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TRANSPORT PHENOMENA IN HYDROGEL MEMBRANES.

COLIN JAMES HAMILTON

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF ASTON IN BIRMINGHAM

MAY 1988

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THE UNIVERSITY OF ASTON IN BIRMINGHAM

TRANSPORT PHENOMENA IN HYDROGEL MEMBRANES.

COLIN JAMES HAMILTON

Submitted for the Degree of Doctor of Philosophy. May 1988

Summary.

In this thesis the factors surrounding the permeation of alkali and alkaline earth metal salts through hydrogel membranes are investigated. Although of relevance to aqueous separations in general, it was with their potential application in sensors that this work was particularly concerned. In order to study the effect that the nature of the solute has on the transport process, a single polymer matrix, poly (2-hydroxyethyl methacrylate), was initially studied. The influence of cation variation in the presence of a fixed anion was looked at, followed by the effect of the anion in the presence of a fixed cation. The anion was found to possess the dominant influence and tended to subsume any influence by the cation. This is explained in terms of the structure-making and structure-breaking characteristics of the ions in their solute-water interactions. Analogies in the transport behaviour of the salts are made with the Hofmeister series.

The effect of the chemical composition of the polymer backbone on the water structuring in the hydrogel and, consequently, transport through the membrane, was investigated by preparing a series of poly (2-hydroxyethyl methacrylate) copolymer membranes and determining the permeability coefficient of salts with a fixed anion. The results were discussed in terms of the "free-volume" model of permeation and the water structuring of the polymer backbone. The ability of ionophores to selectively modulate the permeation of salts through hydrogel membranes was also examined. The results indicated that a dual-sorption model was in operation.

Finally, hydrogels were used as membrane overlays on coated wire ion-selective electrodes that employed conventional plasticised-PVC-valinomycin based sensing membranes. The hydrogel overlays were found to affect the access of the analyte but not the underlying electrochemistry.

Keywords: hydrogel, permeation, permselectivity, Hofmeister series, ion-selective electrode.
to my parents
ACKNOWLEDGEMENTS.

I would like to express my sincere thanks and gratitude to my supervisor Dr. B.J. Tighe for his help, advice, encouragement and guidance throughout the duration of this work.

I would like to thank Dr. S.M. Murphy for both her practical help and useful discussions during my years at Aston.

For financial support, my thanks go to the S.E.R.C. for funding my first two years and the B.T.G. for funding the remaining year.

In addition, I would like to thank the following people: Mr. Phil Corkhill for carrying out the D.S.C. work on my samples, my colleagues in lab. 358 and 248, for their general help, and my flatmates for our many useful discussions throughout the practical work and writing up of this thesis.

Finally, I would like to express my appreciation to Ms. Linda Bennett for her patience and support in the last few hectic months of the writing up.
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<tr>
<td>AZBN</td>
<td>α-azo-bisisobutyronitrile</td>
</tr>
<tr>
<td>CWISE</td>
<td>coated wire ion-selective electrode</td>
</tr>
<tr>
<td>DC-18-crown-6</td>
<td>dicyclohexano-18-crown-6</td>
</tr>
<tr>
<td>DOP</td>
<td>dioctyl phthalate</td>
</tr>
<tr>
<td>DOS</td>
<td>dioctyl sebacate</td>
</tr>
<tr>
<td>D.S.C.</td>
<td>differential scanning calorimetry</td>
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<tr>
<td>Ecell</td>
<td>EMF of cell assembly</td>
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<tr>
<td>EGDM</td>
<td>ethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>EMA</td>
<td>ethyl methacrylate</td>
</tr>
<tr>
<td>EWC</td>
<td>equilibrium water content</td>
</tr>
<tr>
<td>FWC</td>
<td>freezing water content</td>
</tr>
<tr>
<td>HEMA</td>
<td>2-hydroxyethyl methacrylate</td>
</tr>
<tr>
<td>HMA</td>
<td>hexyl methacrylate</td>
</tr>
<tr>
<td>HPA</td>
<td>2-hydroxypropyl acrylate</td>
</tr>
<tr>
<td>HPMA</td>
<td>2-hydroxypropyl methacrylate</td>
</tr>
<tr>
<td>ISFET</td>
<td>ion-selective field effect transistor</td>
</tr>
<tr>
<td>LMA</td>
<td>lauryl methacrylate</td>
</tr>
<tr>
<td>MMA</td>
<td>methyl methacrylate</td>
</tr>
<tr>
<td>MOSFET</td>
<td>metal oxide field effect transistor</td>
</tr>
<tr>
<td>NFWC</td>
<td>non-freezing water content</td>
</tr>
<tr>
<td>PA</td>
<td>polyacrylamide</td>
</tr>
<tr>
<td>PEM-400</td>
<td>methoxy (polyethylene glycol) monomethacrylate</td>
</tr>
<tr>
<td>PVC</td>
<td>poly (vinyl chloride)</td>
</tr>
<tr>
<td>PVP</td>
<td>poly (vinyl pyrrolidone)</td>
</tr>
<tr>
<td>Sm</td>
<td>partition coefficient</td>
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<tr>
<td>St</td>
<td>styrene</td>
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<td>-----</td>
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<td>val</td>
<td>valinomycin</td>
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CHAPTER ONE

