course of this research a similar study to that carried out by Goulding was undertaken using acrylamide based hydrogels of 4 monomeric components. The results are shown in Table III.F and are portrayed in Graph III.4. Only the effect of the addition of water was

TABLE III.F

EFFECT OF MONOMER DILUTION ON THE WATER CONTENTS OF A SERIES OF ACRYLAMIDE BASED HYDROGELS

Wt of H_2O added (g)	ACM	HEMA	MAA	St	% Water Content
-	33	47	10	10	36.6
-	40	40	10	10	40.6
1.0	40	40	10	10	45.1
1.0	45	35	10	10	49.0
1.0	50	30	10	10	51.3
1.5	60	20	10	10	60.7

GRAPH III.4


Key
x - Acrylamide copolymers prepared without water
o - Acrylamide copolymers prepared with 1 g of water
□ - Acrylamide copolymers prepared with 1.5 g of water
% H_2O
70
60
50
40
30
20
30
40
50
60
Concentration of Acrylamide (mol%)

investigated, and the results seem to agree with those found previously. In this study a range of polymers were used and the acrylamide content was increased by gradually replacing the content of 2-hydroxy ethyl methacrylate. A linear increase in water content would be expected with increasing acrylamide content but, as is seen in Graph III.4, the monomer dilution creates a 'step-up' effect in the water content-composition profile.

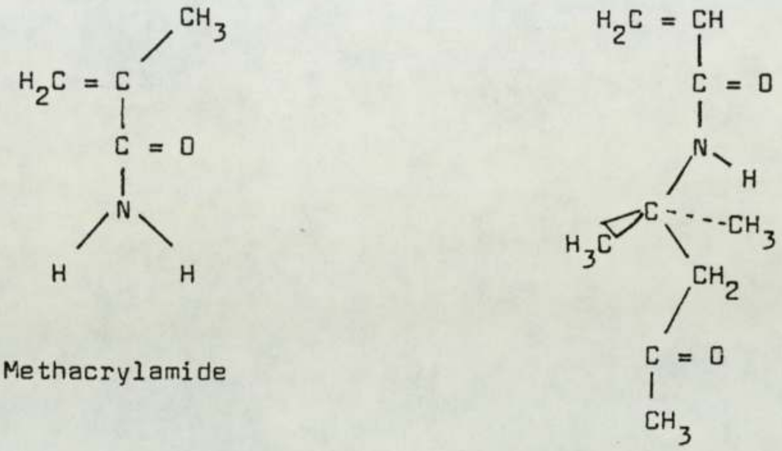
Further studies with high water content hydrogel copolymers at elevated temperatures have indicated that certain compositions are liable to give water contents which are not thermally reversible and show evidence of hysterysis phenomena. The implications of obtaining a hysterysis loop in the water content temperature profile will be discussed at length in Chapter IV. It becomes obvious however that any potential lens material that exhibits this behaviour to an appreciable degree will give rise to acute problems in terms of the stability of the parameters of the contact lens and its fit when the lens is sterilised by autoclaving and fluctuations in the temperature of the eye occur. While no detailed account of the causes of the observed stability problems will be given until the following chapter, it is important to note that the occurrence of temperature hysterysis may be attributed to the interaction between two of the monomeric components of the hydrogel copolymer. This again illustrates the unsuitability of using a hydrophilicity series of individual monomers for selecting constituents of a potential continuous wear contact lens material.

To summarise this section, it must be remembered that any knowledge of the hydrophilicity of various monomers, only becomes useful to the design of the properties of copolymers when the bonding of water to the hydrophilic groups far outweighs interchain bonding between monomer units in the polymer. Not only have the results of these studies cast doubt on the actual validity of a hydrophilicity series, but they have also brought the rationality of an equilibrium water content into question. This is a consequence of the hydration studies of polymers in which interchain bonding between hydrophilic groups is in competition with water-polymer binding. It would seem that over a period of time water absorption increasingly asserts itself over interchain interactions between appropriate functional groups, causing a gradual rise in water content. Hence, in these forms of hydrogels, an equilibrium is rarely, if ever attained and is also unlikely to be prolonged for any period of time as chain rotation and a reformation of interchain hydrogen bonding may also occur in these polymers. In addition to this, those hydrogels that are subject to irreversible changes in water content with varying temperature also give rise to doubts over the concept of a water content at equilibrium, since two samples of the same polymer composition may vary as a result of having different thermal histories.

Thus a knowledge of the relative hydrophilicity of an individual monomer cannot be taken as a useful guideline for the design of a high water content continuous wear contact lens material and a somewhat more empirical method for attaining an appropriate balance of properties has therefore been adopted.

III.4 COMPARISON BETWEEN THE HYDROGELS OF ACRYLAMIDE AND THOSE OF ITS HIGHER DERIVATIVES

In view of the interesting results obtained during this and other research projects with acrylamide copolymers, a number of studies have been undertaken to investigate the effect of structural variation within the acrylamide units on the water contents of these types of hydrogels. During the course of this research particular attention has been focussed on the copolymers of methacrylamide and diacetone acrylamide, since this will give an insight into the effect of substitution at the vinyl and amide positions of acrylamide. The chemical structures of methacrylamide and diacetone acrylamide are shown in Figure III.d.



Methacrylamide

Diacetone acrylamide

Figure III.d

Copolymers of acrylamide and these derivatives with 2-hydroxy ethyl methacrylate have been prepared and the compositions together with the water contents are listed in Table III.G. Before these results, which are portrayed in Graph III.5, are discussed it should be noted that differences in the degrees of solubility of the acrylamide derivatives in 2-hydroxy ethyl methacrylate are easily discernible. It is seen that the limit of solubility of acrylamide in 2-hydroxy ethyl methacrylate is such that copolymer compositions with an acrylamide content greater than 40 mol % require the addition of a solvent such as water to ensure complete dissolution. The solubility of diacetone acrylamide is seen to be greater than that of acrylamide since the 50:50 (mol:mol) copolymer composition with 2-hydroxy ethyl methacrylate is conveniently prepared without the addition of water being necessary. This is in sharp contrast to the behaviour of the methacrylamide based copolymers

TABLE III.G

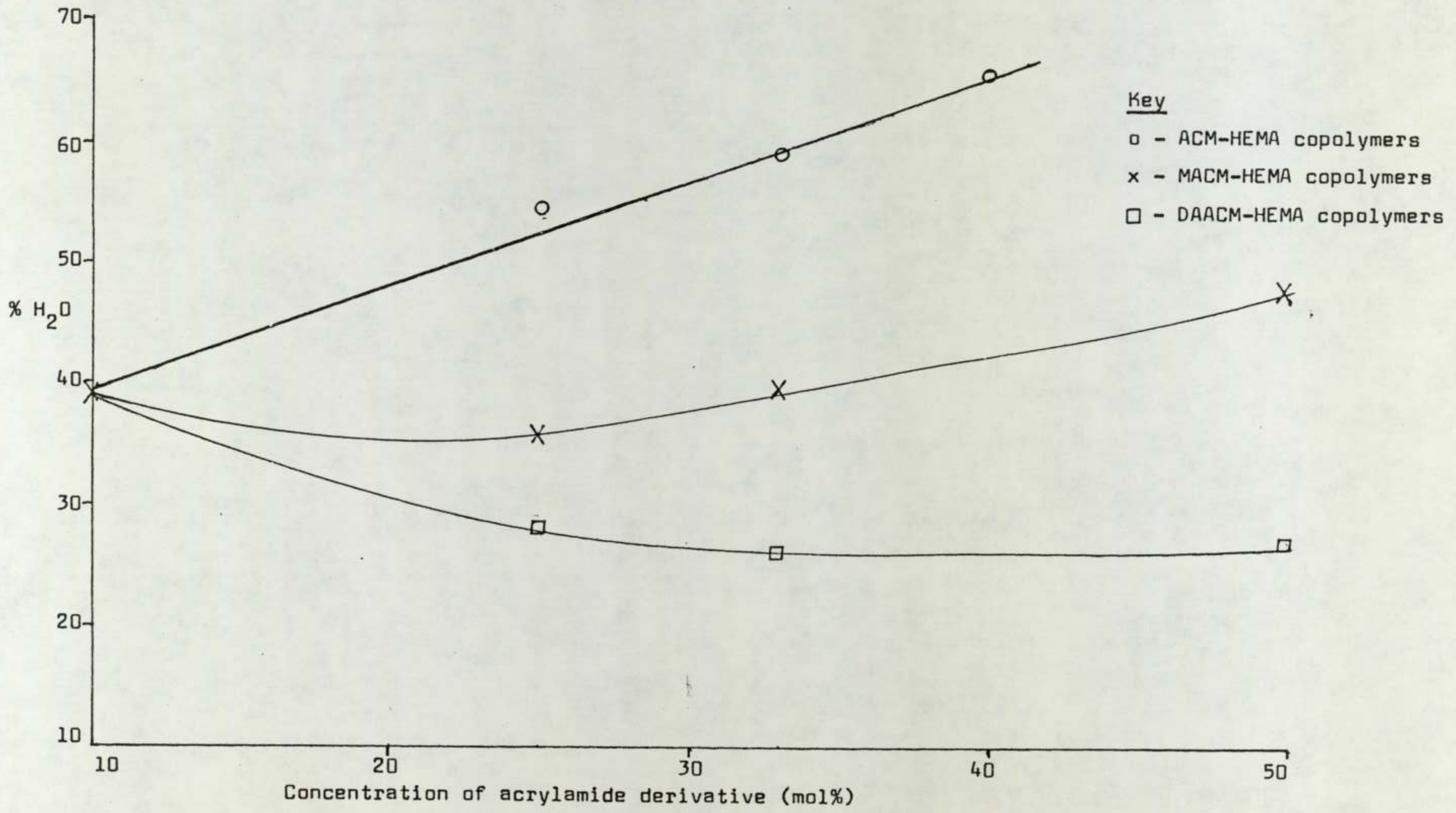
WATER CONTENTS OF 2-HYDROXY ETHYL METHACRYLATE COPOLYMERS WITH ACRYLAMIDE DERIVATIVES

ACM	MACM	DAACM	HEMA	H_2O added (weight %)	% water content
			100		39.0
25			75		56.0
33			67		59.3
40			60		63.7
	25		75		36.2
	33		67	3	39.6
	50		50	15	47.8
		25	75		28.8
		33	67		26.4
		50	50		27.5

as methacrylamide is seen to be less soluble than acrylamide in that 3% by weight of the 33:67 (mol:mol) composition is water. The amount of water to ensure complete dissolution of methacrylamide rises to 15% by weight for the 50:50 (mol:mol) copolymer composition.

The trends for the water contents of these copolymers are shown in Graph III.5 and the difference in behaviour of the acrylamide copolymers and those of its derivatives are clearly illustrated. The copolymers of acrylamide and 2-hydroxy ethyl methacrylate show an almost linear increase in water content as the acrylamide content of the hydrogel composition is raised. The corresponding copolymer compositions of methacrylamide and diacetone acrylamide both show an

GRAPH III.5


70
60
50
40
30
20
10
% H_2O
10
20
30
40
50
Concentration of acrylamide derivative (mol%)
Key
o - ACM-HEMA copolymers
x - MACM-HEMA copolymers
□ - DAACM-HEMA copolymers

initial decrease in water content before beginning to rise above a minimum value. It would seem therefore that the effects of the methyl substituent on the polymer backbone in the methacrylamide compositions and the bulky ketonic group on the amide side chain of diacetone acrylamide copolymers are similar.

The methacrylamide copolymers with 2-hydroxy ethyl methacrylate show that inclusion of methacrylamide units gives rise to a depression of water content until a certain concentration of amide groups are present within the polymer. The amide group of methacrylamide is more polar than the hydroxyl group of 2-hydroxy ethyl methacrylate and this accounts for the rise in water content as the copolymers become increasingly rich in hydrophilic amide units. The initial fall in water content may be explained by an increase in hydrophobic bondings within the copolymer caused by Van der Waals interactions between the methyl substituents on the 2-hydroxy ethyl methacrylate and methacrylamide units. However as the methacrylamide content of the copolymer composition is increased and the restriction of rotation arising from dipole-dipole interactions between the side chains of hydroxy ethyl methacrylate units is replaced by the hydrophilic nature of the amide groups which gradually become sufficient to overcome the hydrophobic Van der Waals attractions between methyl substituents.

While an interpretation of the results obtained for the water contents of methacrylamide containing copolymers has been attempted, the addition of water to the monomeric composition prior to polymerisation brings the validity of the treatment adopted into question. It has been seen from Tables III.E and III.F that the addition of water as a partial solvent for the acrylamide content of a monomeric solution has resulted in the formation of hydrogels with somewhat higher water contents than would be expected. It may therefore be possible to explain the rise in water content observed as the methacrylamide concentration in the monomer feed ratio is increased in an analogous manner. If this is correct however it only serves to support the hypothesis already put forward, since the addition of water prior to polymerisation may be expected to increase the methacrylamide content, and therefore the number of hydrophilic amide groups, within the copolymer. This will give rise to a more dramatic increase in the water content-composition profile than might be expected although the causes of the observed trend remain unaltered.

The behaviour of the copolymers of diacetone acrylamide and 2-hydroxy ethyl methacrylate is similar to that shown by the methacrylamide based compositions but the depression of water content is even more pronounced. The water content decreases dramatically as the concentration of diacetone acrylamide units within the copolymer is increased until a small rise is observed for the 50:50 (mol:mol) composition. Since the only structural difference between diacetone acrylamide and acrylamide itself is the replacement of a hydrogen atom in the amide group by a large 1,1 dimethyl-3-oxy butyl substituent, this is obviously the cause of the striking contrast in hydrophilicity between these monomers. The results obtained for the copolymers of diacetone acrylamide and 2-hydroxy ethyl methacrylate may be explained by an interpretation analogous to that used for the methacrylamide copolymer compositions. The methyl substituents within the 1,1 dimethyl-3-oxy butyl group not only give rise to hydrophobic bondings with the methyl substituent of the hydroxy ethyl methacrylate units but also tend to shield the hydrophilic amide group which inhibit the attraction of water molecules. It is not surprising therefore that the substitution of a hydrophobic unit at the hydrophilic amide site is more effective in causing a depression in water content than the methyl group of methacrylamide. This is confirmed by the fact that the concentration of diacetone acrylamide required to cause a rise in water content is greater than that for methacrylamide due to the shielding of the hydrophilic amide group as previously stated.

A similar study of the copolymers of these acrylamide derivatives with 2-hydroxy propyl acrylate would be expected to show almost identical behaviour and confirm the conclusions previously outlined. Examination of the results obtained, as shown in Table III.H and depicted in Graph III.6, illustrate that this is largely true in the case of the acrylamide and methacrylamide copolymers. The copolymers of diacetone acrylamide however are seen to decrease in water content to a greater extent as the concentration of diacetone acrylamide is increased, and no rise in water content is observed. This is somewhat surprising since 2-hydroxy propyl acrylate is more hydrophilic than its isomer 2-hydroxy ethyl methacrylate and diacetone acrylamide might therefore be expected to depress the water content to a lesser extent. This may be due to the hydrophobic bondings caused by Van der Waals attractions between methyl groups and dipole-dipole interactions in the side chains of the diacetone acrylamide and 2-hydroxy propyl acrylate units being more effective in restricting water absorption than similar bonds formed with methyl substituents on the polymer backbone in copolymers with 2-hydroxy ethyl methacrylate.

To investigate the effect of incorporating diacetone acrylamide in a copolymer composition more fully, the water contents of copolymers of diacetone acrylamide and N-vinyl pyrrolidone have been studied. The results, together with those of Ng for copolymers of N-vinyl pyrrolidone and 2-hydroxy ethyl methacrylate, are shown in Table III.I and Graph III.7.

GRAPH III.6

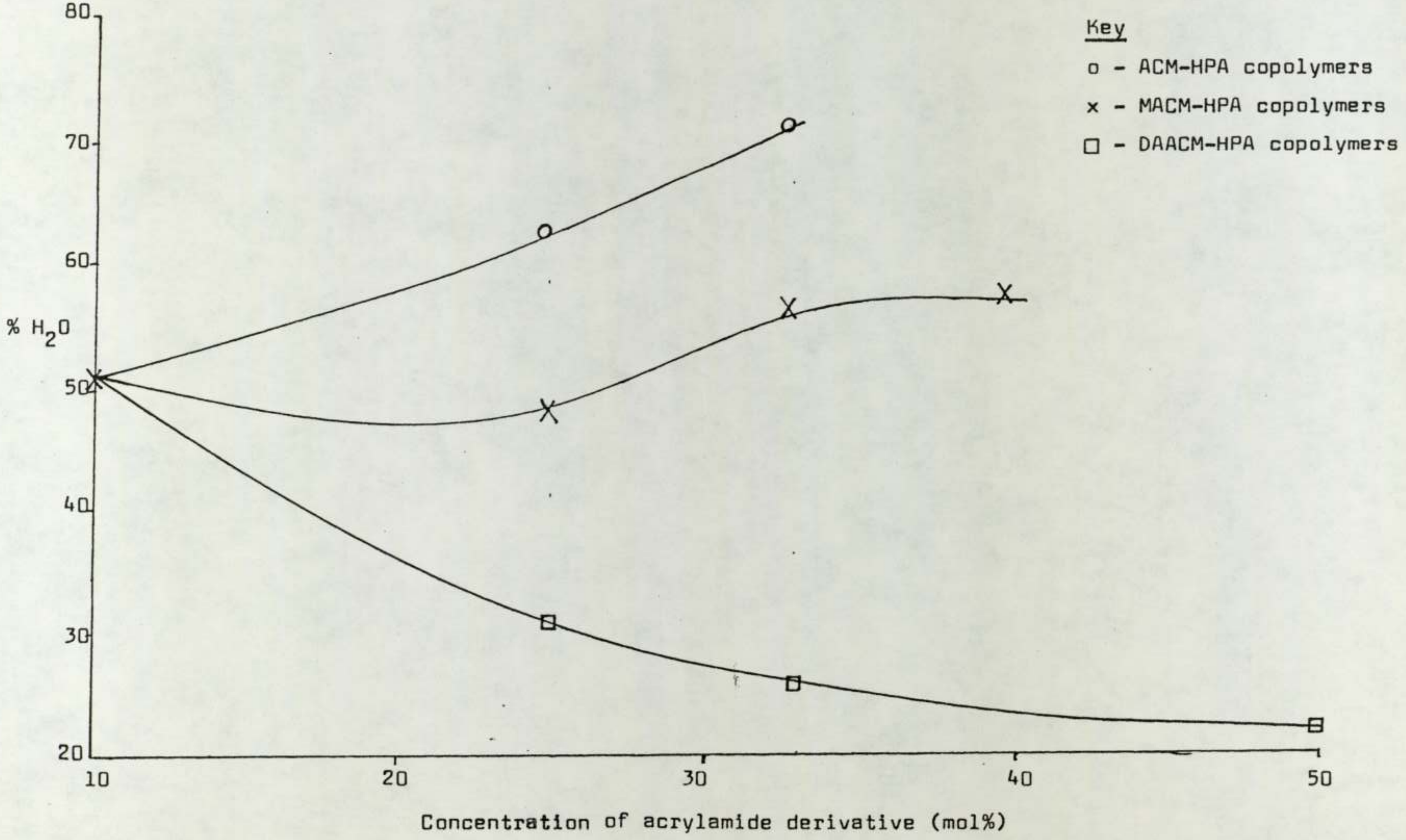

80
70
60
50
40
30
20
% H_2O
10
20
30
40
50
Concentration of acrylamide derivative (mol%)
Key
o - ACM-HPA copolymers
x - MACM-HPA copolymers
□ - DAACM-HPA copolymers

TABLE III.H

WATER CONTENTS OF COPOLYMERS OF 2-HYDROXY PROPYL ACRYLATE WITH ACRYLAMIDE DERIVATIVES

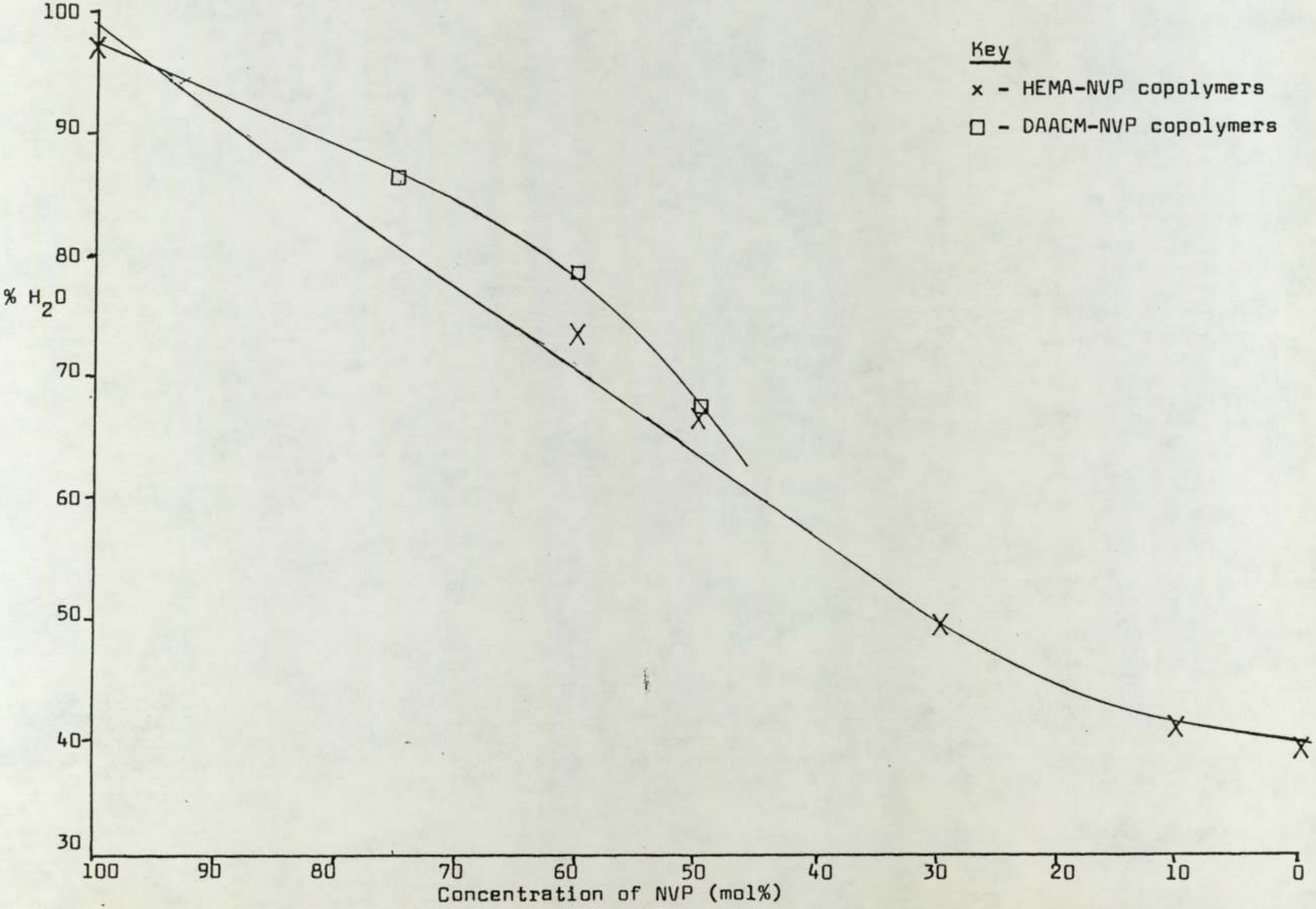
ACM	MACM	DAACM	HPA	H_2O added (weight %)	% Water content
			100		51.0
25			75		61.7
33			67		71.3
	25		75		48.5
	33		67	3	55.7
	40		60	7	56.5
		25	75		30.8
		33	67		25.8
		50	50		22.2

TABLE III.I

WATER CONTENTS OF COPOLYMERS OF N-VINYL PYRROLIDONE WITH DIACETONE ACRYLAMIDE AND 2-HYDROXY ETHYL METHACRYLATE

DAACM	HEMA	NVP	% Water content
		100	97.0
25		75	85.9
40		60	78.5
50		50	66.2
	40	60	73.2
	50	50	66.1
	70	30	49.9
	90	10	40.6

GRAPH III.7


Key
x - HEMA-NVP copolymers
□ - DAACM-NVP copolymers
% H_2O
100
90
80
70
60
50
40
30
100
90
80
70
60
50
40
30
20
10
0
Concentration of NVP (mol%)

The marked curve that starts to form in the water content-composition profile for the diacetone acrylamide copolymers with N-vinyl pyrrolidone tends to indicate that while there is little hydrophobic interaction between the respective monomer units, a degree of hydrophobic bonding is established between diacetone acrylamide units when sufficient are present. The curve for the copolymers of 2-hydroxy ethyl methacrylate and N-vinyl pyrrolidone, although starting below that for the diacetone acrylamide compositions, shows little indication of significant numbers of hydrophobic bondings between the methyl groups present on the polymer backbone.

In view of the somewhat complex nature of the results for the acrylamide derivatives copolymerised with monomers which have shown little interchain interaction with acrylamide itself; those copolymers where a great deal of interchain bonding is expected to exist should prove very interesting. To this end, copolymers of methacrylamide and diacetone acrylamide with acrylic and methacrylic acid have been prepared to investigate the effect of hydrogen bonding on the water contents of compositions containing acrylamide derivatives. The results of this study are listed in Table III.J and some are depicted in Graph III.8.

The first point of note is the increased solubility of methacrylamide in methacrylic acid in comparison to 2-hydroxy ethyl methacrylate and 2-hydroxy propyl acrylate. The 33:67 (mol:mol) copolymer of methacrylamide and methacrylic acid may be prepared without any water being added to the composition to ensure a homogeneous solution. The water contents for the copolymer compositions of methacrylamide and methacrylic acid are seen to decrease steadily until a slight rise of 1% is observed for the 50:50 (mol:mol) composition. It should be remembered however

TABLE III.J

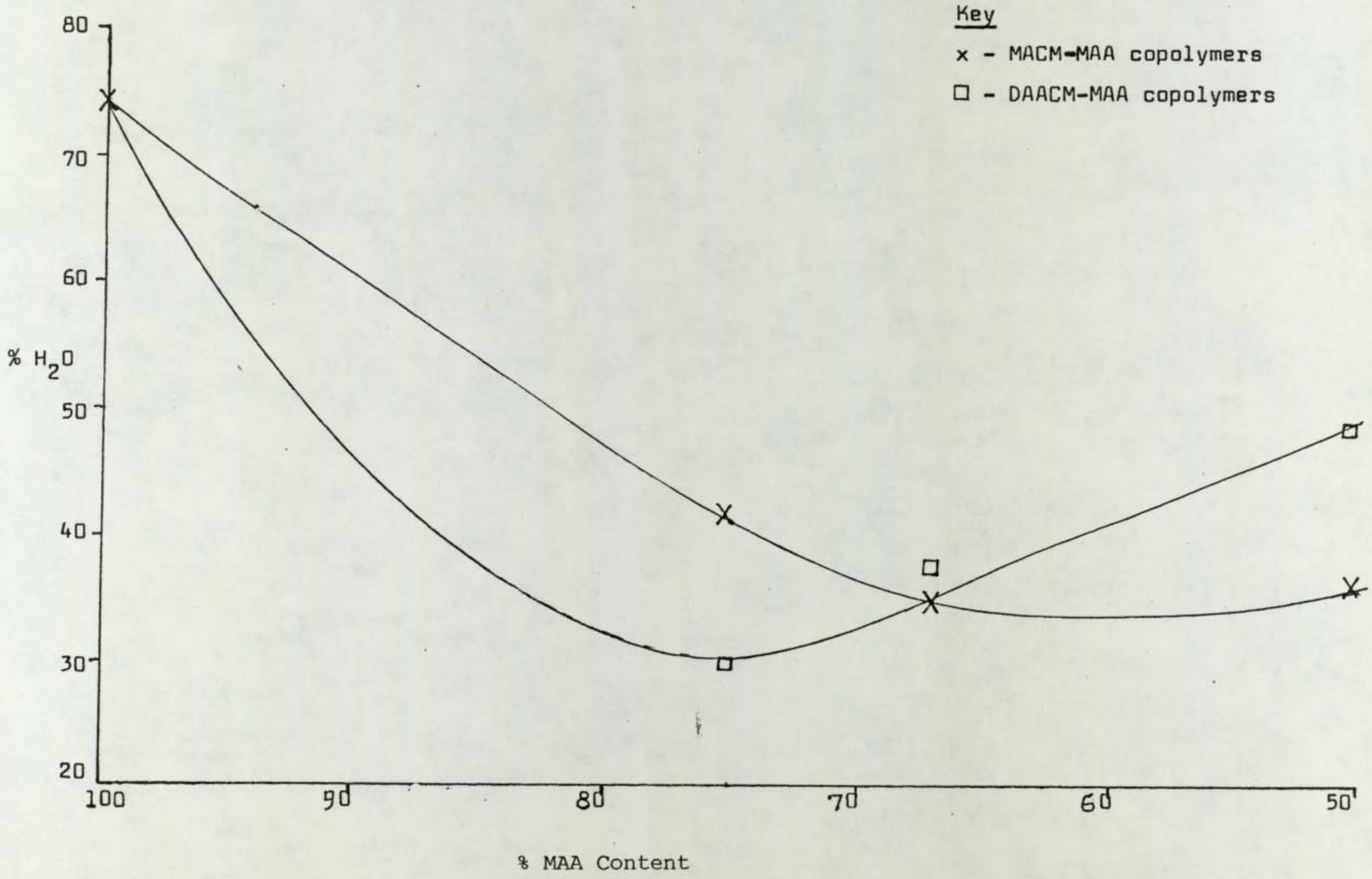
WATER CONTENTS AT VARIOUS PERIODS OF HYDRATION FOR COPOLYMERS OF ACRYLAMIDE DERIVATIVES WITH ACRYLIC ACID AND METHACRYLIC ACID

MACM	DAACM	MAA	AA	H_2O added (Weight %)	% Water Content		
					1 month	3 months	2 years
		100		0	73.5	-	-
25		75		0	41.5	46.6	-
33		67		0	34.7	37.7	-
50		50		10	35.7	37.0	44.2
50			50	10	31.4	-	-
	25	75		0	30.2	29.8	-
	33	67		0	36.4	36.5	-
	50	50		0	48.4	-	-
	50		50	0	24.4	-	-

that the 50:50 (mol:mol) copolymer contains 10% by weight of water to ensure that the methacrylamide content is fully dissolved. The added water would be expected to cause a disruption of hydrogen bonding between the methacrylamide and methacrylic acid units within the hydrogel and give rise to higher water contents. It may be concluded therefore that the behaviour of copolymers of methacrylamide and methacrylic acid is analogous to that of acrylamide and methacrylic acid, with water tending to cause a breakdown in interchain hydrogen bonding in both cases.

The results obtained for the copolymers of diacetone acrylamide and methacrylic acid are seen to differ appreciably from those for the

GRAPH III.8


Key
x - MACM-MAA copolymers
□ - DAACM-MAA copolymers
80
70
60
50
40
30
20
% H_2O
100
90
80
70
60
50
% MAA Content

corresponding methacrylamide copolymers. As the proportion of diacetone acrylamide in the composition is increased the water content of the copolymers is observed to rise almost linearly. This can be attributed to the methyl substituents within the 1,1 dimethyl-3-oxy butyl group of diacetone acrylamide effectively shielding the amide group and preventing it from entering into interchain hydrogen bonding with methacrylic acid units. As the diacetone acrylamide content is increased by reducing the proportion of methacrylic acid groups within the copolymer, there will be an overall loss of hydrogen bonding between carboxylic acid units which will not be substituted for by amide-acid interactions, and a rise in water content will result. It is interesting to note that the shielding effect of the 1,1 dimethyl-3-oxy butyl group which is responsible for the supression of the hydrophilic nature of the amide group also gives rise to a promotion of hydrophilicity when diacetone acrylamide is copolymerised with methacrylic acid.

These results for water contents were taken after one month's hydration, but in the light of the results of Goulding certain copolymers were monitored for the effect of time on the water content. The copolymers of methacrylamide and methacrylic acid were found to undergo a rise in water content with time, although a great deal less than the increase reported for the 50:50 (mol:mol) copolymer of acrylamide and methacrylic acid. Two of the copolymers of diacetone acrylamide and methacrylic acid were also studied for the effect of hydration time on the water content and, as is seen in Table III.J, no appreciable change in water content was found to occur.

These findings can be used to resolve the alternatives proposed to explain the reason for the increases in water content with time, of these type of hydrogels. Examination of the results in Table III.J

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shows that the rise in water contents after 3 months hydration gradually diminishes as the methacrylamide content of the copolymers is increased. If hydrolysis of the amide groups were taking place within the hydrogel network a greater proportion of methacrylamide units would be expected to give rise to a greater degree of hydrolysis and therefore a large increase in water content. This effect is not seen to occur and since no change is observed in the water contents of the diacetone acrylamide based copolymers, the concept of amide group hydrolysis must be somewhat dubious. Indeed amides are known to be the least reactive of carboxylic acid derivatives to water[59] due to the existance of the resonance equilibria shown in Figure III.e.

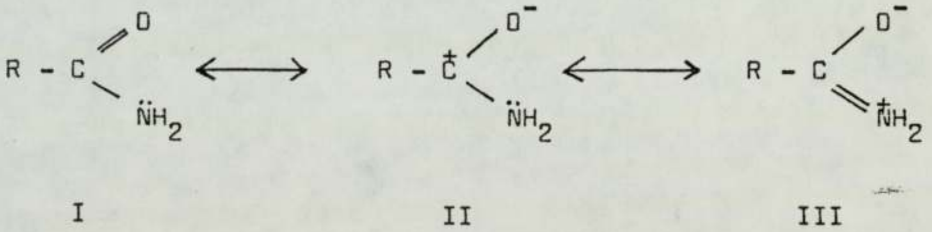


Figure III.e

In resonance form I the lone pair of electrons on the nitrogen atom occupy a p orbital parallel to those p orbitals which constitute the π bond of the carbonyl group. The electron pair then becomes delocalised into the carbonyl group as portrayed by resonance structure III. As the overall contribution of III to the hybrid structure becomes greater the positive charge developed on the carbonyl carbon atom (resonance form II) is diminished and the reactivity of the carbonyl group to nucleophilic attack therefore decreases. Since there is only a small difference in electronegativity between carbon and nitrogen, the electron pair is readily shared increasing the contribution of resonance structure III and causing amides only to undergo hydrolysis in the presence of strong acids or bases.

The alternative hypothesis for the time dependent water contents observed for the copolymers of acrylamide and methacrylic acid was a relaxation of interchain hydrogen bonding within the hydrogel network. Since no appreciable change in the water contents of the copolymers of diacetone acrylamide and methacrylic acid was observed after 3 months hydration, it would seem that the interchain hydrogen bonding between methacrylic acid units does not undergo relaxation. The relaxation of interchain hydrogen bonding within the hydrogel network will therefore only take place between those hydrogen bonds formed by amide and carboxylic acid groups. A close examination of the bond formed between the amide and carboxylic acid groups shows that a number of polar groups remain within the vicinity of the interacting units and are free to attract water molecules. This is represented more clearly in Figure III.f:-

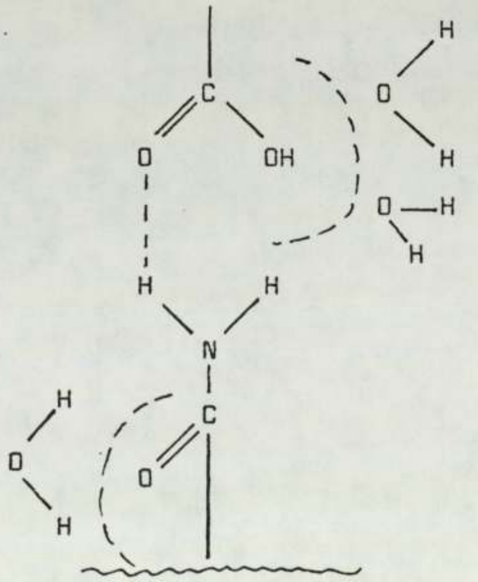


Figure III.f

Interaction of H_2O molecules with the hydroxyl group of carboxylic acid and carbonyl group of amide despite hydrogen bonding

As more water molecules become associated with these polar groups the interchain hydrogen bond between the carbonyl group of the acid and the amidic hydrogen is subjected to increasing amounts of strain until it is finally ruptured. When breakage has occurred these groups are themselves solvated by water molecules causing an increase in water content. This process will not occur with those interchain hydrogen bonds between two carboxylic acid units since both the hydroxyl and carbonyl groups enter into hydrogen bond formation as was seen in figure III.a.

Hydrogen bonding relaxation would therefore only be expected to result in those hydrogels where an appreciable amount of amide-carboxylic acid interaction takes place, such as the copolymers of methacrylic acid with acrylamide and methacrylamide. It is interesting that the copolymers of methacrylamide undergo a smaller rise in water content than those of acrylamide. Indeed the water content of the 50:50 (mol: mol) copolymer of methacrylamide and methacrylic acid rises by 8.5% in 2 years, which is less than half that found for the corresponding acrylamide composition after six months hydration. The implication of this is that the effect of the α methyl substituent on the polymer backbone is not only to form hydrophobic bondings via Van der Waal attractions, but also to restrict the rotation of the polar groups about the backbone. This will prevent the most preferential alignment of the hydrophilic groups in the side chain to allow optimal water obsorption by the hydrogel. The contribution of the methyl group in restricting the rotation about the polymer chain is also a factor in the lower hydrophilicity of 2-hydroxy ethyl methacrylate in comparison to its structural isomer 2-hydroxy propyl acrylate. The trends observed in Graph III.7 for the water contents of copolymers of N-vinyl pyrrolidone and 2-hydroxy ethyl methacrylate are also due to this effect in some part. The restricted rotation is seen to be initially greater than the hydrophobic bondings of the 1,1 dimethyl-3-oxy butyl group of diacetone acrylamide, which gradually become increased as the amide content of the copolymer is raised and depress the water content to a larger extent.

The effect of the restricted chain rotation imposed by the methyl substituent on the water content of a hydrogel can be seen more clearly by considering the results for copolymers of the acrylamide derivatives with acrylic and methacrylic acid. The 50:50 (mol:mol) copolymers of acrylic acid are seen to have lower water contents than the corresponding compositions of methacrylic acid. It would seem therefore that the absence of an α methyl substituent not only allows chain rotation about the polymer backbone to give a preferential arrangement for water absorption but also the optimal configuration for interchain hydrogen bond formation. This leads to a water content of 24.4% for the copolymer of diacetone acrylamide and acrylic acid, which is approximately half that found for the corresponding methacrylic acid composition, due to the optimised hydrogen bonding between acrylic acid units. The water content of the copolymer of methacrylamide and acrylic acid is found to be 31.4%, which is less than 5% lower than that of the corresponding methacrylic acid hydrogel. The presence of the α methyl group in the methacrylamide structure will obviously restrict rotation about the chain to segmental motion only and therefore impede the efficiency of hydrogen bond formation within the network. It should also be noted that these copolymer compositions of methacrylamide include 10% by weight of water which will limit the degree of interchain hydrogen bonding in the hydrogel.

In view of the interesting results obtained in these studies with acrylamide derivatives, the effect of substituting a less bulky group than the 1,1 dimethyl-3-oxy butyl substituent of diacetone acrylamide at the nitrogen atom would also be of value. To this end, the results of a recent study in these laboratories by Stones[60] into the terpolymers of 2-hydroxy propyl acrylate, methyl methacrylate and various acrylamide derivatives are shown in Table III.K. While these results lend support to the general trend of hydrophilicity of the acrylamide derivatives, as outlined in this chapter, the main point of interest is the use of N-hydroxy methyl acrylamide. The data in Table III.K indicates that the effect of substituting a methylol group at the nitrogen atom is to render the monomer slightly less hydrophilic than methacrylamide. This would suggest that the presence of the methylol group at the amide site, as illustrated in Figure III.g, does not shield the hydrophilic unit as effectively as the 1,1 dimethyl-3-oxy butyl group in diacetone acrylamide.

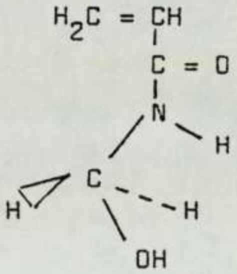


Figure III.g

N-hydroxy methyl acrylamide

The result for the terpolymer with N-hydroxy methyl acrylamide has encouraged the study of certain copolymer compositions including this monomer, during the course of this research. The main point of interest of these compositions was to be the interaction of the secondary amide group with carboxylic acid units to give rise to hydrogen bonding. The results of this study are listed in Table III.K and it is interesting to note that in addition to having a similar hydrophilicity to methacrylamide, N-methylol acrylamide is also just as insoluble. It is seen that all the compositions prepared required

TABLE III.K

WATER CONTENTS OF TERPOLYMERS OF 2-HYDROXY PROPYL ACRYLATE, METHYL METHACRYLATE AND VARIOUS ACRYLAMIDE DERIVATES

HPA	MMA	ACM	MACM	DAACM	HMACM	% Water Content
90	10					33.0
80	10	10				55.0
80	10		10			43.0
80	10			10		31.0
80	10				10	40.5

TABLE III.L

WATER CONTENTS OF N-HYDROXY METHYL ACRYLAMIDE BASED COMPOSITIONS

HMACM	HEMA	HPA	NVP	AA	MAA	H_2O Added (Weight %)	% Water Content
50	50					10	45.6
33			33	33		7	68.8
40		20	20	20		7	67.4
33		10	42		15	6	68.9
45		10	30		15	9	67.8
55		10	20		15	16	63.2

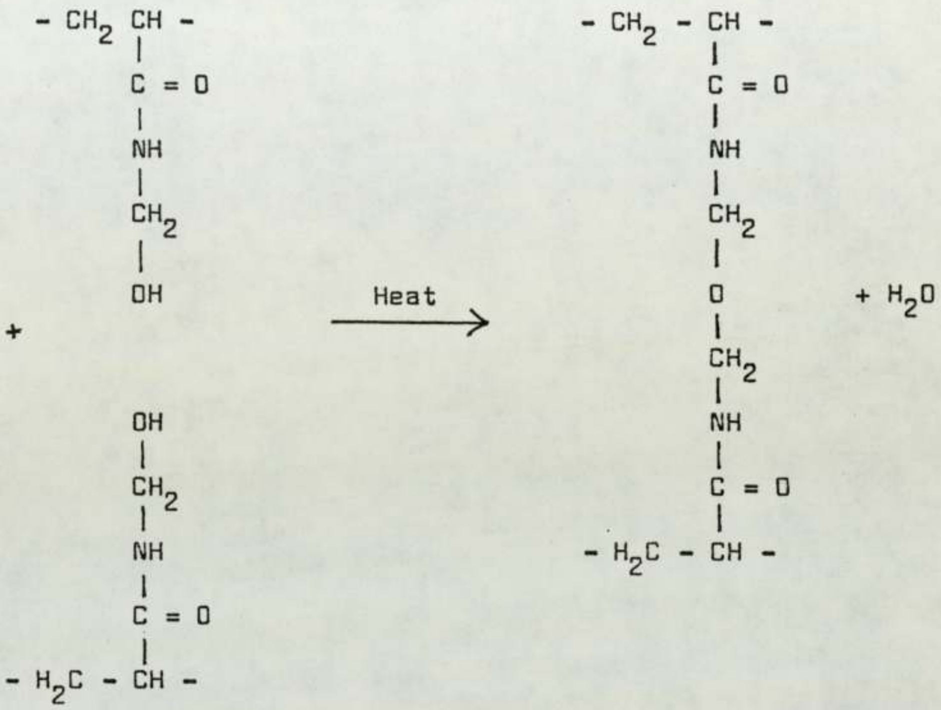
the addition of water and therefore little can be drawn from the validity of these results in relation to interchain hydrogen bonding between the secondary amide groups and the carboxylic acid units. The results in Table III.K show that all compositions of 33 mol % of N-hydroxy methyl acrylamide required the addition of water to obtain a homogeneous comonomer solution which is in contrast to the behaviour of methacrylamide compositions that require no water at this amide concentration. This indicates that while the solubility of N-hydroxy methyl acrylamide in hydrophilic monomers is less than that of methacrylamide, it is far more soluble in water.

The water content of the 50:50 (mol:mol) copolymer of N-hydroxy methyl acrylamide and 2-hydroxy ethyl methacrylate is found to be 45.6%, only 2% less than that for the corresponding composition of methacrylamide. This supports the conclusion that N-hydroxy methyl acrylamide is slightly less hydrophilic than methacrylamide and suggests that any shielding of the amide group by the methylol substituent is compensated for by the presence of the polar hydroxyl group.

In addition to its limited solubility, another major disadvantage of N-hydroxy methyl acrylamide in determining the effect of structure on the water content of its copolymers is that it is known to form intermolecular cross links. One reaction by which this could occur has been suggested (by Hoffman et al)[61] in which an ethereal linkage is produced in the presence of heat with the elimination of water. This is shown more clearly in Figure III.h.

N-hydroxy methyl acrylamide will therefore be of little use in a lathe cut continuous wear lens composition as a rise in cross link density can be expected as lenses are sterilised by autoclaving and a fall in water content will result.

FIGURE III.h



III.5 ASSESSMENT OF STRENGTH OF VARIOUS HYDROGELS

One of the major requirements for any hydrogel polymer to be suitable as a contact lens material is the ability to resist the deforming force applied by the eyelid while being sufficiently pliable to minimise discomfort. The forces imposed on the contact lens during the blink cycle are somewhat complex, yet the compressive mode of deformation can be considered as having most effect.[62] To this end the deformational behaviour of certain hydrogels has been studied, by previous workers and during this research, with the use of a Monk and Wright microindentor. A complete description of the instrument together with specific details of its modification for use with hydrogels has been given by Ng.[40] In view of this, it is sufficient to restrict this discussion of the apparatus to the manner in which it is used to obtain comparisons between hydrogels in terms of deformational resistance.

The pressure exerted by the eyelid during the blink cycle has been reported[62] as being of the order of 2.6×10^4 dynes cm^{-2}. The purpose of the microindentation studies that have been carried out is therefore to measure the deformation produced by applying various loads to a spherical indentor (0.16 cm diameter) at the surface of a hydrogel for a period of 1 minute. If suitable loads are applied, the shapes of the indentation-recovery curves so produced give an indication of the deformational behaviour of a material under pressures close to that exerted by the eyelid.

A number of equations have been developed which may be used to calculate the rigidity modulus of a material from the results of microindentation studies. Hertz derived the theoretical relationship, shown in Equation III.1, for the indentation of an infinitely thick, perfectly elastic solid by a spherical indentor of infinite hardness.

$$\frac{E}{1 - v^2} = \frac{3}{4} \frac{m\,g}{r^{\frac{1}{2}} h^{\frac{3}{2}}} \qquad \text{(III.1)}$$

E = Young's modulus of elasticity

v = Poisson's ratio

m - mass applied to the indentor

g = graviational constant (981 cm sec^{-2})

r - radius of indentor (0.08 cm for hydrogels)

h = depth of indentation

The Hertzian equation can be shown to be consistent with that derived by Pitts[63] to calculate the rigidity modulus, G, of a thick film which is given in Equation III.2.

$$G = \frac{3}{16} \frac{m\,g}{r^{\frac{1}{2}} h^{\frac{3}{2}}} \qquad \text{(III.2)}$$

Combining these equations leads to a relationship between the rigidity modulus and Young's modulus of elasticity of a material as shown in Equation III.3.

$$G = \frac{E}{4(1-v^2)} \qquad \text{(III.3)}$$

Pitts[63] has also derived a theoretical relation for the indentation of thin elastic films which is given in Equation III.4.

$$G = \frac{mg}{2\pi r^2}\left[\frac{t}{h}\right]^3 \qquad \text{(III.4)}$$

t = film thickness

Taylor and Kragh[64] have also considered the effect of film thickness on the degree of indentation and rigidity modulus of an elastic film. This has led to the development of the empirical equation as shown in Equation III.5.

$$G = 0.36\,\frac{mg}{r^2}\left[\frac{t-h}{h}\right]^{\frac{3}{2}} \qquad \text{(III.5)}$$

If the film thickness is sufficiently great with respect to the depth of indentation such that $\frac{t-h}{h}$ approaches t/h then all the equations may be rewritten in a general form shown in Equation III.6.

$$\log m = n \log h + \log kG \qquad \text{(III.6)}$$

The Pitts equation for thin films would be appropriate if n were equal to 3 whereas all other equations predict a value of 1.5 for n.