INTRODUCTION AND LITERATURE SURVEY.
1.1 Introduction.

Hydrogels are a unique class of polymeric materials in that water plays an intimate part in their structure and related properties. The term hydrogel has no clear-cut single definition, but can be used to describe a variety of materials, such as those which are natural in origin like the alginates; or semi-synthetic, such as cellulose acetate; or synthetic, such as polyacrylamide and the polyacrylates. In the case of this study, the term hydrogel will refer to a synthetic crosslinked polymer network that can swell but not dissolve in water. Wichterle and Lim, with their synthesis of poly(2-hydroxyethyl methacrylate) or polyHEMA, were amongst the first to perceive the potential of these materials: particularly in the field of biomedical applications\(^1\), where their interfacial properties with biological fluids exhibit thromboresistant properties. Such materials are, therefore, of interest for in vivo devices.

The imbibed water provides a medium for the transport of water soluble species through the polymer gel, a property which distinguishes them from other polymers. This work is concerned with elucidating the controlling factors in the permeation of alkali and alkaline earth metal salts through synthetic hydrogel membranes. Although this is of relevance to aqueous separations in general, it is with the use of hydrogels in sensors that the work is particularly concerned. Consequently, the work also involves the construction and use of coated-wire ion-selective electrodes as a test-bed system for new membrane formulations of both hydrophobic and hydrophilic polymeric materials.

This chapter will deal with the factors surrounding permeability and permselectivity; the nature of hydrogels and their transport properties; and finally, possible applications of permselective membranes with special reference to electrochemical sensors.
1.2 The Fundamentals of Permeation and Diffusion.

Permeation is a phenomenon in which a certain species or component passes through another substance. The driving force for such a process could be a gradient in concentration, pressure, electrical potential or even temperature. "Permeation" is a general term for mass transmission and covers a number of transport mechanisms, such as reverse osmosis, dialysis, electrophoresis and diffusion.

In the case of diffusion, matter is transported from one point to another under a concentration gradient. Where such a gradient exists, the random motion of molecules yield a net transfer of the species from the region of higher concentration to that of the lower. This is expressed mathematically using Fick's first Law \( J = -D \frac{dC}{dx} \) (equation 1.1). It states that the diffusional flux of a species is proportional to the concentration gradient measured normal to the unit area of the cross-section through which a species diffuses:

\[
J = -D \frac{dC}{dx}
\]

where, \( J \) = flux (mass.length\(^{-2}\).time\(^{-1}\)), \( F \) = total flow rate; \( S \) = area; \( D \) = diffusivity; \( C \) = concentration; \( X \) = space coordinates measured normal to the cross-section.

In membrane transport, if the diffusivity of the membrane is independent of concentration, then using Fick’s first Law, the steady state flow for the inside of the membrane can be expressed as:

\[
F = DS \frac{C_2 - C_1}{L}
\]

(1.2)
where $L membrane thickness.

1.3 Classes of Membrane.

Membranes are often classed as being either heterogeneous or homogeneous in their behaviour. Heterogeneous or porous membranes are regarded as having fixed pores, such that "bulk flow" occurs. That is, flow is convective as opposed to by activated diffusion. It is assumed that principles applying to macroscopic phenomena, such as Poiseuille's Law, also apply at the submicroscopic and molecular level to such membranes. Permeation of gases through a porous film such as glassine will follow Bunsen's effusion law and is proportional to $T^{-1/2},M^{-1/2}$ where $T$ is the temperature, and $M$ is the molecular weight of the permeant $^4$.