Log-log plots of load against depth of indentation for various hydrogels, by a number of workers,[40,65,66] have given gradients of 1.5 or less. It is therefore assumed that Pitts equation for thin films is inapplicable under the conditions of measurement employed. The Hertzian equation (III.1) is generally preferred over the empirical relationship of Taylor and Kragh (III.5) to calculate the rigidity moduli of hydrogels, due to it having a sound theoretical basis and being consistent with Pitts equation for thick films (III.2). It is seen from the general equation (III.6) that the rigidity modulus G may be calculated from the intercept of a plot of log load against log indentation and therefore, by substitution from Equations III.1 and III.2, it is seen that:-

$$\text{Intercept} = \log kG = \log \frac{4r^{\frac{1}{2}}}{3g} \frac{E}{1-v^2} = \log \frac{16r^{\frac{1}{2}}}{3g} G \qquad \text{(III.7)}$$

The load-indentation results for various hydrogels that were obtained during this research are shown in Table III.M, together with those by Ng for poly(2-hydroxy ethyl methacrylate) and Booth[65] for the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate. While these results are portrayed as a log-log plot in Graph III.8, the slopes and intercepts were determined by least squares fit analysis and are listed in Table III.N together with the rigidity moduli calculated from them.

As previously stated, the loads applied were such that the forces exerted on the materials approached eyelid pressure. However, in order to calculate the rigidity modulus in dynes cm^{-2}, the values calculated for the intercept correspond to the logarithm of the mass applied to create an indentation of 1 centimetre. If all the hydrogels tested exhibited true Hertzian behaviour and gave a slope of 1.5, the rigidity moduli calculated in Table III.N would yield a good comparison of the strength of these materials. The only hydrogel tested which was found to obey the Hertzian equation absolutely was poly(2-hydroxy ethyl methacrylate) and this therefore gave the highest calculated value for rigidity modulus. If the results for the materials shown in Table III.M are considered, the highest indentations are found to

TABLE III.M

LOAD-INDENTATION RESULTS FOR VARIOUS HYDROGELS

HEMA

Load (g)	0.14	0.24	0.34	0.48	0.75
Indentation (cm) x 10^4	2.4	3.55	4.7	5.6	7.1

DAACM 50 HEMA 50

Load (g)	0.17	0.24	0.3	0.34	0.75
Indentation (cm) x 10^4	1.1	1.6	2.0	2.7	6.5

DAACM 33 HEMA 67

Load (g)	0.2	0.3	0.34	0.75	1.0
Indentation (cm) x 10^4	1.3	1.95	2.2	5.2	6.9

MACM 33 HEMA 67

Load (g)	0.17	0.2	0.24	0.3	0.48
Indentation (cm) x 10^4	1.1	1.3	1.4	1.6	2.9

MACM 25 HEMA 75

Load (g)	0.2	0.27	0.3	0.48
Indentation (cm) x 10^4	0.8	1.0	1.1	1.8

ACM 33 HPA 67

Load (g)	0.35	0.5	0.75	0.9
Indentation (cm) x 10^4	1.1	1.6	2.1	2.5

GRAPH III.9

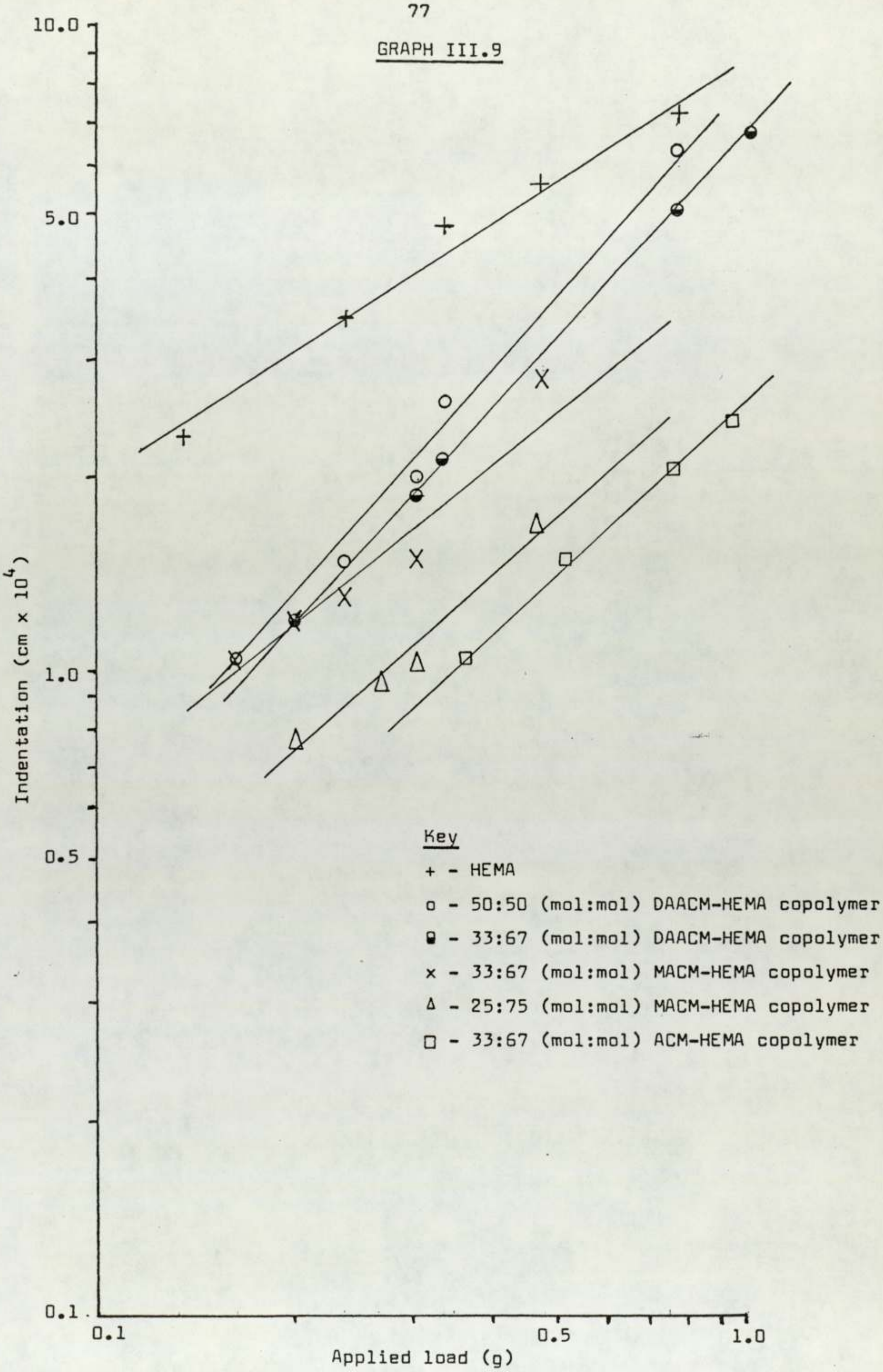

10.0
5.0
1.0
0.5
0.1
Indentation (cm x 10^4)
0.1
0.5
1.0
Applied load (g)
Key
+ - HEMA
o - 50:50 (mol:mol) DAACM-HEMA copolymer
◒ - 33:67 (mol:mol) DAACM-HEMA copolymer
x - 33:67 (mol:mol) MACM-HEMA copolymer
Δ - 25:75 (mol:mol) MACM-HEMA copolymer
□ - 33:67 (mol:mol) ACM-HEMA copolymer

TABLE III.N

DETERMINATION OF RIGIDITY MODULI OF VARIOUS HYDROGELS

Hydrogel	Slope, n	Intercept	$^{E}/_{1-v^{2}}$ Dynes/cm^2	G Dynes/cm^2
HEMA	1.51	4.58	7.91×10^{8}	3.16×10^{9}
DAACM 50 HEMA 50	0.91	2.81	1.67×10^{6}	6.67×10^{6}
DAACM 33 HEMA 67	0.81	2.45	7.26×10^{5}	2.90×10^{6}
MACM 33 HEMA 67	1.23	4.08	3.09×10^{7}	1.24×10^{8}
MACM 25 HEMA 75	1.08	3.72	1.36×10^{7}	5.44×10^{7}
ACM 33 HEMA 67	1.17	4.16	3.74×10^{7}	1.50×10^{8}

Slope and intercept determined by lease squares fit method

$$\text{slope, } n = \frac{a\sum x_1 y_1 - \sum x_1 \sum y_1}{a\sum x_i^2 - (\sum x_1)^2}$$

$$\text{Intercept} = \frac{\sum y_i - n\sum x_1}{a}$$

a = number of observations

occur for poly(2-hydroxy ethyl methacrylate) which would indicate that at approximately eyelid pressure this was the weakest of the hydrogels tested.

Ng[40] has simulated the conditions of eyelid pressure by using a load of 0.34 g in conjunction with a flat ended indentor of 0.126 cm diameter and has reported a deformation of approximately 2 microns for poly(2-hydroxy ethyl methacrylate). A far more meaningful comparison of the results shown in Table III.M, in terms of potential use for contact lens materials, would therefore be the force required to give an indentation of 2 microns with a spherical indentor. Since the slope and intercept for each line has been calculated in Table III.N, the force required to give an indentation of 2 microns may easily be calculated using equation III.6. The results for the hydrogels studied are shown in Table III.O and are portrayed as a function of water content in Graph III.9.

The graph may be conveniently divided into three arbitrary sections of low, medium and high rigidity as shown. The lower portion is seen to contain the copolymers of diacetone acrylamide and 2-hydroxy ethyl methacrylate together with poly(2-hydroxy ethyl methacrylate) itself. The lower rigidity of these materials may be accounted for by the small degree of interchain adhesion within the polymer network due to a deficiency of hydrogen bonding. The hydroxyl and carbonyl groups of 2-hydroxy ethyl methacrylate are unlikely to form a large number of strong hydrogen bonds, although the presence of methacrylic acid impurities may enhance the capabilities of doing so. The amide group of diacetone acrylamide is, as stated previously, effectively shielded by the methyl components of the 1,1 dimethyl-3-oxy butyl substituent attached to it and this limits the amount of

TABLE III.0

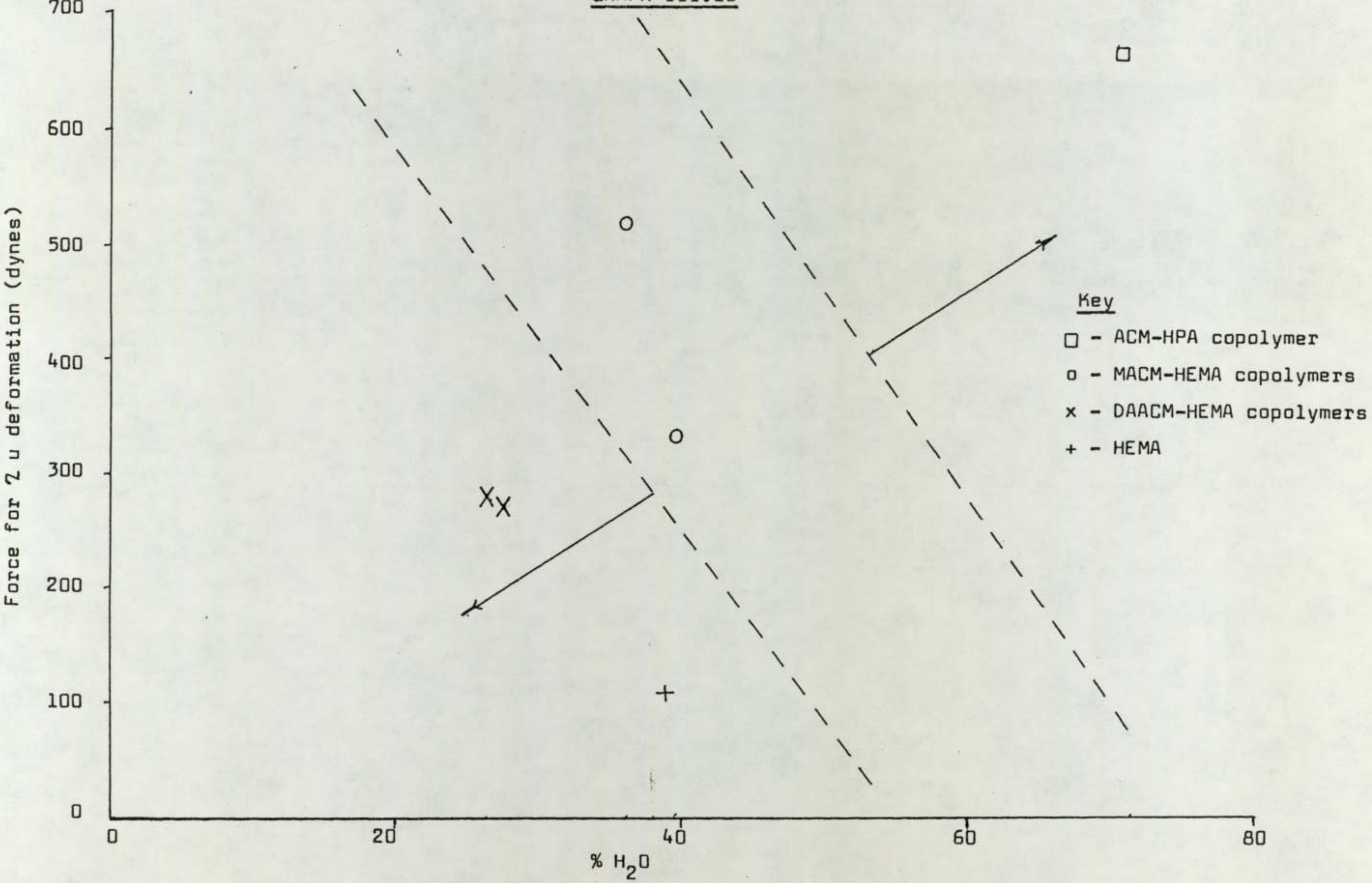
APPLIED FORCE REQUIREMENT FOR AN INDENTATION OF 2 MICRONS FOR VARIOUS HYDROGELS

Hydrogel	% Water Content	Mass (g) for 2μ Indentation	Force (dynes) for 2 μ Indentation
HEMA	39.0	0.108	106
DAACM 50 HEMA 50	27.5	0.278	273
DAACM 33 HEMA 33	26.4	0.284	279
MACM 33 HEMA 67	39.6	0.339	333
MACM 25 HEMA 75	36.2	0.531	521
ACM 33 HPA 67	71.3	0.679	666

interchain hydrogen bond formation within its copolymers.

While neither of the components of the polymers in the lower region of Graph III.9 are capable of strong hydrogen bond formation, this is not the case for the copolymers of methacrylamide and 2-hydroxy ethyl methacrylate which are seen to fall in the middle band of the graph. The primary amide groups of methacrylamide are free to enter into interchain hydrogen bonding and hence the force required to cause a deformation of 2 microns to these polymers is significantly greater than that for those hydrogels in the lower region of Graph III.9. The presence of the α methyl substituents of methacrylamide and 2-hydroxy ethyl methacrylate does however limit the extent to which hydrogen bonding may occur within these copolymers, since the segmental rotation of the amide groups about the polymer backbone is hindered and

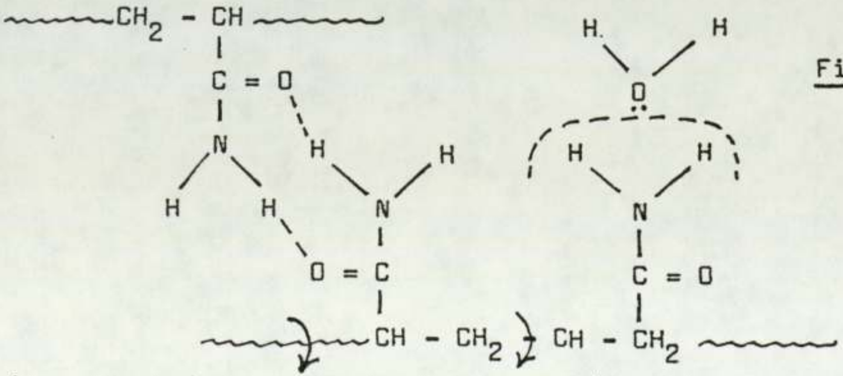
GRAPH III.10


700
600
500
400
300
200
100
0
Force for 2 u deformation (dynes)
0
20
40
60
80
% H_2O
Key
□ - ACM-HPA copolymer
o - MACM-HEMA copolymers
x - DAACM-HEMA copolymers
+ - HEMA

the appropriate groups are unable to adopt the most preferential arrangement for completely effective hydrogen bond formation.

When no α methyl substituents are present on the polymer backbone, as is the case for the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate, the hydrogel may attain a more favourable configuration for interchain hydrogen bond formation and a stronger material results. For this reason the strength of the copolymer of acrylamide and 2-hydroxy propyl acrylate is far greater than that of the other materials tested and therefore lies in the third region (of highest strength) in Graph III.9.

The result obtained for the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate is most interesting in that this material has a high water content of 71.3% in addition to its good deformational properties. This would suggest that while a certain amount of the water within the hydrogel network is free to function as a plasticiser for the material, a high percentage of the water is also strongly hydrogen bonded to the hydrophilic groups of the copolymer. This could partially account for the high strength of the copolymer of acrylamide and 2-hydroxy propyl acrylate as it may serve to hold the polymer chains in a fixed configuration in the hydrated state maintaining the optimal hydrogen bonding formation already achieved. This is more clearly illustrated in Figure III.i:-



<u>Figure III.i</u>

The presence of water molecules bound strongly to one amide group effectively restricts the rotation of the polymer chain which may lead to the rupture of hydrogen bonding between two other amide groups.

The excellent deformational properties of the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate coupled with its high water content encourages the belief that an acrylamide based hydrogel may be appropriate as a continuous wear contact lens material. Certain problems do arise with this material however and these, together with the structural refinements made to overcome them are outlined in the following chapter.

In concluding this chapter on the structure-property relationships of hydrogel copolymers, it must be stated that only the effect of changing the side chains on the water content and deformational properties of these materials has been discussed. It should be remembered however, that the total water content is known to be a controlling factor in several other characteristics of hydrogels, such as the diffusion of small metabolites through the network (although at small pore sizes and for larger metabolites the ratio of bound to free water is important). Another variation in hydrogel structure that may play an important part in these studies is the inclusion of various proportions of di-olefinically substituted species in the network to produce gels of different cross-link density. The cross link density of a polymer is known in other systems to affect the mechanical properties and therefore the dependence of hydrogel properties on the concentration and type of cross-linking agent used will be discussed separately in Chapter V.

CHAPTER FOUR

CHAPTER IV

STABILITY OF ACRYLAMIDE BASED HYDROGELS

IV.1 INTRODUCTION

This chapter is concerned with the refinements made to improve the properties of the 33:67 (mole:mole) copolymer of acrylamide and 2-hydroxy propyl acrylate in order to approach the requirements necessary for a continuous wear contact lens. One of the problems encountered with modified acrylamide copolymers of appropriate water content for a continuous wear lens material has been their dubious hydrolytic and thermal stability. It is obviously vital that any changes in chemical composition of a lens material which give rise to an increased degree of swelling must be identified and corrected. If the stability of a hydrogel material was insufficient to prevent an extension of the contact lens parameters due to increased swelling throughout the extended wear period problems of poor fit would arise. This condition would not only result in reduced optical performance of the lens but would also give rise to an additional degree of protein deposition; the implications of which will be discussed more fully in Chapter VII.

The causes of the problems of instability will be discussed and attributed to the interaction of methacrylic acid groups with residual N-vinyl pyrrolidone monomer. As both components are necessary to the production of a hydrogel material of suitable hydrophilicity and processability, a compromise situation must be achieved.

It therefore becomes necessary to find an appropriate composition in which the interaction between methacrylic acid and N-vinyl pyrrolidone is kept within tolerable limits. The problems associated with the achievement of such a composition will be discussed at the conclusion of the chapter, together with suggestions of other desirable modifications.

IV.2 MODIFICATION OF THE ACRYLAMIDE (33) HYDROXY PROPYL ACRYLATE (67) FORMULATION TO A MORE CONVENIENTLY PROCESSABLE CONTINUOUS WEAR MATERIAL

As previously stated, a semi-empirical study of various co-polymers designed to yield a material of appropriate water content and suitable processability for a lathe cut continuous wear lens was carried out starting from the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate. Certain difficulties associated with the polymerisation of acrylamide compositions were encountered and overcome to a certain extent during the course of this study. The first problem was found to arise from the fact that acrylamide is a solid monomer and has a limited solubility in various liquid monomers such as 2 hydroxy propyl acrylate at room temperature. Since acrylamide is a very hydrophilic monomer a limited acrylamide content will restrict the water content of the hydrogel co-polymers that may be prepared and it is therefore desirable that the amount of acrylamide incorporated in the gel is increased to ensure that the oxygen permeability of the co-polymer is sufficient. The most convenient method of increasing the acrylamide content was found to be by the addition of a small amount of water to the monomer formulation in order to dissolve any acrylamide not taken into solution by liquid monomers. The amount of water added was kept as low as possible, typically not more than 10% of the formulation weight, in order to limit further deterioration of the polymers caused by water acting as a plasticiser.

The results of several studies outlined in Chapter III have indicated that the solubility of acrylamide and its derivatives has been found to increase when included in a co-monomeric composition with methacrylic acid.[27,57,65] Unlike the addition of water which tends to produce hydrogels with inferior mechanical properties,[58] the hydrogen bond forming capabilities of the functional groups of acrylamide and methacrylic acid will give rise to an increase in strength of the copolymer network.

While methacrylic acid lends strength to the network by hydrogen bonding which acts as a form of secondary crosslinking, it therefore leads to a reduction in water content making it essential that further modification of the composition takes place to restore the water content to a level that fulfils the oxygen permeability requirement once more. This problem was remedied by the addition of a hydrophilic liquid monomer such as N-vinyl pyrrolidone, and adjusting the levels of methacrylic acid and hydroxy propyl acrylate within the formulation until a balance was achieved and a hydrogel of appropriate water content and strength for a continuous wear lens was produced.

While this would seem to give a polymer that meets with the requirements for a continuous wear lens material it proves unsatisfactory in that the reactivity ratio of N-vinyl pyrrolidone is considerably lower than the other constituent monomers of the formulation.[68] Hence the resulting hydrogel will be impregnated with residual N-vinyl pyrrolidone monomer and low molecular weight oligomers which lead to tackiness of the rods and then discolouration if a postcure is employed to combine more of the residual monomer in the network. Since any unbound material may be transported into the eye in an 'in vivo' situation and become a possible cause of infection,[69] it is obviously desirable to reduce the residuals to as low a level as possible to facilitate their removal from a lens before its insertion into the eye. This problem is made somewhat more acute in that care must be taken when making the conditions of polymerisation more severe to try to combine more residual monomer, since the polymerisation of acrylamide containing compositions are known to be violent unless mild conditions are used.[70]

This situation was found to be eased somewhat by the addition of styrene to the formulation. Despite being a hydrophobic monomer, styrene polymerises readily at low temperatures, since it has a low reactivity ratio,[68] and tends to increase the rate of gellation whilst lending strength and clarity to the polymer. Thus by adjusting the N-vinyl pyrrolidone-styrene balance of the formulation, polymers of approximately 75% water content with good clarity, strength, processability and a lower residual content were produced as depicted in Table IV.A.[71]

IV.3 INVESTIGATION OF THE PROBLEMS OF STABILITY

While these compositions would appear in principle to be satisfactory for the desired application, more subtle complications were found to arise making the design of a hydrogel as a continuous wear contact lens more complex. The water contents of the polymers listed in Table IV.A were found to be susceptible to 'drift', ie increasing by finite amounts with time, and required approximately 8 weeks to establish an 'equilibrium' value. This is a serious defect, since a drifting water content will be responsible for changes in the lens parameters (such as the radius of curvature of the back surface of the lens), and hence cause poor fit and damage to the eye over a prolonged period.[72]

In addition to the problems arising from the great fluctuations in the water content of these potential lens materials, further complications accrued from the temperature instability of the co-polymers. This proved insufficient in some cases to prevent a vast expansion of dimensions during the sterilisation procedure of autoclaving.

TABLE IV.A

	ACM	MACM	DAACM	NVP	HPA	MAA	St*
1	33			47	10	10	9.0
2	30		10	40	10	10	8.5
3	20	10	10	40	10	10	7.0
4		15	10	55	10	10	5.75
5		20	20	40	10	10	3.75
6	25	5		50	10	10	5.75

Key:-

ACM	Acrylamide
MACM	Methacrylamide
DAACM	Diacetone acrylamide
NVP	N-vinyl pyrrolidone
HPA	Hydroxy propyl acrylate
MAA	Methacrylic acid
St	Styrene

* The figures in the styrene column are calculated on a weight percentage basis whereas all other figures refer to molar percentages. All compositions contained 0.25 weight per cent of polyethylene oxide (molecular weight 400) dimethacrylate as a crossslinking agent.

In an attempt to investigate these phenomena more fully the water contents of various co-polymers intermediate in the design of those shown in Table IV.A, ie having no styrene and various contents of the other monomers, were monitored at several different temperatures. The water contents were calculated by recording the hydrated weight after two weeks hydration in distilled water at the appropriate temperature, starting at 70°C and descending at intervals of 10°C to 40°C, whereupon the samples were dehydrated. The resulting water contents are given in Table IV.B and are plotted as a function of temperature in Graph IV.1,

TABLE IV.B

Composition of Copolymer

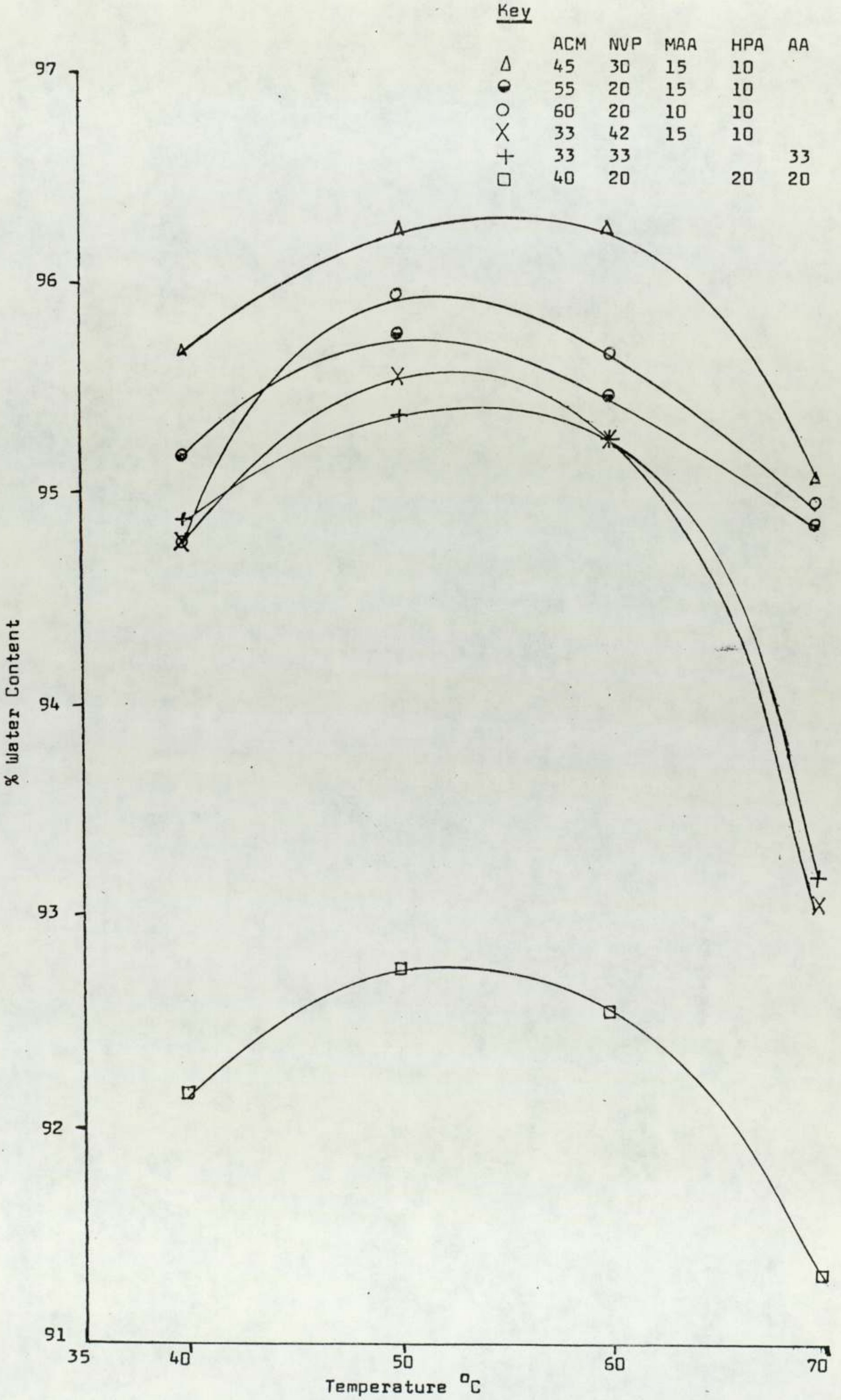
ACM	NVP	HPA	MAA	AA
33	33			33
33	42	10	15	
40	20	20		20
45	30	10	15	
55	20	10	15	
60	20	10	10	

% Water Content at Various temperatures

70°C	60°C	50°C	40°C
93.2	95.3	95.4	94.9
93.1	95.3	95.6	94.8
91.3	92.6	92.8	92.2
95.1	96.3	96.3	95.7
94.9	95.5	95.8	95.2
95.0	95.7	96.0	94.8

which proves most interesting. As each curve attains a maxima between 50°C and 60°C before falling to a lower value at 70°C, the effect was deemed to be a real characteristic rather than a chance experimental observation. These results do not, however, explain the observation that some of these polymers undergoing destruction when autoclaved in lens form since extrapolation of the curves in Graph IV.1 would result in

Graph IV.1


Key
ACM NVP MAA HPA AA
Δ 45 30 15 10
● 55 20 15 10
○ 60 20 10 10
X 33 42 15 10
+ 33 33 33
□ 40 20 20 20
% Water Content
97
96
95
94
93
92
91
35
40
50
60
70
Temperature °C

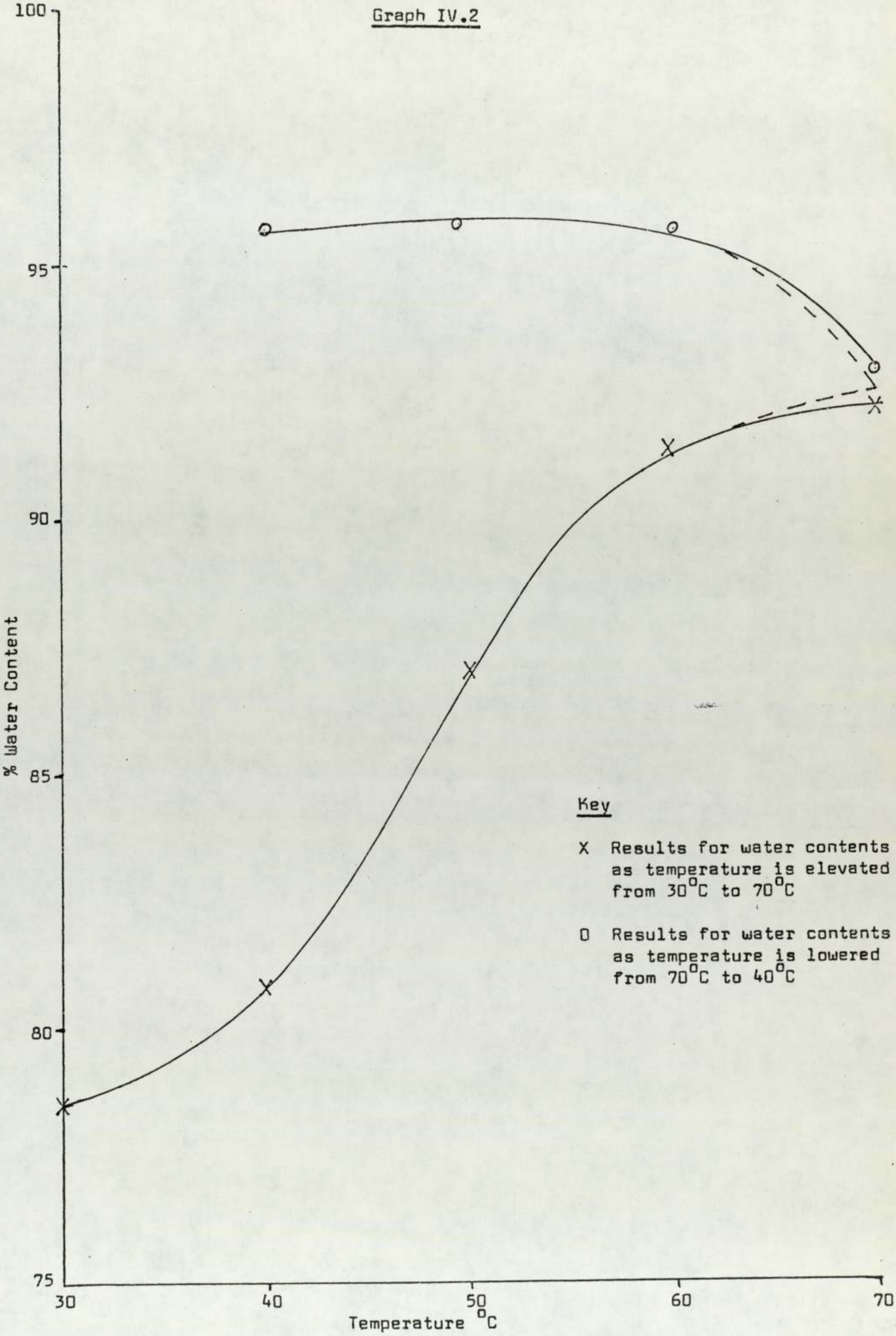
a considerably lower water content at 100°C when compared to that at 60°C. Although the gels were very fragile at 60°C there were no indications of decomposition apart from a strong odour of residual N-vinyl pyrrolidone monomer.

In an attempt to clarify this situation, a further water content-temperature profile of the polymer ACM 45 mol% NVP 35 mol% HPA 10 mol% MAA 10 mol% was obtained. Two sets of samples were used, the first being hydrated at 70°C for 14 days and the temperature then decreased to 40°C at 10°C intervals as before, and the second set being elevated from 30°C to 70°C in a similar manner. The water contents and the resulting plot are shown in Table IV.C and Graph IV.2 and prove most enlightening in that a hysterysis loop is seen to occur. It should be noted that the results for the water contents of both sets of samples agree to within 0.7% at 70°C and hence both curves are extrapolated to an average value. The hysterysis loop gives a clear indication that the

TABLE IV.C

WATER CONTENTS OF ACM 45 NVP 35 HPA 10 MAA 10 AT VARIOUS TEMPERATURES

Temperature °C	Water content as temperature is raised	Water content as temperature is lowered
70	92.1%	92.8%
60	91.3%	95.6%
50	87.0%	95.7%
40	80.8%	95.6%
30	78.6%	



Graph IV.2

100
95
90
85
80
75
% Water Content
30
40
50
60
70
Temperature °C
Key
X Results for water contents as temperature is elevated from 30°C to 70°C
O Results for water contents as temperature is lowered from 70°C to 40°C

problem of temperature stability is related to the drifting water content phenomena that is observed at room temperature, in that the water content of the gel is made non thermally-reversible by the drift becoming greater at higher temperatures.

Having identified that the poor temperature stability of these polymers is a function of their variation in water content at room temperature, the easiest method of resolving which monomers were responsible for these problems was thought to be the systematic exclusion of each in turn from the composition, and then check if any drift in water content occurred. To this end the compositions shown in Table IV.A were modified by the exclusion of methacrylic acid, adjusting the styrene content to the nearest molar percentage and limiting the amount of N-vinyl pyrrolidone to sufficient for the acrylamide content to be dissolved without the addition of water. These new compositions are listed in Table IV.D, and it should be remembered that the figures will bear little resemblance to the corresponding compositions in Table IV.A due to the restricted amount of N-vinyl pyrrolidone added. Where appropriate the compositions are quoted as whole number ratios of monomer contents for convenience. Further experimentation showed that the water content of the fifth of these polymers in lens form reached a steady state within a week. Over the next month the water content was found to be stable to within ± 0.7% which encouraged the belief that the poor stability of the polymers in Table IV.A was caused by methacrylic acid. This hypothesis encouraged a study of the water contents of the materials in Table IV.D at various temperatures from 25°C ascending to 70°C at regular intervals, as a confirmation of the temperature stability dependence on the water content drift.

The results in Table IV.D and the water content-temperature profiles in Graph IV.3 show a decrease in water content over the temperature

TABLE IV.D

Composition of co-polymer

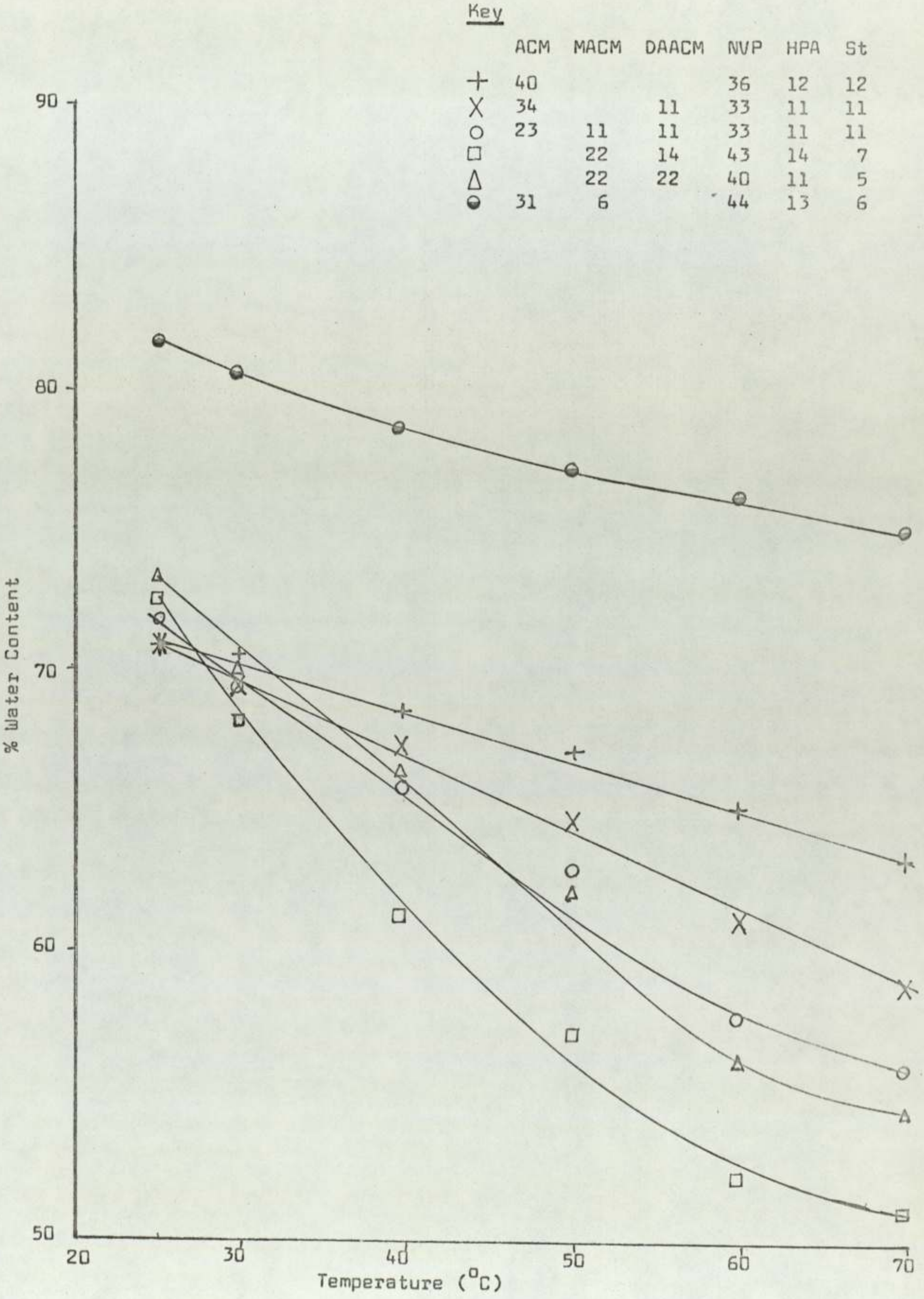
	ACM	MACM	DAACM	NVP	HPA	St
1	40			36	12	12
2	34		11	33	11	11
3	23	11	11	33	11	11
4		22	14	43	14	7
5		22	22	40	11	5
6	31	6		44	13	6

% Water content at various temperatures

	$25^{\circ}C$	$30^{\circ}C$	$40^{\circ}C$	$50^{\circ}C$	$60^{\circ}C$	$70^{\circ}C$
1	71.1	70.5	68.6	67.4	65.5	63.6
2	71.1	69.6	67.5	64.9	61.4	59.1
3	72.0	69.5	66.2	62.9	57.9	56.2
4	72.4	68.4	61.7	57.6	52.6	51.2
5	73.4	70.3	66.3	62.5	56.5	54.7
6	81.6	80.9	79.0	77.7	76.7	75.6

NB All formulations were cross-linked by 0.5 weight per cent of polyethylene oxide (molecular weight 400) dimethacrylate. All water contents were taken after 14 days hydration at the quoted temperatures.

Graph IV.3



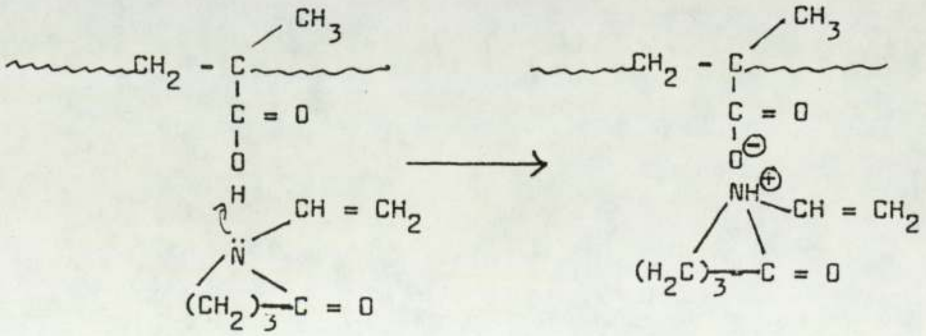
Key

	ACM	MACM	DAACM	NVP	HPA	St
+	40			36	12	12
X	34		11	33	11	11
○	23	11	11	33	11	11
□		22	14	43	14	7
Δ		22	22	40	11	5
●	31	6		44	13	6

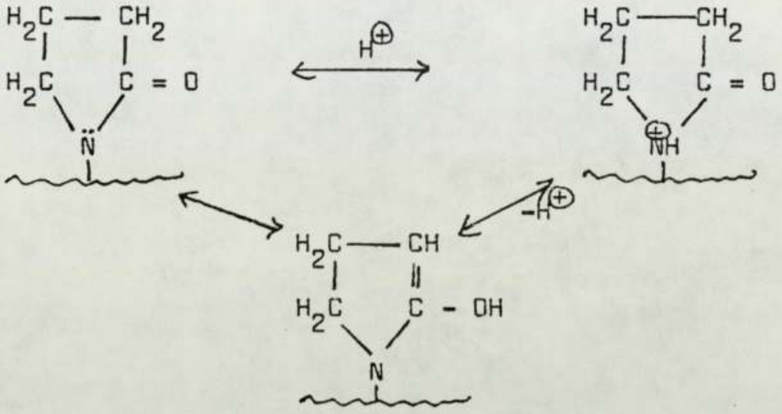
range studied which reinforces the conviction that methacrylic acid gives rise to poor temperature stability properties. This was made more apparent when these gels were found to revert to their former water contents when cooled from 70°C to lower temperatures. With no drift in water content to create hysterysis phenomena the water contents of the polymers fall with increasing temperature due to the Van der Waals forces between the non polar hydrophobic groups being enhanced and giving rise to a form of secondary cross-linking.[40] As may be seen from an examination of the curves, those polymers containing higher levels of methacrylamide and diacetone acrylamide undergo much sharper falls in water content with increasing temperature due to more hydrophobic groups being present and becoming increasingly subject to Van der Waals interactions at higher temperatures.

IV.4 THEORY OF DRIFTING WATER CONTENTS

An examination of the information presented in the previous section leads to the obvious conclusion that methacrylic acid is the prime cause of the poor temperature stability and drifting water content. The mechanism whereby drift occurred was postulated as being due to the interaction between methacrylic acid within the co-polymer and residual N-vinyl pyrrolidone monomer, which is basic, to form ion pairs as depicted in Figure IV.a



Poly vinyl pyrrolidone is thought to undergo a similar protonation when in a low pH media and exhibits keto-enol tautomerism as shown in Figure IV.b[73]



As water will solvate ionic species most readily the residuals will diffuse from the polymer network being replaced by water which packs far more efficiently within the network causing an upward drift in the water content. Hence it becomes incorrect to consider polymers having monomers such as N-vinyl pyrrolidone and methacrylic acid together within their composition as having an equilibrium water content, since the solvation shells surrounding a certain proportion of the hydrophilic groups change as a function of time. For this reason all future references to water contents within this text will mean the apparent water content of the hydrogel after a known period of hydration, unless it is specifically stated that the particular water content has reached an equilibrium value.