With homogeneous membranes it is assumed that there is neither macroscopic phase separation of the polymer and non-polymer components nor any heterogeneity in these components. This means that in this class of membranes there are no macroscopic pores or channels. However, on the molecular scale nothing can be said to be purely homogeneous. Fluctuations of the macromolecular chain segments yields a system of transient pores and channels. Coherent gels such hydrogels are normally placed into this class $^4,^5$.

With a hydrogel, which consists of a water swollen polymer matrix, the concept of "pores" has a different physical meaning to that of the fixed pores of heterogeneous membranes. In hydrogels, pores are fixed neither in size nor location but result from the random movement of chain segments which may exhibit a high degree of mobility due to the plasticising effect of the water. The pores and channels in such systems are, therefore, in a constant state of flux. Permeation through a homogeneous film can be thought of as resulting from two distinct processes: solubility of the penetrant in the polymer, which is a thermodynamic
quantity; and diffusion which is a kinetic quantity relating to the mobility of the penetrant species within the macromolecular matrix.

1.4 Effect of Structure on Diffusion.

Structure and morphology have important influences on the selectivity and rate of diffusion through a polymer membrane. On the macroscale you have factors such as membrane thickness, lamination, asymmetry as well as the size, type and size distribution of pores. On the microscale, degree of crosslinking, chain stiffness, crystallinity, degree of swelling as well as fixed charges, hydrogen bonding, polar group interactions or even simple Van Der Waal attractions will all affect the rate of transport of the permeant 3, 4, 5. In general, it can be said that, factors which decrease the segmental mobility of the polymer chains will decrease the diffusion rate.

1.5 Separation Processes in Membranes.

There are various separation processes that employ membranes 2, 6, 7. These processes are classified in part by the nature of the membrane and in part by the driving force used to generate the fluxes. Since this work is concerned with the membrane transport of water soluble species it may be appropriate to consider a few of the membrane processes used to achieve separation in aqueous media.

Microfiltration.

Microfiltration membranes have a heterogeneous porous structure with pore sizes typically in the range of 0.02 microns to 10 microns. Such membranes, under a driving force of a pressure differential, in the order of a few tens of kilonewtons, allow for relatively high fluxes of water and dissolved species but retain suspended material such as biological fragments, bacteria and silica. The membranes can be regarded as inert sieves through
which the bulk flow of solvent and solute can occur. However, interaction between particles and the membrane surface may occur, especially in aqueous systems due to the presence of electrical double layer effects. Such factors have an influence on membrane lifetime and transport properties of the membrane.

**Ultrafiltration.**

Ultrafiltration is a means by which large molecules or colloid particles can be separated from solvent and low molecular weight solutes, such as salts. The pore sizes of such membranes lies nominally in the range of 1 - 20 nm. Ultrafiltration membranes are classified by the largest molecular weight material that can be transported. This maximum is known as the molecular weight cut-off. Ultrafiltration works in the same way as microfiltration, the difference being a matter of degree rather than kind with respect to the size of particle that can be transmitted.

**Reverse Osmosis.**

Hyperfiltration, more commonly known as "reverse osmosis", is a process whereby virtually all suspended and dissolved material is separated out from solution. This system employs a semipermeable membrane - so called because it allows for the passage of some substances such as the solvent, but not others, such as the solute. Reverse osmosis occurs when the hydrostatic pressure across the membrane exceeds the osmotic pressure, thus resulting in a flow of solvent from the high-concentration side to the low-concentration side. This is the reverse of what occurs with normal osmosis. To get acceptable solvent flow very high pressures must be employed: typically in the range of 8 - 10 Mpa. Unlike microfiltration and ultrafiltration, a simple sieving mechanism cannot explain the separation processes. The active layer of a reverse osmosis membrane is homogeneous and thus pores have no real physical meaning but are an entropic concept caused by segmental motions in
the polymer backbone and pendant side groups. Transport, therefore, occurs not by bulk flow but by a solution-diffusion mechanism (see section 1.6). The mobility of water molecules may exceed that of inorganic ions by two to three orders of magnitude, the low dielectric constant of the polymer resulting in the ions being less soluble in the membrane phase than the water molecules. Non-ionic solutes are more readily soluble in such membranes. The exclusion of these solutes being due to their low mobility relative to water molecules. Reverse osmosis membranes tend to be asymmetric in structure or in the form of thin film composites where a thin, homogeneous solute rejecting skin (20 - 50 nm thick), known as the "active layer," is deposited on a porous substrate which acts as a support.