In order to establish this theory more fully a study of the hydrolytic and temperature stability of a series of co-polymers having a low level of hydrogen bonding, by the inclusion of small but increasing amounts of methacrylic acid, was thought to be of value. To this end the first co-polymer composition in Table IV.D, ACM 40 mol% NVP 36 mol% HPA 12 mol% St 12 mol% was modified by preparing 5 co-polymers with a methacrylic acid content increasing from 1% to 5% and the N-vinyl pyrrolidone level was adjusted to ensure that the acrylamide content was completely dissolved. The resulting compositions are shown in Table IV.E and the figures are corrected to the nearest 0.1%. The water contents of these compositions were monitored over a period of nine months as is shown in Table IV.F together with the calculated standard deviations in each case. From these results for the water contents that are depicted in Graph IV.4, it is seen that the water contents rise to a maximum after 6 months hydration before falling to a level just greater than that observed after four months. Since the drift in water content is no greater than 3.3% in any of the hydrogels under study it might be argued that the results are only caused by random error, however since all the curves in Graphs IV.4 to 6 are almost identical the effect was thought

TABLE IV.E

	ACM	NVP	HPA	St	MAA
1	41.8	31.6	12.7	12.7	1.2
2	41.8	27.6	13.9	13.9	2.8
3	41.4	29.9	12.5	12.5	3.7
4	41.3	28.8	12.5	12.5	4.9
5	40.4	29.2	12.2	12.2	6.0

All compositions were cross linked with 0.5 weight per cent of poly ethylene oxide (molecular weight 400) dimethacrylate

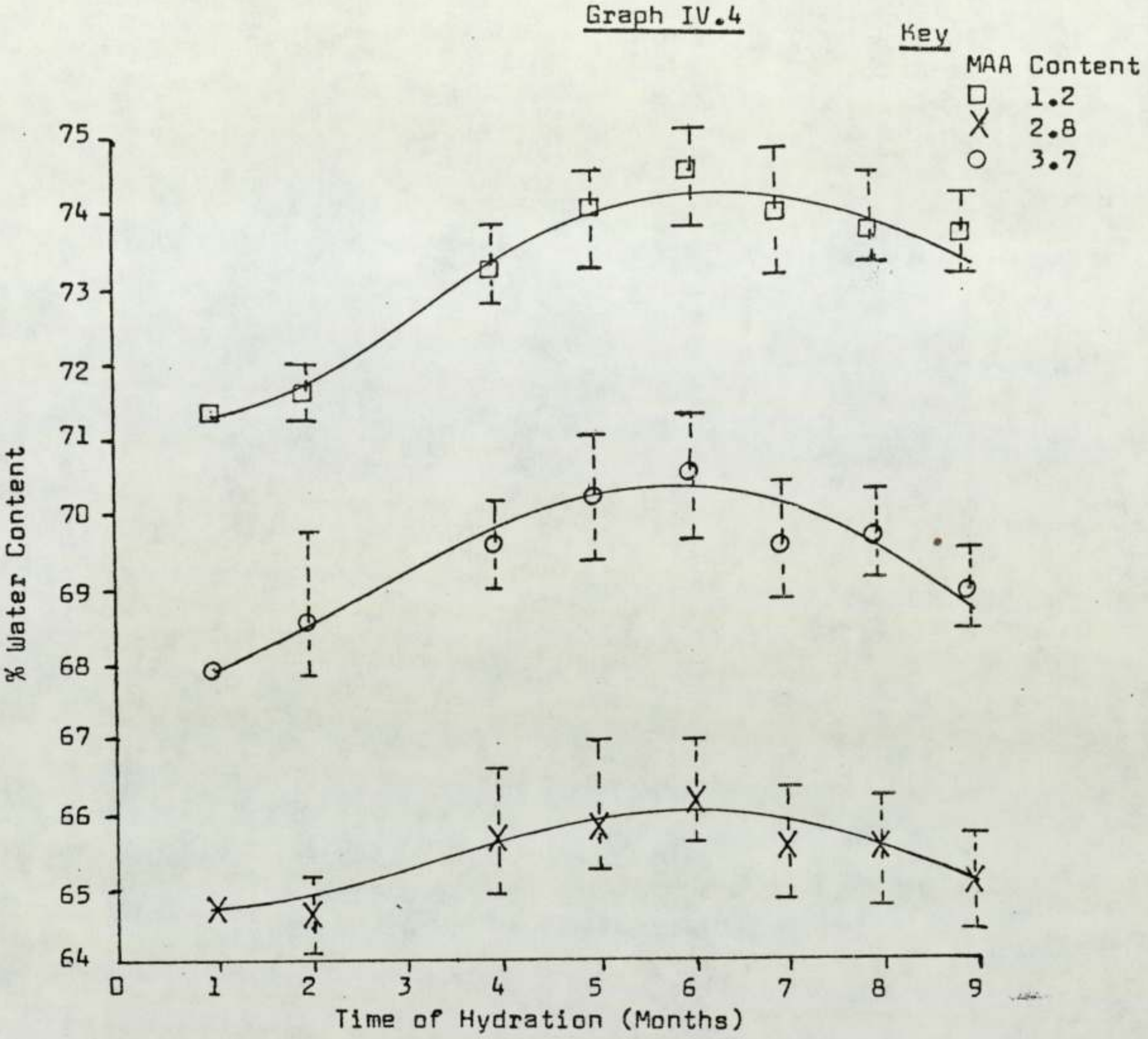
TABLE IV.F

WATER CONTENTS AND STANDARD DEVIATIONS OF POLYMERS OF INCREASING MAA CONTENTS AT VARIOUS HYDRATION TIMES

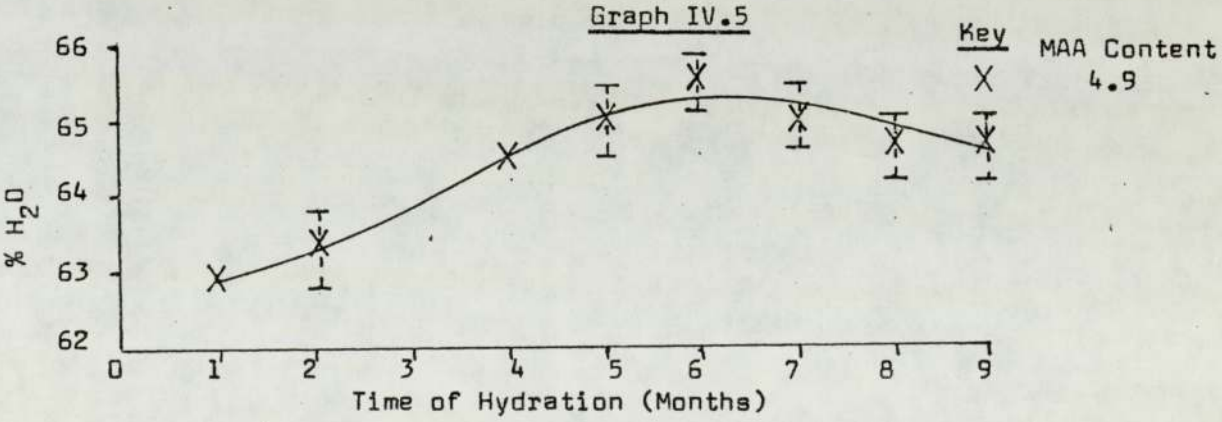
Time of Hydration	MAA Content = 1.2%	MAA Content = 2.8%	MAA Content = 3.7%	MAA Content = 4.9%	MAA Content = 6.0%
1 month	WC = 71.3% S = 0.2%	WC = 64.7% S = 0.1%	WC = 67.9% S = 0.4%	WC = 63.0% S = 0.2%	WC = 62.5% S = 0.1%
2 months	WC = 71.6% S = 0.3%	WC = 64.6% S = 0.6%	WC = 68.5% S = 1.0%	WC = 63.4% S = 0.5%	WC = 63.1% S = 0.5%
4 months	WC = 73.3% S = 0.5%	WC = 65.6% S = 0.8%	WC = 69.6% S = 0.6%	WC = 64.5% S = 0.3%	WC = 64.3% S = 0.4%
5 months	WC = 74.0% S = 0.7%	WC = 65.7% S = 1.1%	WC = 70.2% S = 0.9%	WC = 65.0% S = 0.5%	WC = 65.0% S = 0.6%
6 months	WC = 74.5% S = 0.7%	WC = 66.1% S = 0.8%	WC = 70.5% S = 0.9%	WC = 65.5% S = 0.4%	WC = 65.8% S = 1.1%
7 months	WC = 74.0% S = 0.9%	WC = 65.5% S = 0.8%	WC = 69.5% S = 0.8%	WC = 65.0% S = 0.4%	WC = 65.0% S = 1.1%
8 months	WC = 73.9% S = 0.6%	WC = 65.5% S = 0.8%	WC = 69.7% S = 0.6%	WC = 64.7% S = 0.4%	WC = 65.0% S = 1.3%
9 months	WC = 73.7% S = 0.6%	WC = 65.0% S = 0.7%	WC = 68.9% S = 0.5%	WC = 64.7% S = 0.4%	WC = 64.8% S = 1.1%

S = standard deviation

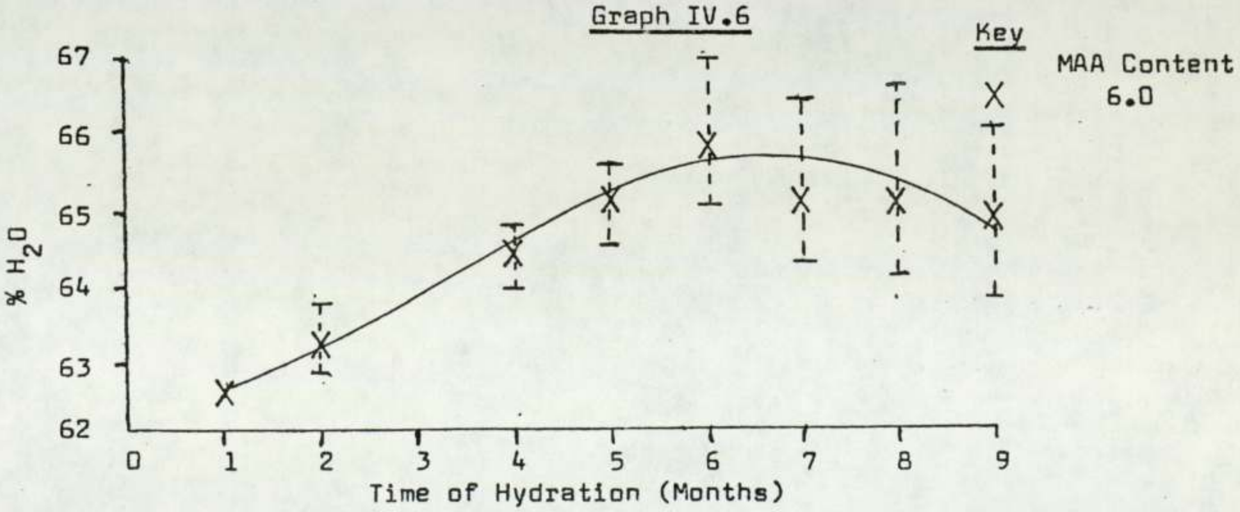
Graph IV.4



Graph IV.5



Graph IV.6



to be a real characteristic of these materials. It would be expected from an examination of the content of methacrylic acid within each of the compositions that the water content of the co-polymers should fall as the hydrogen bonding conveyed by methacrylic acid increases. This is not seen to occur in the second and third co-polymers prepared, having 2.8% and 3.7% of methacrylic acid respectively, since in the latter composition a greater N-vinyl pyrrolidone content is present.

The curves observed in Graphs IV.4 to 6 tend to support the hypothesis that the instability of these hydrogels is indeed due to the formation of a methacrylic acid-N-vinyl pyrrolidone complex giving rise to a drifting water content. In fact the shape of the curves and the respective error bars would seem to indicate that two possible competing effects are seen to occur. The first effect is the residual N-vinyl pyrrolidone monomer, after remaining within the polymer network by binding with methacrylic acid, becoming dissociated and slowly diffusing from the network causing a rise in water content. The standard deviations of the water contents as shown in Table IV.F illustrate this effect since a rise in deviation is observed after the first month, indicating that a different rate of diffusion of residual N-vinyl pyrrolidone from the polymer network occurred due to different sample weights giving different surface to volume ratios from which diffusion may take place. The second effect is an increase in hydrogen bonding through the methacrylic acid groups becoming increasingly freed from N-vinyl pyrrolidone monomer and hence after six months the re-assertion of hydrogen bonding overcomes the drift in water content, causing it to decrease and level out after nine months.

The temperature stability of these co-polymers was also examined over the range 30°C to 60°C with the water contents being monitored at regular intervals for a month, although for only 14 days at 30°C. These results are shown in Tables IV.G to J and Graphs IV.5 to 9, and an increase in the rate of drift of the water contents with temperature is observed for each material, in addition to an increase in water content itself with temperature. It is worthwhile to note that these tendencies become more pronounced as the methacrylic acid content of the co-polymer composition is increased. These results may be explained by the increase in temperature bringing about a decrease in hydrogen bonding over a period of time causing an increase in water content. It is, however, more likely that the rate of dissociation of the methacrylic acid-N-vinyl pyrrolidone complex and the diffusion of the residual monomer from the network increases at higher temperatures.[56,74,75] This view is supported by the fact that the residual fractions of each co-polymer are seen to increase with temperature, as is shown in Table IV.K and Graph IV.12.

Further justification of the hypothesis of methacrylic acid-N-vinyl pyrrolidone interaction was sought by the study of an exaggerated representation of the situation occurring in those previous examples where drifts in the water content were found. To this end, the effect of swelling various co-polymers, containing varying amounts of methacrylic acid, in a water-N-vinyl pyrrolidone mixture was studied. The results, as shown in Table IV.L, were obtained by first hydrating samples of each co-polymer in distilled water and then determining the water content (which was found to be nearly reproducibly attained within 7 days in each case). The weights of the dehydrated samples used to calculate the equilibrium water contents were also used throughout the remainder of the study to obtain the apparent water contents of the co-polymers in different hydrating media, since any attempt to dehydrate after hydrating

TABLE IV.G

WATER CONTENTS OF POLYMERS WITH INCREASING MAA CONTENT AT VARIOUS HYDRATION TIMES AT 30°C

Time of Hydration	MAA Content = 1.2%	MAA Content = 2.8%	MAA Content = 3.7%	MAA Content = 4.9%	MAA Content = 6.0%
5 days	71.1%	62.6%	67.5%	62.1%	62.3%
8 days	71.1%	62.7%	68.0%	62.5%	62.5%
12 days	71.8%	62.9%	68.3%	62.7%	62.9%
14 days	72.0%	63.0%	68.3%	62.8%	63.1%

TABLE IV.H

WATER CONTENTS OF POLYMERS WITH INCREASING MAA CONTENTS AT VARIOUS HYDRATION TIMES AT 40°C

Time of Hydration	MAA Content = 1.2%	MAA Content = 2.8%	MAA Content = 3.7%	MAA Content = 4.9%	MAA Content = 6.0%
1 day	72.0%	62.6%	67.7%	62.7%	63.0%
5 days	72.6%	62.8%	68.5%	63.2%	63.7%
7 days	74.7%	63.3%	68.9%	63.7%	63.9%
11 days	75.0%	63.6%	69.3%	64.4%	64.7%
14 days	75.7%	64.1%	70.0%	65.1%	65.6%
18 days	76.2%	64.6%	71.0%	66.3%	66.7%
22 days	76.7%	64.9%	71.5%	67.3%	67.8%
25 days	77.0%	65.5%	72.3%	68.2%	68.6%
28 days	77.8%	65.8%	72.8%	68.7%	68.9%
32 days	78.4%	66.4%	73.5%	69.4%	69.8%

TABLE IV.I

WATER CONTENTS OF POLYMERS WITH INCREASING MAA CONTENTS AT VARIOUS HYDRATION TIMES AT 51°C

Time of Hydration	MAA Content = 1.2%	MAA Content = 2.8%	MAA Content = 3.7%	MAA Content = 4.9%	MAA Content = 6.0%
3 days	74.4%	64.8%	73.3%	69.5%	70.8%
5 days	74.6%	65.2%	73.7%	70.4%	71.8%
7 days	74.9%	65.5%	74.4%	71.2%	72.9%
12 days	75.7%	66.4%	75.7%	73.1%	75.1%
14 days	76.2%	66.9%	76.5%	74.0%	76.0%
19 days	76.8%	67.7%	78.1%	75.6%	77.6%
21 days	77.5%	68.0%	78.8%	76.3%	78.2%
27 days	78.2%	69.1%	79.8%	77.7%	79.8%
34 days	79.3%	70.0%	80.5%	79.2%	81.1%

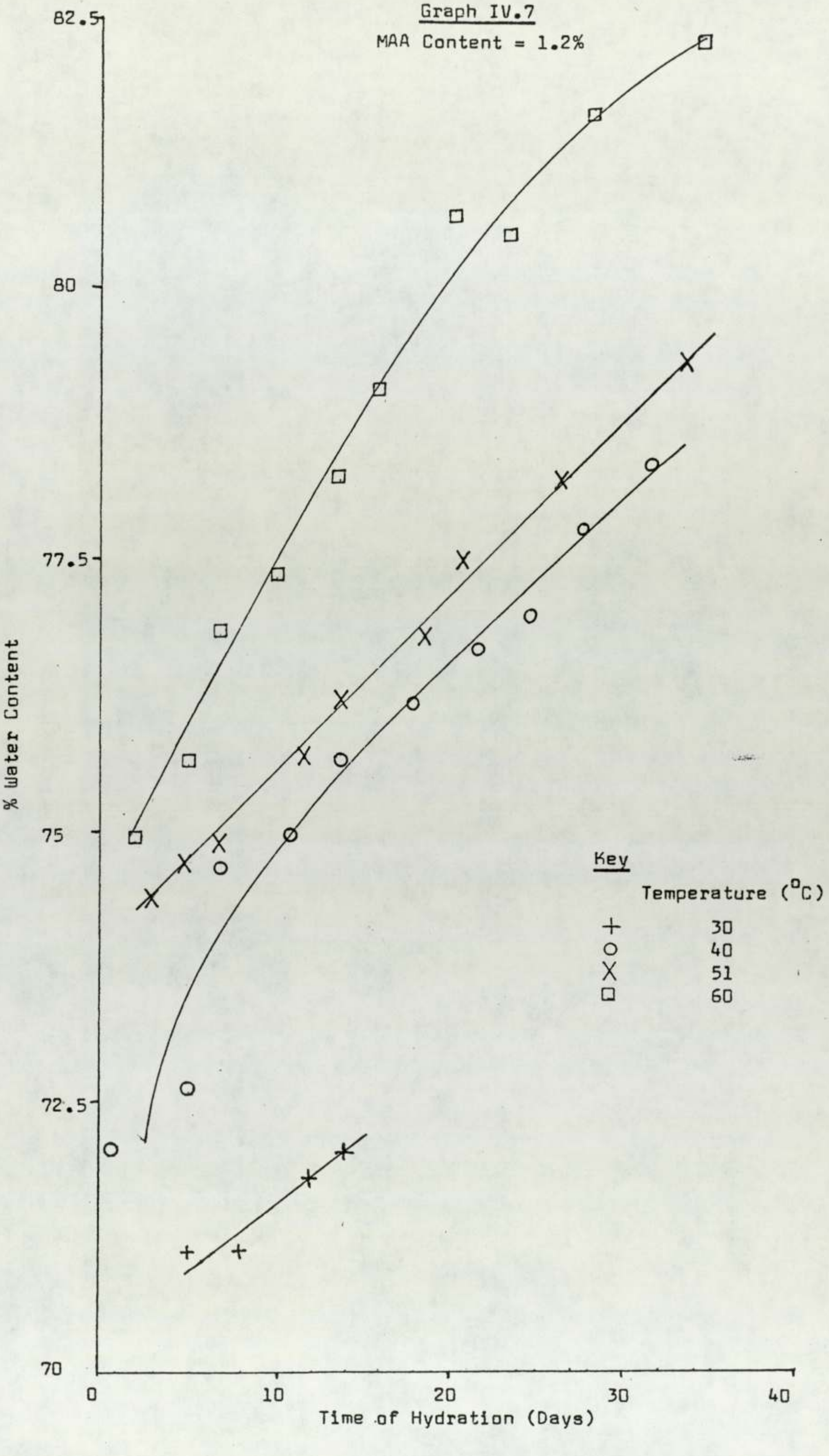
TABLE IV.J

WATER CONTENTS OF POLYMERS WITH INCREASING MAA CONTENTS AT VARIOUS HYDRATION TIMES AT 60°C

Time of Hydration	MAA Content = 1.2%	MAA Content = 2.8%	MAA Content = 3.7%	MAA Content = 4.9%	MAA Content = 6.0%
2 days	74.9%	67.6%	78.8%	75.8%	79.1%
7 days	76.8%	69.0%	80.5%	78.0%	81.3%
10 days	77.3%	69.7%	81.4%	79.2%	82.0%
14 days	78.2%	70.7%	82.4%	80.5%	83.1%
16 days	79.1%	71.2%	83.2%	80.9%	83.7%
21 days	80.7%	71.8%	83.8%	81.5%	84.7%
24 days	80.5%	72.0%	84.2%	82.1%	85.2%
28 days	81.6%	72.8%	84.7%	83.2%	85.9%
35 days	82.3%	73.6%	85.7%	83.9%	86.6%

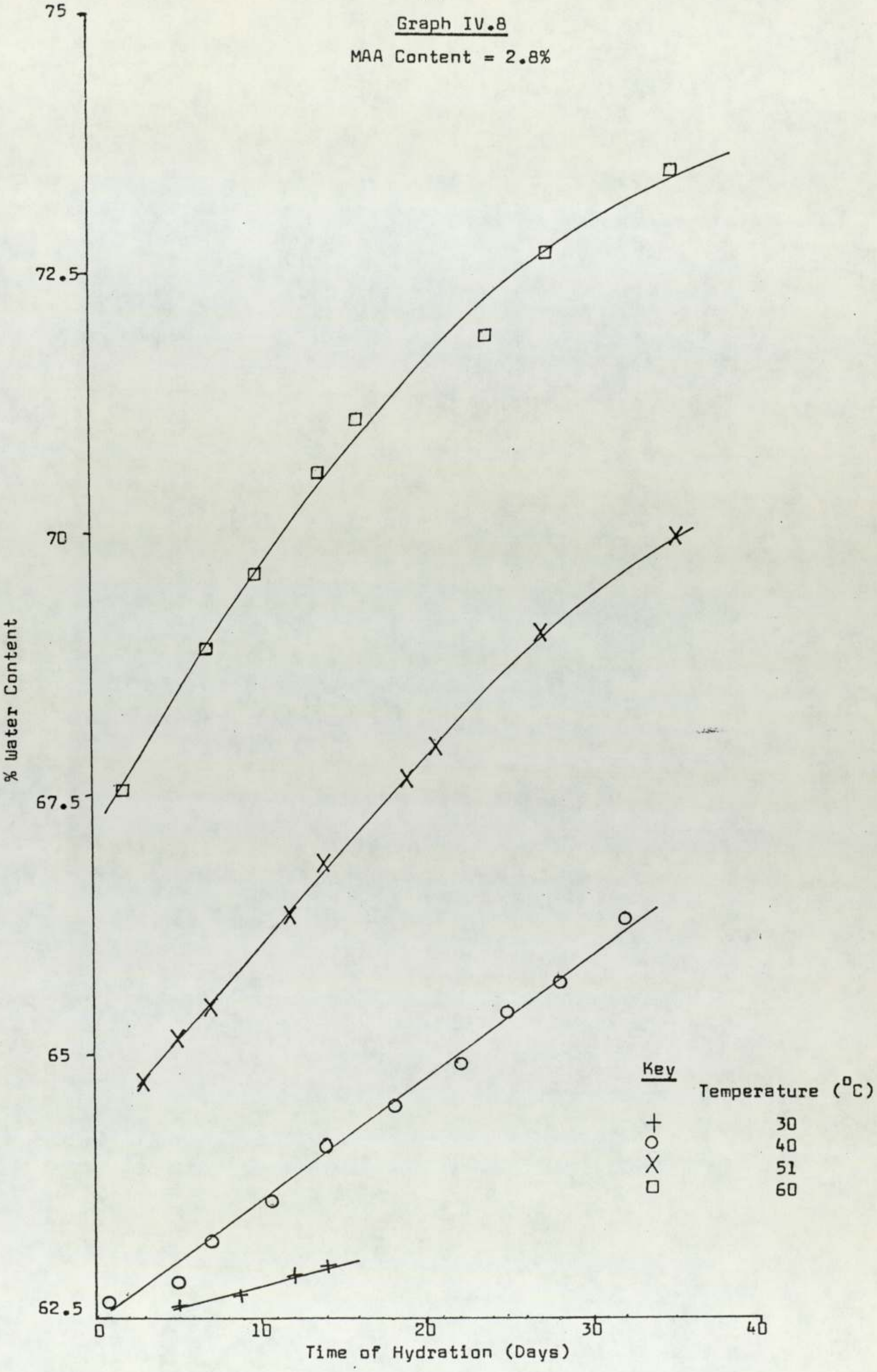
Graph IV.7

MAA Content = 1.2%



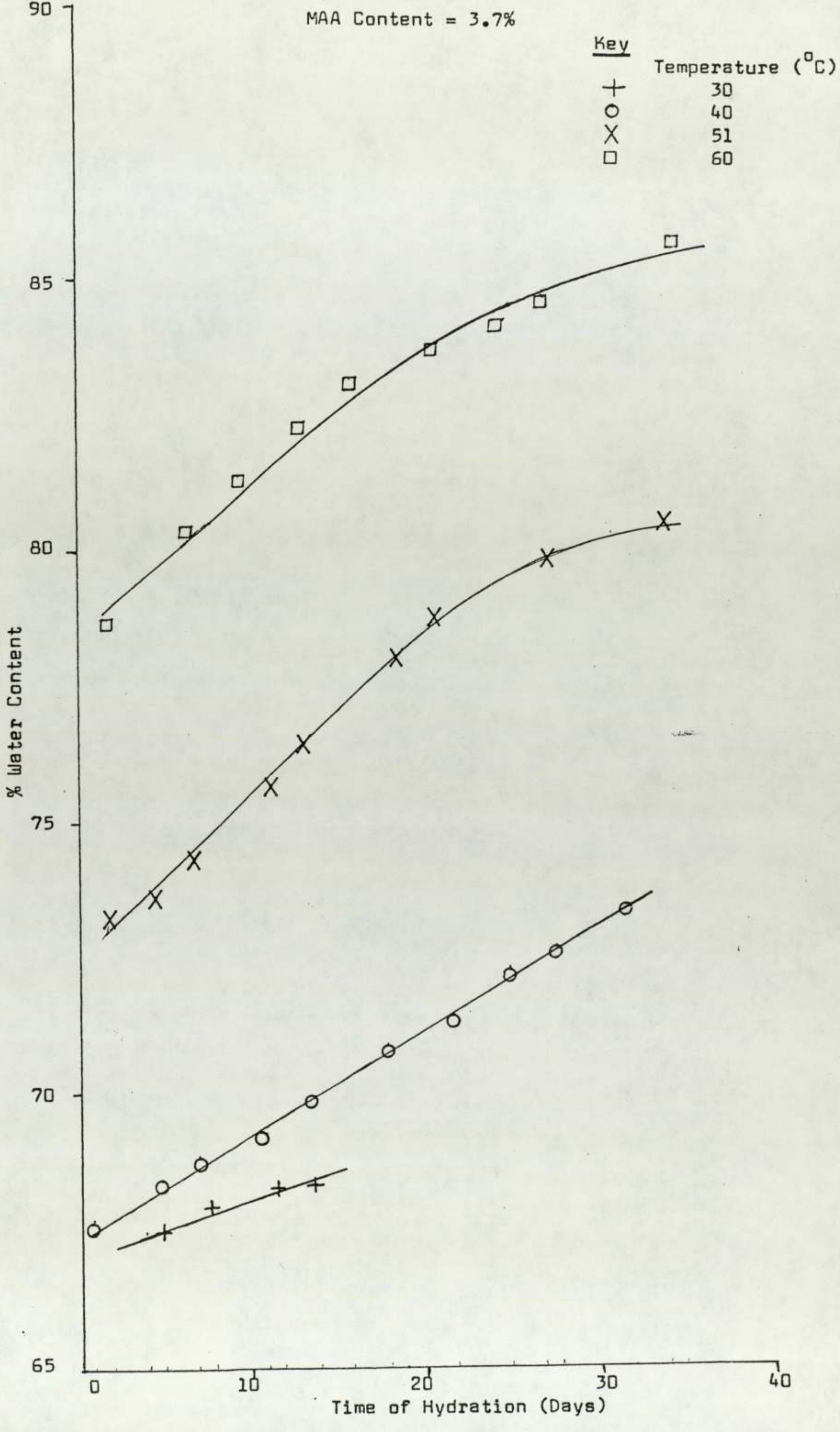
Graph IV.8

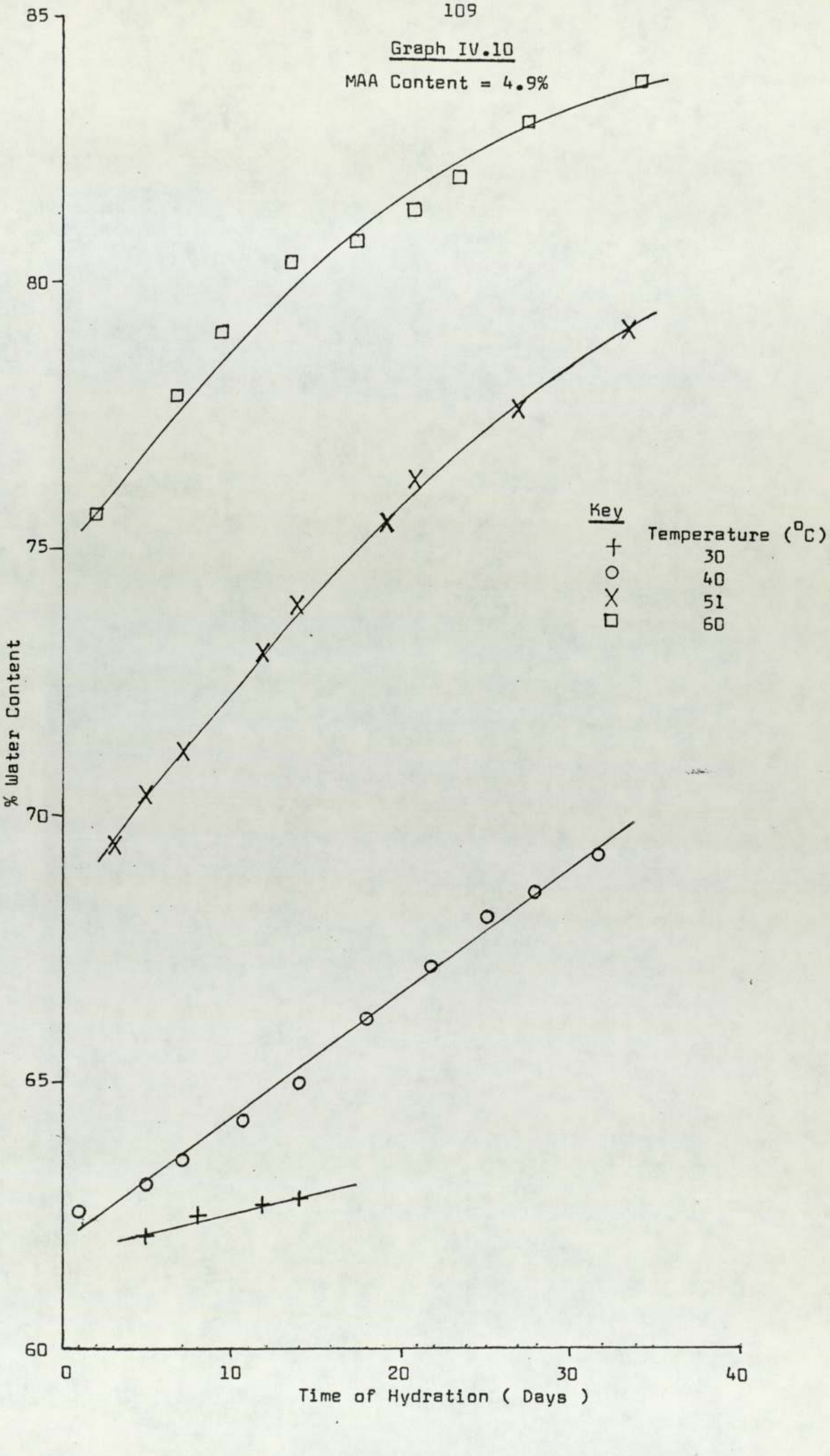
MAA Content = 2.8%



Graph IV.9

MAA Content = 3.7%




Graph IV.10
MAA Content = 4.9%
% Water Content
Time of Hydration (Days)
85
80
75
70
65
60
0
10
20
30
40
Key
Temperature (°C)
+ 30
○ 40
X 51
□ 60

Graph IV.11

MAA Content = 6.0%

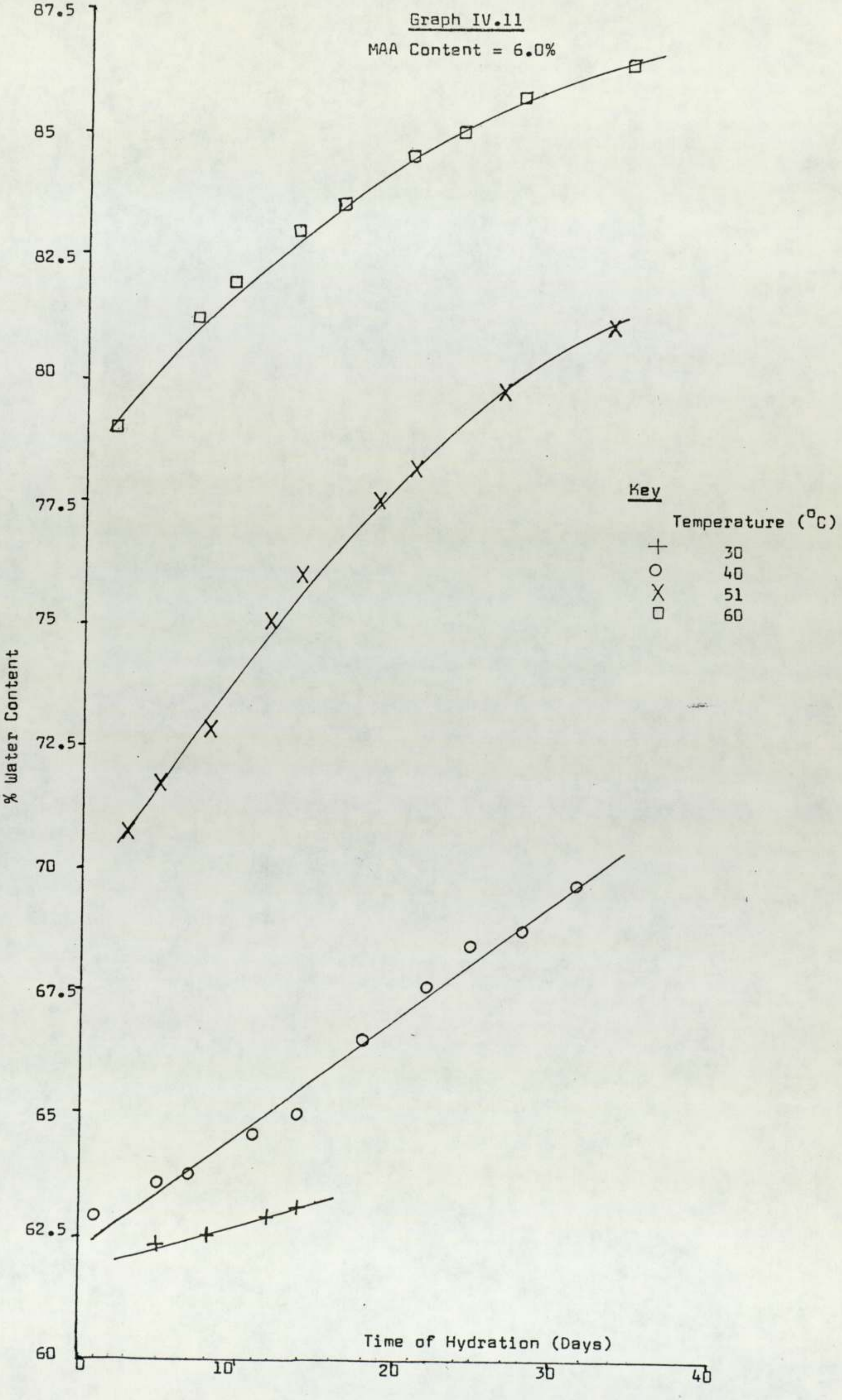


TABLE IV.K

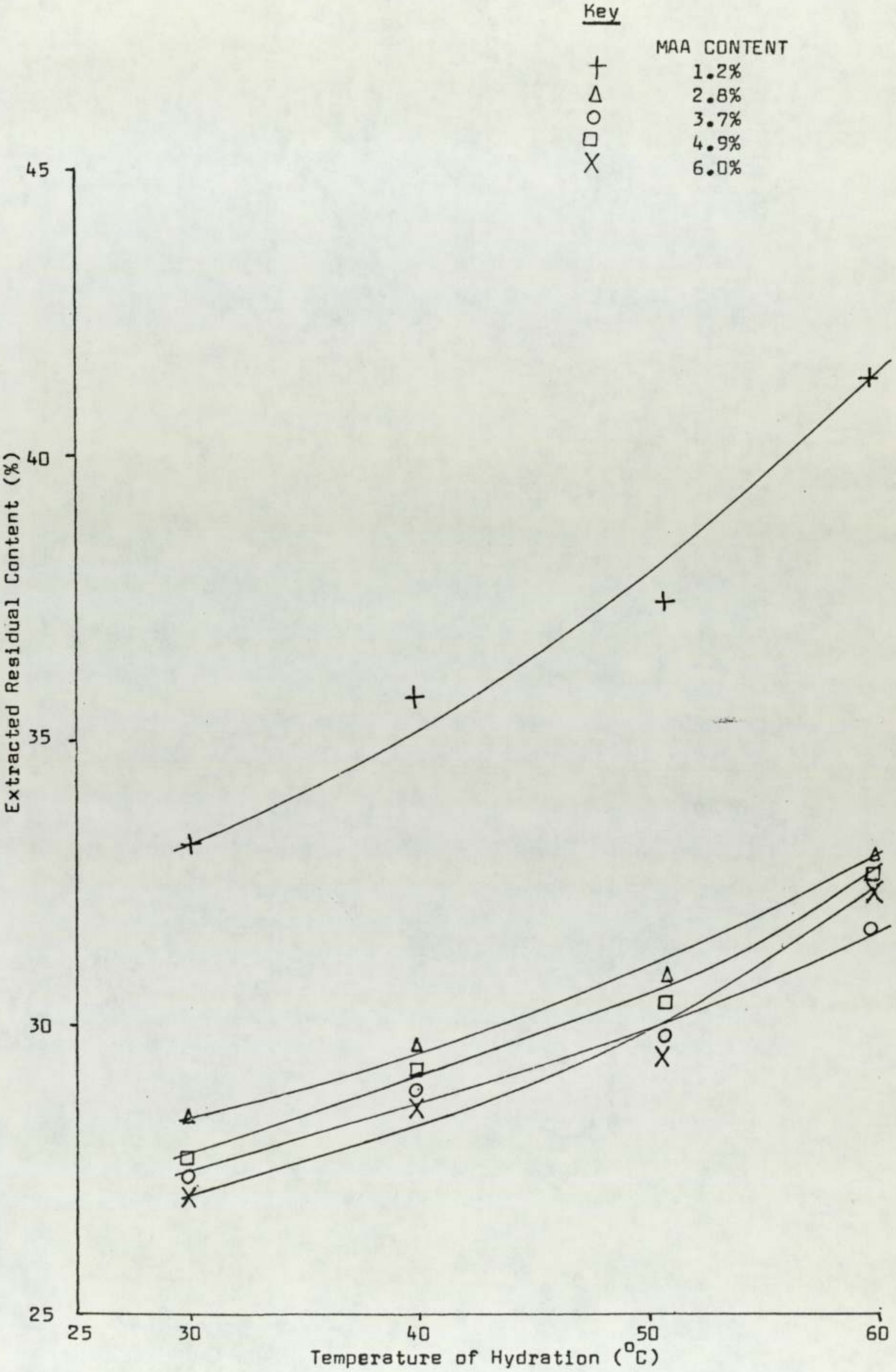
RESIDUALS OF POLYMERS WITH INCREASING MAA CONTENT AT VARIOUS TEMPERATURES

MAA Content of co-polymer	Residuals at 30°C	Residuals at 40°C	Residuals at 51°C	Residuals at 60°C
1.2%	33.2%	35.8%	37.5%	41.4%
2.8%	28.4%	29.6%	30.9%	32.9%
3.7%	27.5%	28.9%	29.8%	31.8%
4.9%	27.6%	29.2%	30.6%	32.8%
6.0%	27.1%	28.6%	29.7%	32.6%

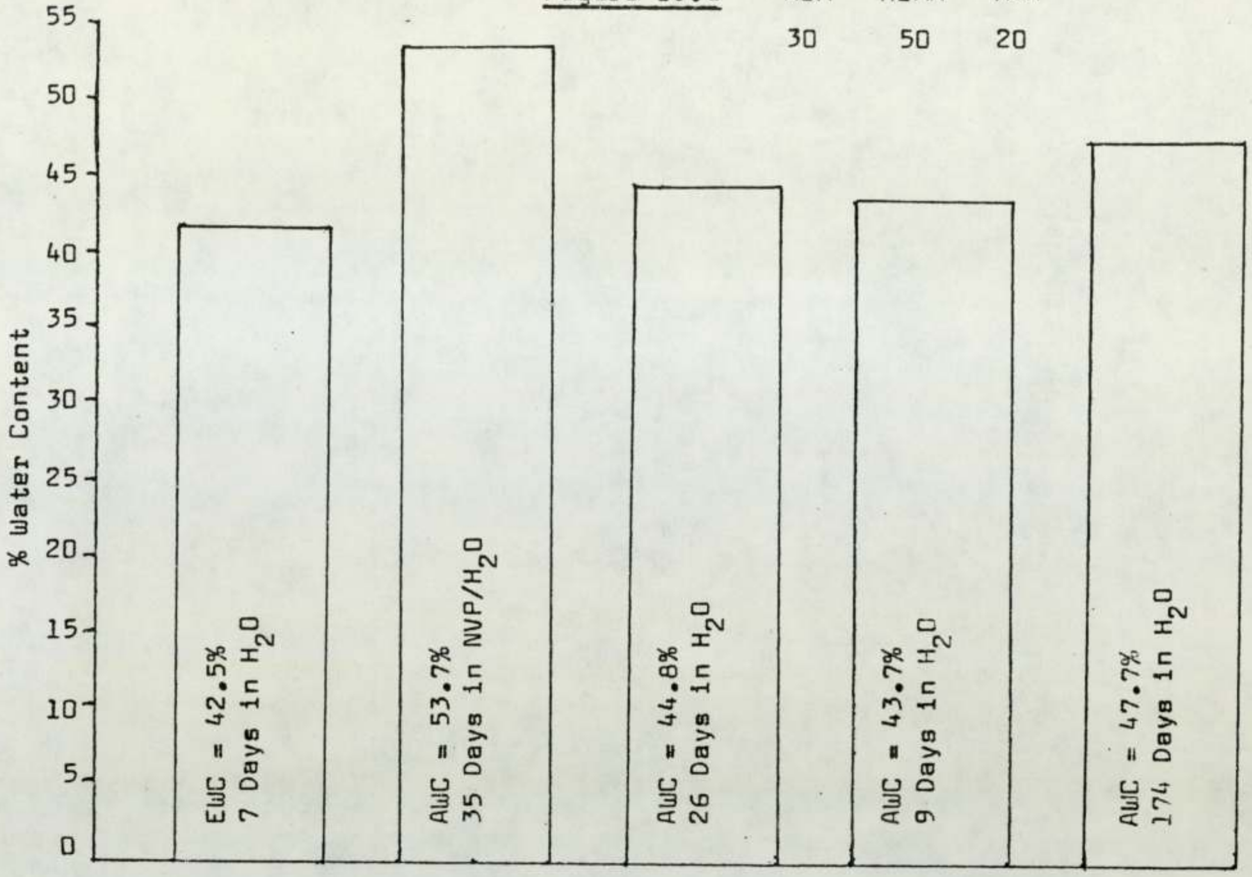
TABLE IV.L

Copolymer Compositions				Water Contents in various hydrating media for varying periods of time				
ACM	HEMA	MAA	St	EWC (H_2O) 7 Days	AWC (NVP/H_2O) 36 Days	AWC (H_2O 26 Days	AWC (New H_2O) 9 Days	AWC 174 Days
50	30	10	10	51.3%	61.0%	55.7%	54.8%	57.6%
60	20	10	10	60.7%	68.8%	65.6%	64.0%	66.5%
30	50	20		42.5%	53.7%	44.8%	43.7%	47.7%
40	40	20		50.3%	61.3%	54.0%	52.2%	58.3%
33	33	33		37.5%	53.1%	47.3%	44.45%	55.3%

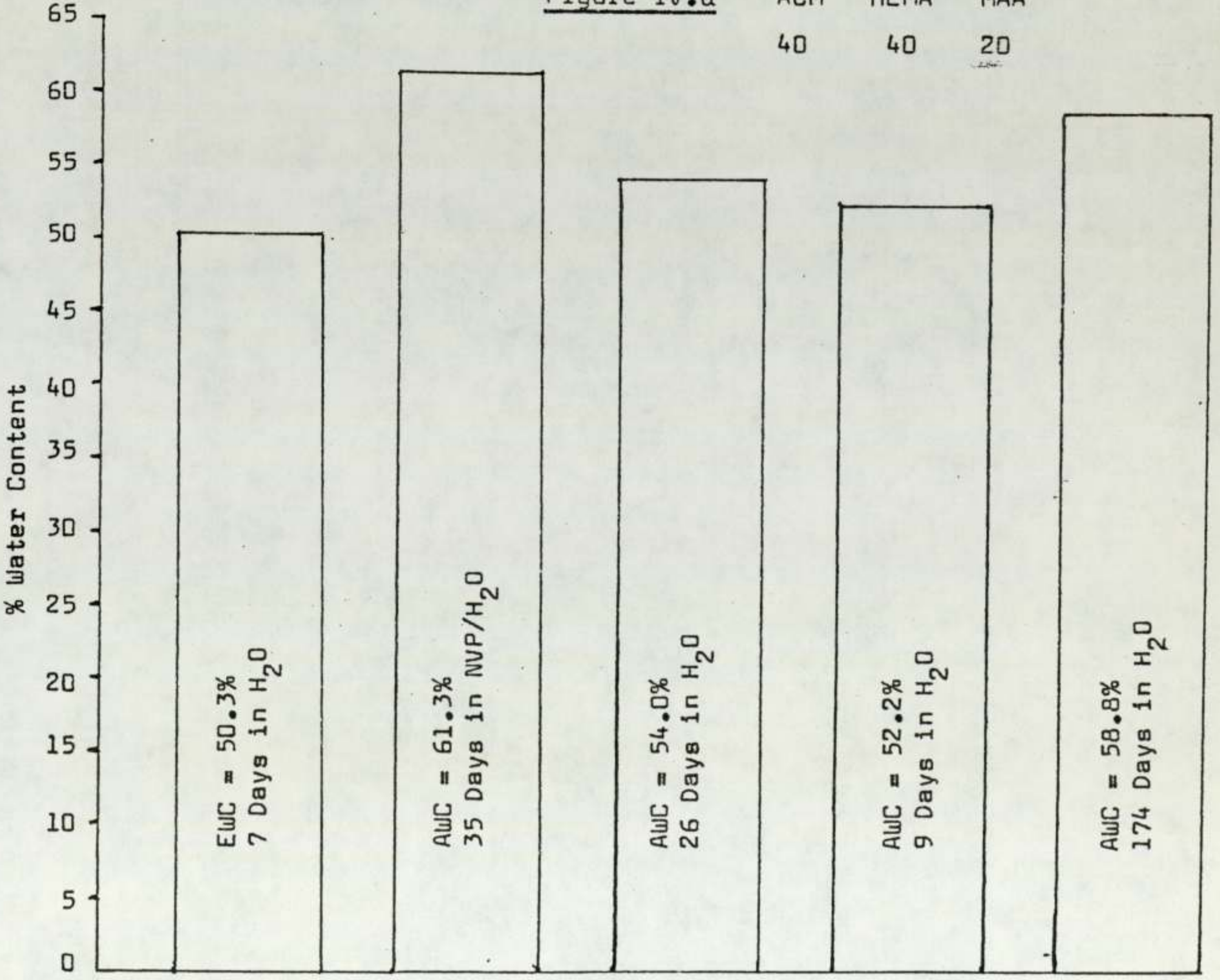
Graph IV.12


Key
MAA CONTENT
+ 1.2%
Δ 2.8%
○ 3.7%
□ 4.9%
X 6.0%
45
40
35
30
25
Extracted Residual Content (%)
25
30
40
50
60
Temperature of Hydration (^oC)

in N-vinyl pyrrolidone would lead to polymerisation of the monomer within the existing polymer network. The dehydrated samples were therefore rehydrated in a water-N-vinyl pyrrolidone mixture (6:1 volume ratio) for a month before the apparent water contents were calculated and the samples again hydrated in distilled water for another month whereupon the water contents were re-calculated. The distilled water was then changed for a second time and the apparent water contents were again re-calculated after 9 days and 6 months hydration. The results, as shown in Table IV.L, are depicted in Figures IV.c to g and show the same trends in each case indicating that this behaviour is a real effect rather than a chance result of experimental error. The apparent water content of each material, when hydrated in the N-vinyl pyrrolidone-water mixture, is seen to rise to a level greater than the equilibrium value of the water content calculated previously. It should be noted that the value of the rise in apparent water content over that found after 7 days hydration increases as the methacrylic acid content of each co-polymer is increased, and this is in keeping with the theory of methacrylic acid-N-vinyl pyrrolidone complex formation as previously outlined. On removal of this hydrating medium and its replacement with distilled water, a dramatic fall in the apparent water content is observed although it remains above the value originally obtained. Since the water content does not revert to its original equilibrium level, it would appear that a proportion of the N-vinyl pyrrolidone monomer is still bound to the methacrylic acid groups within the polymer network, preventing a complete re-assertion of hydrogen bonding. A further fall in water content is observed after 9 days hydration in a second portion of distilled water, which lends more support to the explanations already put forward, but an upward drift in the apparent



<u>Figure IV.c</u> ACM HEMA MAA
30 50 20



<u>Figure IV.d</u> ACM HEMA MAA
40 40 20

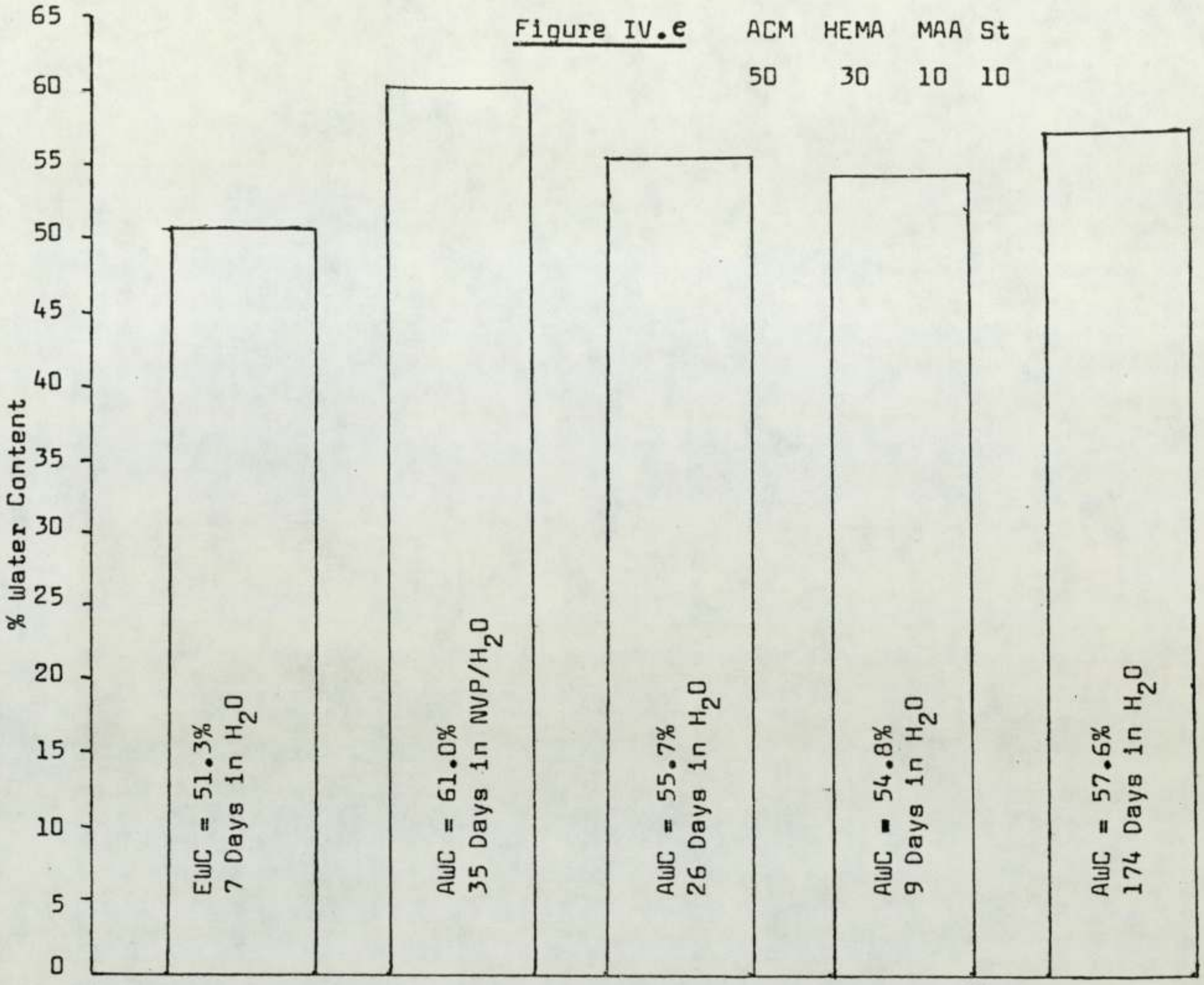


Figure IV.e

ACM HEMA MAA St
50 30 10 10

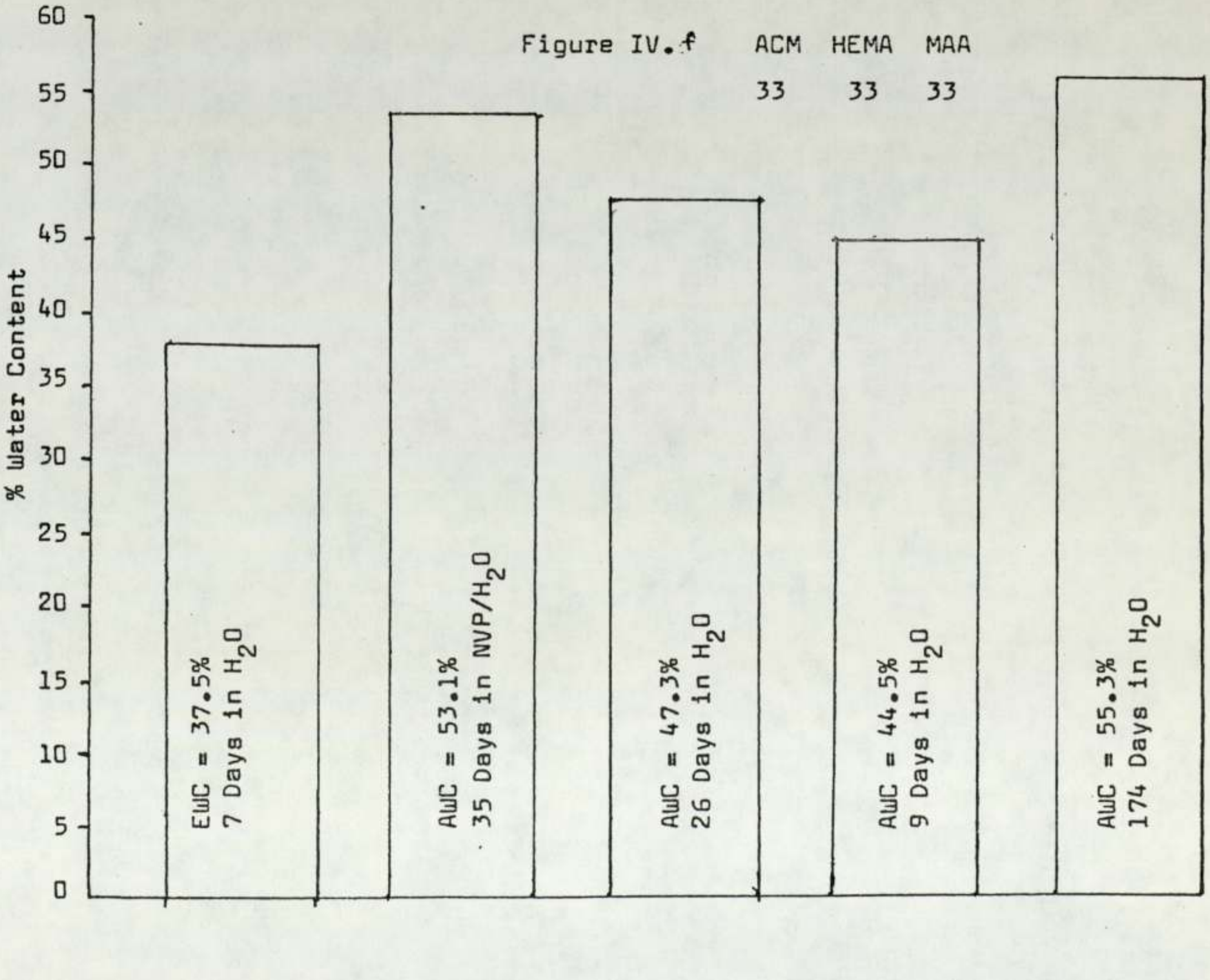
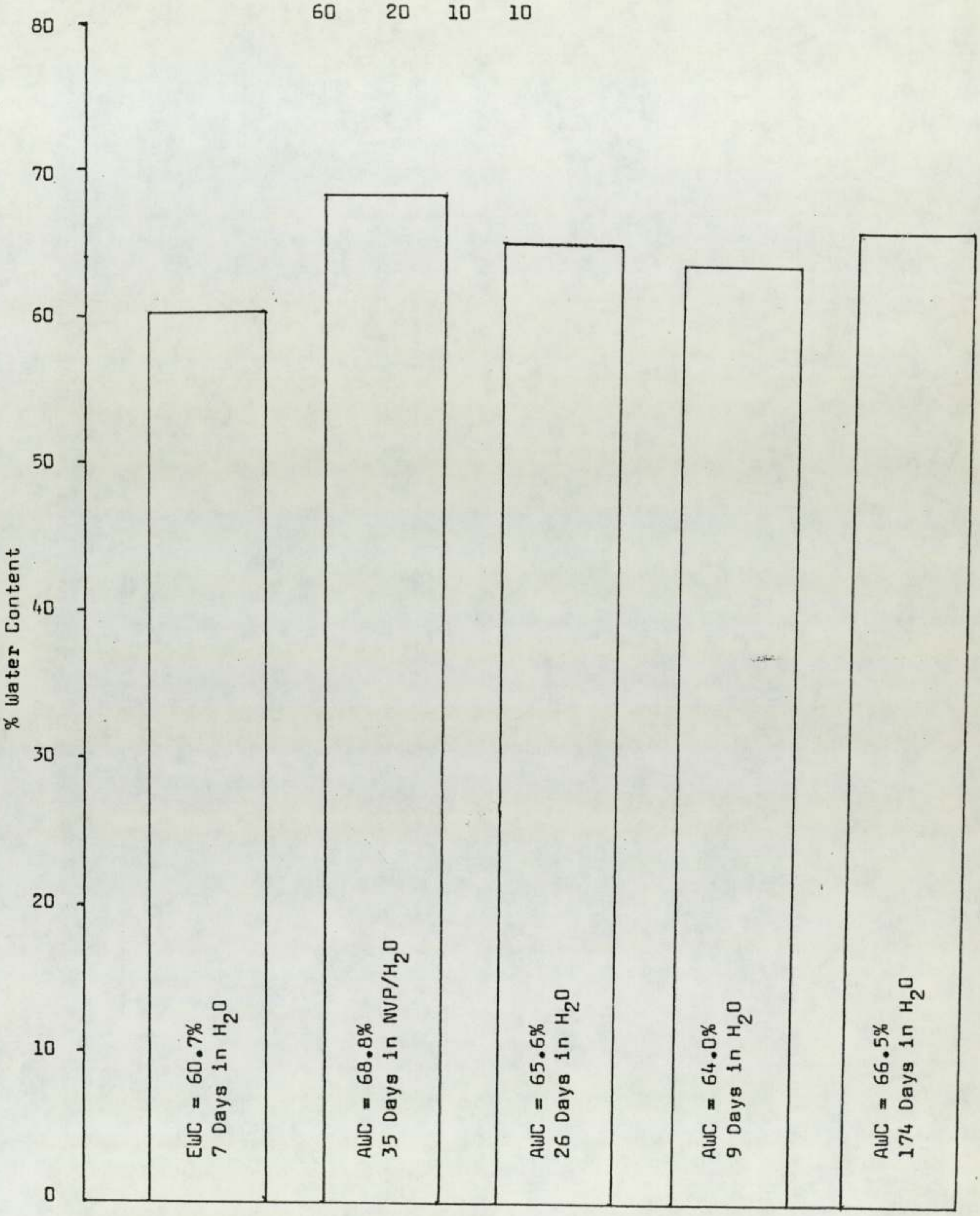


Figure IV.f

ACM HEMA MAA
33 33 33

Figure IV.9

ACM	HEMA	MAA	St
60	20	10	10



water content is then seen after another 6 months hydration. The reason for this is not thought to be a reabsorbtion of N-vinyl pyrrolidone into the gel, since the water content of each hydrogel rose above that observed before water replaced the water-N-vinyl pyrrolidone mixture as the hydrating media.

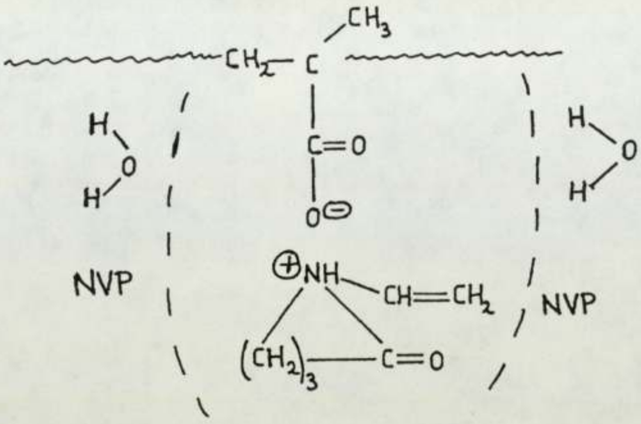
The explanation of this effect is therefore considered to be the formation of the protonated quaternary ammonium ion of the basic N-vinyl pyrrolidone monomer being solvated by other molecules of N-vinyl pyrrolidone, which undergo a gradual exchange with water molecules giving rise to upward drift in water content. This may be illustrated more clearly by considering the changes in the solvation shell surrounding the components of the methacrylic acid-N-vinyl pyrrolidone complex in the form of a series of equations.

As was depicted earlier in Equation IV.a the methacrylic acid groups within the polymer attract the basic N-vinyl pyrrolidone monomer giving rise to the formation of a complex, which prevents the methacrylic acid group from hydrogen bonding and causes the apparent water content to increase. This complex, since it is ionic in nature, will be strongly solvated by molecules of both N-vinyl pyrrolidone and water, as is depicted in Figure IV.c. For the purposes of distinction in the following equations, N-vinyl pyrrolidone molecules within a solvation shell will be denoted by NVP rather than a structural formula.

The number of molecules of water and N-vinyl pyrrolidone monomer directly associated with a complex of this type will only be of the order of 2 or 3 rather than the several shown in Figure IV.h.

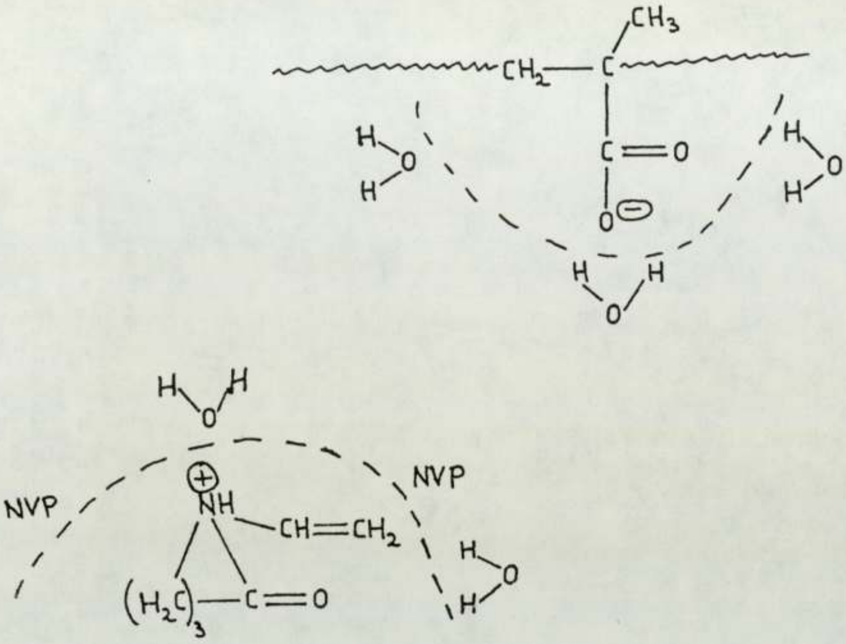
It should be remembered however that a solvation shell of this type will be vastly extended by both N-vinyl pyrrolidone and water molecules binding to the molecules of the preceeding layer of the solvation

Figure IV.h Solvation of MAA-NVP Complex by Water and NVP



shell. Two gradual processes are now thought to occur, firstly the methacrylic acid groups within the network that have not entered into complex formation with N-vinyl pyrrolidone molecules undergo chain rotation to reform hydrogen bonds with other groups in the polymer. The second process is the breakdown of the complex to produce the ion pair components separately solvated, the carboxylate anion by water molecules and the quaternary ammonium ion by molecules of both N-vinyl pyrrolidone and water. Since the quaternary ammonium ion of N-vinyl pyrrolidone will act only as a weak electrolyte, its dissociation to give a separately solvated ionic species will be slow even in a dilute solution. Hence when the N-vinyl pyrrolidone-water hydrating medium is changed to one of distilled water, the process of chain rotation followed by the reformation of certain number of hydrogen bonds takes place first, which accounts for a fall in water content while not a complete reversion to the equilibrium values. This is again seen upon a second change of water, but over a period of time the dissociation of the ion pair complex becomes more complete giving rise to two distinct and separate solvation shells as shown in Figure IV.i .

Figure IV.i Complete Dissociation of the MAA-NVP Complex



It should be remembered that as water replaces the N-vinyl pyrrolidone-water mixture, increasing amounts of N-vinyl pyrrolidone monomer are removed from the solvation shell of the quaternary ammonium ion and are substituted by water molecules, which pack into shells far more effectively. This also leads to a drift in the water content of the polymer.

It was thought that the best means of testing this theory would be to swell certain polymers in a more basic solution than N-vinyl pyrrolidone to produce a complex that is a stronger electrolyte. For this reason, those polymers listed in Table IV.E were swollen in a sodium bicarbonate-saline solution (35g$NaHCO_3$-9gNacl in 1 litre of distilled water) as were certain polymers which were modifications of the acrylamide containing gels listed in Table IV.A. The results, as shown in Tables IV.M and N, were obtained by hydrating the dehydrated samples, used in the calculation of the water contents, first in the

TABLE IV.M

Copolymer Compositions						Water Contents in Various Hydrating Media for Varying Periods of Time				
ACM	MACM	DAACM	NVP	HPA	St	H_2O 25 Days	$NaHCO_3$/$NaCl$ 27 Days	H_2O 8 Days	H_2O 196 Days	H_2O 267 Days
33			47	10	10	76.8%	80.5%	91.1%	92.6%	92.9%
30		10	40	10	10	75.8%	76.1%	87.1%	88.7%	89.1%
20	10	10	40	10	10	76.5%	76.3%	83.2%	84.7%	85.4%
25	5		55	10	5	88.7%	90.5%	94.5%	96.3%	96.5%

TABLE IV.N

Copolymer Composition					Water Contents in Various Hydrating Media for Varying Periods of Time				
ACM	NVP	HPA	St	MAA	H_2O 32 Days	$NaHCO_3$/$NaCl$ 27 Days	H_2O 8 Days	H_2O 196 Days	H_2O 267 Days
41.8	31.6	12.7	12.7	1.2	71.3%	77.0%	91.3%	91.6%	91.9%
41.8	27.6	13.9	13.9	2.8	64.7%	74.9%	91.3%	91.4%	91.7%
41.4	29.9	12.5	12.5	3.7	67.9%	79.8%	94.2%	94.2%	94.5%
41.3	28.8	12.5	12.5	4.9	63.0%	79.9%	93.8%	93.6%	94.0%
40.4	29.2	12.2	12.2	6.0	62.5%	83.5%	96.5%	96.5%	96.7%

sodium bicarbonate-saline solution and then in distilled water. The trends shown seem to be the same in each case, but the magnitude of the changes varies according to the methacrylic acid content of each co-polymer. Those co-polymers having no methacrylic acid in their composition, as shown in Table IV.M, undergo only a small change in water content when hydrated in the sodium bicarbonate-saline solution, but a far greater rise in water content is observed when this hydrating solution is changed to distilled water. This behaviour proves interesting when contrasted with that of those polymers containing methacrylic acid which show a greater increase in water content when hydrated in sodium bicarbonate-saline solution. It should also be noted that the rise in water content is seen to increase regularly with the increasing water content. Once again a dramatic increase in water content is observed when the hydrating medium is changed to distilled water, after which there seems to be very little fluctuation in water content over a period of nine months.

These observations may be explained on the basis of acidic impurities, probably acrylic acid in hydroxy propyl acrylate, being present in those compositions from which methacrylic acid was excluded giving rise to the formation of the sodium salt of the carboxylic acid within the network. Since the rise in water content on hydrating in sodium bicarbonate-saline solution is less than 4%, whereas the co-polymer having only 1.2% methacrylic acid, as seen in Table IV.N, shows an increase of almost 7%, it is thought that the impurities of acrylic acid are not greater than 0.5%. The dramatic rise in water content on changing the hydration media to distilled water lends support to the theory, previously advanced in this chapter, of the dissociation of the quaternary ammonium complex between N-vinyl pyrrolidone and methacrylic acid. Thus after treatment with sodium bicarbonate-saline solution, the addition of distilled water leads to a more dilute solution in which almost complete dissociation of the sodium salt takes place, since it is a reasonably strong electrolyte, and therefore very little change in water content is observed over a long period of time. This behaviour is distinct from the case in which the quaternary ammonium ion of N-vinyl pyrrolidone causes the formation of an ion pair within the network, since this is a far weaker electrolyte and will only undergo dissociation to solvated ionic species very slowly to give an increasing water content over a period time.

IV.5 CONCLUSIONS

In order to prepare a high water content hydrogel of this type as a potential continuous wear contact lens material it therefore becomes necessary to restrict the concentration of methacrylic acid within the copolymer composition. While this will lead to a reduction in complex formation between methacrylic acid and N-vinyl pyrrolidone monomer which gives rise to a changing water content with time, it will also place limitations upon the strength of the hydrogel networks which may be prepared. In an effort to alleviate this problem a study of the effects of using different crosslinking agents has been carried out and will be described in the following chapter.

CHAPTER FIVE

CHAPTER V

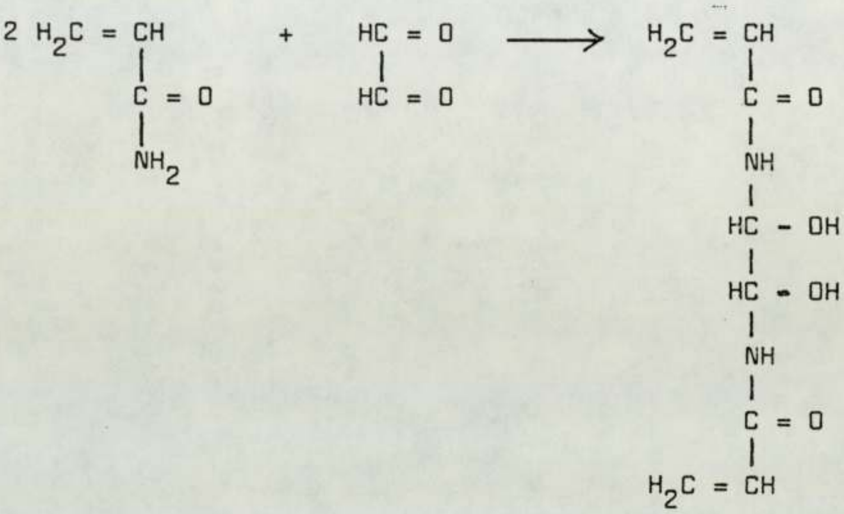
THE EFFECT OF VARIOUS CROSS-LINKING AGENTS ON THE PROPERTIES OF HYDROGEL POLYMERS

V.1i INTRODUCTION

As was stated at the end of Chapter III, those properties of a hydrogel that are relevant to the design of continuous wear contact lens are not only dependent upon the structure of the side chain groups of the polymer but also the type and distribution of cross-links throughout the network.[41] Since all the results obtained in Chapter III relate to polymers containing identical amounts of the same cross-linking agent, it may be argued that a satisfactory material for continuous wear may be achieved by modifying only the copolymer composition. However as a consequence of the stability problems of the materials discussed in Chapter IV, it becomes apparent that the amount of methacrylic acid included in a potential continuous wear contact lens formulation must either be strictly limited or eliminated completely. While this may give rise to a polymer with a water content which is suitably stable; the degree of interchain adhesion from hydrogen bonding would become considerably reduced and might even cause the strength of the hydrogel to become unacceptable. This chapter is therefore concerned with the study of various cross-linking agents and their effect on both the water content and the deformational properties of hydrogel polymers. As many polymers are known to have better mechanical properties at higher cross-link densities, it may be possible to produce a material of sufficient strength despite the absence of the contribution to hydrogen bonding supplied by the methacrylic acid groups.

V.lii PREPARATION OF DIHYDROXY ETHYLENE BIS ACRYLAMIDE

The method employed for the preparation of the cross-linking agent dihydroxy ethylene bis acrylamide was that described by Yoshizawa et al.[77] The product is conveniently isolated from the facile reaction of acrylamide and glyoxal as illustrated in Figure V.a -



A solution of acrylamide in anisole was added to a 41% aqueous solution of glyoxal and the mixture was stirred continuously for 3 days. A pH of 7 was maintained throughout the course of the reaction by the careful addition of sodium bicarbonate.

A white precipitate of the cross-linking agent began to form after 1 day and gradually increased as the reaction proceeded to completion. After 3 days the reaction was deemed complete and the precipitate was filtered, washed with methanol and dried under vacuum. The product was found to melt within the temperature range 143-145°C, which is in good agreement with the literature value of 143°C. The reaction yield was determined to be approximately 75%.

V.2i EFFECT OF CROSS-LINKING ON THE WATER CONTENT OF A HYDROGEL

Although it has been reported that the water content of poly(2-hydroxy ethyl methacrylate) remained almost unaffected by an increase from 0.3% to 3.0% in the concentration of the cross-link agent tetra ethylene glycol dimethacrylate,[78] it has also been noted by several workers that hydrogels of high water content show far greater dependence in this property on the degree of cross-linking within the network.[79,80,81]

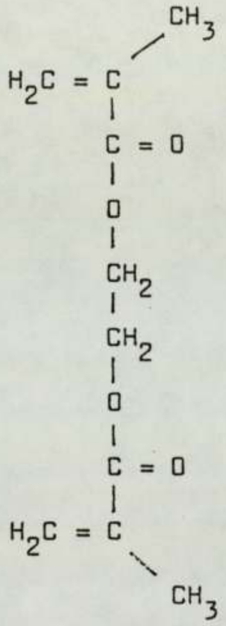
Preliminary studies, carried out during the course of this research, have shown that the water contents of copolymers containing acrylamide derivatives are indeed dependent on the type of cross-linking agent used. The results are shown in Table V.A, from which it is seen that those

TABLE V.A

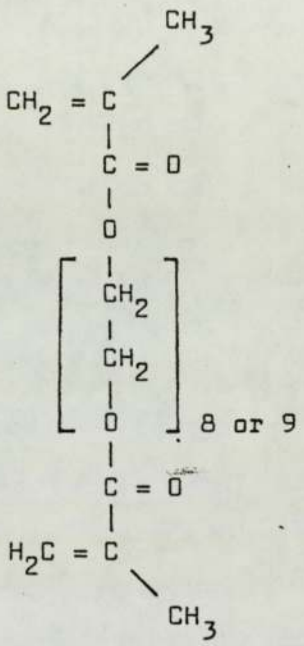
WATER CONTENTS OF VARIOUS HYDROGEL COPOLYMERS CROSS-LINKED BY EDMA OR PEO(400)DMA

Hydrogel Copolymer	Cross-Linking Agent		% Water Content
	EDMA	PEO(400)DMA	
DAACM 50)	1.0 wt%		27.5
HEMA 50)		1.0 wt%	23.1
DAACM 50)	1.0 wt%		24.4
AA 50)		1.0 wt%	22.8
MACM 50)	1.0 wt%		31.4
AA 50)		1.0 wt%	23.8
MACM 50)	1.0 wt%		35.7
MAA 50)		1.0 wt%	33.1

hydrogels cross-linked with polyethylene oxide (molecular weight = 400) dimethacrylate were found to have a lower water content than those of identical copolymer structure which were cross-linked by ethylene glycol dimethacrylate. While the same weight of cross-linking agent was added to each co-monomer formulation from which the hydrogels were prepared, it should be remembered that this will produce a higher molar concentration of ethylene glycol dimethacrylate within the network due to its lower molecular weight. This may be seen more clearly by studying the structures of the cross-linking agents in Figure V.b -



EDMA (Molecular weight = 198)



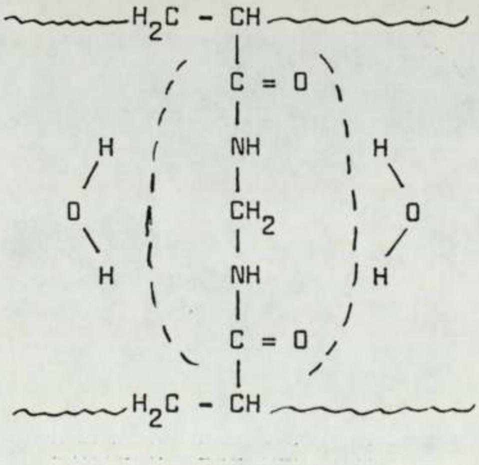
PEO(400)DMA (Molecular weight = 554)

Ng[40] has found that a depression of water content results from increasing the concentration of ethylene glycol dimethacrylate within the hydrogel network. This would indicate that the size, nature and distribution of cross-links throughout the hydrogel network will have a marked effect on the properties exhibited by the polymer, since a lower molar concentration of one cross-linking agent is seen to have a more pronounced effect on water content than a higher concentration of another.

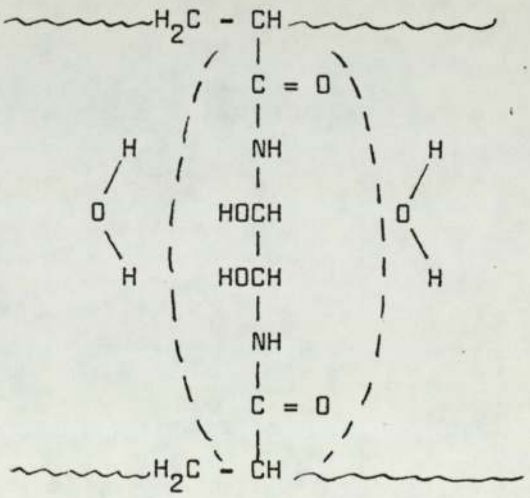
V.2ii VARIATION OF WATER CONTENT WITH STRUCTURE AND CONCENTRATION OF DIVINYL CROSS-LINKING AGENTS

The observations referred to in the previous section have led to a study, carried out in these laboratories by Patel[82] (under the guidance of the author) using varying concentrations of several cross-linking agents with one copolymer formulation. The water contents of hydrogels prepared from the co-monomer composition acrylamide (33 mole%), N-vinyl pyrrolidone (47 mole%), 2-hydroxy propyl acrylate (10 mole%) and styrene (10 mole%) with a number of cross-linking agents have been measured and are displayed in Table V.8 and Graph V.1.

Those hydrogels which were cross-linked with the acrylamide based cross-linking agents, methylene bis acrylamide and dihydroxy ethylene bis acrylamide, are seen to have higher water contents throughout the range of concentrations studied. This behaviour may be attributed to the polarity of the two amidic groups within these cross-linking agents which may enhance the hydrophilicity of the copolymer as illustrated in Figure V.c -



Methylene bis acrylamide



Dihydroxy ethylene bis acrylamide

TABLE V.8

EFFECT ON THE WATER CONTENT OF THE HYDROGEL ACM33 NVP47 HPA10 St10 BY VARIOUS CROSS-LINKING AGENTS AT DIFFERING CONCENTRATIONS

EDMA

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.14	0.28	0.55	1.11	2.78
% Water Content	81.4	76.3	71.2	69.5	59.6

PEO(200)DMA

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.08	0.16	0.31	0.62	1.55
% Water Content	82.5	73.4	72.8	72.1	66.5

PEO(400)DMA

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.05	0.10	0.20	0.40	0.99
% Water Content	73.2	69.9	66.5	61.0	54.2

MBACM

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.18	0.36	0.71	1.43	3.56
% Water Content	90.0	85.9	84.0	73.9	66.5

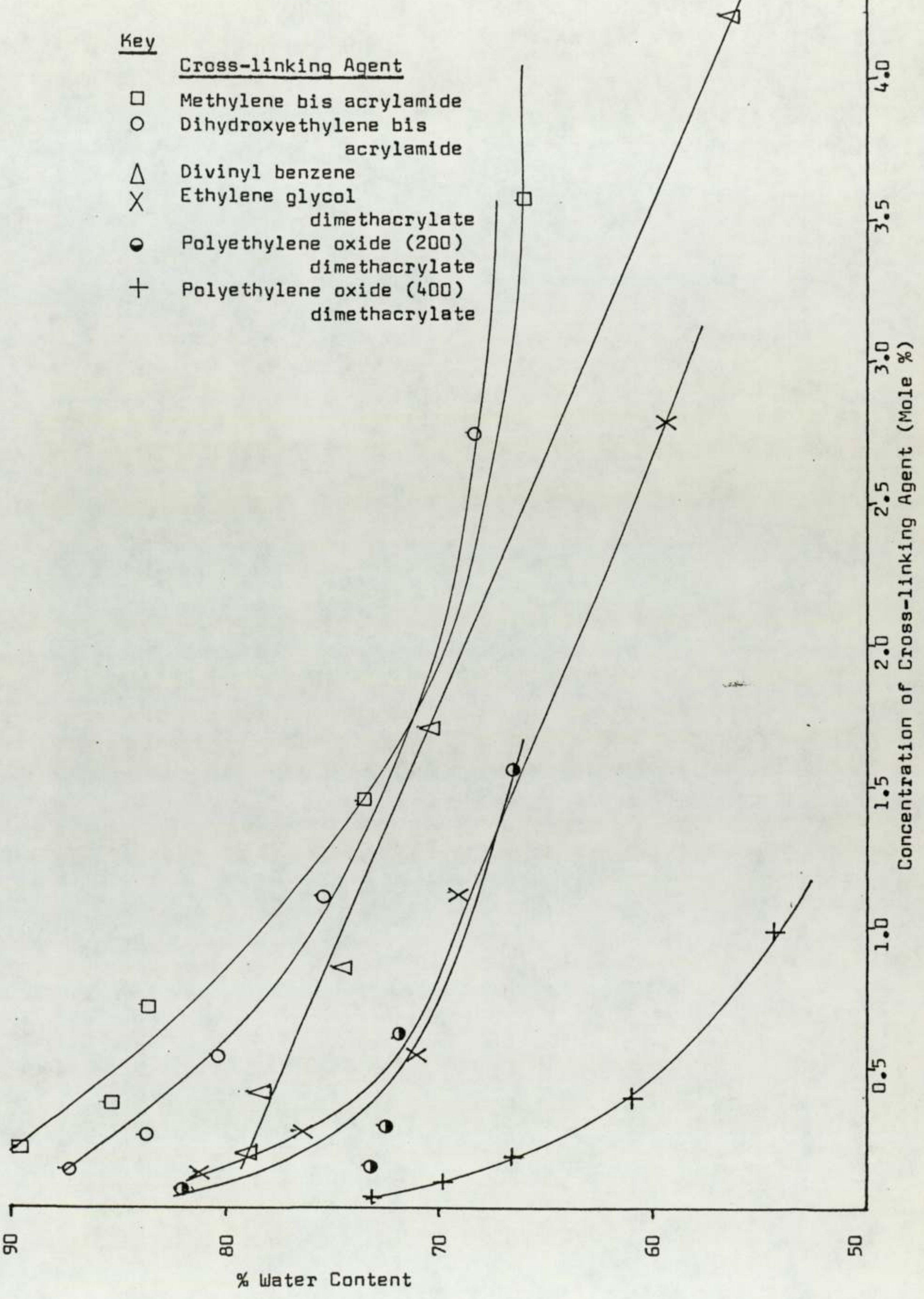
DHEBACM

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.14	0.27	0.55	1.10	2.75
% Water Content	87.8	84.1	80.9	75.9	68.7

DVB

% by weight	0.25	0.5	1.0	2.0	5.0
Mole %	0.21	0.42	0.85	1.69	4.23
% Water Content	79.4	79.0	75.0	70.9	56.9

Graph V.1


Key
Cross-linking Agent
□ Methylene bis acrylamide
○ Dihydroxyethylene bis acrylamide
△ Divinyl benzene
X Ethylene glycol dimethacrylate
◒ Polyethylene oxide (200) dimethacrylate
+ Polyethylene oxide (400) dimethacrylate
Concentration of Cross-linking Agent (Mole %)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
% Water Content
90
80
70
60
50

It should be stressed that these acrylamide based cross-linking agents only enhance hydrophilicity with respect to those hydrogels cross-linked by other reagents. Graph V.1 shows that an increase in the concentration of cross-linking agent leads to a decrease in water content. The presence of two hydroxyl groups in the structure of dihydroxy ethylene bis acrylamide might be expected to increase the water content of hydrogels to a greater extent than those cross-linked with methylene bis acrylamide, but this is not seen to be the case at low concentrations. There may be several explanations for this behaviour, but the solubilities of each cross-linking agent in the constituent monomers of the copolymer could give rise to a more favourable distribution of methylene bis acrylamide units within the hydrogel network and the presence of hydroxyl groups in dihydroxy ethylene bis acrylamide will also increase the capability for hydrogen bond formation.

The dimethacrylate derivatives studied gave similar curves to those obtained for the acrylamide based cross-linking agents. It is apparent, however, that the dimethacrylate cross-linking agents produce cross-linked hydrogels of lower water content due to the absence of polar substituents, such as amide groups, within their structures. As the distance between the vinylic groups in each cross-linking agent is increased by the inclusion of ethylene oxide units, a decrease in the water contents of the hydrogels produced are seen to occur. The difference in water contents of hydrogels cross-linked with ethylene glycol dimethacrylate and poly ethylene oxide (av molecular weight = 200) dimethacrylate is seen from Graph V.1 to be small. A much more marked difference is observed however when those hydrogels with cross-links of polyethylene oxide (molecular weight = 400) dimethacrylate are considered. The additional ethylene oxide units present in hydrogels cross-linked with poly ethylene oxide (molecular weight = 400) dimethacrylate would therefore seem to give rise to a greater degree of hydrophobic bondings in the network, via Van der Waals attractions and dipole-dipole interactions, to bring about a significant depression in water content.

Those hydrogels cross-linked with divinyl benzene were found to undergo a linear decrease in water content as the concentration of cross-linking agent was increased. This may be attributed to the phenyl group of divinyl benzene causing an increase in the degree to which the steric hindrance, due to the presence of styrene in the copolymer, restricts the absorption of water by the hydrogel network.

V.2iii VARIATION OF WATER CONTENT WITH A TRIVINYL SUBSTITUTED CROSS-LINKING AGENT

A further study on cross-linking agents in hydrogels has been undertaken in these laboratories, under the guidance of the author, to investigate the differences between compounds having 2 or 3 vinylic sites available for cross-linking.[83] The 25:75 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate was cross-linked by conventional reagents such as methylene bis acrylamide and ethylene glycol dimethacrylate in addition to 1,1,1 trimethylol propane trimethacrylate, which has a structure containing 3 olefinic unsaturated groups, as shown in Figure V.d.

The results of this study are shown in Table V.C and portrayed in Graph V.2. It is seen that methylene bis acrylamide again proves to be the most hydrophilic of the cross-linking agents used, for the same reasons stated previously in this chapter. It should be noted however that the inclusion of methylene bis acrylamide gave rise to linear decrease in water content as the concentration of the cross-linking

TABLE V.C

WATER CONTENTS OF THE HYDROGEL ACM25 HPA75 AT VARYING CONCENTRATIONS OF 3 CROSS-LINKING AGENTS

TMPTMA

% by Weight	Mole %	% Water Content
0.25	0.08	71.3
0.5	0.17	70.0
1.0	0.34	66.5
2.0	0.68	62.4
5.0	1.70	48.2

MBACM

% by Weight	Mole %	% Water Content
0.5	0.37	72.0
1.0	0.74	67.4
2.0	1.48	65.2
5.0	2.96	50.8

EDMA

% by Weight	Mole %	% Water Content
0.5	0.28	61.7
1.0	0.58	52.8
2.0	1.16	49.7
5.0	2.82	47.9

Graph V.2

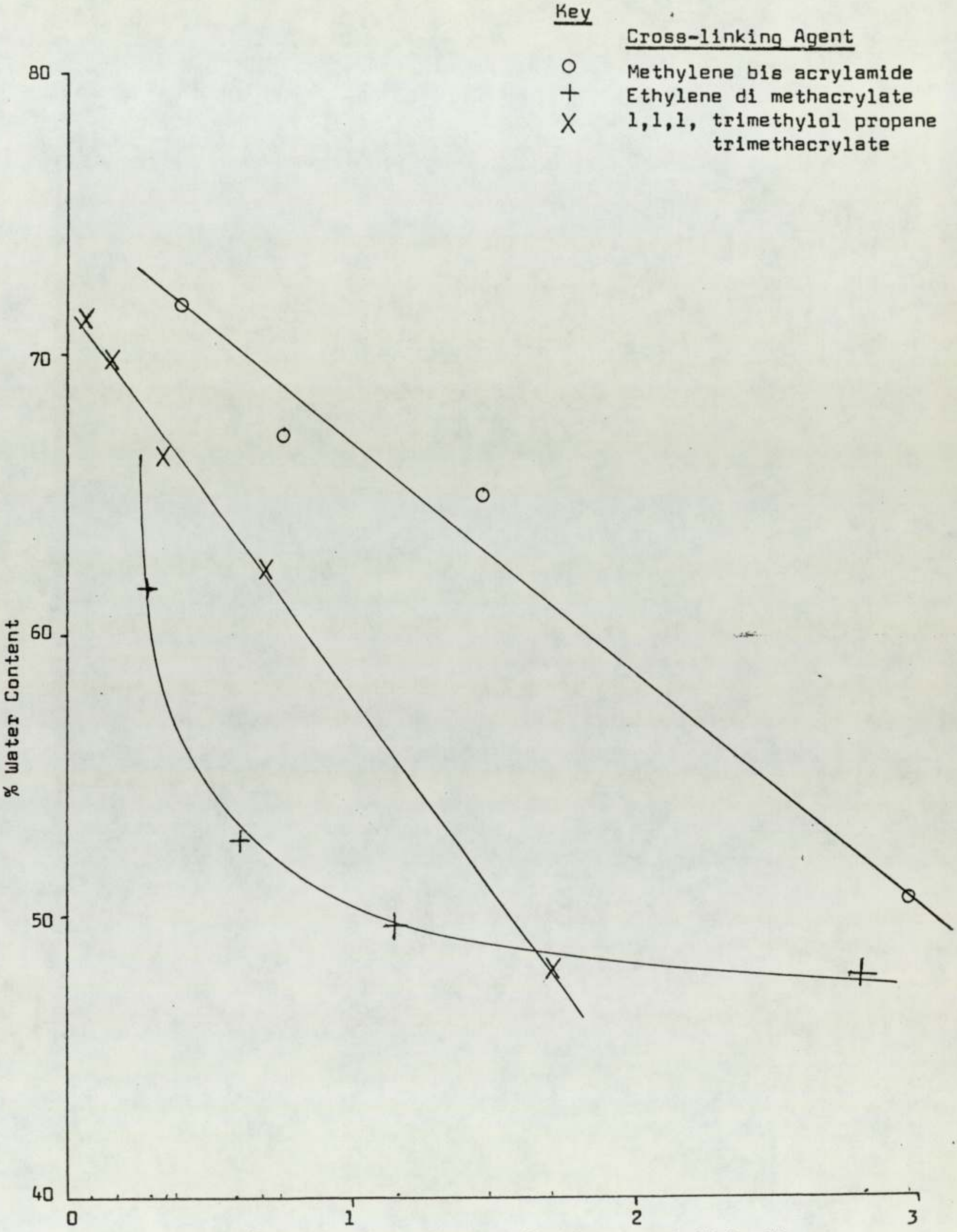
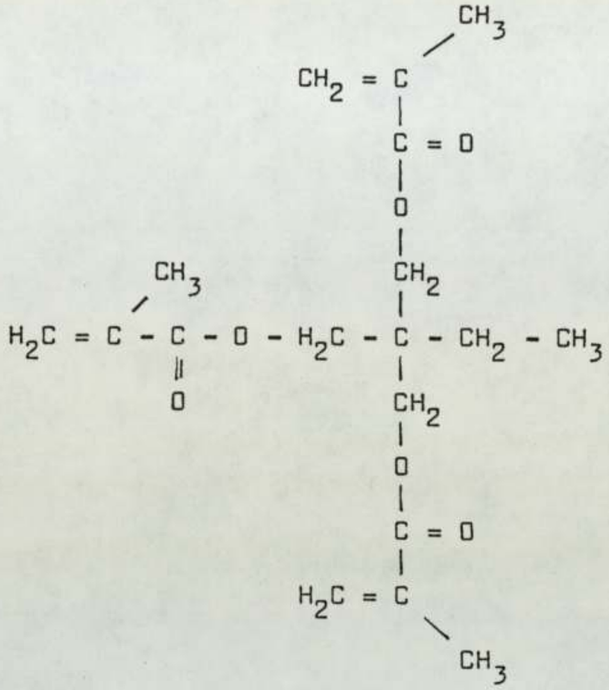

Key
Cross-linking Agent
○ Methylene bis acrylamide
+ Ethylene di methacrylate
X 1,1,1, trimethylol propane trimethacrylate
80
70
60
50
40
% Water Content
0
1
2
3
Concentration of cross-linking agent (Mole %)

FIGURE V.d



1,1,1 trimethylol propane trimethacrylate

agent was increased. This would suggest that a different distribution of methylene bis acrylamide units takes place within the 25:75 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate compared to that with the more complicated network used by Patel[82], in which a less severe depression of water content was observed.

The results for the water contents of hydrogels cross-linked by ethylene glycol dimethacrylate show a similar trend to those obtained for the more complex polymers containing the same cross-linking agent. It may therefore be assumed that analogous distributions of ethylene glycol dimethacrylate within each network have occurred in both cases.

The behaviour of the trimethacrylate cross-linking agent is quite interesting in that, at low concentrations, it is of intermediate hydrophilicity, between methylene bis acrylamide and ethylene glycol dimethacrylate. As the concentration is increased however, a rapid linear decrease in water content is observed and gels containing more than 1.7 mole% of trimethylol propane trimethacrylate are found to have a lower water content than those containing the same amount of ethylene glycol dimethacrylate. This behaviour is to be expected since the trimethacrylate derivative will produce a copolymer containing 3-dimensional cross-links as opposed to linear cross-link formation in the other cases. The actual number of cross-links occurring within the copolymer network will therefore be expected to increase at a greater rate for those hydrogels cross-linked by the trimethacrylate. Thus a rapid depression in water content is observed as the molar percentage of 1,1,1 trimethylol propane trimethacrylate is increased.

V.3i DETERMINATION OF THE CROSS-LINK DENSITY OF HYDROGELS

Ng has described a method by which the cross-link density of a hydrogel polymer may be calculated, using the Monk and Wright microindentor.[40] The equations employed to determine the cross-link density from microindentation measurements may be shown to be consistent with the Mooney, Rivlin, Saunders equation, for rubber vulcanisates, by using a number of accepted approximations. The Mooney, Rivlin, Saunders equation[84,85] which enables the calculation of cross-link density (via the elastic constant C_1) from tensile stress-strain measurements is shown in Equation V.1 -

$$f = 2Ao\ (\lambda - \lambda^{-2})(C_1 + \lambda^{-1} C_2) \qquad \ldots V.1$$

f = Applied force

Ao = Area of sample

λ = Extension ratio

C_1, C_2 = Elastic constants

For highly swollen networks, the elastic constant C_2 approaches zero[86] and the Mooney, Rivlin, Saunders equation may therefore be re-written as shown in Equation V.2

$$f = 2Ao(\lambda - \lambda^{-2})C_1\, Vr^{-\frac{1}{3}} \qquad \text{...V.2}$$

Vr = Volume fraction of polymer in swollen gel

The elastic constant C_1 may be used to determine the physically manifested intercross-link molecular weight (Mcphys) from the relationship given in Equation V.3

$$2C_1 = \frac{.RT}{\text{Mcphys}} \qquad \text{...V.3}$$

R = Gas constant

T = Temperature (^{o}K)

The determination of C_1 from tensile stress-strain experiments presents several complications when applied to hydrogels and the compression modulus approach as described by Cluff, Glading and Pariser[87] has been adopted. It can be shown that the extension ratio term in Equation V.2 can be replaced as shown in Equation V.4

$$(\lambda - \lambda^{-2}) = \frac{3\Delta h}{hs} \qquad \text{...V.4}$$

Δh = Compressional deformation (indentation) produced by force f

hs = Initial height (thickness) of swollen sample

It should be noted that this relationship only holds for small deformations. If this expression is now substituted into Equation V.2, a means of calculating C_1 (and therefore Mcphys) can be obtained from Equation V.5

$$\frac{f}{\Delta h} = 2C_1 \frac{3Ao\ Vr^{-\frac{1}{3}}}{hs} \qquad \ldots V.5$$

A plot of force against indentation should therefore produce a straight line and enable C_1 to be determined from the gradient.

The microindentation technique employed in this work involved measuring the deformation produced by a flat-ended cylindrical indentor of 0.126 cm diameter at various loads. The area of the sample undergoing deformation, Ao, is therefore constant in each case and is equal to 1.25×10^{-2} cm^2 ($\pi d^2/4$). As stated previously this treatment is only valid for highly swollen networks, with $Vr \leq 0.3$. It was therefore necessary to swell all the hydrogels used in this work in a polar solvent such as dimethyl formamide. The value of Vr[41] in each case was calculated from the relationship shown in Equation V.6

$$Vr = \frac{W_1\ D_2}{W_2\ D_1} \qquad \ldots V.6$$

W_1 = Weight of dehydrated polymer
D_1 = Density of dehydrated polymer
W_2 = Weight of gel swollen in dimethyl formamide
D_2 = Density of gel swollen in dimethyl formamide

The respective densities were determined by using a Davenport density gradient column.

It should be remembered that this treatment is based upon the approximate relation given in Equation V.4, however an exact equation may be derived and is written in terms of parameters suitable for the microindentation technique in Equation V.7[88,89]

$$C_1 = \frac{f\ Vr^{\frac{1}{3}}}{2Ao} \left[\frac{hs^3 - 2hs^2\Delta h + hs\,\Delta h^2}{3hs\,\Delta h^2 - 3hs^2\Delta h - \Delta h^3}\right] \qquad \ldots V.7$$

A study by Melley and Stuckey[90], with natural rubber cross-linked by dicumyl peroxide, has shown that little discernable difference in the values of C_1 computed using both equations V.5 and V.7 can be detected for small deformations.

If Equations V.5 and V.3 are used to determine the values of C_1 and Mcphys respectively, a measure of the cross-link density of a hydrogel network may be found from Equation V.8

$$\nu = \frac{1}{2\ \text{Mcphys}} \qquad \text{...V.8}$$

Since the value of Mcphys will be affected by the number of chain entanglements within the network, the values of the 'cross-link densities' calculated in this work will be greater than the true value. Since each of the determinations carried out during the course of this work involved only those polymers prepared from the composition acrylamide (33 mole%), N-vinyl pyrrolidone (47 mole%), 2-hydroxy propyl acrylate (10 mole%) and styrene (10 mole%), a reasonable comparison of the efficiency of each cross-linking agent may be attained.