**Dialysis.**

In a broad sense, dialysis refers to a process separating one chemical species from another in a liquid solution through semipermeable membranes, by means of their unequal diffusion rates through the membrane. In ordinary dialysis the transport of the solute through the membrane is achieved by imposing a concentration gradient across the membrane - there is no pressure differential in dialysis. If the mixture contains more than one electrolyte; and the interionic interaction amongst ions of the same sign is insignificant then the governing equation in ordinary dialysis is the diffusion equation: (equation 1.2).

In Donnan dialysis the interionic interaction plays an important rôle, and the Donnan equilibrium is maintained at the membrane-solution interface. Normally, "Donnan dialysis" is limited to the dialysis of electrolyte solutes with an ion exchange membrane. The term can be extended to all cases where the Donnan equilibrium has a significant effect such as in neutral membranes where the membrane is permselective with respect to one of the ions present in the solution. However, the Donnan effect may be subsumed if the solvent on the
low-concentration side is continually renewed.

Electrodialysis.
The driving force in dialysis is a chemical potential caused by a transmembrane concentration gradient. In the case of electrodialysis there is a second force: an electrical potential difference. This electrical potential is usually applied opposite to the concentration gradient in order to create a more concentrated salt solution. Consequently, this process is sometimes used as an alternative to reverse osmosis. Neutral membranes are not used since they would tend to pass anions and cations in opposite directions in the electric field and thus fail to achieve the desired concentration of solute. The membranes employed are made of polyelectrolytes which selectively allow for the passage of ions of counter-charge to the polymer: thus, cation transport is selected for by anionic membranes and anion transport by cationic membranes. The electrical potential used in such systems is typically in the range of 1 - 2 V per cell pair.

1.6 The Nature of Water in Hydrogels.
The water absorbed by a hydrogel network is quantitatively represented by the equilibrium water content, EWC, the ratio of the weight of water in the hydrogel to the weight of the hydrogel at equilibrium hydration, expressed as a percentage (equation 2.2). The EWC is arguably the most important single property of a hydrogel, influencing as it does the permeability, mechanical, surface and other properties of the gel 4, 8-11. There is a great deal of evidence to suggest that water in polymers can exist in more than one state 12-15 and that these states of water in the hydrogel will also affect its properties. Thus the water present in a polymer network exists in a continuum of states between two extremes. These are, water strongly associated with the polymer network through hydrogen bonding, sometimes called "bound" or non-freezing water, and water with a much greater degree of
mobility, unaffected by the polymeric environment and sometimes referred to as "free" or "freezing" water. The properties of a hydrogel are therefore strongly influenced both by the EWC of the hydrogel and by the ratio of freezing to non-freezing water.

Although transport models tend mainly to relate the permeability or diffusivity to the overall EWC \(^{16,17}\) there have been studies into the effect water structuring in the hydrogel network may have on transport properties \(^{14,18,19}\). For example, oxygen transport was found to be negligible in styrene-HEMA copolymers that contained no freezing water in comparison to copolymers in which freezing and non-freezing water was present \(^{14}\). Similar findings were made with water binding studies on cellulose acetate for use in reverse osmosis membranes for desalination, where a low freezing water content promotes salt rejection \(^{20}\). This is generally explained in terms of the permeants ability to partition in the different water regions. Hydrophilic solutes such as sodium chloride require the presence of freezing water in order to partition in the membrane \(^{21}\).

1.7 The Blood Compatibility of Hydrogels.

As was mentioned in the introduction to this chapter, one of the properties of hydrogels is their relative biocompatibility compared with hydrophobic polymers. In applications of membranes such as in sensors to monitor components in blood, in hemodialysis and liver support, it is necessary to eliminate thrombus formation. The exposure of blood to an artificial surface usually results in the adsorption of blood proteins. This can be followed by the deposition of platelets which, in turn frequently leads to the formation of a thrombus or blood clot. Although the potential of hydrogels as blood compatible materials has been appreciated for some time \(^1,22\) progress has been slow due to the complicated nature of the interaction of blood with synthetic polymers which leaves many aspects surrounding thrombus formation still unresolved \(^{23}\).
The formation of an adsorbed protein layer is generally regarded as the first step in the interaction of blood with an artificial surface. In general, hydrogels adsorb less protein than hydrophobic materials and the protein is less strongly bound \(^{22}\). The coagulation time of blood in contact with various polymers was found to be related to the critical surface tension of the polymers such that high surface-free energies have faster thrombus formation than low-energy ones \(^{23}\). This feature of a low surface-free energy is generally found to be prerequisite for a material to possess good thromboresistant properties \(^{24}\). The ideal biomaterial, therefore, should have an interfacial free energy as low as possible. Andrade suggested that in an aqueous environment the ideal boundary for blood would be water containing the correct composition of ions and small solute molecules \(^{25}\). The nearest compromise to this ideal is hydrogels.