V.3ii VARIATION OF HYDROGEL PROPERTIES WITH MEASURED CROSS-LINK DENSITY

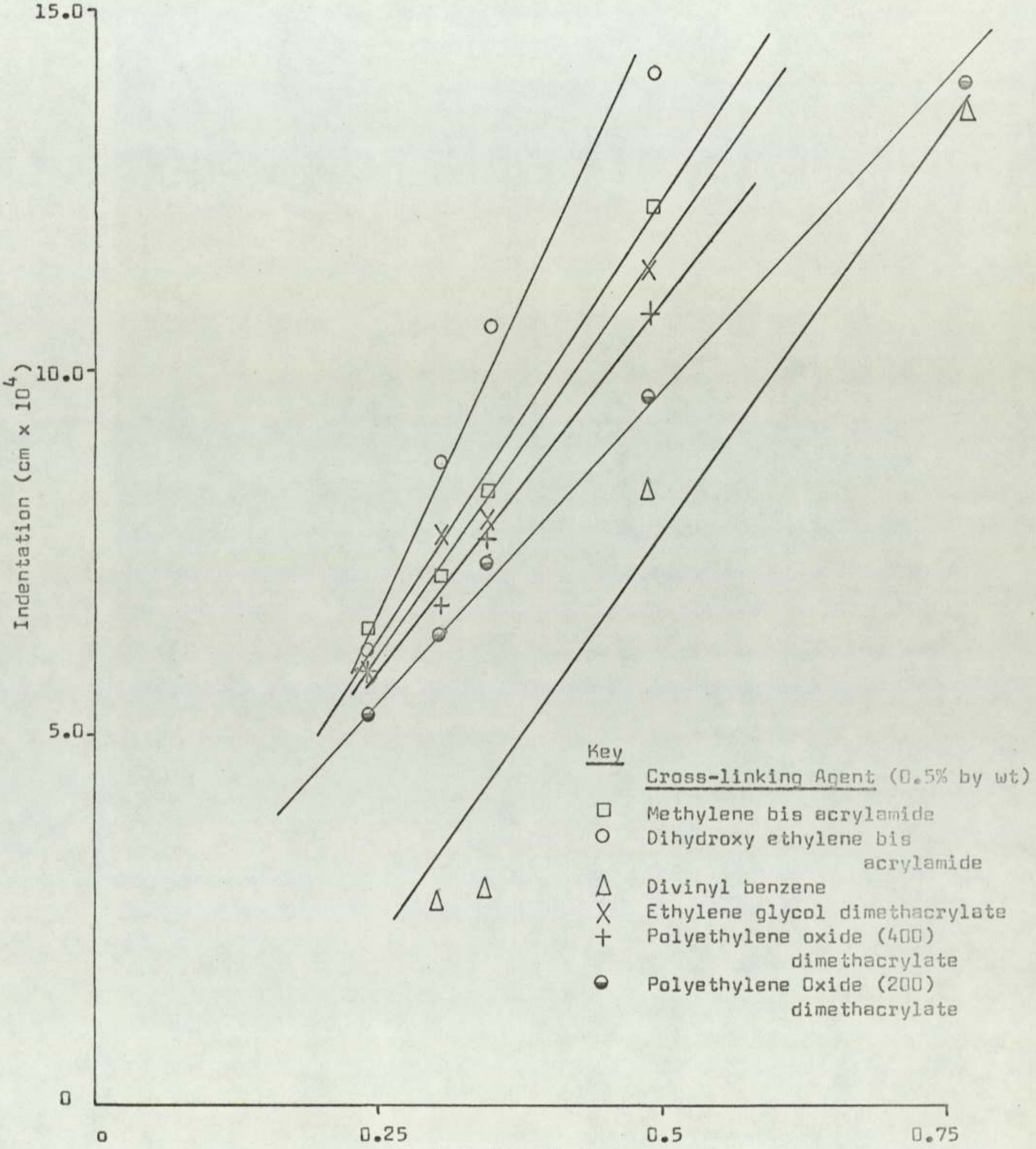
The indentations produced by a flat ended indentor (0.126 cm diameter) with various loads on hydrogels swollen in dimethyl formamide were measured and the results are shown in Table V.D. Those hydrogels tested contained either 0.5% by weight or 5.0% by weight of the cross-linking agents listed in Table V.B. From the results in Table V.D, plots of load against indentation may be made and these are shown in Graphs V.3 and V.4 for the 0.5% by weight and the 5.0% by weight concentrations respectively.

TABLE V.D

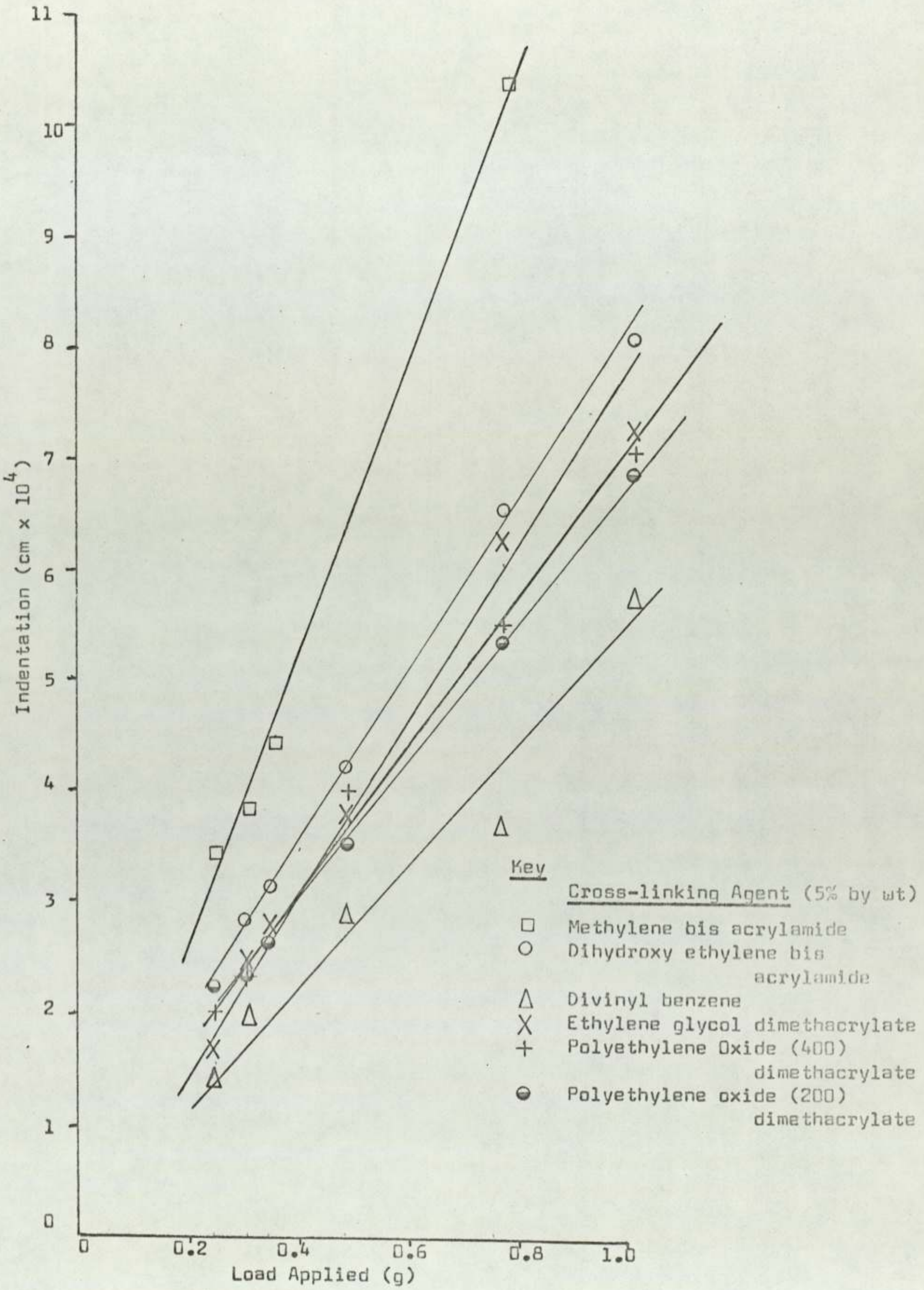
MICROINDENTATION RESULTS FOR THE COPOLYMER ACM33 NVP47 HPA10 St10 WITH VARYING AMOUNTS OF DIFFERENT CROSS-LINKING AGENTS

Cross-Linking Agent	% By Weight	Mole %	Indentation (μ) at Various Loads (g)						
			0.24	0.3	0.34	0.48	0.75	1.0	2.0
EDMA	0.5	0.28	5.9	7.8	8.0	11.45	-	-	-
EDMA	5.0	2.78	1.7	2.5	2.8	3.8	6.3	7.3	-
PEO(200)DMA	0.5	0.16	5.4	6.5	7.5	9.7	13.9	-	-
PEO(200)DMA	5.0	1.55	2.2	2.4	2.6	3.6	6.55	7.0	13.3
PEO(400)DMA	0.5	0.10	5.9	6.8	7.7	10.8	-	-	-
PEO(400)DMA	5.0	0.99	2.0	2.4	-	4.0	5.45	7.1	-
MBACM	0.5	0.36	6.4	7.1	8.35	12.3	-	-	-
MBACM	5.0	3.55	3.5	3.9	4.5	-	10.5	-	-
DHEBACM	0.5	0.27	6.2	8.7	10.7	14.2	-	-	-
DHEBACM	5.0	2.75	2.2	2.8	3.1	4.2	6.1	8.1	-
DVB	0.5	0.42	-	2.9	3.1	8.5	13.8	-	-
DVB	5.0	4.23	1.6	2.1	-	3.0	3.8	5.9	11.2

Graph V.3


15.0
10.0
5.0
0
Indentation (cm x 10^4)
o
0.25
0.5
0.75
Load Applied (g)
Key
Cross-linking Agent (0.5% by wt)
□ Methylene bis acrylamide
○ Dihydroxy ethylene bis acrylamide
△ Divinyl benzene
X Ethylene glycol dimethacrylate
+ Polyethylene oxide (400) dimethacrylate
◒ Polyethylene Oxide (200) dimethacrylate

Graph V.4



11
10
9
8
7
6
5
4
3
2
1
0
Indentation (cm x 10^4)
0
0.2
0.4
0.6
0.8
1.0
Load Applied (g)
Key
Cross-linking Agent (5% by wt)
□ Methylene bis acrylamide
○ Dihydroxy ethylene bis acrylamide
△ Divinyl benzene
X Ethylene glycol dimethacrylate
+ Polyethylene Oxide (400) dimethacrylate
● Polyethylene oxide (200) dimethacrylate

From the slopes determined from graphs V.3 and V.4, values of C_1 (and therefore the cross-link density) may be calculated by the method outlined in the previous section. The actual magnitude of the values obtained for C_1 are in reasonable agreement with those found by Melley and Stuckey[90] for natural rubber cross-linked by dicumyl peroxide, in that they are found to be lower by a factor of approximately 10. This seems acceptable since the errors involved in the determination of C_1 by the micro-indentation technique are probably greater than those experienced when using micro-compression or stress-strain methods for natural rubber. It should also be remembered that the cross-linking of natural rubber by dicumyl peroxide is carried out under different conditions to those employed for the copolymers prepared during this research.

V.3ii(a) VARIATION OF CROSS-LINK DENSITY WITH MOLAR CONCENTRATION OF CROSS-LINKING AGENT

The results for C_1 and the measured cross-link density for the hydrogels studied are shown in Table V.E and are portrayed as a function of the molar percentage of cross-linking agent added in Graph V.5. A high degree of scatter of the points in this graph is apparent. Two possible interpretations of these results are therefore represented by the straight line and curve shown. Both of these alternatives are seen to be subject to large deviations in certain cases and these will be discussed together with the implications of each interpretation.

V.3ii(b) DEVIATIONS AND IMPLICATIONS ARISING FROM THE PROPOSED LINEAR RELATIONSHIP

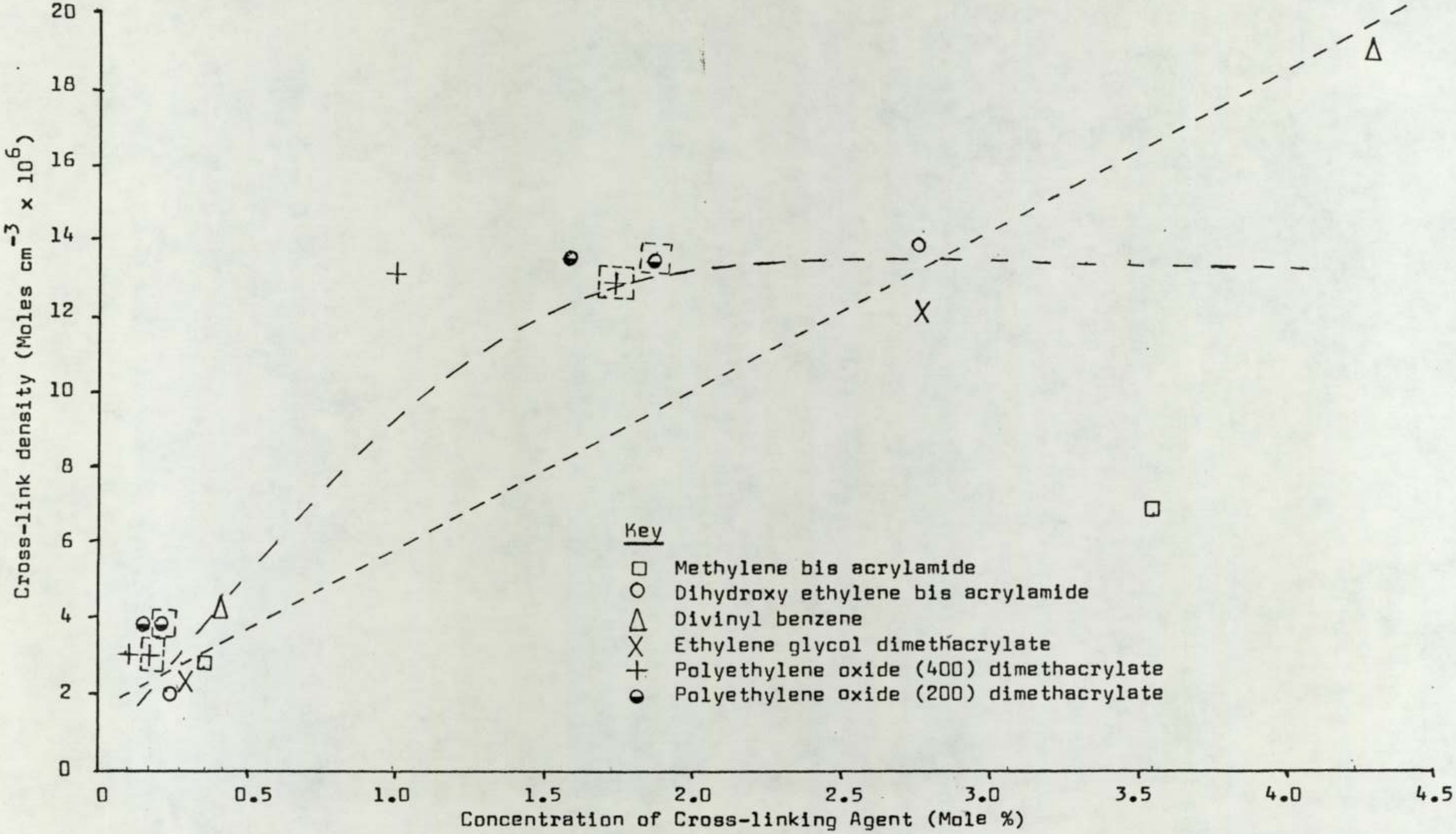
A linear increase in cross-link density with the molar percentage of cross-linking agent added would tend to suggest that the interchain

TABLE V.E

CROSS-LINK DENSITY DETERMINATION FOR COPOLYMERS OF ACM33 NVP47 HPA10 St10 WITH DIFFERENT CROSS-LINKING AGENTS

Cross-Linking Agent	Mole % Added	Slope × 10^{-3} g cm^{-1}	hs × 10^{3} cm	V_R	C_1 g cm^{-2}	Mcphys × 10^{-5} mol^{-1} cm^{3}	ν(CLD) × 10^{6} mol cm^{-3}
EDMA	0.28	0.46	25.4	0.066	63	1.97	2.54
EDMA	2.78	1.22	30.4	0.303	332	0.37	13.37
PEO(200)DMA	0.16 (0.18)	0.63	24.1	0.115	98	1.27	3.94
PEO(200)DMA	1.55 (1.84)	1.62	25.4	0.236	340	0.36	13.69
PEO(400)DMA	0.10 (0.17)	0.52	23.0	0.104	75	1.70	3.02
PEO(400)DMA	0.99 (1.73)	1.26	29.2	0.291	325	0.38	13.09
MBACM	0.36	0.38	25.0	0.120	62.5	1.84	2.72
MBACM	3.55	0.70	26.7	0.277	165	0.75	6.64
DHEBACM	0.27	0.33	25.4	0.139	58	2.14	2.34
DHEBACM	2.75	1.33	29.2	0.319	354	0.35	14.26
DVB	0.42	0.67	26.7	0.073	113.5	1.09	4.57
DVB	4.23	1.74	30.4	0.312	478	0.26	19.25

Graph V.5


Cross-link density (Moles cm^{-3} x 10^{6})
0
2
4
6
8
10
12
14
16
18
20
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
Concentration of Cross-linking Agent (Mole %)
Key
□ Methylene bis acrylamide
○ Dihydroxy ethylene bis acrylamide
△ Divinyl benzene
X Ethylene glycol dimethacrylate
+ Polyethylene oxide (400) dimethacrylate
◒ Polyethylene oxide (200) dimethacrylate

bond linkage formation is very effective throughout the whole concentration range studied. Those hydrogel polymers cross-linked with high concentrations (5% by weight) of methylene bis acrylamide and the polyethylene oxide dimethacrylate derivatives are seen to give rise to the greatest deviations from the linear relationship proposed.

In the case of methylene bis acrylamide an unexpectedly low cross-link density is apparent, which may be attributed to the precipitation of a portion of the solid divinyl cross-linking agent from the co-monomer solution prior to polymerisation. The gels cross-linked by polyethylene oxide dimethacrylate derivatives may be contrasted to those with methylene bis acrylamide in that unusually high cross-link densities are produced. It will be noted however that two sets of points for each concentration of the polyethylene oxide dimethacrylate derivatives has been plotted in Graph V.5 and the reasons for this will be given before the discussion is continued.

A possible explanation of the high cross-link densities produced by the polyethylene oxide dimethacrylate derivatives could be found if both compounds were to be impure and contain substantial amounts of ethylene glycol dimethacrylate. If this were true, the effective molecular weights of both compositions would be considerably reduced and give rise to a large increase in the actual molar concentration of cross-linking agent added. Since this might result in these cross-linking agents being in agreement with the proposed linear relationship, samples of both were provided for analysis by gel permeation chromatography. The results of this study are given in Tables V.F and V.G together with the respective chromatograms in Figures V.e and V.f.

TABLE V.F

GPC RESULTS FOR POLYETHYLENE OXIDE (MOLECULAR WEIGHT 200) DIMETHACRYLATE OBTAINED USING STRYRAGEL COLUMNS AND TETRAHYDROFURAN SOLVENT AT A FLOW RATE OF 1 ml/min

Retention Volume Counts	Polymer H Values	D_w/D_v (%) Values	Calibrated* M Values $\times 10^{-3}$	Polymer M Values $\times 10^{-3}$	LogM Values	D_w/DLogM Values
109	0.00	0.00	0.3200	0.2766	2.4434	0.00
110	0.60	0.77	0.2950	0.2573	2.4104	0.54
111	1.30	1.66	0.2730	0.2418	2.3834	1.23
112	4.30	5.48	0.2550	0.2287	2.3592	4.35
113	8.40	10.71	0.2400	0.2187	2.3398	9.13
114	11.70	14.92	0.2280	0.2083	2.3187	13.47
115	11.50	14.67	0.2170	0.1954	2.2909	13.85
116	10.50	13.39	0.2050	0.1904	2.2796	13.56
117	10.70	13.65	0.1970	0.1823	2.2607	14.52
118	8.70	11.10	0.1890	0.1742	2.2409	12.43
119	4.20	5.36	0.1810	0.1679	2.2250	6.23
120	2.00	2.55	0.1740	0.1626	2.2112	3.15
121	1.80	2.30	0.1680	0.1574	2.1894	2.90
122	1.60	2.04	0.1610	0.1495	2.1746	2.71
123	0.80	1.02	0.1550	0.1434	2.1565	1.39
124	0.30	0.38	0.1490	0.1373	2.1377	0.54
125	0.00	0.00	0.1430	0.1332	2.1244	0.00

* This calibration was derived from polystyrene standards using values of Mark-Houwink constants of $K = 1.2 \times 10^{-4}$ $\alpha = 0.71$ for polyethylene oxide (200) dimethacrylate. This is an obvious source of error since chains of polystyrene will coil in a different manner to polyethylene oxide. A more precise interpretation of the chromatogram is therefore given in the text.

TABLE V.G

GPC RESULTS FOR POLYETHYLENE OXIDE (MOLECULAR WEIGHT 400) DIMETHACRYLATE OBTAINED USING STYRAGEL COLUMNS AND TETRAHYDROFURAN SOLVENT AT A FLOW RATE OF 1 ml/min

Retention Volume Counts	Polymer H Values	D_w/D_v (%) Values	Calibrated* M Values × 10^{-3}	Polymer M Values × 10^{-3}	LogM Values	D_w/DLogM Values
103	0.00	0.00	0.6300	0.5109	2.7083	0.00
104	0.20	0.23	0.5550	0.4432	2.6465	0.10
105	0.30	0.35	0.4850	0.3960	2.5976	0.17
106	0.40	0.46	0.4300	0.3563	2.5518	0.24
107	0.50	0.58	0.3850	0.3296	2.5144	0.33
108	0.50	0.58	0.3500	0.2997	2.4766	0.36
109	0.50	0.58	0.3200	0.2776	2.4434	0.38
110	0.50	0.58	0.2950	0.2573	2.4104	0.43
111	1.30	1.50	0.2730	0.2418	2.3834	1.18
112	4.90	5.67	0.2550	0.2287	2.3592	4.76
113	11.60	13.43	0.2400	0.2187	2.3398	12.13
114	18.90	21.88	0.2280	0.2083	2.3187	20.91
115	20.00	23.15	0.2170	0.1954	2.2909	23.16
116	12.60	14.58	0.2050	0.1904	2.2796	15.64
117	5.90	6.83	0.1970	0.1823	2.2607	7.70
118	2.90	3.36	0.1890	0.1742	2.2409	3.98
119	1.20	1.39	0.1810	0.1679	2.2250	1.71
120	0.70	0.81	0.1740	0.1626	2.2112	1.06
121	0.70	0.81	0.1680	0.1547	2.1894	1.08
122	1.00	1.16	0.1610	0.1495	2.1746	1.63
123	1.30	1.50	0.1550	0.1434	2.1565	2.17
124	0.50	0.58	0.1490	0.1373	2.1377	0.86
125	0.00	0.00	0.1430	0.1332	2.1244	0.00

* Calibration derived from polystyrene standards, using values for Mark-Houwink constants of $K = 1.2 \times 10^{-4}$ $\alpha = 0.71$ for polyethylene oxide (400) dimethacrylate. This is an obvious source of error since polystyrene chains will coil in a different manner to those of polyethylene oxide. A more precise interpretation of the chromatogram is therefore given in the text.

Figure IV.e Gel Permeation Chromatogram of Polyethylene Oxide (200) Dimethacrylate

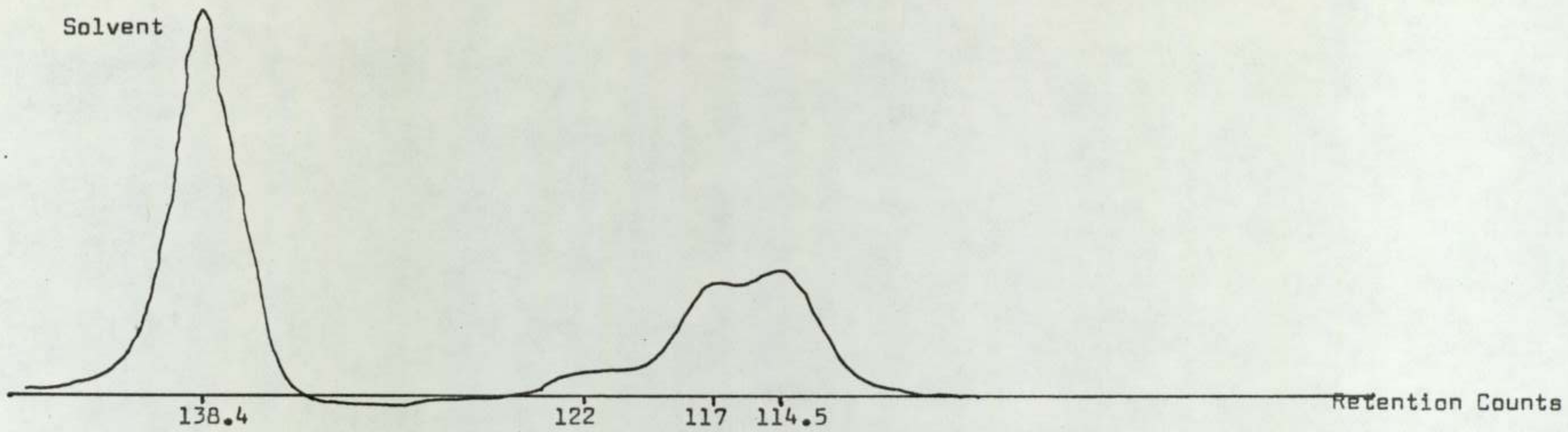
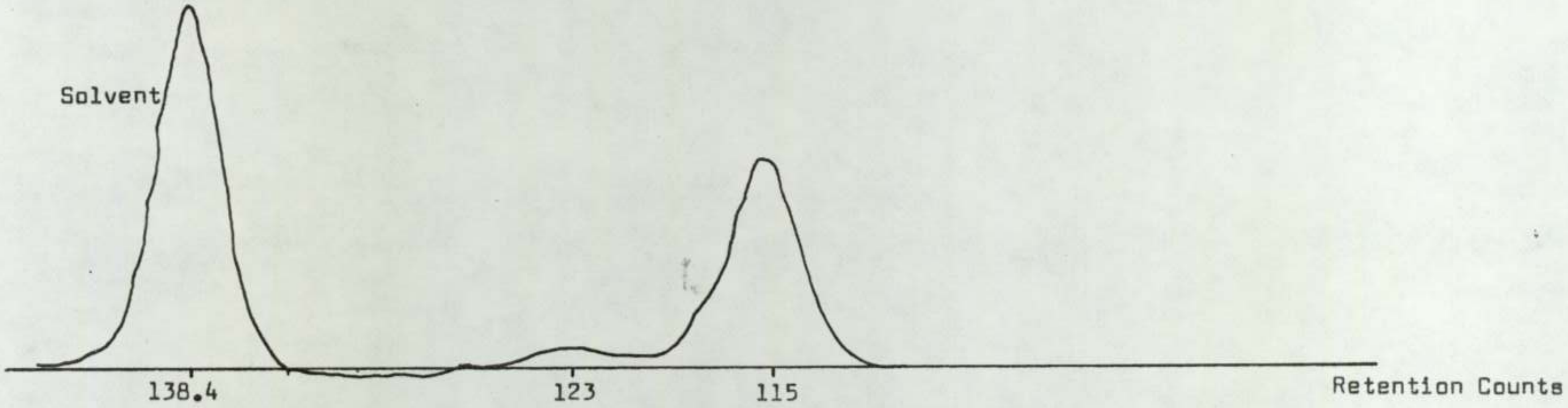


Figure IV.f Gel Permeation Chromatogram of Polyethylene Oxide (400) Dimethacrylate



V.3ii(c) INTERPRETATION OF GEL PERMEATION CHROMATOGRAMS

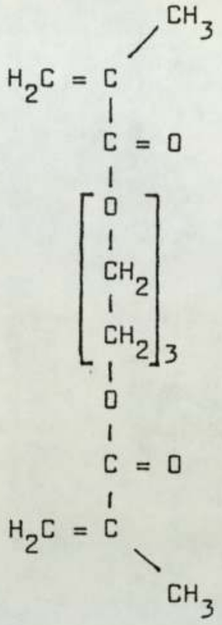
The results from the gel permeation chromatographic study may be interpreted satisfactorily by assuming that the chains of the poly ethylene oxide dimethacrylate derivatives are coiled in the same manner as that of ethylene glycol dimethacrylate and have an almost identical excluded volume.

The chromatogram obtained for poly ethylene oxide (molecular weight = 400) dimethacrylate shows a fairly monodispersive pattern with a small initial peak at a retention volume count of approximately 121 followed by a peak at 115. That for the lower molecular weight derivative also shows an identical small peak at 121 together with a very broad peak which would indicate the presence of two more components in the sample. One of these components has a retention volume count of 114.5, and can therefore be assigned to the same species at 115 in the chromatogram of polyethylene oxide (molecular weight = 400) dimethacrylate, whereas another compound of lower molecular weight gives rise to the peak at 117.

If the small initial peaks in both chromatograms are assigned to the presence of impurities of ethylene glycol dimethacrylate in the samples the remainder of the peaks may be interpreted. The peak at 115 can be shown to correspond to a molecular weight of 286 which is consistent with a dimethacrylate compound having 3 ethylene oxide groups as illustrated by the structure in Figure V.g.

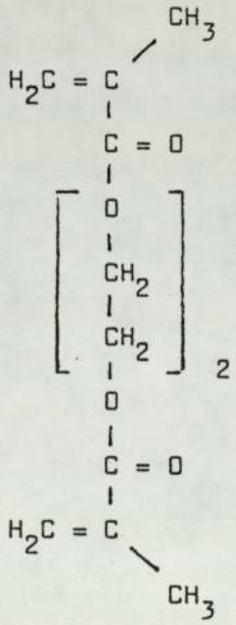
As previously stated this compound is also responsible for the peak at a retention volume count of 114.5 in the second chromatogram. The peak at a retention volume count of 117 in the second chromatogram is consistent with a species of molecular weight 242 which corresponds to a dimethylate having two ethylene oxide units as shown in Figure V.h.

FIGURE V.g



True structure of cross-linking agent supplied as polyethylene oxide (molecular weight = 400) dimethacrylate

FIGURE V.h



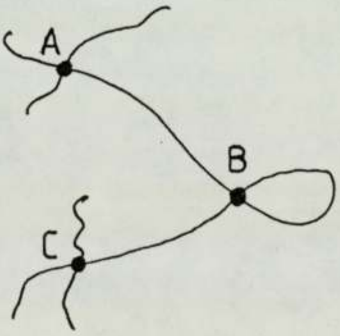
One component of the cross-linking agent supplied as polyethylene oxide (molecular weight = 200) dimethacrylate

The true molecular weight of the cross-linking agent supplied as polyethylene oxide (molecular weight = 400) is therefore 286, since the peak due to ethylene glycol dimethacrylate shows that only small amounts are present. The chromatogram for polyethylene oxide (molecular weight = 200) dimethacrylate shows approximately equal peak areas for both components present which would indicate a 50:50 mixture and an average molecular weight of 264 can therefore be assumed. These molecular weights have been used to calculate the true molar concentrations of the cross-linking agents added and the corrected points are therefore shown in Graph V.5 together with the original ones.

Even when the corrected points for these cross-linking agents are considered, a large deviation from the proposed linear relationship is still apparent. This could possibly be due to the fact that the ethylene oxide dimethacrylate derivatives have a greater inter chain distance between the vinyl cross-linking sites than any of the other cross-linking agents studied. There may therefore be a greater degree of chain entanglements within these networks via the interaction of the poly ethylene oxide groups of the cross-linking agent. While this would be expected to affect the microindentation measurements made, it should also be remembered that in a highly swollen network the polymer chain may extricate itself from chain entanglements.

V.3ii(d) DEVIATIONS AND IMPLICATIONS ARISING FROM THE PROPOSED CURVE

An alternative explanation of the results in Table V.E may therefore be appropriate in the light of the study on the ethylene oxide dimethacrylate derivatives. The curve shown in Graph V.5 could possibly yield a better interpretation of the efficiency of the cross-linking agents studied. As the concentration of added cross-linking agent is increased, the efficiency of the formation of cross-links throughout the network might be expected to decrease due to greater amounts remaining as unreacted residual monomer. The cross-linking agent which shows a very marked deviation from the curve shown in Graph V.5 is divinyl benzene which is known to be the most reactive species used during the course of this research. It would therefore be expected that hydrogels cross-linked with divinyl benzene in high concentrations might produce networks of higher cross-link densities with respect to those copolymers containing cross-linking agents of a lower monomer reactivity ratio. It is also possible that, at high concentrations, certain cross-linking agents form a significant number of intramolecular cross-links,[91] as depicted in Figure V.i -



Intermolecular cross-linking between polymer chains has occurred at sites A and C whereas an intramolecular cross-link is formed at site B which results in a network imperfection.

Since divinyl benzene is of greater reactivity it may be expected to produce cross-linked gels with fewer network imperfections of this type.

V.3ii(e) SWELLING OF HYDROGELS OF HIGH CROSS-LINK DENSITY IN POLAR SOLVENTS

Since both interpretations of the results obtained during this study rely on viable explanations of the behaviour of cross-linking agents at high concentrations, further experimental investigation over a wide concentration range would be appropriate. This was attempted using 25: 75 (mol:mol) copolymers of acrylamide and 2-hydroxy propyl acrylate, cross-linked with various amounts of 1,1,1 trimethylol propane trimethacrylate.

A successful completion of this study proved impossible however, since those copolymers containing large amounts of the trimethacrylate cross-linking agent were found to fracture after a few hours hydration in dimethyl formamide. This phenomena prevented a complete investigation of the cross-link density of these materials, throughout a wide concentration range of added cross-linking agent, and further work on 1,1,1 trimethylol propane trimethacrylate was therefore abandoned. It is however, quite interesting to speculate upon the mechanism by which the breakdown of these gels in dimethyl formamide occurs. When a polymer consisting of a cross-linked network structure is placed in a solvent, absorption of the fluid occurs and the polymer swells rather than becoming dissolved. As the solvent is absorbed, portions of the polymer chains between cross-linking sites will be compelled to assume increasingly elongated configurations which will produce an elastic retractive force in opposition to the swelling process. A state of equilibrium swelling may therefore be attained when these forces are in balance, provided that no chemical interaction takes place between the polymer and the swelling media.[92] In the case of hydrogel networks swollen in very polar solvents, such as dimethyl formamide, large amounts of fluid will be absorbed. However, when the network contains a large number of cross-linking sites, as might be expected to be provided by a large concentration of trimethacrylate units, a greater elastic retractive force may also be developed. In this case the assertion of both forces, swelling and retractive, may become so great as to cause fragmentation of the polymer before equilibrium swelling can be attained.

V.4i DEPENDENCE OF THE DEFORMATIONAL PROPERTIES OF HYDROGELS ON CROSS-LINK DENSITY

Those polymers which were used in the cross-link density determinations, as outlined in the previous section, were also subjected to mechanical-deformation by using the Monk Wright micro indentor. The experimental method and interpretations employed were identical to that described in Chapter III, with varying loads being applied to a spherical indentor at the surface of a water swollen gel in order to determine the relative rigidity of each polymer.

The results obtained during this study are shown in Table V.H. From this data, the deformational force required to produce an indentation of 2 microns may be calculated by the same method as that described in Chapter III. The results for each copolymer are as shown in Table V.I and are plotted as a function of measured cross-link density and water content in Graphs V.6 and V.7 respectively.

The immediate conclusion to be drawn from the results illustrated in Graphs V.6 and V.7 is that the force required for an indentation of 2 microns rises with cross-link density (and therefore decreasing water content). Since the cross-link density of these hydrogels has been shown, from Graph V.1, to determine the water content and therefore the plasticising level within these copolymers, it is difficult to determine the separate contributions of each variable on the deformational properties of hydrogels.

It may be thought that the cross-link density is only instrumental in affecting the rigidity of hydrogels by altering the effect of the water content as a plasticiser. This is seen not to be the case however, since examination of Graph V.7 shows that the rigidity of hydrogels cross-linked by a high concentration of the bis acrylamide derivatives is far below that of the copolymer containing a mixture of triethylene

TABLE V.H

MICROINDENTATION RESULTS FOR THE WATER SWOLLEN HYDROGEL ACM33 NVP47 HPA10 St10 WITH VARYING AMOUNTS OF DIFFERENT CROSS-LINKING AGENTS

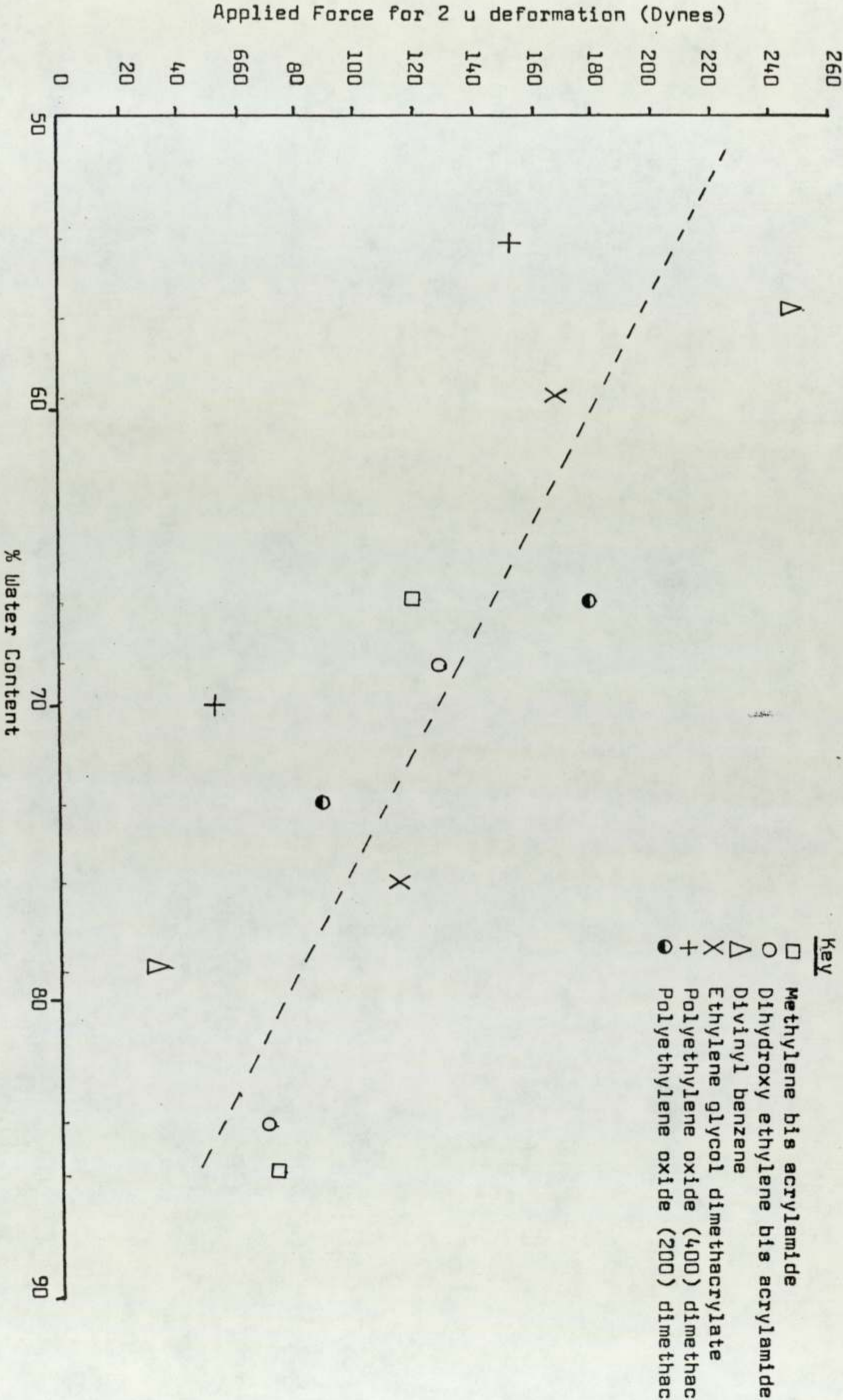
Cross-Linking Agent	% By Weight	Mole %	Indentation (μ) at Various Loads (g)							
			0.14	0.24	0.3	0.34	0.48	0.75	1.0	2.0
EDMA	0.5	0.28	-	4.4	5.0	6.9	10.4	14.2	-	-
EDMA	5.0	2.78	1.95	2.3	-	-	4.4	7.6	10.5	-
PEO(200)DMA	0.5	0.18	-	4.3	6.75	8.35	10.9	14.2	-	-
PEO(200)DMA	5.0	1.84	1.7	2.4	-	-	3.9	6.7	9.05	14.1
PEO(400)DMA	0.5	0.17	-	5.8	7.2	9.8	10.9	14.2	-	-
PEO(400)DMA	5.0	1.73	1.9	2.9	-	3.4	5.4	7.4	-	-
MBACM	0.5	0.36	-	6.5	9.15	9.4	14.2	-	-	-
MBACM	5.0	3.55	-	4.0	5.35	6.7	10.5	14.2	-	-
DHEBACM	0.5	0.27	-	7.0	8.1	9.4	14.0	-	-	-
DHEBACM	5.0	2.75	-	2.9	-	-	5.7	6.7	11.7	13.6
DVB	0.5	0.42	-	7.6	9.4	-	12.8	-	-	-
DVB	5.0	4.23	-	1.95	-	-	3.4	5.0	8.55	13.3

TABLE V.I

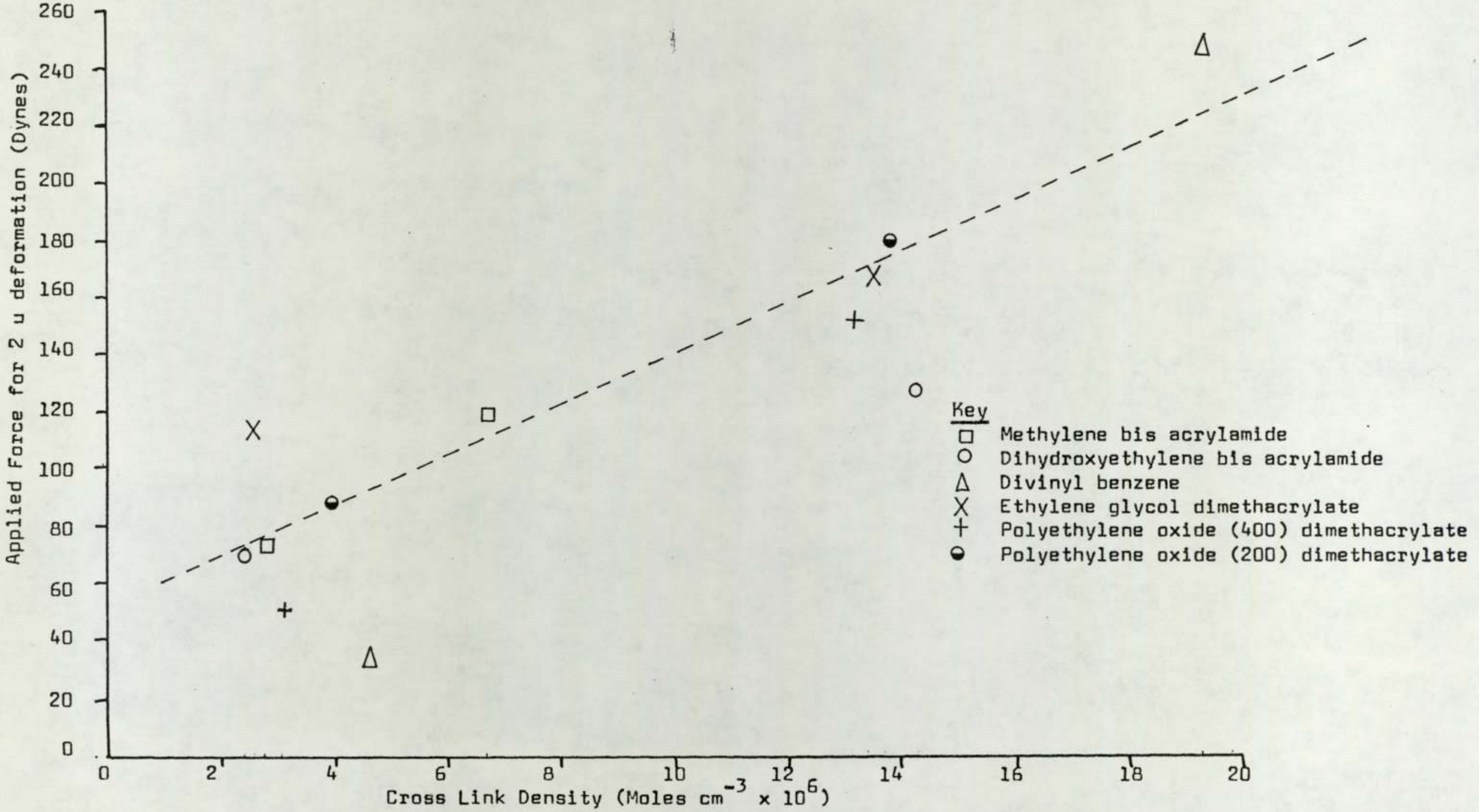
CALCULATION OF THE FORCE REQUIRED FOR AN INDENTATION OF 2 MICRONS IN HYDROGELS CONTAINING VARYING AMOUNTS OF DIFFERENT CROSS-LINKING AGENTS

Cross Linking Agent	Mole %	$\nu \times 10^6$ (CLD) mol cm^{-3}	% Water Content	Slope g/micron	Intercept	Mass (g) for 2 μ Indent^n	Force (Dynes)
EDMA	0.28	2.54	76.3	1.09	-2.06	0.116	114
EDMA	2.78	13.37	59.6	0.89	-3.02	0.172	169
PEO(200)DMA	0.18	3.94	73.4	0.98	-2.68	0.092	90
PEO(200)DMA	1.84	13.69	66.5	0.83	-3.09	0.183	180
PEO(400)DMA	0.17	3.02	69.9	0.75	-2.73	0.052	51
PEO(400)DMA	1.73	13.09	54.2	0.82	-3.03	0.155	152
MBACM	0.36	2.72	85.9	1.09	-2.50	0.079	75
MBACM	3.55	6.64	66.5	1.14	-2.66	0.123	121
DHEBACM	0.27	2.34	84.1	1.02	-2.54	0.073	72
DHEBACM	2.75	14.26	68.7	0.75	-3.04	0.132	129
DVB	0.42	4.57	79.0	0.74	-2.65	0.038	37
DVB	4.23	19.25	56.9	0.94	-3.142	0.256	251

Graph V.6


Applied Force for 2 u deformation (Dynes)
260
240
220
200
180
160
140
120
100
80
660
40
20
0
50
60
70
80
90
% Water Content
Key
□ Methylene bis acrylamide
○ Dihydroxy ethylene bis acrylamide
△ Divinyl benzene
X Ethylene glycol dimethacrylate
+ Polyethylene oxide (400) dimethacrylate
◐ Polyethylene oxide (200) dimethacrylate

Graph V.7


Applied Force for 2 u deformation (Dynes)
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
Cross Link Density (Moles cm^{-3} x 10^{6})
Key
□ Methylene bis acrylamide
○ Dihydroxyethylene bis acrylamide
Δ Divinyl benzene
X Ethylene glycol dimethacrylate
+ Polyethylene oxide (400) dimethacrylate
◒ Polyethylene oxide (200) dimethacrylate

oxide and diethylene oxide dimethacrylate. As each of these hydrogels are of approximately the same water content, the effect of cross-link density on the deformational properties is obviously dependent on the type and distribution of the cross-links throughout the copolymer network. This is seen to be true since the lower rigidity of gels containing methylene bis acrylamide can be attributed to its reduced cross-link density which is caused by precipitation of the cross-linking agent. The same reasoning cannot be applied to the gels cross-linked by dihydroxy ethylene bis acrylamide and the chemical nature of the cross-links formed may therefore be the cause of its lower resistance to deformation with respect to those gels containing dimethacrylate cross-links.

Having established that the type and distribution of cross-linking agents throughout the network will be expected to have a pronounced effect on the deformational properties of hydrogels, it seems worthwhile to divide the discussion of the results obtained according to the nature of the cross-linking agent.

V.4ii(a) HYDROGELS CROSS-LINKED BY DIVINYL BENZENE

The results for networks containing divinyl benzene are interesting in that at the lower cross-linking agent concentration a gel having the least resistance to 2 microns indentation is produced. At the higher concentration however, the rigidity of the network formed is greater than any of the other compositions studied. While this may appear to be an anomalous result, it should be remembered that gels cross-linked by a high concentration of divinyl benzene were found to have the greatest cross-link density of all the copolymers studied. It must therefore be assumed that the greater number of cross-links formed gives rise to the increased rigidity, although from the result at the lower concentration, divinyl benzene is seen to be ineffective in reinforcing the strength of hydrogels.

V.4ii(b) HYDROGELS CROSS-LINKED BY BIS ACRYLAMIDE DERIVATIVES

Examination of the variance of the resistance to 2 microns deformation as a function of water content shown in Graph V.7 reveals that the results for both bis acrylamide derivatives are almost identical for each concentration studied. At the lower concentration this is as expected since the hydrogel networks produced are seen (from Table V.I) to have similar cross-link densities and water contents. The results at the higher concentration however are somewhat surprising, since the network cross-linked by dihydroxy ethylene bis acrylamide has a significantly greater cross-link density than that supplied by methylene bis acrylamide. It may therefore be that the water content of these hydrogels cross-linked by the bis acrylamide derivatives is the controlling factor in determining the deformational properties of the polymer. This behaviour is in marked contrast to that thought responsible for the large difference in rigidity between gels containing bis acrylamide derivatives and dimethacrylate derivatives as cross-linking agents. Another explanation may therefore be appropriate, and it is possible that dihydroxy ethylene bis acrylamide is simply far less effective than methylene bis acrylamide in increasing the rigidity of hydrogels at higher cross-link densities.

V.4ii(c) HYDROGELS CROSS-LINKED BY DIMETHACRYLATE DERIVATIVES

The results for the dimethacrylate cross-linking agents are generally higher in rigidity than those for hydrogels cross-linked by the bis acrylamide derivatives. At the lower cross-linking agent concentration this may be attributed to the lower water contents of gels containing the dimethacrylate derivatives, since it is seen from Graph V.6 that all the materials have similar cross-link densities. It is interesting to note however that the cross-linking agent found to consist of triethylene oxide dimethacrylate is a notable exception, in that it has a low resistance to 2 microns indentation despite having a water content which is less than any of the other copolymers of comparable cross-link density. Since the cross-linking agent supplied as poly ethylene oxide (mol wt = 200) dimethacrylate has been identified as a mixture of triethylene oxide dimethacrylate and diethylene oxide dimethacrylate, it is seen from Graph V.7 that the diethylene oxide dimethacrylate component is responsible for the increased rigidity with respect to gels containing triethylene oxide dimethacrylate only. This trend is also observed at the higher cross-linking agent concentration with the rigidity of gels containing diethylene oxide dimethacrylate even having a greater rigidity than those cross-linked by ethylene glycol dimethacrylate. This behaviour would lend support to the observation made for the bis acrylamide derivatives, that only small changes in the chemical structure of the cross-linking agent may produce notable differences in the rigidity of the resulting hydrogel network.

V.4iii DISCUSSION OF RIGIDITY IN RELATION TO REQUIREMENTS FOR A CONTINUOUS WEAR CONTACT LENS MATERIAL

From the results obtained during this study it is seen that while the increase of cross-link density within a hydrogel network may benefit the mechanical properties somewhat, it will also give rise to a drastic decrease in water content. If the values for the force required to produce an indentation of 2 microns obtained during this study are compared to those for the more simple acrylamide based copolymers given in Chapter 3 a quite marked difference is observed. The rigidities of the copolymers containing acrylamide derivatives are seen to be far greater than those found for the more complicated composition used during the study on cross-linking agents. This may be attributed to the lower water contents of the more simple copolymers which would obviously have a lesser plasticising effect on the network giving rise to greater rigidity. One exception to this explanation however is the 33:67 (mol:mol) copolymer of acrylamide and 2-hydroxy propyl acrylate which has both a high water content (71.3%) and a high resistance to 2 microns indentation. As stated in Chapter III, this may be attributed to hydrogen bonding between amide units of acrylamide and the carbonyl and hydroxyl groups of 2-hydroxy propyl acrylate. Since all these groups are present within the copolymer composition used in this study it may appear strange that such a great difference in rigidity has resulted. It should be remembered however that the presence of N-vinyl pyrrolidone and styrene units within the chain structure may cause hindrance to hydrogen bond formation. This is expected to be significantly lower anyway, due to only 10 mole% of 2-hydroxy propyl acrylate being included in the copolymer composition used in this work. This explanation is supported by the results of lathe cutting trials carried out in the research department of Kelvin Lenses Limited.[93] While samples of the 4 component composition used in the cross-linking agent study were deemed to be of insufficient strength as a continuous wear lens material, lenses cut from the copolymer of acrylamide and 2-hydroxy propyl acrylate proved acceptable in terms of cutting, polishing and strength.

As the use of the acrylamide-2-hydroxy propyl acrylate copolymer is unacceptable for a continuous wear contact lens material because of the reasons given in Chapter IV, a means of reinforcing a weaker composition must be found. Since the results in Table V.I and Graphs V.6 and V.7 indicate that, at a cross-link density which will yield a water content which is appropriate for continuous wear, ethylene glycol dimethacrylate gives the best deformational properties, it was adopted as the cross-linking agent to be used in all further research.

Despite this the results indicate that a monomer capable of strong hydrogen bond formation, such as methacrylic acid, should also be included in any composition for potential continual wear applications to give the material an acceptable degree of strength. There will therefore be a need for further modification of the polymer in an attempt to limit the interaction between methacrylic acid groups and residual N-vinyl pyrrolidone which caused the problems of stability outlined in Chapter IV. This will be dealt with in the following chapter.

CHAPTER SIX

CHAPTER VI

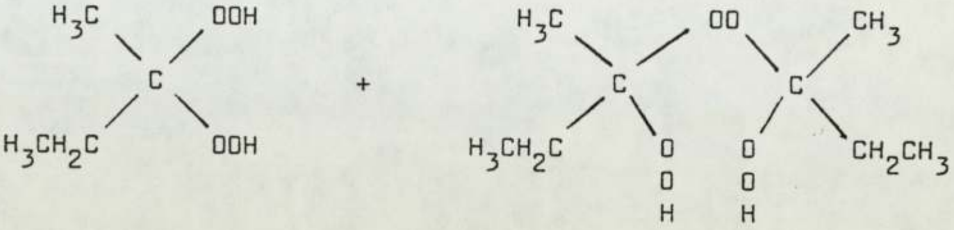
EFFECTS OF POLYMERISATION CONDITIONS ON THE PROPERTIES OF HYDROGELS RELEVANT TO THE PRODUCTION OF A LATHE-CUT CONTINUOUS WEAR CONTACT LENS

VI.1 INTRODUCTION

From the experimental evidence produced in Chapter IV, it was concluded that a high water content hydrogel of satisfactory stability might only be achieved by the elimination, or severe restriction, of the interaction between methacrylic acid groups and residual N-vinyl pyrrolidone monomer. In the preceeding chapter however, it was noted that a hydrogel having sufficient strength at high water contents could not be attained without the introduction of a higher degree of interchain hydrogen bonding, via the inclusion of a number of methacrylic acid units within the polymer network. It is therefore desirable to incorporate as much N-vinyl pyrrolidone as possible in the chain structure, in order to limit the complex formation with methacrylic acid, which gives rise to poor stability.

A semi-empirical study of the effect of the polymerisation conditions on the relevant properties of the polymers produced has therefore been undertaken. It should be stressed that the theory and mechanisms of the thermally initiated free-radical polymerisation of vinyl monomers are widely known and documented.[92,94,95] This discussion will therefore be limited to a survey of the differing effects of the polymerisation conditions on the water content, the residual fraction extractable by water and the optical clarity of the polymer rods produced.

The polymerisations studied were initiated by methyl ethyl ketone peroxide, which is supplied as a mixture of various structures, as illustrated in Figure VI.a -



+ other more complex structures

Figure VI. Structure of methyl ethyl ketone peroxide

The use of methyl ethyl ketone peroxide as an initiator to produce polymers intended for biomedical applications may seem somewhat surprising, as it is generally used in conjunction with transition metal ions (such as cobalt) to activate fast polyester resin cures at room temperature.[95] The production of free radicals for this initiation scheme is via the reaction of the hydroperoxide groups with the cobalt promoter, as illustrated in Figures VI.b and VI.c -

$$ROOH + Co^{2+} \longrightarrow RO^{\bullet} + \bar{O}H + Co^{3+}$$ Figure VI.b

$$ROOH + Co^{3+} \longrightarrow ROO^{\bullet} + H^{+} + Co^{2+}$$ Figure VI.c

It should be noted that the cationic promoter used may also react with the free radicals generated and thus inhibit polymerisation, as shown in Figure VI.d -

$$RO + Co^{2+} \longrightarrow RO^{-} + Co^{3+}$$ Figure VI.d

As the polymers produced in this study were initiated solely by a thermal process, with no addition of a transition metal ion promoter, the use of methyl ethyl ketone peroxide as a suitable initiator for these materials may be questionable. It must be remembered however, that methyl ethyl ketone peroxide was employed for producing polymer rods suitable for manufacture into lathe-cut contact lens prior to the commencement of this research project. In addition to this a recent survey of the toxicological characteristics of contact lenses manufactured from rods prepared using methyl ethyl ketone peroxide has shown the material to be acceptable for continuous wear.[97] This would suggest that any residual initiator or monomers remaining after polymerisation that are toxicologically active species may be easily extracted by a facile hydration procedure.

While this would justify the study undertaken, further experimentation into the production of polymer rods, using initiators more usually associated with materials for biomedical applications, has continued. To this end the results obtained from a pilot production scheme carried out at Kelvin Lenses research laboratories, with various initiators are also included and are used to suggest whether optimal conditions for the preparation of polymer rods are of use.

VI.2 INVESTIGATION OF THE EFFECTS OF VARYING POLYMERISATION CONDITIONS ON POLYMER PROPERTIES

A series of polymer rods were prepared from the monomeric composition: acrylamide (41.4 mol%), N-vinyl pyrrolidone (29.9 mol%), 2-hydroxy propyl acrylate (12.5 mol%), methacrylic acid (3.7 mol%). This formulation being identical to that used during the earlier stability studies, as outlined in Chapter IV. The polymerisations were carried out using a range of initiator concentrations, from 0.5% to 3.0% by weight of the total monomeric composition, at temperatures of 40°C, 50°C and 60°C for varying cure times. Upon completion of polymerisation, sections of each rod were taken and subjected to a postcure of one hour at temperatures of 80°C, 90°C and 100°C respectively while one portion was retained without further postcuring. A survey of the optical clarity of each sample prepared was carried out while water content and residual fraction determinations were performed using thin polished discs, cut from each section of the polymer rods. The results of these studies are shown in Tables VI.A to VI.L. In order to facilitate the discussion of these results, the effect of varying polymerisation conditions on the properties of unpostcured materials will be considered before making comparisons with those subjected to a postcure.

VI.3i EFFECT OF POLYMERISATION CONDITIONS ON THE WATER CONTENT OF POLYMERS PREPARED WITHOUT POSTCURE

Ng[40] has reported that variations in the conditions under which 2-hydroxy ethyl methacrylate is polymerised have produced hydrogels of differing water contents. Polymers prepared at higher initiator concentrations for shorter periods were recognised as having elevated water contents due to the presence of more chain ends facilitating the swelling process of the hydrogel. It is therefore to be expected that the molecular weight distribution and average chain length of the polymers produced during this study will be responsible for variations in the water contents of these hydrogels.

Due to the interaction between methacrylic acid groups and residual N-vinyl pyrrolidone monomer the stability of the materials studied may be sufficiently variable to produce results which mask the effects of differing initiation conditions. In order to minimise the effects of stability on water content each determination was carried out after a hydration time of 1 month precisely.

In order to present a more appropriate discussion, the effect of varying each of the three facets of the polymerisation conditions (ie initiator concentration, temperature of polymerisation and time of polymerisation) on the water content will be considered separately.

VI.3ii EFFECT OF INITIATOR CONCENTRATION ON WATER CONTENT

As the initiator concentration within a co-monomer composition is increased, a higher number of free radicals may be expected to be produced giving rise to the formation of more growing chain radicals. An increase in the number of growing chain radicals will also shorten the time of propagation during the polymerisation process, since the rate of termination will also be increased by the chain radicals having a greater probability of undergoing recombination or disproportionation via chain transfer of a hydrogen atom.

The water contents of hydrogels prepared using higher concentrations of methyl ethyl ketone peroxide would therefore be expected to be greater than those for materials with a lower initiator content, due to the presence of a higher number of shorter chains. The results shown in Tables VI.A to VI.C would generally lend support to this hypothesis, although certain anomalies are seen to occur in some cases. This is illustrated by the water content-initiator concentration profile shown in Graph VI.1. The results for polymers prepared at 50°C are seen to rise to a peak with no appreciable difference in water content arising from an increase of 2% to 3% by weight in initiator concentration. This behaviour may be attributed to the tendency of hydroperoxide and peroxide initiators to undergo decomposition in part by a self-induced radical chain process.[97] This involves the radicals released upon thermal decomposition of the initiator reacting with other initiator molecules

TABLE VI.A

EFFECT OF VARYING POLYMERISATION CONDITIONS ON POLYMER PROPERTIES OF RODS PREPARED AT 40°C

Time of Polymerisation	Optical Clarity	% Water Content	% Residuals
Initiator Content = 0.5% by Weight			
7 Days	Pale Yellow	57.2	32.4
10 Days	Pale Yellow	59.3	31.0
14 Days	Pale Yellow	68.6	29.4
Initiator Content = 1.0% by Weight			
3 Days	Clear	60.1	30.6
7 Days	Clear	60.9	30.0
14 Days	Pale Yellow	60.4	31.3
21 Days	Pale Yellow	61.3	29.1
Initiator Content = 2.0% by Weight			
1 Day	Clear	63.3	32.3
7 Days	Clear	64.6	31.1
10 Days	Clear	61.7	31.8
Initiator Content = 3.0% by Weight			
1 Day	Clear	67.2	36.0
7 Days	Clear	68.7	36.0
10 Days	Clear	65.4	33.9

TABLE VI.8

EFFECT OF VARYING POLYMERISATION CONDITIONS ON POLYMER PROPERTIES OF RODS PREPARED AT 50°C

Time of Polymerisation	Optical Clarity	% Water Content	% Residuals
Initiator Content = 0.5% by Weight			
5 Days	Clear	61.3	28.8
7 Days	Clear	61.2	29.0
10 Days	Pale Yellow	61.3	28.4
14 Days	Pale Yellow	62.2	28.6
Initiator Content = 1.0% by Weight			
3 Days	Clear	61.1	29.0
5 Days	Clear	61.9	28.6
7 Days	Clear	61.7	28.1
10 Days	Clear	62.2	28.0
14 Days	Pale Yellow	62.5	26.8
Initiator Content = 2.0% by Weight			
3 Days	Clear	65.5	31.3
5 Days	Clear	65.2	30.8
7 Days	Clear	65.5	31.0
10 Days	Clear	66.0	29.3
Initiator Content = 3.0% by Weight			
3 Days	Clear	64.7	33.6
5 Days	Clear	65.4	33.2
7 Days	Clear	65.3	33.0
10 Days	Clear	65.0	32.4
14 Days	Pale Yellow	65.6	30.9

TABLE VI.C

EFFECT OF VARYING POLYMERISATION CONDITIONS ON POLYMER PROPERTIES OF RODS PREPARED AT 60°C

Time of Polymerisation	Optical Clarity	% Water Content	% Residuals
Initiator Content = 0.5% by Weight			
7 Days	Pale Yellow	63.3	27.8
14 Days	Yellow	63.3	27.5
21 Days	Dark Yellow	63.5	27.3
Initiator Content = 1.0% by Weight			
7 Days	Clear	64.1	28.8
14 Days	Pale Yellow	64.4	28.7
21 Days	Pale Yellow	64.4	28.6
Initiator Content = 2.0% by Weight			
3 Days	Clear	65.1	30.9
10 Days	Pale Yellow	65.2	30.3
14 Days	Yellow	65.4	30.0
Initiator Content = 3.0% by Weight			
3 Days	Clear	67.1	34.3
10 Days	Pale Yellow	66.9	33.7
14 Days	Pale Yellow	67.9	33.2

to combine with one portion of the species and simultaneously release another radical. The overall result is the net loss of an initiator molecule although the number of free radicals for initiation remains unchanged.

At high initiator concentrations this process of self-induced initiator decomposition (illustrated in Figure VI.e) can be expected to be appreciable and give rise to gel formation at an effectively lower initiator concentration.

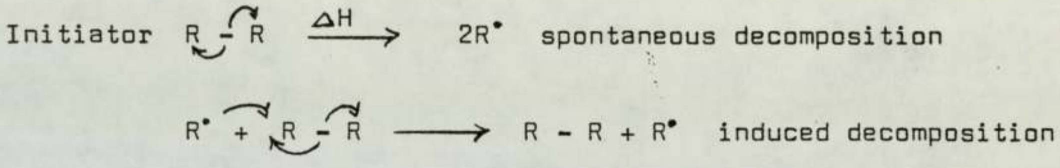


Figure VI.e

The results would suggest that for polymerisation with a 3% initiator concentration at 50°C, the reaction proceeds via induced decomposition and is completed before all the initiator is consumed.

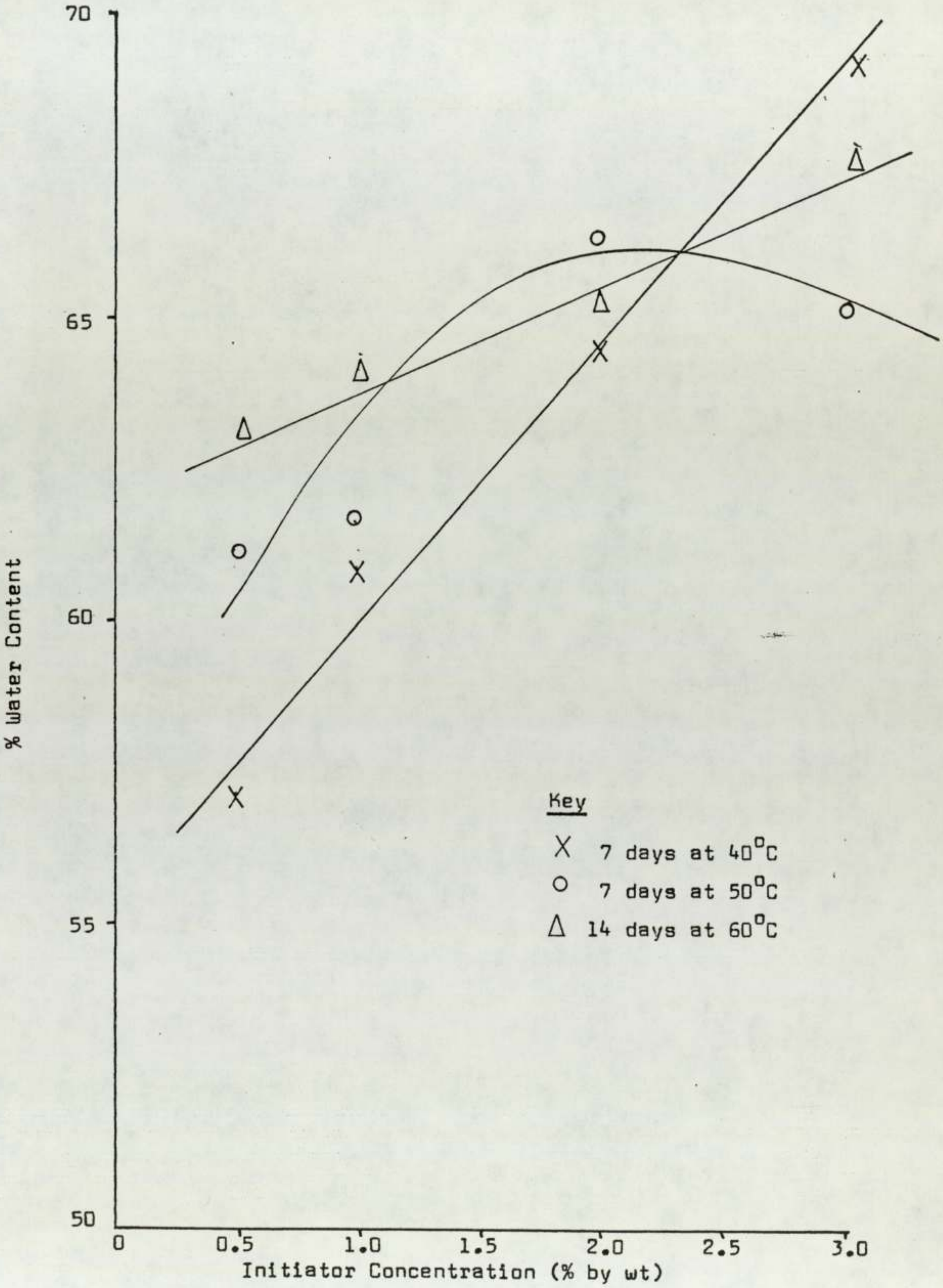
To justify this concept for this trend in the water content-initiator concentration profile at 50°C, the reasons why this behaviour is not observed at 40°C and 60°C should be examined. The induced decomposition mechanism would be expected to become enhanced at higher polymerisation temperatures. It should be remembered however that at 60°C the rate of reaction between the free radical formed by the initiator and a monomer unit to give a primary radical species will also increase. This reaction is illustrated in Figure VI.f -

$$R^{\bullet} + M \longrightarrow M_1^{\bullet}$$

Figure VI.f

Primary radical formation

Graph VI.1


70
65
60
55
50
0
0.5
1.0
1.5
2.0
2.5
3.0
% Water Content
Initiator Concentration (% by wt)
Key
X 7 days at 40°C
○ 7 days at 50°C
Δ 14 days at 60°C

The results in Tables VI.A to VI.C would therefore suggest that at 60°C the rate of formation is sufficiently fast to limit induced decomposition at high initiator concentrations. At 40°C the reaction time for the polymerisation is possibly sufficiently long for those initiator molecules that enter into induced decomposition to undergo further thermal dissociation and initiate polymerisation.

VI.3iii EFFECT OF POLYMERISATION TEMPERATURE ON WATER CONTENT

It was observed in the previous section that an increase in initiator concentration generally led to a rise in water content by increasing both the number of initiating species and the rate of termination of the polymerisation process. A change in polymerisation temperature will however affect all three stages of the reaction mechanism; initiation, propagation and termination. The change in water content with increasing polymerisation temperature is therefore less predictable than that for an increase in initiator concentration. Close scrutiny of the results in Tables VI.A to VI.C show that as the polymerisation temperature is raised an increase in water content is generally observed.

One of the few anomalies that may be found, is again the result for polymers prepared at 50°C with an initiator concentration of 3% by weight of methyl ethyl ketone peroxide. Once more the reason for this can be attributed to the induced initiator decomposition process as outlined in the previous section. Any other irregularities in the general trend of an increase in water content with a rise in the temperature of polymerisation may possibly be due to differences produced in the ratio of the rates of propagation and termination. This may give rise to fluctuations in the molecular weight distribution and average chain length of the polymers produced. Another explanation of those results which are not satisfactorily resolved by the concepts already advanced may be the mode of termination of the polymerisation reaction. Both possible steps of the termination via radical recombination and disproportion are shown in Figures VI.g and VI.h -

$$M\dot{x} + M\dot{y} \longrightarrow Mx + y$$

Figure VI.g
Termination via radical recombination

$$M\dot{x} + M\dot{y} \longrightarrow Mx + My$$

Figure VI.h
Termination via disproportion

An increase in the extent of termination via disproportionation will lead to a reduction in the average chain length of the resulting polymer and therefore an increase in the water content. Should a greater degree of radical recombination take place to terminate the polymerisation process, a polymer of higher molecular weight distribution and lower water content will result.

VI.3iv EFFECT OF POLYMERISATION TIME ON WATER CONTENT

The results shown in Tables VI.A to VI.C show little variation in water content with the time of polymerisation at temperatures of 50°C and 60°C. The only appreciable changes of water content with reaction time are seen to occur at 40°C. At an initiation concentration of 0.5% of methyl ethyl ketone peroxide the water content of the hydrogels produced are seen to rise with increasing polymerisation time. This behaviour may be contrasted with that at 1% initiator concentration, where no appreciable variation in water content is observed, and the fall in water content after 7 days polymerisation for materials having higher initiator contents.

The polymers prepared with a 0.5% by weight concentration of methyl ethyl ketone peroxide are most interesting in that the water contents found are the lowest (57.2% for 7 days reaction) and highest (68.6%) for 14 days reaction) of any recorded throughout the whole study. The low initiator concentration and temperature used will give rise to a small conversion of initiator to free radical species and therefore a long period (~ 6 days) before gellation takes place. This would suggest that the reason for the low water contents observed after reaction times of 7 days and 10 days are due to incomplete polymerisation in that only a small proportion of N-vinyl pyrrolidone has become incorporated in the network. As N-vinyl pyrrolidone has a lower reactivity ratio than any other monomeric component used in this study, this would seem a reasonable supposition.[72] The low reactivity ratio of N-vinyl pyrrolidone can be attributed to the difficulty with which the monomer reacts with different free radical species within the growing polymer chain. The most favourable time within the duration of the reaction for the incorporation of N-vinyl pyrrolidone is therefore at the stage of formation of primary free radicals, as illustrated earlier in Figure VI.f. Since fewer free radicals will be formed during the initiation stage under these conditions, polymers containing less N-vinyl pyrrolidone will be produced.

The polymerisation conditions used will also lead to a lower water content, since the hydrogel produced will consist of a lower number of long chains. Once again this is due to the low conversion of initiator to free radicals, since this will ensure a longer propagation time as fewer species are present to enter into termination reactions via disproportionation and radical recombination.

As the time of polymerisation is increased to 14 days at 40°C a huge rise in water content is apparent. This phenomena may be attributed to the polymerisation of the residual N-vinyl pyrrolidone by reaction with free radicals from initiator molecules that are slow to undergo decomposition. As N-vinyl pyrrolidone molecules are capable of readily adding to a growing chain in order to yield homopolymers, the formation of long chains of poly(N-vinyl pyrrolidone) within the network at extended reaction times will lead to the production of a more hydrophilic hydrogel.

The results for hydrogels prepared with a 1.0% (by weight) initiator concentration at 40°C show little discernable change in water content over the polymerisation period studied. This may be due to a greater number of free radicals being formed by the initiator decomposition giving rise to the formation of polymers having a larger number of shorter chains in comparison with those produced at an initiator content of 0.5%. It should also be remembered that an increase in the number of free radicals formed will lead to a greater amount of N-vinyl pyrrolidone incorporated at the stage of primary radical creation. This increase in the N-vinyl pyrrolidone proportion within the network will limit the variation in water content with polymerisation time, as the tendency to produce chains of N-vinyl pyrrolidone homopolymer will be reduced.

At higher initiator concentrations of 2% and 3% of methyl ethyl ketone peroxide an even greater number of free radical initiating species will be formed. While this may lead to more NVP being incorporated during the formation of primary radicals, the rate of termination of the polymerisation will also increase giving rise to a shorter propagation time. At a temperature of 40°C complete conversion of high initiator concentrations cannot be expected but nevertheless gellation is seen to occur within 24 hours. This shorter gellation time will ensure that concentrations of both initiator and residual N-vinyl pyrrolidone will remain. Owing to the structure of methyl ethyl ketone peroxide containing two hydroperoxide groups, it is possible to obtain polymer chains terminated by a species containing an unreacted hydroperoxide group. It is therefore likely that such groups may react over a longer period of time and initiate further polymerisation with residual N-vinyl pyrrolidone monomer to effectively increase the polymer chain length. This process is represented in Figure VI.i -

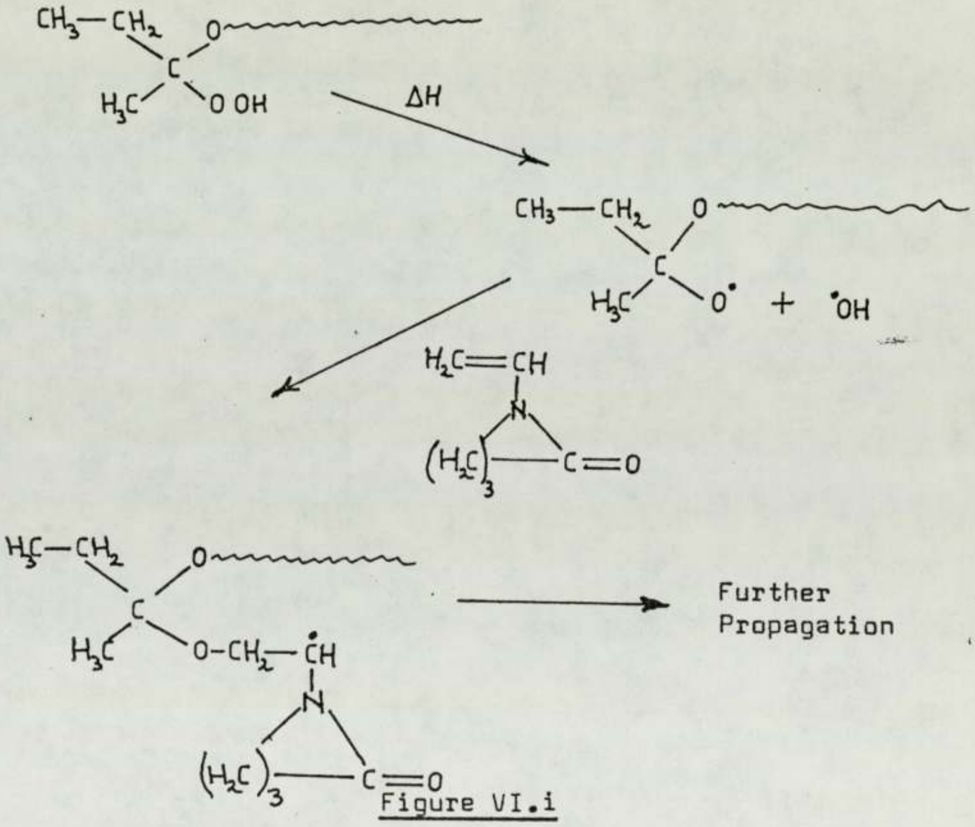


Figure VI.i

Since it is likely that the number of N-vinyl pyrrolidone units extending the chain length will be reasonably small, due to the presence of other initiator molecules leading to termination, this process may lead to a decrease in water content which is observed after 10 days polymerisation.

These effects will not be as noticeable at polymerisation temperatures of 50^{0}C and 60^{0}C since a far greater conversion of initiator to free radical species takes place together with an enhancement of the reactivity of N-vinyl pyrrolidone. The reactions described earlier in this section are therefore much more rare at elevated polymerisation temperatures and therefore little variation in water content with reaction time is observed.

VI.4i EFFECT OF POLYMERISATION CONDITIONS ON THE RESIDUAL FRACTION OF POLYMERS PREPARED WITHOUT POSTCURE

Whereas the molecular weight distribution and average chain length are the governing factors which control the variation in water content with polymerisation conditions, the same is not true for changes in the residual fraction. The relative rates of the propagation and termination stages of the polymerisation reaction will determine the amounts of material that are extractable during the hydration period. The trends of the residual fraction variation may not therefore be predictable from the trends observed for the water contents; ie an increase in water content may not necessarily correspond to a decrease in the residual fraction.

VI.4ii EFFECT OF INITIATOR CONCENTRATION ON THE % RESIDUAL FRACTION

At each polymerisation temperature studied a similar trend in the results obtained for the variation of % residual content with initiator concentration is seen from Tables VI.A to VI.C. While the % residuals of samples prepared with 0.5% and 1.0% of methyl ethyl ketone peroxide are seen to be approximately equal for each of the polymerisation temperatures employed, a gradual rise is observed at the higher initiator levels of 2% and 3%. This may seem somewhat surprising since a higher initiator concentration might be expected to produce a more efficient polymerisation reaction, with a greater proportion of the component monomers becoming incorporated within the gel network. That this is not seen to be the case may be attributed to the greater number of free radicals formed during the initiation stage of the polymerisation. As stated previously, in the effects on the variation in water content, this will not only increase the rate of initiation but also the termination of the polymerisation process. It would therefore seem that the time of propagation is most important in determining the residual contents of the materials produced.

At high initiator concentrations the increased rate of termination, via the greater number of free radical initiating species, is responsible for limiting the length of the polymer chains and also forming oligomeric, uncrosslinked species which can be extracted upon hydration. This phenomena will therefore be responsible for the general increase in % residual fraction of the polymers as the initiator concentration is raised.

The only exception to this general behaviour is due to the results obtained for polymers with an initiator concentration of 0.5% methyl ethyl ketone peroxide, at 40°C. The reasons for this anomaly will be fully discussed in the later section VI.4iv.

VI.4iii EFFECT OF POLYMERISATION TEMPERATURE ON % RESIDUAL FRACTION

A comparison of the results in Tables VI.A to VI.C indicates that only a small decrease in the residual fraction is observed, as the temperature of polymerisation is increased. It is also noticeable that the results for those samples prepared using high initiator concentrations at 50°C show little difference to those obtained for the corresponding polymers at 60°C. There is however, a discernable decrease in these results with respect to the residual fractions determined for materials prepared at 40°C.

These observations may be rationalised by remembering that the magnitude of the residual fraction will be governed by the relative rates of propagation and chain termination. It would seem therefore, that polymerisations carried out at 50°C and 60°C would have similar times of propagation and therefore incorporate similar amounts of monomer units within the polymer network. The difference in water contents observed may seem strange in view of this, but it should be remembered that at 60°C the decomposition of initiator to free radicals will be far more efficient and give rise to a polymer with a greater number of shorter chains. The results for materials prepared at 40°C show a greater residual fraction, which may be attributed to the slower rate of propagation at the lower temperature. The differences between the results for materials polymerised at 40°C in comparison to those at 50°C and 60°C are therefore seen to be most marked at high initiator concentrations.

VI.4iv EFFECT OF POLYMERISATION TIME ON THE % RESIDUAL FRACTION

As the % residual fraction is dependent upon the rate of polymerisation, very little variation with the polymerisation time is to be expected after gellation has occured. The results in Tables VI.A to VI.C tend to support this, although a noticeable variation is seen to occur for the polymers prepared at 40°C with an initiator concentration of 0.5% methyl ethyl ketone peroxide. The reason for the observed variation can be attributed to the very slow rate of polymerisation under these conditions, leading to incomplete polymerisation even after 10 days. As the reaction proceeds to completion however, chains of poly N-vinyl pyrrolidone are formed giving rise to an appreciable fall in the residual content after 14 days at 40°C. This will give rise to the anomalous behaviour noted in the variation of % residual content with initiator concentration.

In general the results for polymerisations at 40°C and 50°C show a small drop in the % residual content after a polymerisation time of 14 days or longer. This may be due to reactions occuring at chain ends with unreacted hydroperoxide groups as illustrated earlier in Figure VI.i. The same behaviour is not observed at 60°C however, due to the efficiency of initiator decomposition to free radical species being far greater and therefore yielding very few unreacted hydroperoxide groups at chain ends within the polymer network.

VI.5i EFFECT OF POLYMERISATION CONDITIONS ON THE OPTICAL CLARITY OF POLYMERS PREPARED WITHOUT POSTCURE

The production of a material of correct optical quality will be dependent upon the extent to which large blocks of N-vinyl pyrrolidone are formed within the polymer network, leading to a yellow discolouration of the resulting polymer. The results for unpostcured samples shown in Tables VI.A to VI.C indicate few observed changes with variable polymerisation conditions. It is therefore more convenient to discuss the results of this study in a single section, rather than give the effects of varying initiator concentration, temperature and polymerisation time separately.

An increase in initiator concentration is seen to give rise to a general decrease in the tendency of the polymer to become discoloured by the inclusion of blocks of N-vinyl pyrrolidone. This can be accounted for by an increase in the number of growing chains during the propagation stage of polymerisation which will give rise to an increased rate of termination. The extent to which blocks of N-vinyl pyrrolidone will be formed therefore becomes limited for the same reasons governing the variation of the residual fraction with initiator concentrations as outlined earlier in Section VI.4ii.

The optical clarity of the polymers produced is seen to undergo deterioration with increasing polymerisation temperature. Little discernable difference can be seen between the results obtained for polymers prepared at 40°C and 50°C, although a marked yellow discolouration is apparent for several polymers with a polymerisation temperature of 60°C. It would seem therefore, that at 60°C sufficient heat energy to overcome the activation energy for the addition of successive N-vinyl pyrrolidone units to the growing polymer chain is supplied. This will increase the formation of blocks of N-vinyl pyrrolidone within the polymer network to give rise to a greater degree of discolouration of the materials produced.

The results in Tables VI.A to VI.C show a gradual increase in discolouration with polymerisation time, particularly for those polymers prepared at 60°C. This can be attributed to the formation of blocks of homopolymeric chains of N-vinyl pyrrolidone becoming bound to the network after gellation of the polymer has taken place.

It is interesting to note that the results of this study indicate that changes in the optical clarity of these materials do not coincide with the changes in water content or residual fraction, as discussed earlier. It should be remembered however that the nature of the residual materials, ie unreacted monomers or low molecular weight oligomeric chains that remain unbound to the main network, may also give rise to the discolouration of polymers. Thus a material containing a high concentration of residual N-vinyl pyrrolidone monomer is more liable to give rise to a product with yellow discolouration after gellation, than one containing a greater number of oligomers which are liable to be extracted upon hydration. As a greater degree of discolouration is seen to occur at 60°C, via the formation of blocks of N-vinyl pyrrolidone, the effects of postcures at elevated temperatures may give an insight into the nature of the components of the residual fraction.

VI.6i EFFECTS OF POSTCURING ON POLYMER PROPERTIES

As polymers are subjected to a postcure at an elevated temperature, the fraction of the initiator concentration remaining unreacted during the polymerisation process may be converted to free radicals, giving rise to further polymerisation of residual monomer units. The majority of the residual monomer content can be expected to consist of N-vinyl pyrrolidone and its further incorporation in the polymer network would be beneficial by enhancing the water content and reducing the residual fraction of the material. It should be remembered however, that formation of a number of chains consisting of N-vinyl pyrrolidone blocks has given rise to a yellow discolouration of the polymers which would be a serious disadvantage for materials intended for contact lens applications. A balance between the conditions under which the polymerisation is carried out and the temperature of postcure should therefore be found in order to optimise the water content, residual fraction and optical clarity of a potential lens material. In view of this the effects of postcuring at various temperatures on each of these properties will be discussed separately in the following sections.

VI.6ii EFFECT OF POSTCURE ON WATER CONTENT

The results for the study of the variation in water content with postcure are shown in Tables VI.D to VI.F. A rise in water content with respect to the unpostcured samples is observed in almost every case for those polymers subjected to elevated temperatures for one hour. This is to be expected as an increase in the N-vinyl pyrrolidone content of a polymer should lead to hydrogel of enhanced hydrophilicity. It should be noted that the increase in water content, as a result of postcuring at elevated temperatures, becomes less marked as the temperature of polymerisation is raised. This is seen from the very small changes in water content resulting from postcuring samples polymerised at 60^{o}C. The extent of incorporation of more N-vinyl pyrrolidone during postcuring would therefore seem to decrease with increasing polymerisation temperature, which is to be expected due to the more effective conversion of the initiator to free radicals and the greater reactivity of monomers at higher temperatures. Thus for polymers prepared at 60^{o}C, the composition of the residual materials will consist mainly of oligomers of N-vinyl pyrrolidone, rather than unreacted monomer and their further reaction at higher temperatures will be limited by a far lower concentration of unconverted initiator.

One of the few exceptions to this general trend of a more pronounced effect of postcuring at lower polymerisation temperatures is seen to occur for the polymer prepared with 0.5% of methyl ethyl ketone peroxide at 40^{o}C for 14 days. This would lend support to the explanation for the variation of water content with polymerisation time for materials prepared under these conditions, as outlined earlier in Section VI.3iv.

The remainder of the results for the polymers prepared at 40^{o}C show

TABLE VI.D

EFFECT OF POSTCURE ON THE WATER CONTENT OF POLYMERS PREPARED AT 40°C

Time of Polymerisation	Water Content (%) at Various Postcures			
	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	57.2	65.5	68.1	65.7
10 Days	59.3	64.8	66.4	64.7
14 Days	68.6	68.4	68.7	67.7
1.0% Initiator				
3 Days	60.1	66.6	67.2	67.2
7 Days	60.9	65.8	66.6	66.8
14 Days	60.4	65.8	65.9	65.8
21 Days	61.3	65.6	66.4	66.5
2.0% Initiator				
1 Day	63.3	66.8	67.8	67.2
7 Days	64.6	66.7	67.8	67.2
10 Days	61.7	65.6	66.7	66.3
3.0% Initiator				
1 Day	67.2	69.6	69.3	68.7
7 Days	68.7	69.3	69.3	69.4
10 Days	65.4	68.3	67.1	66.9

TABLE VI.E

EFFECT OF POSTCURE ON THE WATER CONTENT OF POLYMERS PREPARED AT 50°C

	Water Content (%) at Various Postcures			
Time of Polymerisation	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
5 Days	61.3	64.2	65.1	66.0
7 Days	61.2	64.4	64.5	65.3
10 Days	61.3	63.5	65.0	65.4
14 Days	62.2	63.2	64.8	65.0
1.0% Initiator				
3 Days	61.1	64.7	65.0	65.9
5 Days	61.9	65.6	65.4	64.7
7 Days	61.7	64.9	65.1	65.6
10 Days	62.2	64.0	65.1	65.6
14 Days	62.5	63.5	63.9	63.8
2.0% Initiator				
3 Days	65.5	69.0	68.4	67.9
5 Days	65.2	67.9	67.9	67.6
7 Days	65.5	67.7	67.4	67.4
10 Days	66.0	67.6	67.2	67.2
3.0% Initiator				
3 Days	64.7	67.3	66.6	67.5
5 Days	65.4	67.8	68.0	67.3
7 Days	65.3	67.3	66.7	68.4
10 Days	65.0	67.0	66.9	67.3
14 Days	65.6	66.4	66.2	66.2

TABLE VI.F

EFFECT OF POSTCURE ON THE WATER CONTENT OF POLYMERS PREPARED AT 60°C

	Water Content (%) at Various Postcures			
Time of Polymerisation	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	63.3	63.6	64.5	65.5
14 Days	63.3	63.2	63.6	64.2
21 Days	63.5	63.5	63.9	64.3
1.0% Initiator				
7 Days	64.1	64.9	65.7	65.4
14 Days	64.4	64.5	64.6	65.2
21 Days	64.4	64.9	64.8	64.6
2.0% Initiator				
3 Days	65.1	66.9	66.9	67.6
10 Days	65.2	65.4	65.6	66.0
14 Days	65.4	65.9	65.4	65.6
3.0% Initiator				
3 Days	67.1	68.6	68.7	68.5
10 Days	66.9	67.9	67.8	67.7
14 Days	67.9	67.2	67.3	67.6

an expected trend for the effect of postcure on water content as the initiator concentration is increased. As the initiator concentration rises the increase in water content produced by subjecting the polymers to a postcure is seen to diminish. This is quite reasonable, since the increase of initiator content at low polymerisation temperatures will give rise to a high concentration of unconverted initiator molecules, which will lead to the formation of a greater number of short chains of N-vinyl pyrrolidone upon postcuring at higher temperatures. The formation of shorter chains of N-vinyl pyrrolidone within the polymer network will clearly be less effective in enhancing the hydrophilicity of these materials with respect to those prepared with a lower initiator concentration, where postcuring would be expected to incorporate longer chains of residual monomer units.

The same trend in the effect of postcure on water content is also observed in the results for polymers prepared at 50°C, although less pronounced. At a polymerisation temperature of 60°C however, the results in Table VI.F show that the effective enhancement of water content by postcures at elevated temperatures is greatly diminished. This may be attributed to the increased efficiency of the conversion of initiator to free radical species at 60°C giving rise to a greater degree of consumption of initiator molecules during the polymerisation process. Since less initiator molecules will remain unreacted after polymerisation at 60°C, the effect of the postcure to increase water content by incorporation of residual N-vinyl pyrrolidone in the polymer network is reduced. If this explanation is correct the results for polymers prepared with lower initiator concentrations should have water contents which are less susceptible to change after being postcured at higher temperatures. The results for polymers with initiator concentrations of 0.5% and 1.0% by weight of methyl ethyl ketone peroxide tend to substantiate this supposition.

As might be expected the time of polymerisation is seen to give rise to little effect on the enhancement of water content produced by postcuring. The only noticeable change produced by polymerisation time is seen to arise for the polymers prepared with an initiator content of 0.5% at 40°C. The reasons for this variation were stated earlier in this discussion.

VI.6iii EFFECT OF POSTCURE ON THE % RESIDUAL FRACTION

From the results on the variation of water content with postcure, it is to be expected that a decrease in the % residual fraction will be seen as postcuring causes the polymerisation of residual N-vinyl pyrrolidone monomer. The results shown in Tables VI.G to VI.I not only verify this expectation but also illustrate the variation in the composition of the % residual fraction at different polymerisation temperatures. As the temperature of polymerisation is increased, the reduction in the % residual fraction due to subjecting the polymers to postcure is seen to decrease. This would be explained by the amount of residual N-vinyl pyrrolidone monomer within the total extractable material decreasing at higher polymerisation temperatures. As the reactivity of N-vinyl pyrrolidone is greater at higher temperatures, the formation of chains of poly N-vinyl pyrrolidone which may be extracted from the network upon hydration would be expected to increase with temperature. Thus for polymerisation at 60°C the % residual fraction contains less unreacted monomer with respect to that at 40°C and the decrease caused by postcuring is much less marked.

While no experimentation into the chemical composition of the

TABLE VI.G

EFFECT OF POSTCURE ON THE RESIDUAL FRACTION OF POLYMERS AT 40°C

Time of Polymerisation	Residuals (%) at Various Postcures			
	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	32.4	23.3	22.9	21.2
10 Days	31.0	21.8	21.2	20.0
14 Days	29.4	22.9	21.9	21.0
1.0% Initiator				
3 Days	30.6	24.5	19.2	18.7
7 Days	30.0	24.1	21.4	20.1
14 Days	31.3	23.7	21.9	20.3
21 Days	29.1	24.6	22.4	21.9
2.0% Initiator				
1 Day	32.3	27.0	27.8	25.8
7 Days	31.1	26.3	26.9	25.4
10 Days	31.8	26.5	28.1	25.5
3.0% Initiator				
1 Day	36.0	33.5	31.9	29.9
7 Days	36.0	33.5	32.2	30.3
10 Days	33.9	30.6	29.9	28.0

TABLE VI.H

EFFECT OF POSTCURE ON THE RESIDUAL FRACTION OF POLYMERS AT 50°C

Time of Polymerisation	Residuals (%) at Various Postcures			
	No Postcure	1 Hour 80^{o}C	1 Hour 90^{o}C	1 HOur 100^{o}C
0.5% Initiator				
5 Days	28.8	24.7	25.3	20.3
7 Days	29.0	25.4	25.2	23.1
10 Days	28.4	25.5	25.9	23.4
14 Days	28.6	25.6	25.4	24.0
1.0% Initiator				
3 Days	29.0	24.7	23.8	20.0
5 Days	28.6	23.6	23.0	22.8
7 Days	28.1	25.3	22.3	22.1
10 Days	28.0	25.9	23.6	20.9
14 Days	26.8	26.4	24.5	24.5
2.0% Initiator				
3 Days	31.3	27.7	25.0	23.9
5 Days	30.8	29.9	25.1	23.9
7 Days	31.0	29.0	25.4	25.4
10 Days	29.3	28.9	26.8	24.5
3.0% Initiator				
3 Days	33.6	31.2	30.4	26.3
5 Days	33.2	29.8	28.8	28.2
7 Days	33.0	29.8	29.9	28.8
10 Days	32.4	29.3	29.4	27.5
14 Days	30.9	29.7	29.5	23.3

TABLE VI.I

EFFECT OF POSTCURE ON THE RESIDUAL FRACTION OF POLYMERS AT 60°C

Time of Polymerisation	Residuals (%) at Various Postcures			
	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	27.8	26.7	25.7	24.3
14 Days	27.5	27.1	26.1	24.9
21 Days	27.3	26.8	26.6	25.5
1.0% Initiator				
7 Days	28.8	28.0	26.6	26.6
14 Days	28.7	27.9	26.9	26.0
21 Days	28.6	27.8	27.2	27.0
2.0% Initiator				
3 Days	30.4	28.5	27.6	27.2
10 Days	30.3	29.8	28.7	28.0
14 Days	30.0	30.1	29.2	28.9
3.0% Initiator				
3 Days	34.3	32.5	30.4	30.8
10 Days	33.7	32.7	32.0	31.0
14 Days	33.2	32.4	32.4	32.4

extractable fraction of these hydrogels has been carried out during this research, the decomposition of N-vinyl pyrrolidone monomer in the presence of acids has been widely documented.[99] A fuller account of the problems which may arise from the occurrence of these reactions will be given at the conclusion of this chapter, in the light of results obtained with other initiating systems.

The results in Tables VI.G to VI.I also show that the fall in the % residual fraction produced by postcuring decreases as the initiator content is raised, although very little difference is observed at a polymerisation temperature of 60°C. This trend can also be explained by the increase in the formation of low molecular weight poly N-vinyl pyrrolidone at higher initiator concentrations which will constitute a greater proportion of the total % residual fraction. Those polymers prepared at 60°C will however contain a sufficiently small concentration of N-vinyl pyrrolidone monomer, to give rise to the effect of the postcure in reducing the % residual fraction becoming independent of the added initiator concentration.

As expected varying the time of polymerisation shows no noticeable changes to the effect of the postcure on the % residual fraction.

VI.6iv EFFECT OF POSTCURE ON OPTICAL CLARITY

The results in Tables VI.D to VI.I for the variation of water content and % residual fraction with postcures at elevated temperatures indicate that these properties of the polymers generally tend to improve as the postcuring temperature is increased. Thus a postcure at 100°C is usually seen to give rise to a hydrogel of higher water content and a lower residual content with respect to a polymer prepared under the same conditions but subjected to postcuring at lower temperatures. It may therefore be considered beneficial to subject a potential contact lens material to very high temperature postcures in order to enhance these properties of the material. The results for the study of the variation of optical clarity with postcure, as shown in Tables VI.J to VI.L, clearly indicate that high temperatures rapidly give rise to discolouration of the polymers. Thus a postcure which gives rise to an appropriate balance of properties must be selected.

As stated earlier, in Section VI.5i, the discolouration of polymers can be attributed to the formation of chains of poly N-vinyl pyrrolidone above a certain concentration. High temperature postcures which give rise to a greater degree of incorporation of blocks of N-vinyl pyrrolidone are therefore seen to produce polymers with more discolouration. Once more the proportions of N-vinyl pyrrolidone present in the residual fraction will determine the degree to which discolouration takes place upon postcuring. The most marked changes in optical clarity after subjection to postcure are therefore seen to occur for those polymers prepared at 40°C, where materials which are clear after polymerisation become orange or brown at 100°C. At higher polymerisation temperatures the discolouration of materials caused by postcuring is much more difficult to assess due to the varying nature of the residuals produced in each case. It is noticeable however that for most polymers, a postcure at a temperature above 80°C will give rise to a yellow discolouration.

In the introduction to this chapter the use of methyl ethyl ketone peroxide as a suitable initiator was questioned. The results of this study would tend to reinforce the doubts over its applicability. It should be reiterated however, that toxicological studies have revealed that the residual materials may be extracted to give a polymer of acceptable sterility.[97] Furthermore the results of investigations

TABLE VI.J

EFFECT OF POSTCURE ON THE OPTICAL CLARITY OF POLYMERS AT 40°C

	Optical Clarity at Various Postcures			
Time of Polymerisation	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	Pale Yellow	Yellow	Dark Yellow	Dark Orange
10 Days	Pale Yellow	Yellow	Dark Yellow	Light Orange
14 Days	Pale Yellow	Pale Yellow	Pale Yellow	Dark Yellow
1.0% Initiator				
3 Days	Clear	Clear	Pale Yellow	Yellow
7 Days	Clear	Clear	Pale Yellow	Yellow
14 Days	Pale Yellow	Pale Yellow	Yellow	Yellow
21 Days	Pale Yellow	Pale Yellow	Pale Yellow	Yellow
2.0% Initiator				
1 Day	Clear	Yellow	Yellow	Dark Orange
7 Days	Clear	Pale Yellow	Yellow	Orange
10 Days	Clear	Clear	Yellow	Orange
3.0% Initiator				
1 Day	Clear	Pale Yellow	Dark Yellow	Brown
7 Days	Clear	Pale Yellow	Dark Yellow	Brown
10 Days	Clear	Clear	Yellow	Dark Yellow

TABLE VI.K

EFFECT OF POSTCURE ON THE OPTICAL CLARITY OF POLYMERS AT 50°C

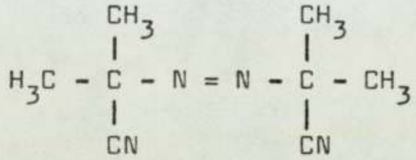
Time of Polymerisation	Optical Clarity at Various Postcures			
	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
5 Days	Clear	Clear	Clear	Pale Yellow
7 Days	Clear	Clear	Pale Yellow	Pale Yellow
10 Days	Pale Yellow	Pale Yellow	Yellow	Yellow
14 Days	Pale Yellow	Pale Yellow	Yellow	Dark Yellow
1.0% Initiator				
3 Days	Clear	Clear	Clear	Dark Yellow
5 Days	Clear	Clear	Pale Yellow	Yellow
7 Days	Clear	Clear	Pale Yellow	Yellow
10 Days	Pale Yellow	Pale Yellow	Pale Yellow	Dark Yellow
14 Days	Pale Yellow	Pale Yellow	Yellow	Yellow
2.0% Initiator				
3 Days	Clear	Clear	Clear	Dark Yellow
5 Days	Clear	Clear	Pale Yellow	Dark Yellow
7 Days	Clear	Clear	Pale Yellow	Yellow
10 Days	Clear	Clear	Pale Yellow	Yellow
3.0% Initiator				
3 Days	Clear	Clear	Clear	Dark Yellow
5 Days	Clear	Clear	Pale Yellow	Dark Yellow
7 Days	Clear	Clear	Clear	Yellow
10 Days	Clear	Clear	Yellow	Dark Yellow
14 Days	Pale Yellow	Pale Yellow	Yellow	Dark Yellow

TABLE VI.L

EFFECT OF POSTCURE ON THE OPTICAL CLARITY OF POLYMERS AT 60°C

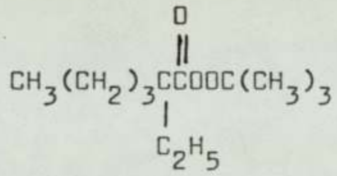
Time of Polymerisation	Optical Clarity at Various Postcures			
	No Postcure	1 Hour 80°C	1 Hour 90°C	1 Hour 100°C
0.5% Initiator				
7 Days	Pale Yellow	Pale Yellow	Pale Yellow	Yellow
14 Days	Yellow	Yellow	Yellow	Dark Yellow
21 Days	Dark Yellow	Dark Yellow	Dark Yellow	Dark Yellow
1.0% Initiator				
7 Days	Clear	Clear	Pale Yellow	Yellow
14 Days	Pale Yellow	Pale Yellow	Pale Yellow	Dark Yellow
21 Days	Pale Yellow	Yellow	Dark Yellow	Dark Yellow
2.0% Initiator				
3 Days	Clear	Clear	Pale Yellow	Yellow
10 Days	Pale Yellow	Pale Yellow	Yellow	Yellow
14 Days	Yellow	Yellow	Yellow	Yellow
3.0% Initiator				
3 Days	Clear	Clear	Pale Yellow	Yellow
10 Days	Pale Yellow	Pale Yellow	Pale Yellow	Dark Yellow
14 Days	Pale Yellow	Pale Yellow	Yellow	Dark Yellow

undertaken in the research laboratories of Kelvin Lenses Limited[100], as shown in Table VI.M, indicate that the use of other initiators widely used in the polymer industry give rise to similar problems to those experienced with methyl ethyl ketone peroxide. The names and formulae of the initiators employed during the pilot production scheme are given in Figures VI.j to VI.n.



$$H_3C - \underset{\underset{CN}{|}}{\overset{\overset{CH_3}{|}}{C}} - N = N - \underset{\underset{CN}{|}}{\overset{\overset{CH_3}{|}}{C}} - CH_3$$

Figure VI.j
AZBN: Azo bis isobutyro nitrile



$$CH_3(CH_2)_3\underset{\underset{C_2H_5}{|}}{C}\overset{\overset{O}{\|}}{C}OOC(CH_3)_3$$

Figure VI.k
TBPO: Tertiary butyl peroctoate

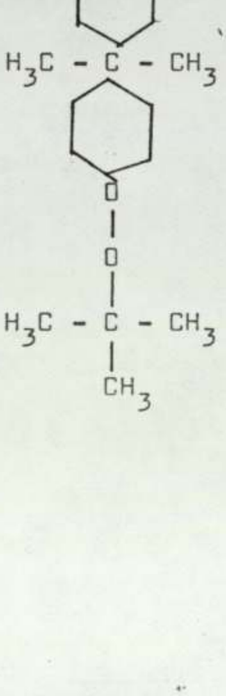


Figure VI.1
DTBCHPDC: 2,2 Bis (4,4-di-tertiary butyl peroxycyclohexyl) propane (Di-tertiary butyl cyclohexyl propane dicarbonate)

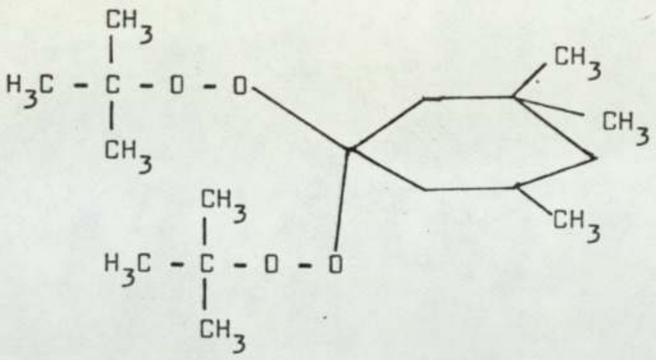
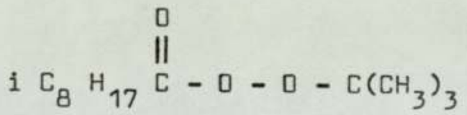


Figure VI.m

TMCPK: 3,3,5-Trimethyl 1,1 bis(tertiary butyl peroxy) cyclohexane
(Trimethyl cyclohexyl per ketal)



$$i\,C_8H_{17}\overset{\displaystyle O}{\overset{\|}{C}} - O - O - C(CH_3)_3$$

Figure VI.n

TBPIN: Tertiary butyl per isononanoate

The results from Table VI.M would suggest that polymers prepared using azo bis isobutyronitrile and tertiary butyl peroctoate are worth further investigation as viable alternatives to methyl ethyl ketone peroxide.

In concluding this chapter it must be stressed that despite the use of optimal bulk polymerisation conditions and initiating system, the decomposition reactions of N-vinyl pyrrolidone monomer will prevent the preparation of a hydrogel of this type which is completely free from residual materials. Two of the most common decomposition reactions of N-vinyl pyrrolidone are shown in Figure VI.o.[99]

Since these reactions are likely to occur during the bulk polymerisation process, the choice of a preferred initiator and polymerisation conditions is made on an empirical basis. Any initiator which will produce polymer rods of good optical quality and appropriate water

TABLE VI.M

RESULTS OF A PILOT PRODUCTION SCHEME FOR THE COMPOSITION ACM33 NVP47 HPA10 St10, CARRIED OUT BY KELVIN LENSES LIMITED RESEARCH DEPARTMENT

Initiator	Concentration (Wt %)	Polymerisation Time and Temperature (°C)		Post Cure	Optical Clarity
AZBN	0.1	143 hours	50°C	2 hours 100°C	Pale Yellow
AZBN	0.1	58 hours	60°C	5 hours 100°C	Light Brown
AZBN	0.1	58 hours	70°C	5 hours 100°C	Dark Brown
TBPO	0.13	143 hours	50°C	2 hours 100°C	Pale Yellow
TBPO	0.13	58 hours	60°C	5 hours 100°C	Light Brown
TBPO	0.13	58 hours	70°C	5 hours 100°C	Light Brown
DTBCHPDC	0.24	10 days	40°C	77 hours 70°C	Ungelled
DTBCHPDC	0.24	59 hours	50°C	77 hours 70°C	Ungelled
MEKP	1.0	7 days 3 days	40°C 60°C	2 hours 80°C	Pale Yellow
TMCPK	0.18	140 hours 2 days	50°C 70°C	1 day 100°C	Light Brown
TMCPK	0.18	58 hours	60°C	5 hours 100°C	Light Brown
TMCPK	0.18	58 hours	70°C	5 hours 100°C	Light Brown
TBPIN	0.14	140 hours	50°C	1 day 100°C	Light Brown
TBPIN	0.14	58 hours	60°C	5 hours 100°C	Light Brown
TBPIN	0.14	58 hours	70°C	5 hours 100°C	Light Brown

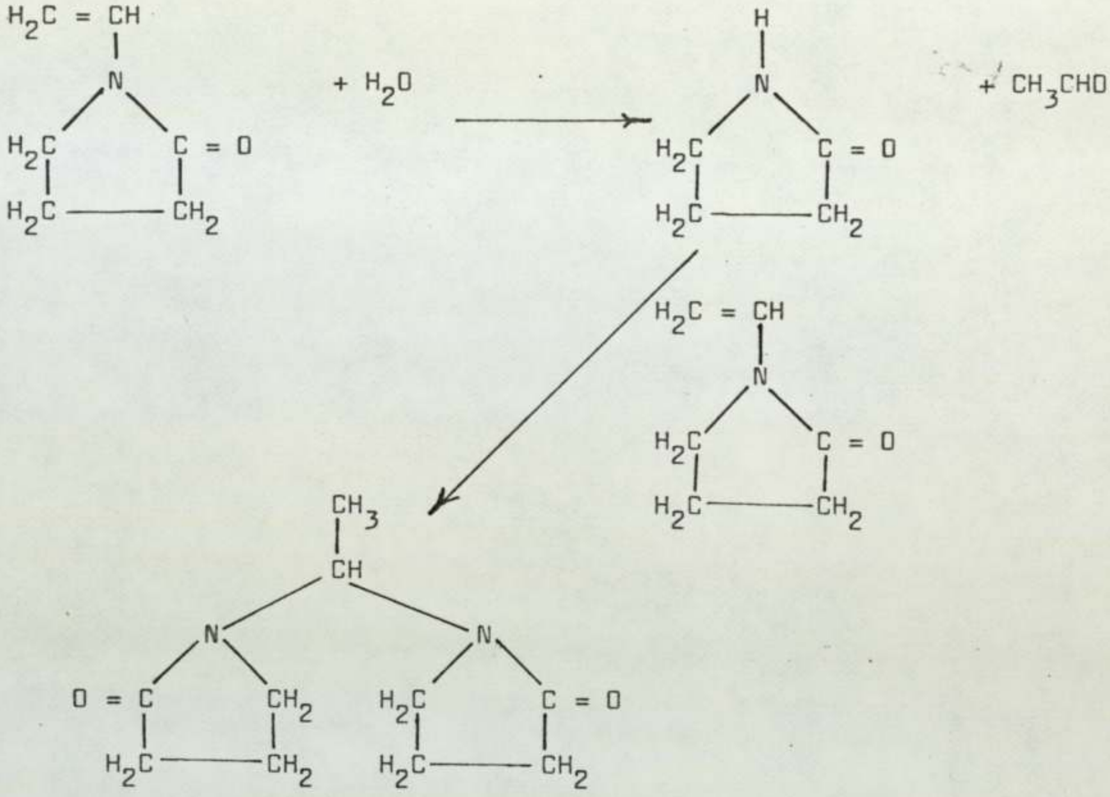


Figure VI.o

content without giving rise to problems of toxicological activity may therefore be deemed suitable for this type of polymerisation. The selection of a particular initiator to overcome the problem of drifting water contents is of no real value since methacrylic acid is likely to interact with some of the decomposition products of N-vinyl pyrrolidone in a similar manner to that shown in Chapter IV with the monomer itself. The problems of stability as outlined in this chapter are therefore best controlled by reducing the concentration of methacrylic acid to a level which produces a drift in water content within tolerable limits.

CHAPTER SEVEN

CHAPTER VII

MODIFICATION OF HYDROGEL SURFACES TO MEET THE REQUIREMENTS FOR CONTINUOUS WEAR CONTACT LENSES

VII.1 INTRODUCTION

As was explained in Chapter I, the cornea consists of a rather complex sandwich-like structure whose bulk and surface properties are governed separately by the stroma and epithelium respectively. These elements of the corneal structure are of widely differing natures and the preparation of a hydrophilic material which may successfully mimic the desirable properties of each layer therefore presents a number of synthetic problems.[15] The previous chapters of this thesis have been concerned with the complications associated with the preparation of a hydrogel polymer of appropriate bulk properties (eg water content, stability and mechanical strength) to meet the pre-requisites for a continuous wear contact lens. Having attained a suitable balance of bulk properties that will satisfy the requirements of corneal metabolism over an extended period, the surface must be modified to ensure that the optical clarity and oxygen permeability of the lens is maintained throughout the whole of the continuous wear cycle. A number of possible routes for producing a suitably surface modified hydrogel for a continuous wear contact lens material have been examined during the course of this research and these will be outlined in the following section.

VII.2 APPROACHES TO OBTAINING A SATISFACTORILY SURFACE MODIFIED LENS MATERIAL FOR CONTINUOUS WEAR

One of the major problems encountered in recent years with soft contact lenses is the progressive formation of surface deposits. These deposits have been shown to be of an essentially proteinaceous nature but in addition, cholesterol, mucopoly saccharides, lipoidal and ionic species are also encountered.[101,102] The problem is not an isolated one as many similar processes are known to occur whenever materials are brought into contact with protein containing biological solutions. The study of available information related to, for example, blood clotting, dental plaque formation and marine fouling has provided useful guides as to the way in which the problem may be minimised. A more complete summary of the background to this problem has recently been compiled by Baker and Tighe.[103]

Hydrogel polymers used for daily wear soft contact lenses are generally cleansed from proteinaceous surface deposits by periodically soaking the lenses in solutions containing a species of known anti-bacterial, antifungal or antiviral activity. A wide variety of soaking solutions have been marketed for different types of soft contact lenses. In every case however the concentration of the active species included must be confined to narrow limits in order to maintain the activity against lens contaminants and yet ensure that the accumulation of the active species within the bulk or at the surface of the lens is less than that which might prove toxic to the cornea.[104] While some soaking solutions are in fact used in conjunction with extended wear contact lens materials (ie those worn for a period of 2 or 3 weeks prior to removal for cleansing), their application for a continuous wear programme (1 to 2 years) presents serious problems. The most easily recognisable of these is to maintain a permanence of effective cleansing over the complete wearing cycle, while ensuring that the toxicity of the active species remains within tolerable limits.[73] At present no suitable soaking solution which is not toxic to the cornea over a long period of time is known and the use of a cleansing or sterilizing solution with continuous wear contact lens would therefore be inappropriate.

Although the removal of surface deposits from a continuous wear contact lens should preferably occur by a different means to the soaking method employed for daily wear soft contact lenses, the requirements for the maintenance of both materials remain essentially the same. These requirements have been summarised to include the following:-[104]

1 The maintenance of the hydrated state of the lens

2 Minimising or completely eradicating the presence of potentially pathogenic bacteria, fungi or viruses

3 The protection of the lens material from the invasion of fungi

4 The maintenance of the surface of the lens free from deposited material from tear fluid.

In the course of these studies the latter requirement has provided the main focus of attention, since the protection of the eye from pathogenic organisms is easier to achieve than the prevention of surface deposits. The extent to which the deposition of debris occurs on a lens surface is dependent upon two major factors:-[104]

a) The amount and character of protein and lipid elements in the tear fluid of an individual lens wearer

b) The character of the lens surface.

The interaction of a hydrogel surface with tear fluid is therefore of great importance in the design of an extended wear contact lens material. The structure of the tear fluid is known to consist of lipid, aqueous and mucous layers[101] and it is the action of the latter which gives rise to the accumulation of proteinaceous material, oils and calciferous deposits leading to a loss of optical clarity and discomfort. Studies have shown that the denatured protein lysozyme is often present as an adsorbed lens surface deposit, caused by epitheal degeneration.[104]

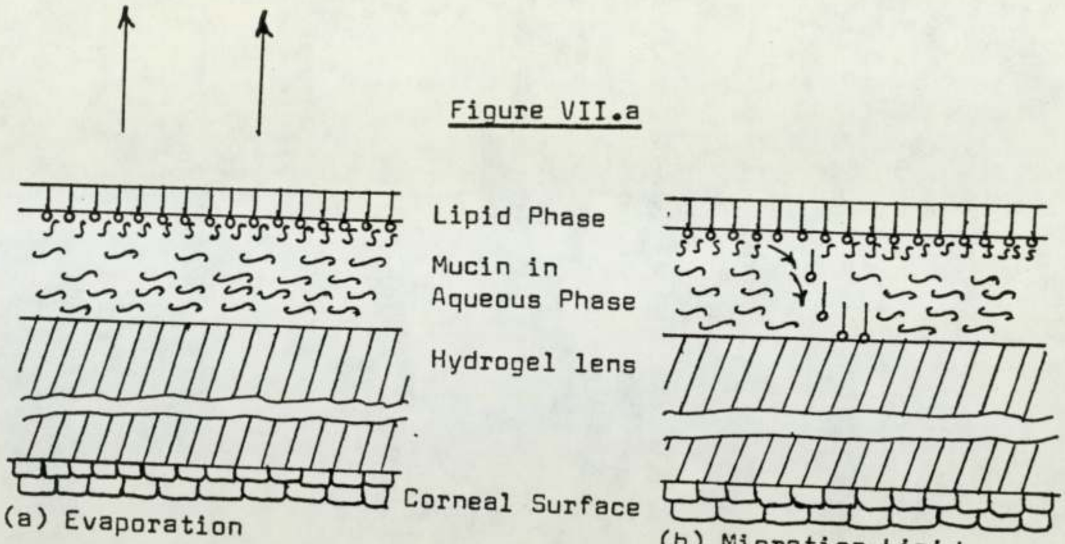
It has been postulated that the presence of lysozyme may lead to an autoimmune reaction which will encourage infections such as stapphylococcus and the development of acute conjunctivitis.[105]

A possible mechanism for the adsorption of proteins on a hydrogel contact lens surface has recently been outlined by Tighe[103] and is portrayed in Figure VII.a. The adsorption of denatured proteins at specific sites on a hydrogel surface may in turn initiate the growth of microbial species with the mucin rich aqueous phase of the tear fluid acting as a nutrient for the propagating cultures.[101]

Hydrogels of sufficiently high water contents for use as continuous wear contact lenses depend upon the presence of polar groups containing oxygen or nitrogen atoms to confer hydrophilicity, and therefore tissue compatability, upon the polymer. This will give rise to a high energy surface in hydrogels of high water content and result in increased adhesive characteristics leading to a greater degree of protein adsorption.[43]

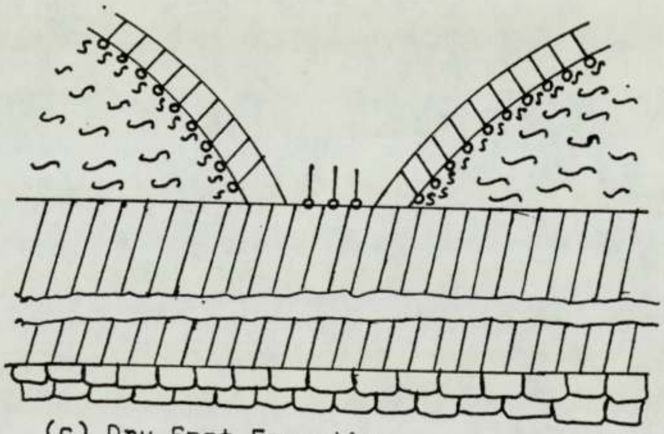
On the basis of this summary of the background to the problem of surface deposits on hydrogel polymers three principals of possible promise in overcoming this problem have been studied during this research. Each of the approaches adopted has involved the modification of existing materials with appropriate bulk properties for continuous wear contact lenses and these may be briefly summarised as follows. The first is to match the surface tension of the hydrogel material to that of natural cellular tissue (in so far as this is possible).[107] The second possibility is to induce a negative charge at the polymer surface and thereby reduce surface deposition by electrostatic repulsion (the interior surface of blood vessels are also known to carry a negative charge).[108] The third is to bind a species having detergent and/or

Figure VII.a

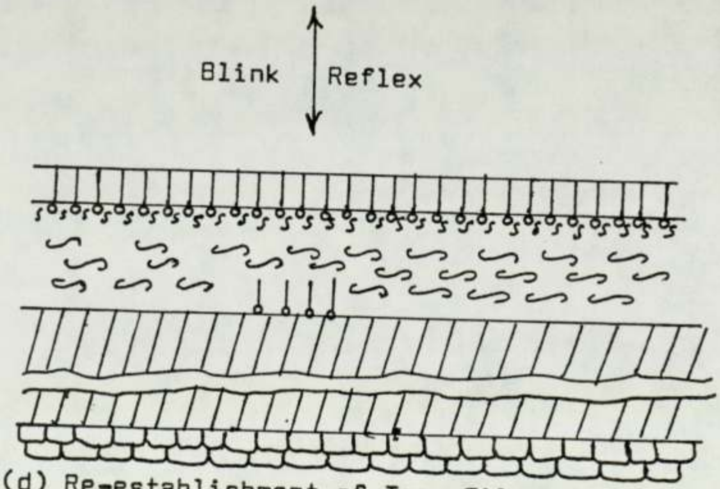


(a) Evaporation

(b) Migration Lipid

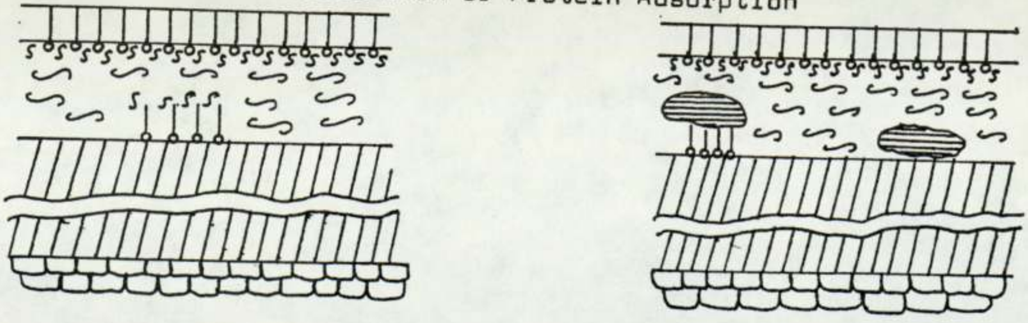


(c) Dry Spot Formation



(d) Re-establishment of Tear Film

Solubilisation or Protein Adsorption



antibacterial qualities to the polymer surface.[109] It should be emphasised that these possible routes to the design of a hydrogel with appropriate protein-polymer surface interactions for an extended wear contact lens material are only broad generalisations and that the thinking behind them is somewhat more subtle, particularly in relation to cell surface modelling. More detailed descriptions of the manner in which each of these concepts may be adapted for the preparation of potential extended wear lens materials will be given in the following sections.

VII.3i MATCHING SURFACE TENSION OF HYDROGELS WITH THAT OF NATURAL CELLULAR MATERIAL

In the previous section it was noted that the polar groups within the structure of a hydrogel polymer will give rise to high energy surfaces which will in turn lead to a greater degree of adsorption of denatured proteins. The most convenient method of studying the correlation between bioadhesion and surface energy is in terms of the critical surface tension of a material to be placed in contact with a biological solution.[110] As surface forces are known to exist in both liquids and solids, the critical surface tension of a solid surface may be defined as being equal to the surface tension of a liquid which will just wet it, ie spread evenly over the solid surface rather than forming discrete droplets. Another quantity that is often used in describing the relationships between polymer surface characteristics and bioadhesion is the interfacial tension. This is defined as the difference between the critical surface tension of the appropriate solid surface and the surface tension of the biological solution.

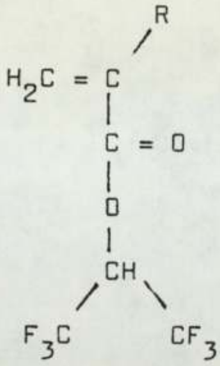
A great deal of conflict exists between various research groups as to the optimum interfacial and surface properties of a hydrogel polymer for it to be suitable as a biocompatible implant material. There are however two approaches to the problem of the criteria for biocompatibility which have received widespread support. The first is known as the 'Minimal Interfacial Energy' hypothesis and suggests that a low interfacial tension (of the order of 5 dynes cm^{-1} or less) between a hydrogel and the aqueous phase of the biological solution should reduce the tendency towards protein adsorption.[111] The major alternative to this approach is the 'Moderate Surface Energy' hypothesis which is based upon the study of the properties of materials found to be successful as long term implants. This work would suggest that a material with a critical surface tension of 20 to 30 dynes cm^{-1} would be most appropriate for biocompatibility,[112] particularly if a large number of methyl groups were present within the surface structure.

Whereas both these hypotheses have been developed from general considerations of the interactions between materials and protein-containing solutions in any biological environment, they can be utilised when dealing with the specific problems arising from hydrogel contact lenses encountering tear fluid. This research has therefore been concerned with the preparation of an appropriate hydrogel polymer having a sufficiently low surface energy to give rise to reduced adhesional characteristics when in contact with tear fluid. As a number of hydrogel co-polymers with appropriate bulk properties in terms of oxygen permeability, mechanical strength etc, for a continuous wear contact lens are undergoing pre-clinical and toxicological trials, this research has involved the modification of existing compositions rather than attempt the development of a completely novel material. To this end two approaches have been employed to obtain a hydrogel with reduced surface protein deposition in tear fluid. The first has involved the incorporation of a monomer containing fluorinated substituents during the polymerisation process and the second is by the preparation of a suitable interpenetrating polymer network. The reasons for adopting each of these approaches together with the methods of preparation employed will now be given in greater detail.

VI.3ii INCORPORATION OF FLUORINATED MONOMERS TO PRODUCE A HYDROGEL OF REDUCED SURFACE ENERGY

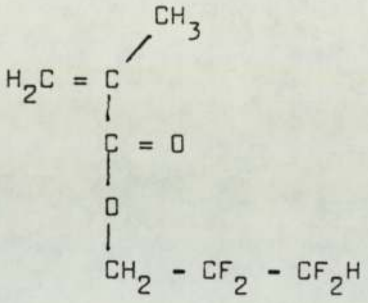
Polymers containing a number of fluoro substituents are known to exhibit low intermolecular forces at the air-solid interface and hence give rise to reduced surface adhesive characteristics.[113,114] This has encouraged the study of copolymers of hydrogels and fluorinated monomers, carried out in these laboratories by Barnes.[43] The surface energies of 90:10 (mol:mol) copolymers of 2-hydroxy propyl acrylate and various fluoro alkyl acrylates and methacrylates have been calculated and are shown in Tables VII.A and VII.B for both the dehydrated polymers and hydrogels. The structural formulae of each of the fluorinated monomers used during this study are given in Figure VII.b.

It becomes apparent from Table VII.A that the inclusion of fluorinated species within a hydrogel structure does indeed yield a material of lower surface energy, with respect to that of the corresponding homopolymer containing no fluoro groups, due to the reduction produced in the polar component. This would indicate that an appreciable number of fluorinated groups are positioned within the surface structural layers of the polymer. The ease of rotation of the polymer backbone[102] can give rise to this effect by the chains adopting a suitable configuration to allow large numbers of fluorinated groups in the side chain to concentrate at the polymer surface. The heat generated during the lathe-cut process used to fabricate the contact lens surface may also lead to an enhancement



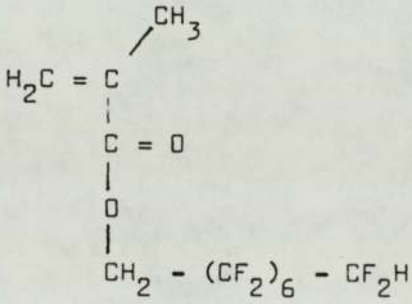
HFIPA $R = H$; hexafluoro isopropyl acrylate

HFIPMA $R = CH_3$; hexafluoro isopropyl methacrylate



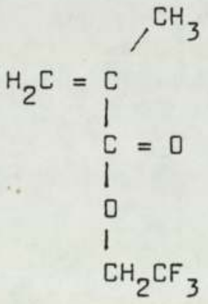
1,1,3 trihydroperfluoro propyl methacrylate

1,1,3 THPFPMA



1,1,7 trihydroperfluoro heptyl methacrylate

1,1,7 THPFHMA



2,2,2 trifluoro ethyl methacrylate

2,2,2 TFEMA

Figure VII.b Structures of Various Fluorinated Monomers

TABLE VII.A

SURFACE ENERGIES OF 2-HYDROXY PROPYL ACRYLATE COPOLYMERS WITH FLUORINATED MONOMERS (90:10 mol:mol) FOR DEHYDRATED SAMPLES

Fluorinated Monomer	Contact Angles		Surface Energies (dynes cm^{-1})		
	Water	Di-iodo methane	γd	γp	γTotal
None	55	41	31.8	19.0	50.8
Hexafluoro isopropyl acrylate	74	19	44.6	4.55	49.15
Hexafluoro isopropyl methacrylate	69	30	39.4	7.9	47.3
1,1,3 trihydro perfluoro propyl methacrylate	75	28	41.5	4.8	46.3
1,1,7 trihydro perfluoro heptyl methacrylate	85	15	48.1	1.0	49.1
2,2,2 trifluoro ethyl methacrylate	70	32	38.7	7.7	46.4

TABLE VII.B

WATER CONTENTS AND DERIVED POLAR COMPONENTS OF SURFACE ENERGIES OF 2-HYDROXY PROPYL ACRYLATE COMPOSITIONS WITH VARIOUS FLUORINATED MONOMERS (90:10 mol:mol) FOR HYDRATED SAMPLES

Fluorinated Monomer	Contact Angle Octane	Polar Component γp dynes cm^{-1}	% Water Content
Hexafluoro isopropyl acrylate	141	23	27.9
Hexafluoro isopropyl methacrylate	137	21	21.1
1,1,3 trihydro perfluoro propyl methacrylate	136	21	31.3
1,1,7 trihydro perfluoro heptyl methacrylate	133	20	20.5
2,2,2 trifluoro ethyl methacrylate	142	23	30.0
None	148	24.6	50.0

of this effect, which would in turn yield an increased concentration of fluorinated substituents at the surface.

While this hypothesis tends to augur well for the potential of fluorinated polymers for contact lens applications, it is the results obtained for the hydrated gels which will determine their true worth. These results are shown in Table VII.8, with the Hamilton contact angles of n-octane on the hydrated polymers and the polar component of the surface free energy being tabulated alongside the respective water contents for each hydrogel. A comparison between these results and those obtained for the dehydrated polymers shows that an appreciable increase in the polar component of the surface energy has taken place upon hydration. This trend is to be somewhat expected due to the presence of water molecules in the surface layers of the hydrated gels, but of greater importance is the far more dramatic increase in the polar component of the surface energy for fluorine containing polymers with respect to that observed for poly(2-hydroxy propyl acrylate).

It would seem appropriate to explain these results by suggesting that chain rotation of the polymer backbone takes place giving rise to a re-orientation of the fluorinated substituents from the surface layers into the bulk of the hydrated gel and their replacement by hydrophilic groups. The depression in the water content of poly(2-hydroxy propyl acrylate) observed due to the inclusion of fluorinated species would, at first sight, tend to support this supposition. It must be remembered however that upon formation of a copolymer containing fluorinated groups, a certain proportion of them will be positioned within the bulk of the material while the remainder are orientated at the surface. The fall in water content observed is expected to be due to the hydrophobic nature of fluorine atoms in the bulk, but gives no indication that any repositioning of fluorinated species has taken place upon hydration of the copolymer.

In the absence of further information on the dispersive component, and therefore the total value of the surface energy of the hydrated gels, it is difficult to make an informed assumption as to the nature of the composition of these surfaces in terms of the abundance of fluorinated species. It is possible however that the observed increase in the polar component of the surface free energy may be attributed to a change in the ratio of bound to free water at the surface of fluorine containing polymers with respect to that present in poly(2-hydroxy propyl acrylate). The presence of hydrophobic fluorine atoms in the surface layers can be expected to disrupt the binding of water molecules around the polar hydroxyl groups and therefore give rise to a greater proportion of free water. This may in turn lead to the upsurgence observed in the polar component of the surface energy, although it should be stressed that experimental verification of this hypothesis, by measuring the ratio of bound to free water at a hydrogel surface, would present several technical problems.[81]

The conclusion that can be drawn from the results shown in Table VII.8 with a good deal of certainty is that the choice of the concentration of fluorinated monomer to be used in a potential composition for continuous wear lenses must be restricted to a very low level. A molar concentration of only 10% of the fluorinated monomer is seen to produce a large decrease in the water content of the resulting copolymer in comparison with that of poly(2-hydroxy propyl acrylate). It would seem therefore, that the maximum concentration of fluorinated monomers to be used in conjunction with an existing co-monomer composition to produce a continuous wear contact lens material must be less than 5%.

Barnes has described the effect of varying the length and number of fluorinated components in the side chain upon the observed decrease in the polar component of the free energy.[43] This treatment would seem somewhat superfluous however when selecting a suitable fluorinated monomer for inclusion in a continuous wear contact lens composition. This becomes apparent by considering that the techniques employed for measuring the surface energy are carried out using samples of copolymer membranes prepared between sheets of poly(ethylene terephthalate). The nature of the polymer surface, in terms of the configuration of both hydrophilic and hydrophobic groups, will undoubtedly be affected by this method of fabrication.[102] This type of surface may therefore differ widely from that of a lathe cut contact lens prepared using an identical comonomer composition. When the problems of the hydrophobic nature of the fluorinated monomers are also taken into account, the difficulties in achieving a satisfactory continuous wear contact lens material containing fluorinated species may be appreciated.

One part of this research has been concerned with monitoring the depression in water content caused by the incorporation of small concentrations of fluorinated monomers in various continuous wear lens compositions. In order to obtain a closer approximation to the in use conditions of these materials, the water content determinations have been carried out using lathe cut lenses hydrated in buffered saline. The co-monomer compositions used during this study are given in Figure VII.c.

The water contents of materials prepared using these compositions in conjunction with fluorinated monomers are shown in Table VII.C.

Composition 1

Acrylamide	33 mole %
N-vinyl pyrrolidone	47 mole %
2-hydroxy propyl acrylate	10 mole %
Styrene	10 mole %
Methacrylic acid	1% by weight

Composition 2

Acrylamide	20 mole %
Methacrylamide	10 mole %
Diacetone acrylamide	10 mole %
N-vinyl pyrrolidone	40 mole %
2-hydroxy propyl acrylate	10 mole %
Styrene	10 mole %
Methacrylic acid	2% by weight

Composition 3

Methacrylamide	20 mole %
Diacetone acrylamide	20 mole %
N-vinyl pyrrolidone	40 mole %
2-hydroxy propyl acrylate	10 mole %
Styrene	10 mole %
Methacrylic acid	2% by weight

Figure VII.c

TABLE VII.C

WATER CONTENTS OF POTENTIAL CONTINUOUS WEAR CONTACT LENSES CONTAINING VARIOUS FLUORINATED MONOMERS

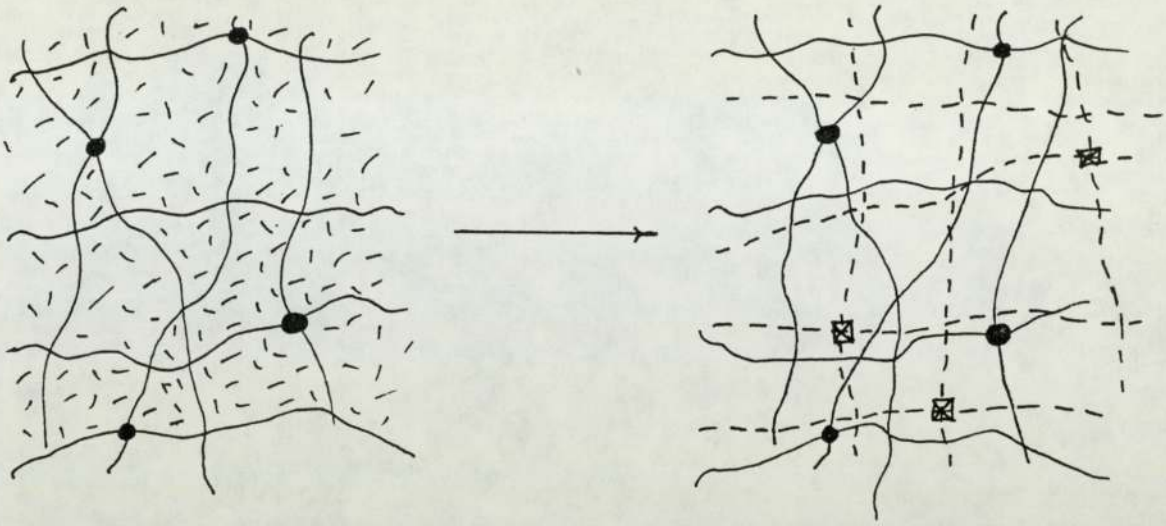
Fluoro Monomer	Concentration	% Water Content
Composition 1		
None	-	73.8
HFIPMA	1% by wt	74.4
HFIPMA	2% by wt	73.4
1,1,3 THPFPMA	1% by wt	73.3
1,1,3 THPFPMA	2% by wt	72.8
Composition 2		
None	-	76.3
HFIPMA	1% by wt	75.6
HFIPMA	2% by wt	74.2
1,1,3 THPFPMA	1% by wt	75.6
1,1,3 THPFPMA	2% by wt	74.5
Composition 3		
None	-	66.5
HFIPMA	2% by wt	65.9
1,1,3 THPFPMA	1% by wt	67.2
1,1,3 THPFPMA	2% by wt	68.1

Once more a general depression in water content is observed as the concentration of the fluorinated monomer is increased. Those few instances where this is not seen to occur may be due to the presence of methacrylic acid impurities in the fluorinated monomer used. A hydrogel material to be used as an extended wear contact lens material should have a water content of not less than 65% at the eye temperature of 34°C, in order to maintain satisfactory corneal respiration.[27] This would suggest that a water content of approximately 70% might be required at room temperature. The results in Table VII.C would therefore suggest that composition 3 is unsuitable as a continuous wear lens material while the concentration of fluorinated monomer added to compositions 1 and 2 should not exceed 3% by weight.

VII.3iii THE SYNTHESIS OF AN INTERPENETRATING POLYMER NETWORK TO PRODUCE A HYDROGEL MATERIAL OF REDUCED SURFACE ENERGY

In view of the complications arising from the use of fluorinated species to obtain a hydrogel material of favourable bio-adhesive characteristics, an alternative approach involving the synthesis of an interpenetrating polymer network has been undertaken during the course of this research. An interpenetrating polymer network may be thought of as a special form of polymer blend which is prepared by swelling a cross-linked polymer network with another monomer containing a cross-linking agent and initiator, followed by polymerisation of the second component 'in situ'. Sperling has represented this process by the schematic illustration shown in Figure VII.d.[115]

In the case of interpenetrating networks prepared from hydrogels, it is usual to swell the polymer in an appropriate organic solvent eg methanol prior to immersion in the monomer which is to constitute the second component of the composite material.



Polymer swollen by monomer

Interpenetrating polymer network

Figure VII.d

As might be expected, several workers have demonstrated that the mechanical properties of some interpenetrating polymer networks are significantly enhanced with respect to the individual strengths of the component polymers from which the material is fabricated.[116] The aspect of interpenetrating polymer networks which has attracted most attention in terms of the design of contact lens materials, has been the observation of the fall in critical surface tension with the composition of materials prepared from emulsions of polyurethane and polyacrylate by Frisch et al.[117] It would seem therefore that the secondary network tends to exert a greater influence on the surface properties of an interpenetrating polymer network than the structure of the first polymer which is swollen by the second monomeric component.

This premise has led to the use of methyl methacrylate in conjunction with hydrogels to produce interpenetrating polymer networks of suitable processability for lathe cut contact lens materials. Methyl methacrylate is widely favoured as the secondary network in the formation of such composite materials, since the homopolymer exhibits the same gross critical surface tension as that of the cornea itself.[15] A typical patented preparation has involved the swelling of a hydrogel copolymer of N-vinyl pyrrolidone and methyl methacrylate in methanol followed by immersion in methyl methacrylate monomer containing allyl methacrylate as a crosslinking agent and a suitable initiator. The interpenetrating polymer network having a secondary network of crosslinked methyl methacrylate may then be formed by various means, eg exposure to ultra violet radiation, thermal polymerisation etc.[118]

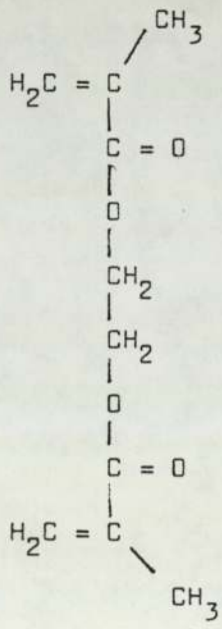
An obvious drawback to the successful adoption of these materials for soft contact lenses becomes apparent from the reports of several workers upon the tendency of interpenetrating polymer networks to exhibit reduced degrees of swelling with respect to their individual polymeric components. Indeed the water content of interpenetrating polymer networks prepared from hydrogels and methyl methacrylate have been shown to fall from 70% to 2%, depending upon the time of immersion in the hydrophobic monomer.[118] This behaviour is reasonably predictable, since the entanglement of hydrophobic chains of poly(methyl methacrylate) with the primary network structure as illustrated in Figure VII.c will increase with the concentration of monomer swollen into the hydrogel and cause greater disruption to the water binding ability of the hydrophilic groups present. In order to prepare an interpenetrating polymer network of sufficient oxygen permeability to maintain corneal metabolism over an extended period, it therefore becomes essential to control the amount of methyl methacrylate monomer swollen into the hydrogel network and polymerised in situ.

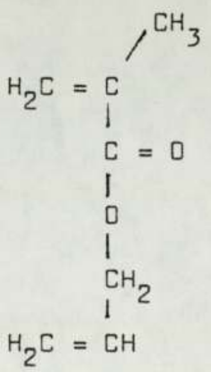
Recent experimentation carried out in these laboratories by Benyahia,[119] under the supervision of the author, have however resulted in the production of materials with methyl methacrylate as the secondary network yet having a water content in excess of 70%. The interpenetrating polymer networks were prepared by swelling an acrylamide based hydrogel in methanol for 1 week followed by immersion in methyl methacrylate monomer together with ethylene dimethacrylate and uranyl nitrate for various periods of time, prior to irradiation under ultra violet light for three hours. Water content determinations were carried out on lenses cut from the materials prepared and the results of this study are shown in Table VII.D. No significant decrease in the water contents of these materials can be discerned from the table, which gives rise to conflict with the results of earlier workers using similar materials. While this may at first suggest that no appreciable polymerisation of methyl methacrylate within the hydrogel network has taken place, it should be stressed that all the lenses manufactured during this study were found to hydrate randomly with some being seen to distort to a noticeable extent. These observations would tend to indicate that some degree of incorporation of the hydrophobic chains of methyl methacrylate within the hydrogel network has taken place.

In order to try and reconcile the apparent contradiction between these results and those patented by earlier workers[118] it seems worthwhile to compare the methods of preparation employed in each case. If the assumption is made that the differences in structure between the hydrogel copolymers used in each case will produce no significant difference to the polymerisation of methyl methacrylate, the only remaining disparities are the choices of initiator and crosslinking agent. The initiator used during this study was uranyl nitrate which is known to complex with

N-vinyl pyrrolidone[120] and it is therefore possible that this will occur when the initiator comes into contact with residual monomer units within the hydrogel network. This will prevent the satisfactory initiation of the methyl methacrylate component, and explain why little reduction in the water contents of the resulting materials is apparent. It is seen from Table VII.D however that the % residual fraction of the materials synthesised are consistently lower than that of the original hydrogel network which would indicate that swelling in methanol effectively removes most of the residuals prior to immersion in methyl methacrylate.

In view of this observation, an alternative explanation of the disparity in results should be sought. The use of ethylene dimethacrylate as the crosslinking agent in preference to allyl methacrylate may indeed give rise to the observed differences. It is seen from Figure VII.e that ethylene dimethacrylate has a greater molecular size than allyl methacrylate and will therefore permeate throughout a swollen hydrogel network to a lesser degree.





Allyl methacrylate
(Molecular weight = 126)

Ethylene dimethacrylate
(Molecular weight = 198)

Figure VII.e

TABLE VII.D

WATER CONTENTS OF MATERIALS PREPARED FROM ACM40 NVP35 HPA15 St10 MAA 2% by wt IMMERSED IN METHYL METHACRYLATE FOR VARIOUS LENGTHS OF TIME

Time of immersion (hours)	% Water Content	% Residual Fraction
0	75.1	11.5
1	73.4	4.0
2	73.7	3.5
3	74.7	1.9
6	73.8	3.0
24	73.5	6.6

TABLE VII.E

VARIATION IN WATER CONTENTS OF COPOLYMERS CONTAINING METHACRYLIC ACID AFTER HYDRATION IN SODIUM BICORBONATE SOLUTION

Molar Percentages					H_2O for 32 Days	$NaHCO_3/NaCl$ for 27 Days	H_2O for 8 Days
ACM	NVP	HPA	St	MAA			
41.8	31.6	12.6	12.7	1.2	71.3	77.0	91.3
41.8	27.6	13.9	13.9	2.8	64.7	74.9	91.3
41.4	29.9	12.5	12.5	3.7	67.9	79.8	94.2
41.3	28.8	12.5	12.5	4.9	63.0	79.8	93.8
40.4	29.2	12.2	12.2	6.0	62.5	83.5	96.5

As the permeability of a species is known to be inversely proportional to its molecular weight, ethylene dimethacrylate may be expected to diffuse into a swollen hydrogel network at only about half the rate of methyl methacrylate monomer (molecular weight = 100). Since the original concentration of ethylene dimethacrylate was only 1% of that of methyl methacrylate, it would seem that the second component of the interpenetrating polymer network is only bound by chain entanglements. This would explain why no significant variation in water content is observed with the time of immersion in methyl methacrylate, since the interchain spacing of the first network will remain largely unaffected by a secondary component which is not cross-linked.

Further experiments with materials prepared by immersion of swollen hydrogels in ethylene dimethacrylate and uranyl nitrate followed by ultra violet irradiation have shown that polymerisation of the cross-linking agent takes place only at the hydrogel surface and no appreciable diffusion into the bulk is discernible.[119] This evidence tends to support the supposition that methyl methacrylate will polymerise within a hydrogel network without being cross-linked by ethylene dimethacrylate, and will only be bound to the primary polymer structure by chain entanglements. In view of this suggested structure, one might expect the component chains of the interpenetrating polymer network to be extricated from chain entanglements upon hydrating the material, giving rise to diffusion of poly(methyl methacrylate) from the hydrogel. Such a process would however involve a decrease in the entropy of the system and the diffusion of the methyl methacrylate component from the interpenetrating polymer network structure is therefore likely to be energetically unfavoured.

As this portion of the research work has only recently been undertaken, no determination of the surface characteristics of these materials has been carried out at the time of submitting this thesis. When these results are available however a much clearer insight into the viability of this method of preparing hydrogels with appropriately modified surface characteristics for continuous wear contact lenses will be obtained.

VII.4i PREVENTION OF THE ACCUMULATION OF PROTEINACEOUS DEBRIS BY THE INDUCEMENT OF A NEGATIVE CHARGE AT THE POLYMER SURFACE

A great deal of conflict exists between various research groups concerning the definitive criteria necessary for a material to exhibit any degree of biocompatibility within an appropriate biological environment.[114] It would seem reasonable to assume however that the most promising approach to be adopted would be by modelling the desired interfacial and surface characteristics on those of the endothelial cell surface.[108,110] A part of this research has therefore been concentrated upon efforts to develop a negatively charged species at a hydrogel surface in order to emulate the interior surface of blood vessels which also carry such a charge. It would therefore appear that one of the factors necessary for the prevention of blood clotting arises from electrostatic repulsions and it may also be possible to prevent protein deposition from tear fluid by the same process. Two possible routes to the inducement of a negative charge at the surface of a potential continuous wear contact lens material have been examined during the course of this research and each will now be described in more detail in the following sections.

VII.4ii PRODUCTION OF A NEGATIVELY CHARGED SURFACE BY NEUTRALISATION OF METHACRYLIC ACID GROUPS TO PRODUCE CARBOXYLATE ANIONS

The first attempt to produce a hydrogel copolymer having a negatively charged surface during this research has involved the preparation of appropriate copolymers, with suitable oxygen permeability and mechanical properties, containing methacrylic acid groups. The carboxylic acid groups within the side chain of the copolymer may then be partly or completely converted to the sodium carboxylate salt by treating the hydrogel with sodium bicarbonate solutions of varying concentrations. As a fraction of the carboxylate anions produced can be expected to be positioned at the hydrogel surface, a greater degree of repulsion of proteinaceous debris would be anticipated with respect to that observed for the untreated material.

If inducement of a negative charge at the hydrogel surface could be effected by such a simple process, the problem of overcoming protein deposition on these contact lens materials would be quite readily solved. The true situation is far more complicated however as treatment of a polymer containing methylacrylic acid as a component with sodium bicarbonate solution will result in the neutralisation of some carboxylic acid groups within the bulk of the hydrogel, in addition to those positioned at the surface. The effects of treating hydrogels of this type with sodium bicarbonate have been discussed in Chapter IV, but some of the results are again shown in Table VII.E in order to underline the great increase in water content that is caused by the formation of ionic species within the polymer network.

As was seen in Chapter IV, the stability of these types of materials must be carefully monitored to ensure that problems of expanding lens size will not be encountered during periods of extended wear. The extent to which neutralisation of a portion of the carboxylic acid groups is carried out must therefore be carefully regulated in order to overcome problems of poor fit for a high water content continuous wear lens material.

This would involve the modification of potential lens compositions in order that an appropriate balance of properties, ie in terms of water content, oxygen permeability, mechanical strength etc, could be achieved following the neutralisation process. As a great deal of research effort has been spent in the development of these compositions for clinical trials, further modifications in structure at a late stage in the research programme is obviously undesirable.

Another point to be considered when dealing with hydrogel materials containing carboxylate anions is that the behaviour observed in an in vitro experiment using distilled water as the hydrating media may show very little similarity to the in vivo situation, when interactions between the tear fluid and the contact lens will take place. While the exact composition of tear fluid may vary from individual to individual[104] it is known to contain a number of cationic species including some divalent cations.[121] These ions are capable of diffusion into the bulk of the hydrogel network where they may react with two carboxylate anions to form an ionically bridged crosslink. This process is depicted in Figure VII.f.

The result of this process will be a decrease in the water content and therefore the dimensions of the contact lens in an in vivo situation causing acute problems in fitting.

The carboxylate anions within the surface layers of the hydrogel network are also liable to react with divalent cations present in the tear fluid. This can lead to an increasing degree of protein becoming associated with the polymer surface with a divalent cation acting as a

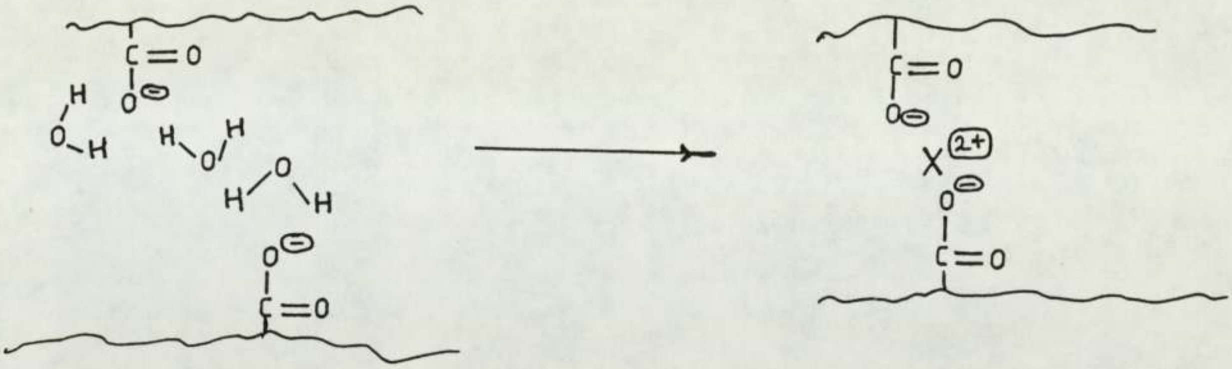


Figure VII.f

bridge between the anionic groups of the hydrogel and those within the protein structure. It should be noted that while the presence of divalent cations in tear fluid threatens to negate the use of this method as a means of preventing protein deposition, recent studies by separate research groups have indicated that divalent ions of magnesium and calcium will not readily displace monovalent sodium ions which are associated with the carboxylate groups.[120,122] As magnesium and calcium ions are the most common form of divalent cations found in tear fluid, the potential problems outlined are only likely to give rise to minor observable effects. If however a more reactive species such as divalent zinc ions were present to an appreciable degree the applicability of this method of protein repulsion would be in serious doubt.

The presence of other cationic species in tear fluid eg Na^+ ions may also be expected to give rise to a greater number of carboxylate anions being positioned at the surface due to chain rotation within the polymer being brought about by electrostatic attractions. This possibility is portrayed diagramatically in Figure VII.g.

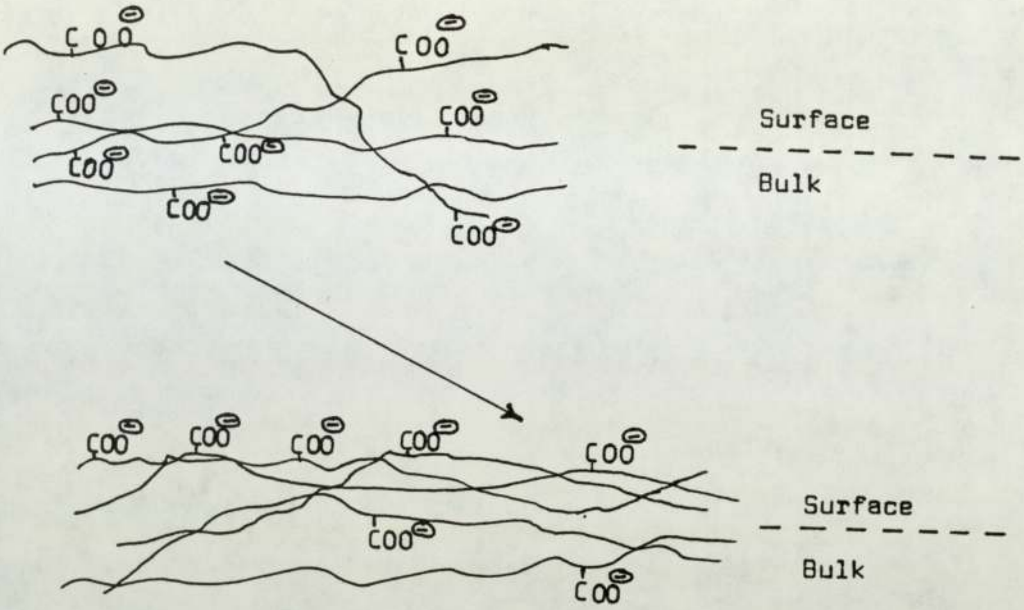


Figure VII.g

Hydrogel with carboxylate anions distributed throughout surface and bulk

Electrostatic attractions of cationic species can cause chain rotations to position more carboxylate anions at the surface. NB This is probably a localised effect with not all chains within the bulk of the network being affected.

If this effect were to occur upon hydration in tear fluid, it raises the question of the potential use of this method to prevent protein deposition. While a greater number of carboxylate anions positioned at the polymer surface might be expected to increase the degree of electrostatic repulsion to proteinaceous debris, it should be remembered that the presence of hydrophilic ionic species in the surface structure will give rise to a great increase in surface energy. The degree of protein deposition upon these types of materials will therefore be dependent upon which of these factors is dominant in controlling the mechanism of the adhesion of proteins to the polymer surface. It is probable therefore that protein repulsion is most effective at some critical surface concentration of carboxylate anions, below which the increased surface energy and wettability will overcome the electrostatic repulsions produced by these groups.

This method of overcoming the accumulation of protein on lens materials therefore seems to be unsatisfactory as the concentration of anions at the surface will be dependent upon the composition of the tear fluid with which the polymer is in contact. It is however possible to utilise the philosophy of this method, provided that a species carrying a negative charge can be chemically bound to the polymer surface at a known concentration. One potential route to achieving this aim will be outlined in the following section.

VII.4iii INCORPORATION OF SODIUM HEPARINATE AS THE INITIATOR OF A METHYL METHACRYLATE COMPONENT IN INTERPENETRATING POLYMER NETWORKS

Heparin, or rather its sodium salt, is a mucopoly saccharide with a molecular weight in the region of 15,000 to 20,000 and is widely used in biomedical applications for its anti-coagulent properties.[123] While the exact structure of heparin has yet to be ellucidated, it has been recognised in part to consist of the tetrameric species shown in anionic form in Figure VII.h[124]

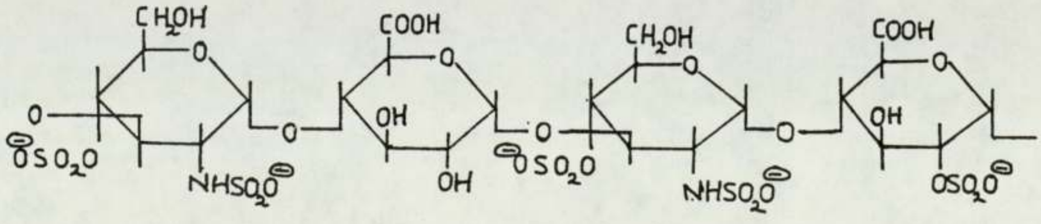


Figure VII.h

As mentioned earlier the study of the blood clotting process has yielded a valuable insight into the manner in which protein deposition may be reduced. While the mechanism of blood clotting is far more complex than that of contact lens spoilation from tear fluid, the phenomena of protein deposition is common to both since protein deposition is the first key step leading to coagulation.[125] Only when certain proteins, such as fibrinogen or gamma globulins, have denatured upon a surface will favourable conditions for platelet adhesion ensue and blood thrombus formation take place.[123] As only small amounts of heparin have been found to be required for effective prevention of blood coagulation, many attempts have been made to bind it to polymeric materials.[126,127] Amongst the more successful efforts undertaken has been the work of Labarre, Boffa and Jozefowicz[128] in which the radical polymerisation of methyl methacrylate was carried out using an initiator system of sodium heparinate and cerium (Ce^{4+}) ions. The reaction of cerium ions with the hydroxyl groups in the tetrameric unit of heparin will produce a heparin radical which, in the process of initiating free radical polymerisation, will become covalently bound to the resulting polymer. This reaction sequence is thought to yield a graft copolymer of heparin and methyl methacrylate by a similar mechanism to that proposed by Gaylord[129] for the polymerisation of methyl methacrylate with cellulose.

The problem faced in this research was however to incorporate heparin at the surface of a hydrogel copolymer with suitable bulk properties for a continuous wear contact lens. In order to achieve this, the preparation of an interpenetrating polymer network was carried out by the use of a graft copolymer of methyl methacrylate and heparin as the secondary network component of the composite material.

The attraction of this approach to localising a species carrying a negative charge at the surface of a hydrogel copolymer is two fold. The first arises from the large size of the complex heparin molecule which is too great to enable penetration of the pores in the hydrogel surface structure. Thus the sodium heparinate end groups of the graft copolymer will congregate at the hydrogel surface, while the methyl methacrylate portion of the secondary component will produce an interpenetrating network via chain entanglements within the bulk of the hydrogel. This gives rise to the second favourable aspect of this method, in that the formation of an interpenetrating polymer network will be instrumental in reducing the surface energy of the composite material. This is most important since, as was stressed in the previous section, the incorporation of hydrophilic anionic species at a polymer surface will lead to an increase in the wettability of the surface. The presence of an anionic species at the surface as a component of an interpenetrating polymer network may therefore be expected to offset the tendency for a higher surface energy to be produced.

In order to effect the formation of an interpenetrating polymer network via heparin initiated graft copolymerisation with methyl methacrylate a modification to the method used by Labarre, Boffa and Jozefowicz[128] has been employed.[119] The sodium salt of heparin was dissolved in a dilute solution of nitric acid ($\sim$ 0.25 m) and after degassing with nitrogen a solution of ammonium cerium nitrate is added immediately followed by the hydrogel network swollen with methyl methacrylate monomer. The reaction was allowed to proceed for one hour at 40°C before being stopped by the addition of an excess of ferrous sulphate. The interpenetrating polymer network formed was washed with a methanolic aqueous solution of sodium hydroxide until neutralisation of the nitric acid had been achieved. This step is necessary to ensure that the heparin molecule becomes bound to the hydrogel surface in the form of its anionic sodium salt. Studies with graft copolymers of acidic heparin and methyl methacrylate have found that these materials exhibit no significant anticoagulent activity.[128]

The process of treating the product with sodium hydroxide solution does lead to certain problems however. The sodium hydroxide will not only neutralise the acidic groups within the heparin structure but also attack any methacrylic acid sites within the bulk of the primary hydrogel network. This will give rise to the same 'in vivo' hazards as those discussed in the previous section with a large increase in swell resulting. Indeed experiments carried out on interpenetrating polymer networks prepared by this route show that materials undergo a loss of dimensional stability upon swelling in water.[119] The resulting swollen material is seen to comprise of opaque regions due to hydrophobic chains of poly methyl methacrylate surrounded by a transparent highly swollen hydrogel network due to the presence of carboxylate anions.

Several modifications to the method of preparation may be made in order to remedy this situation. The most obvious approach is to omit methacrylic acid from the composition of the primary hydrogel network and therefore prevent any conversion to carboxylate anions upon treatment of the final product with sodium hydroxide solution. An alternative solution would be to carry out the reaction in aqueous solution rather than dilute nitric acid. The latter appears to be the most profitable approach since the reaction should be carried out using either a finished hydrogel lens or a polymer blank with the front lens surface already lathe cut. This is necessary to prevent the heparin portion of the interpenetrating polymer network which lies at the surface from being removed during the lens fabrication process. The exclusion of methacrylic acid from the hydrogel composition should therefore be avoided as it has been found to lead to complications in the lens manufacturing process. While the production of heparin radicals via the reaction with cerium (Ce^{4+}) ions is likely to proceed more rapidly in acidic media, the use of an aqueous solution will give rise to far fewer complications with the final product.

As was the case for the more conventional preparation of interpenetrating polymer networks discussed earlier in this chapter, a number of materials have been prepared using heparin initiated methyl methacrylate secondary components and are currently being evaluated. While the initial indications of these studies seem promising, no definite results in terms of surface adhesion or protein deposition have been received at the time of submitting this thesis and further modifications may be necessary as part of a continuing research programme.

VII.5 INCORPORATION OF A SPECIES OF KNOWN ANTI-MICROBIAL ACTIVITY TO PRODUCE HYDROGELS WITH REDUCED LIABILITY TO SURFACE SPOILATION

One of the major sources of the prevention of eye infection is the presence of the protein lysozyme in the tear fluid. The production of lysozyme is thought to proceed via the degeneration of the ethelium[105] to yield a species with high anti-bacterial activity due to enzymic cleavage of the cell wall. The activity is lost when the protein denatures and forms a surface deposit which could lead to a gradual loss in the overall resistance of the eye to infection by micro-organisms.[108] In conventional contact lens wear lysozyme deficiency is rarely a problem as both lens surfaces are in contact with tear fluid, promoting flow via the pumping action of the blink cycle which will distribute more of the active species from the epithelium throughout the tear fluid. This may not be the case for high water content materials used for extended wear contact lenses however, as the posterior lens surface may be tightly fitted to the eye allowing little tear fluid to flow.

In order to overcome this potential problem of surface growth of bacterial colonies on high water content lenses, the incorporation of a monomer having anti-bacterial properties into a suitable composition would seem highly desirable. Any monomer having a substituent which exhibits antimicrobial activity should preferably contain an acrylate or methacrylate group also as this will facilitate its co-polymerisation within a hydrogel composition. A great deal of interest has been focussed on the synthesis of monomers of this type, both in the course of this research and by other workers.[43,109] The esters of para-hydroxy benzoic acid have been widely studied as preservatives due to their effectiveness at low concentrations and their reported synergistic activity when two esters have been used in conjunction.[130,132] The anti-bacterial action produced by these types of compounds has been found to deteriorate however, when they are bound to a polymer chain.[133] The inclusion of aromatic halogen substituents has been reported to enhance the bacterial resistance of compounds of this type[134] which has encouraged the synthesis of a halogenated phenolic acrylate ester. This was first carried out in these laboratories by Barnes[43] who employed the esterification reaction of 2,6 dibromo-4-hydroxy phenol with acryloyl chloride. The reaction is carried out in the presence of sodium hydroxide and may be expected to proceed via the mechanism illustrated in Figure VII.i.

The acrylic ester was isolated and copolymerised within a hydrogel network to yield a material with a greater degree of resistance to bacterial surface growth than unmodified copolymers.

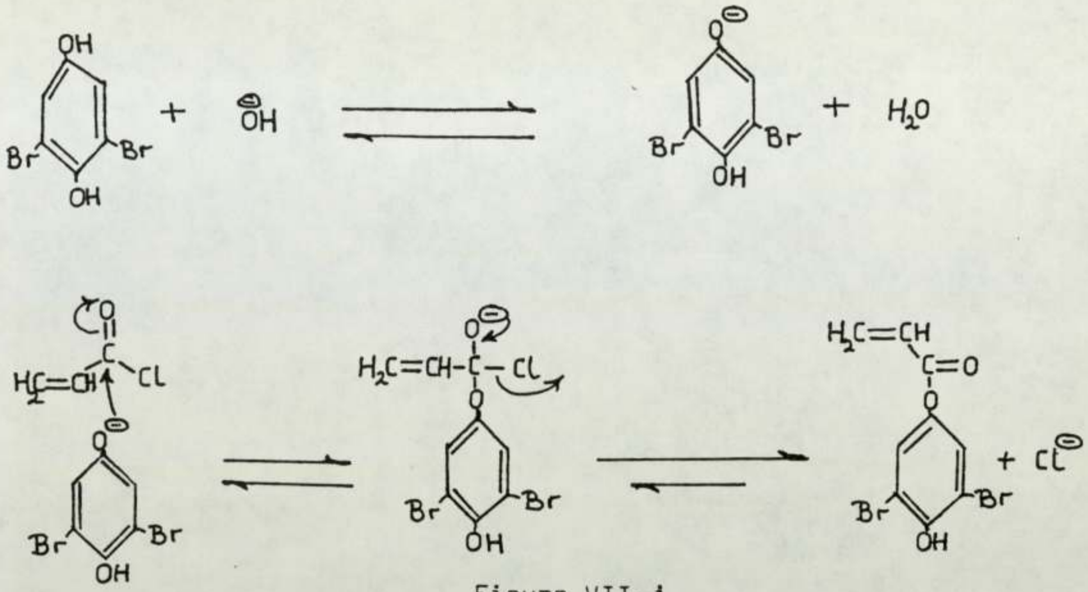


Figure VII.i

This line of research was pursued by the author during the course of an MSc degree.[135] The synthesis of an anti-bacterial monomer was effected via a similar method to that used by Barnes, but in order to promote a greater degree of hydrophilicity the production of an amidic derivative was sought. This was carried out via the reaction of acryloyl chloride with 4-amino 2,6-dibromo phenol, with dimethyl formamide solvent in the presence of triethylamine. The proposed reaction mechanism is portrayed in Figure VII.j.

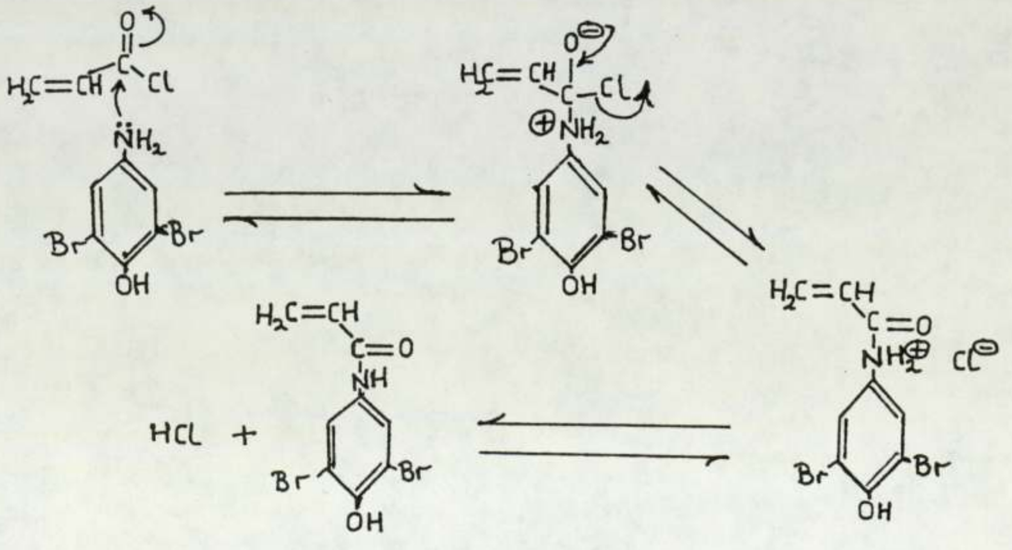


Figure VII.j

The reaction temperature was maintained at 0°C during the addition of acryloyl chloride followed by gentle warming for 30 minutes. The inclusion of triethylamine in the reaction mixture is to remove hydrogen chloride by the formation of a quaternary ammonium salt and therefore displace the equilibria towards a higher yield of the phenolic derivative of acrylamide. A number of differences in the physical properties of the reaction product and the parent amine were found and these are summarised in Table VII.F together with the outstanding features of the infra red, ultra violet and nuclear magnetic resonance spectra of the reaction product.

Complications have arisen however when attempting to produce a hydrogel incorporating a sufficiently high concentration of the synthesised phenolic monomer to ensure antimicrobial activity as phenols are known to inhibit polymerisation by acting as free radical scavengers. Co-monomeric compositions of 2-hydroxy ethyl methacrylate containing more than 2% by weight of the phenolic monomer were not found to undergo gellation when normal conditions of polymerisation (ie 0.1% by weight of azo bis isobutyronitrile initiator at 65°C for 3 days) were employed. At higher initiator concentrations (ie 3% by weight of methyl ethyl ketone peroxide), a greater concentration of the phenolic derivative may be incorporated but this may in turn lead to problems of the type discussed in Chapter VI.

Although a number of materials have been synthesised and are currently undergoing evaluation in order to ascertain the appropriate concentration of the phenolic derivative of acrylamide which is necessary to obtain a sufficient degree of bacteriostatic action in artificial tear fluid, no fully conclusive results have yet been confirmed.

TABLE VII.F

DIFFERENCES BETWEEN REACTION PRODUCT AND PARENT AMINE

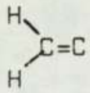
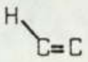
DIFFERENCES IN PHYSICAL PROPERTIES

Physical Property	Reaction Product	Starting Material
Nitrogen content (by elemental analysis)	4.4%	
Melting Point	148°C	194°C
Solvent for UV spectra	Ethanol	Dimethyl Formamide
Peaks in UV spectra	270 mμ (broad)	320 mμ
Solvent for NMR spectra	Acetone	Dimethyl sulphoxide

MAJOR DIFFERENCES IN IR SPECTRA OF THE REACTION PRODUCT

Frequency of absorption (cm^{-1})	Group Assignment
1660 (carbonyl stretch)	Amide I
1530 (N-H bending mode)	Amide II
3020	N-H stretch
3070 (C-H stretching mode)	Vinyl group
990) 970) (C-H bending mode) 1390)	" "
1600 (C=C stretch)	" "

MAJOR DIFFERENCES IN NMR SPECTRA OF THE REACTION PRODUCT

Field strength and type of peak	Group Assignment
3.5 - 3.9 (Multiplet)	Vinyl protons 
4.2 - 4.4 (Triplet)	Vinyl proton 

VII.6 CONCLUSIONS

The successful surface modification of hydrogels in order to prevent excessive deposits of proteinaceous debris is obviously of great importance when considering the design of a continuous wear contact lens material. While this portion of the research has been a success in terms of the synthesis of a number of materials with potentially lower surface-protein adhesive characteristics. As this research project forms part of an ongoing programme into the applications of surface modified hydrogels as biomaterials, a great deal of evaluation of the materials synthesised, in terms of relating surface characteristics to protein deposition, remains to be completed. At the present time it is impossible to predict which of the approaches adopted to obtain a material with reduced surface deposition of proteins will be of most use. When more data is available, one of the methods of producing a surface modified hydrogel may be selected and used as a basis for further experimentation in order to prepare a polymer which may be mass produced for marketing as a continuous wear contact lens material.

CHAPTER EIGHT

CHAPTER VIII

THE DEVELOPMENT OF A DURABLE EXTENDED WEAR CONTACT LENS - SUMMARY AND CONCLUSIONS

VIII.1 INTRODUCTION

While the previous chapter was concerned with the structural refinements necessary to produce a material with appropriate surface properties for a continuous wear contact lens; sufficient research upon the bulk properties (as outlined in Chapters III to VI) has been carried out to enable the production of a hydrogel co-polymer suitable for extended wearing. The steps involved in taking a potentially promising contact lens material to a marketable commodity are outlined below giving a summary of results obtained with co-polymers whose chemical development has been described earlier in this thesis.

VIII.2i LENS MANUFACTURE

The most common technique of lens fabrication is lathe cutting and has been the only technique examined with the high water content materials described, at this time. Initial trials have involved the routine evaluation of the ease of cutting of a dehydrated material in rod form. The materials were cut in such a way as to produce a dehydrated lens of less than 10 mm diameter with a back curve optical radius of 6.7 mm and a front curve calculated (from cutting tables based on the expansion factor) to give a small positive power. Poly (methyl methacrylate) is frequently regarded as a standard material in this respect.

It is apparent that the balance between the toughness and brittleness of a material, which governs the ease of its cutting, will be difficult to predict by conventional physical testing and the most convenient assessment can be made by the practical procedure outlined above. The method of preparation of the polymer in rod form is therefore most important in obtaining a material which may be lathe cut easily. In order to prepare materials having a reproducible ease of cutting, it is necessary to ensure that each of the monomers to be used has been purified by an appropriate method (as outlined in Chapter II) and that the final composition is 'degassed' with nitrogen for 20 minutes prior to the commencement of the polymerisation process. The conditions under which the polymerisation reaction is carried out will also affect the processability of the final material and it is necessary to ensure that each rod is fully cured and also subjected to an appropriate postcure at elevated temperature under vacuum. This procedure is aimed at reducing the concentration of residual materials (either unreacted monomer or low molecular weight oligomers) within the polymer network as these tend to have a plasticising effect upon the material and make cutting difficult. A more detailed account of the effects of reaction time, temperature of polymerisation, initiator concentration and postcuring conditions upon some relevant properties of the polymers produced has been given in Chapter VI. While this study has led to the production of materials under appropriate conditions to give rise to a satisfactory ease of cutting, it must be stressed that further modifications to a polymer composition (eg the addition of fluorinated monomers or the production of an interpenetrating polymer network) will alter the degree of toughness or brittleness and therefore the cuttability also. Any changes in composition should therefore be accompanied by modifications to the conditions of polymerisation in order to ensure that the ease of cutting of the material is retained.

In addition to residual monomers causing plasticisation of the polymer rod, the absorption of moisture from the atmosphere into the highly hydrophilic network will also give rise to the same effect. The material is therefore stored in a drying oven at approximately 40°C immediately prior to lathing. The lens form is cut in the manner described earlier in this section and is then subjected to polishing in order to produce a smooth surface finish of appropriate optical quality. It should be stressed that the polishing procedure is used to remove surface irregularities produced during the lathe cut process rather than forming a specific optical radius other than that already cut. The back curve of the contact lens is generally cut from the polymer blank and polished prior to repeating the process for the front surface. Polishing the back curve is usually carried out by affixing the partially formed lens to a rotating brass chuck with wax and oscillating the back curve in contact with an appropriately sized polishing cloth to produce an evenly smooth surface. The front curve is polished in an analogous manner and any wax is removed by washing with an appropriate solvent. A variety of particulate polishing compounds (not unlike Brasso) are available, but in order to avoid hydration of the lens during the process, formulations of aluminium oxide lubricated with distilled parafin are very popular.[136]

VIII.2ii HYDRATION AND LENS REPRODUCIBILITY

One of the most important aspects of the manufacture of lathe cut soft contact lenses is having sufficient knowledge of the lens material to be certain that a dehydrated lens will produce an undistorted fully hydrated lens of dimensions predictable from expansion tables. In order to ensure that this will occur with the materials developed during the course of this research, tests have been carried out at Kelvin Lenses Research Laboratories using several samples cut from an individual polymer rod and several rods of each particular composition. The results of these tests have indicated that all the materials developed will produce a satisfactory hydrated lens,[137] provided that the normal preparative polymerisation precautions, as outlined in an earlier section (eg monomer purification, degassing, temperature control etc) are employed.

VIII.2iii LENS PARAMETERS AND THEIR STABILITY

The finished contact lenses are subjected to a comprehensive inspection of relevant lens parameters prior to any fitting into a patient's eyes. The back curvature optical radius, the lens diameter and the optical power of each lens are all checked using optical equipment developed by Kelvin Lenses Limited, while the centre thickness is monitored with a micrometer. Each of these parameters are monitored at regular intervals upon prolonged lens storage and after being sterilised by autoclaving.[137]

It was suggested earlier in Chapter IV that no chemical change in these types of acrylamide based hydrogels could be detected upon autoclaving and problems of stability were caused by the interaction of methacrylic acid and N-vinyl pyrrolidone. The checking of lens parameters after autoclaving is a very important test however as no known high water content lens material that is commercially available is able to tolerate repeated sterilisation by autoclaving without undergoing some shift in lens parameters. This becomes apparent from the results shown[137] in Tables VIII.A to C for two materials developed during this research (compositions 1 and 2, as outlined in Chapter VII) and Duragel which is a high water

TABLE VIII.A

CHANGES IN PARAMETERS OF COMPOSITION 1 ON HYDRATION AND AUTOCLAVING

Lens Parameters						Expansion Factors (of Dry)			
Dry		4-Days Hyd		Autoclaved		4-Days Hyd		Autoclaved	
Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam
4.97	7.85	7.40	12.00	7.50	12.35	1.49	1.53	1.52	1.57
4.99	7.85	7.20	12.00	7.40	12.30	1.44	1.53	1.48	1.57
4.98	8.00	7.30	12.20	7.40	13.00	1.47	1.53	1.49	1.63
4.96	7.90	7.30	12.10	7.40	12.40	1.47	1.53	1.49	1.57
4.97	7.90	7.30	12.10	7.30	12.40	1.47	1.53	1.47	1.57
4.96	7.90	7.30	12.05	7.60	12.40	1.47	1.53	1.53	1.57
4.96	7.90	7.30	12.00	7.50	12.30	1.47	1.52	1.51	1.56
4.95	7.90	7.40	12.00	7.40	12.35	1.49	1.52	1.49	1.56
4.97	7.90	7.40	12.00	7.70	12.25	1.49	1.52	1.55	1.55
4.97	7.85	7.40	12.10	7.60	12.35	1.49	1.54	1.53	1.57
4.97	7.90	7.30	12.05	7.50	12.50	1.47	1.53	1.51	1.58
5.00	7.85	7.50	12.00	7.50	12.30	1.50	1.53	1.57	1.54
Means						1.48	1.53	1.51	1.57

TABLE VIII.B

CHANGES IN PARAMETERS OF COMPOSITION 2 ON HYDRATION AND AUTOCLAVING

Lens Parameters						Expansion Factors			
Dry		4-Days Hyd		Autoclaved		4-Days Hyd		Autoclaved	
Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam
5.81	-	8.40	-	8.40	-	1.45	-	1.45	-
5.80	8.65	8.50	13.30	8.20	13.10	1.47	1.54	1.41	1.51
5.81	-	8.50	-	8.70	-	1.46	-	1.50	-
5.80	8.70	8.20	13.45	8.50	13.15	1.41	1.55	1.47	1.51
5.78	8.70	8.50	13.30	8.40	13.15	1.47	1.53	1.45	1.51
5.80	8.65	8.50	13.35	8.40	13.15	1.47	1.54	1.45	1.52
Means						1.46	1.54	1.46	1.51

TABLE VIII.C

CHANGES IN PARAMETERS OF DURAGEL ON HYDRATION AND AUTOCLAVING

Lens Parameters						Expansion Factors			
Dry		4-Days Hyd		Autoclaved		4-Days Hyd		Autoclaved	
Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam	Bcor	Diam
5.52	8.70	8.50	13.35	-	13.50	1.54	1.53	-	1.55
5.51	8.70	8.40	13.35	8.10	13.65	1.53	1.53	1.47	1.57
5.52	8.75	8.60	13.45	8.40	13.55	1.56	1.54	1.52	1.55
5.52	8.70	8.50	13.35	8.80	13.55	1.54	1.53	1.59	1.56
5.52	8.65	8.60	13.35	8.80	13.40	1.56	1.54	1.59	1.55
5.50	8.70	8.60	13.40	8.50	13.50	1.56	1.54	1.55	1.55
				Means		1.55	1.54	1.54	1.56

content lens material (~73.5%) marketed by Cooper Vision Limited.[48-50] The results of these preliminary trials tend to indicate that the behaviour of materials developed during this project is at least comparable to that of a potential competitor which is currently available. Indeed further trials carried out by subjecting these materials to an increased number of autoclave cycles have shown that lenses of Duragel tended to become distorted after 3 cycles of autoclaving or greater. This was not seen to be the case for compositions 1 and 2 however which were found to show good reproducibility of bulk properties both between individual lenses and batches of materials upon successive autoclave cycles. Of these two materials, composition 2 containing substituted acrylamides seems preferable to composition 1 on the basis of the long term viability of the system to repeated autoclaving.

VIII.3 TOXICOLOGY

A great deal of care must be taken prior to the full scale commercial manufacture of a hydrophilic contact lens material to ensure that the lenses will produce no toxicological interaction with the eye when fitted. The most likely cause of such a toxic effect is the presence of low molecular weight residual materials after the completion of the polymerisation process. While part of this research has been devoted to the optimisation of the conditions of polymerisation to produce hydrogels with reduced residual fractions (as outlined in Chapter VI), it is obviously not possible to produce a material prepared from a number of monomeric components that is free from residuals due to differences in monomer reactivity ratios. This is most apparent for the highly reactive acrylamide, which is known to give rise to explosions during polymerisation,[71] and the far less active N-vinyl pyrrolidone which is the main source of residual material. While every attempt is made to remove the residual materials during hydration of the lenses in suitable solutions, tests on the lenses to determine any potential source of eye irritation are also necessary.[69]

The necessary toxicological studies associated with the materials developed during this research have been carried out at the laboratories of the Huntingdon Research Centre[97] and only a brief summary of the principal tests used will be given here.

Each of the tests employed were carried out according to the manner prescribed by the United States Pharmacopeia XIX.[138] An assessment of the acute systemic toxicity to mice of each of the monomers used in the preparation of the materials developed during this project was obtained using the LD50 test (ie lowest dosage required to kill 50% of the animals). The results of these studies have indicated that the toxicity of the monomers in question was not significantly different from other vinylic and acrylic compounds used in the contact lens manufacturing industry. It should be stressed that the general conclusion of most toxicologists that pure hydrogel polymers are biologically inert on acute tissue exposure and that no monomers should remain in the finished lens provided that a satisfactory hydration procedure is adopted.

A number of other relevant tests are also carried out on the polymeric material according to the protocol of the United States Pharmacopeia XIX.[138] These include implantation tests and most relevant of all the examination of extractables. This latter test involves the Vavian extraction of a large number of lenses that have been fabricated and hydrated according to normal manufacturing procedure. Hydration is generally carried out in a chosen hydrating fluid for 3 days prior to extraction in sesame oil. The extract from the lenses is then introduced into a rabbit via an intracutaneous injection in order to assess any toxic effects or irritation. Neither of the acrylamide based polymers (compositions 1 and 2) tested in this manner showed any adverse reactions and were deemed satisfactory for further implantation trials.

The implantation trials for these materials have been carried out by fitting lenses into the eyes of rabbits and observing any irritation produced which may be classified according to the grading scheme proposed by the Food and Drug Administration of the United States of America.[139] Although rabbit eyes are the most widely recommended species for examining ocular toxicity they have proved to be a poor model for assessing soft contact lens materials. In addition to having a very different profile to that of human eyes, the blink rate of rabbits is much slower and therefore less likely to cause an adverse reaction.[69] There are a number of additional complications in using rabbits for continuous wear studies as several of the animals have been found to reject the lenses before the completion of the test period and even tear or eat the lenses.[97] These trials must therefore be viewed as only being of minor importance in comparison to wearing schedules completed by human subjects.

VIII.4 WEARER TRIALS WITH HUMAN PATIENTS

The wearer trials associated with the first of the materials developed during this research for potential continuous wear contact lenses were carried out on a patient population of 27, approximately 25% of whom had worn contact lenses previously. Initial wearing of lenses was restricted to short periods of daily wear in one eye which was gradually extended to full daily wear of the lenses in both eyes. This was in turn extended to overnight wear after a successful period of 4 weeks wearing on a complete daily basis.[140]

As might be expected in initial wearing trials a number of problems will be encountered with a novel contact lens material. The first of these is the interaction of residual monomers within the lens material with the tissue of the eye resulting in adverse reactions[69], as discussed earlier in this chapter. The lenses are also fitted in a loose fashion in preliminary wearing trials in order to minimise metabolic changes within the corneal structure that may result from disruption to the flow of tear fluid. As more expertise is gained in fitting this particular type of lens material and other complications in wearing are overcome, the poor visual acuity which may result from a loose fitting lens can be overcome.[73] Another potential problem with contact lens materials to be worn overnight on a long term basis is the possibility of a change in the lens parameters with time. This is caused by the lids closing during sleep preventing a heat loss from the lens to the atmosphere which maintains the lens material at the temperature of the eye. The elevation in temperature will bring about a change in water content which will in turn give rise to an expansion in lens parameters and alter the fit of the lens. Other variables which will effect the water content of the lens material such as the pH and tonicity of the tear fluid will also result in changes of fit in the lenses. The extent to which these effects will cause changes in the lens parameters will be dependent upon the nature of an individual's tear fluid[104] and therefore a general assessment of how great a problem this will prove cannot be predicted.

As with most novel contact lens materials, it has taken some time to develop fitting expertise in order to achieve a correct balance of fit during a daily wearing cycle. The results of the initial wearing trials obtained with the first material developed during this research (composition 1) are somewhat encouraging. The clinician responsible for fitting the lenses has described the material as being kind to eye and little difficulty was experienced in the eyes becoming adapted to wearing the lenses.[140] The results of the trials for the daily wearing schedules were good and 12 of the initial patient population of 27 were selected to continue the project to the extended wear phase. At this stage of the wearing trials clinical complications began to arise and made it necessary for 10 of the 12 subjects to terminate lens wear. The complications were thought to occur for a number of reasons, but in the opinion of the clinician corneal odema was not a problem which indicates that the oxygen permeability of the lens material is suitable for continuous lens wear. It is possible that difficulties are arising from cycling of the lens over the eye during sleep causing changes in the water content of the lens material which, in conjunction with the effect of temperature variation described earlier, will alter the lens parameters and fitting. As a greater number of patients are subjected to extended wearing of this lens material, this contribution to the complications experienced may be overcome by improved fitting practice. It is also possible that the improved stability to autoclaving found for composition 2 in comparison to that of composition 1 may be important in minimising the complications arising from extended lens wear. A second series of wearing trials using lenses manufactured from composition 2 are therefore in progress but have yet to reach completion.

VIII.5 SUMMARY

The aims of this research project have been fulfilled to a large extent with every possibility of the materials developed during this work being marketed in the near future. While some degree of modification to compositions 1 and 2 may be necessary prior to marketing the finished product, particularly in relation to the methods available to achieving a suitably adapted polymer surface as outlined in Chapter VII, sufficient technical expertise has been developed during this project to facilitate any appropriate adjustments. The 'in vitro' behaviour of the materials developed during this research is currently being compared to that of some hydrogels which are marketed as high water content contact lenses. While this evaluation is still proceeding, some early results for the deposition of the protein albumin[141], as shown in table VIII.D have been obtained using a radioactive tracer (I^{125}) technique and seem most encouraging. No firm conclusions should be drawn solely from these results as they were obtained under static conditions (ie allowing polymer samples to stand in biological solutions containing radioactive labelled protein). Until more information has been compiled from results obtained with systems which more closely assimilate the pumping action of the eyelid it cannot yet be claimed that those materials prepared during this research exhibit a reduced tendency for proteinaceous spoilation.

It is most important to realise however that from the results obtained during this research, the correct balance of properties may be obtained to tailor make a material appropriate for a continuous wear contact lens. When definite conclusions have been arrived at following the completion of the series of material evaluations now in progress, any final minor adjustments to the hydrogel properties in terms of cross-link density (which controls the stiffness of the polymer), surface modification (controlling protein deposition) and the water content (controlling the oxygen permeability) may be made. Upon

TABLE VIII.D

DEPOSITION OF ALBUMIN UNDER STATIC CONDITIONS ON MATERIALS DEVELOPED DURING THIS RESEARCH AND THOSE MATERIALS CURRENTLY AVAILABLE COMMERCIALLY

Contact Lens Product	Manufacturer	Composition of Material	Weight of protein deposited (x 10^{-8} g/lens)
Permalens	Cooper-Vision Optics	NVP, HEMA, MAA	1,700
Duragel	Cooper-Vision Optics	Amido-amino Copolymer	8,000
Eurolens	Kelvin Lenses Limited	Poly(HEMA)	1,400
Sauflon	Contact Lens Manufacturing	NVP, MMA	6,000
Composition 1	This research	see Chapter VIII	1,800
Composition 1 + Fluoro monomer	This research	see Chapter VII (2% HFIPMA)	600
Composition 2	This research	see Chapter VII	940

completion of the 'fine tuning' of the compositions developed during this research, a hydrogel for continuous wear contact lenses may be manufactured and marketed.

CHAPTER NINE

CHAPTER IX

CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

The outstanding conclusion to be drawn from this research is that the main objective of tailoring the properties of an acrylamide based hydrogel to meet the demands of a continuous wear contact lens has been successfully completed, with the production of a material which may soon become commercially available. In order to achieve this however, several aspects of the behaviour of the acrylamide based hydrogels prepared could not be subjected to as full an investigation as their interest merited. These will now be listed together with suggestions of studies which may be undertaken to gain a clearer understanding of the behaviour of these polymers.

The formation, breakdown and re-assertion of interchain hydrogen bonding between amide and carboxylic acid groups should be subjected to a more exhaustive investigation. Techniques which may be used for the determination of the ratio of free to bound water within a hydrogel network such as differential scanning calorimetry and nuclear magnetic resonance spectroscopy may give valuable information on how these components of the water content are affected by the breakdown of hydrogen bonding (whether as a result of hydration time, elevated hydration temperature or diluent added to the monomeric composition). If this line of research was carried out in conjunction with micropenetrometry studies it might be possible to guage the relative importance of interchain hydrogen bonding and the ratio of bound to free water within the network upon the deformational properties of these types of hydrogels.

The same techniques could also be used to extend this study to include the effects of varying the type and density of cross-links within the hydrogel network upon the deformational behaviour and water absorption of the polymers prepared in the course of this research. This may in turn yield an explanation of the observed deviation from Hertzian behaviour of these hydrogels.

The observed behaviour which has been attributed to the interaction of N-vinyl pyrrolidone monomer and methacrylic acid groups within the hydrogel network could also be further investigated by using similar experimental techniques. If the behaviour of these materials proved identical to that of acrylamide-methacrylic acid copolymers, it may be that the effects of N-vinyl pyrrolidone-methacrylic acid interaction is due to hydrogen bonding breakdown rather than the formation of ionic species as postulated in Chapter IV. It would be interesting to study any ionic interaction between aqueous solutions of poly(vinyl pyrrolidone) and poly(methacrylic acid) by potentiometric titration while studies using differential scanning calorimetry on the extracted materials of hydrogels prepared during this research might also yield interesting results.

The latter study would also be of use in order to clarify the results of the survey on the initiator and polymerisation conditions in Chapter VI. Techniques such as gas-liquid chromotography and viscometry could also be used to determine the amounts of N-vinyl pyrrolidone present as residual monomer or homopolymer in the extracted materials. It would be more useful to carry out these studies with suitable copolymer pairs having similar monomer reactivity ratios (such as acrylonitrile and N-vinyl pyrrolidone) and widely different ones (ie acrylamide and N-vinyl pyrrolidone) together with a suitable terpolymer containing all three components.

The synthetic routes for obtaining a suitably surface modified hydrogel as outlined in Chapter VII are of great importance as they form an integral part of the planned marketing programme for the introduction of a Mark II lens having improved surface properties which will overcome the problems of proteinaceous deposits. Of those methods described in Chapter VII, work on the incorporation of fluorinated monomers is at an advanced stage although studies relating the surface energies of these compositions to the degree of protein deposition should be carried out forthwith. This work may then be extended to the other methods for surface modification, especially the heparin initiated formation of an interpenetrating polymer network, in order to determine which offers most promise for general biomedical applications in addition to potential continuous wear contact lens materials. More detailed studies into the properties of these materials may then be carried out in order to characterise the composition of the surface structure and an attempt to develop an experimental technique which will give information on the nature of water (ie free or bound) at the hydrogel surface can be made. This would be of immense value in making an assessment of the properties of hydrogels necessary for an enhanced degree of biocompatibility.

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