The lumen of a blood vessel is negatively charged due to the presence of mucopolysaccharides such as heparin sulphate and chondroitin sulphate. This negative charge is believed to be partially responsible for the thromboresistance of blood vessels \(^{23}\). It has, however, been found that the introduction of negative charge into hydrogels has little or no effect on blood compatibility \(^{26, 27}\). Ratner found that incorporating the negatively charged monomer, methacrylic acid into poly HEMA grafts had no apparent effect on the thrombogeneity of the material \(^{27}\), and Bruck discovered that neutral hydrogels performed at least as well if not better than negatively charged ones, leading him to conclude that other factors such as the rôle of water and possibly surface compliance are decisive in the thromboresistance and biocompatibility of hydrogels \(^{26}\).

An other important feature in blood compatibility may be the existence of microdomains of hydrophilic and hydrophobic sites at the polymer surface \(^{27, 28}\). This could explain the
comparatively good thromboresistant properties of poly HEMA, since this polymer exhibits amphiphilic properties due to the presence of hydrophilic hydroxy-groups on the side chains and the hydrophobic groups of alpha-methyl and methylene on the polymer backbone (see figure 2.1) \(^{28}\). Using copolymers it is possible to change the balance of hydrophobic and hydrophilic sites: Ratner found HEMA-EMA copolymer showed greater blood compatibility than either of the homo-polymers poly HEMA and poly EMA (poly ethylmethacrylate).

Water structuring is known to be of importance in biological phenomena \(^{22}\). Therefore the thromboresistant properties of a hydrogel may not be a simple function of the amount of water held within the polymer matrix but related to aspects of the hydrogel that influence the water structure such as monomer used, pore structure and crosslink density \(^{22,25}\).

The comparatively good blood compatibility of hydrogels has meant that these materials are potentially useful as thromboresistant coatings for any implant or device that comes into contact with blood.

1.8 Transport Phenomena in Hydrogels.

Various studies have been made into the basic nature of transport through hydrogels, particularly for small molecular weight species \(^{16,17,29-34}\). An understanding of transport, and thus an ability to influence permeability and permselectivity, is important in applications such as reverse osmosis, kidney dialysis, sensors and drug release. A universally satisfactory transport model has not yet been realised but they mainly all try and relate the permeability or diffusivity to the overall amount of water in the gel matrix. In a study of dissolved oxygen permeation through a range of hydrogels, Tighe and Ng found
the log of permeability coefficient to be linearly related to the overall EWC. This empirical observation was later confirmed by Feurer et al. and Refojo and Leong. All these studies indicated that the oxygen permeabilities were dependent upon the water content alone and were independent of the type of monomer used in the polymer.

A feature of hydrogel membranes in gas transport studies, that distinguishes them from hydrophobic membranes, is their significantly reduced "boundary layer effect." In the case of hydrophobic polymers the "gaseous" oxygen permeability coefficient is greater than the corresponding "dissolved" permeability coefficient (transport of oxygen across a membrane separating two aqueous phases). This is due to hydrophobic polymers possessing an added resistance to transport known as the "boundary layer effect" which is caused by the high interfacial tension between the polymer and water. This can be reduced by increasing the surface hydrophilicity of the membrane.

The free-volume model proposed by Yasuda et al. is, perhaps, the one that has been applied most successfully to the study of solute transport through hydrogels. This model applies to homogeneous water swollen polymer matrices. In such hydrogels, pores are fixed neither in size nor location but result from the random fluctuations of chain segments which may exhibit a high degree of mobility due to the plasticizing effect of the water. The pores and channels in such systems are, therefore, in a constant state of flux. The free-volume or "hole" model takes a partly thermodynamic, partly statistical approach. It assumes that the transported species is associated only with the water phase, with its diffusion being located next to a suitable hole that is both unobstructed and large enough to accept the permeant. The energy required to form a "hole" being the Helmholtz free energy. Their diffusion into the polymer occurs by local activated jumps of the penetrant molecules from one to another unoccupied "hole". The activation energy takes into account rotation of
a few monomer segments near the penetrant and perhaps some bond stretching. The term "holes" does not refer to actual voids in the matrix but is meant entropically to indicate the probability of creating either sorption sites for the penetrant or diffusion channels in the hydrogel matrix through which the penetrant species can move from one site to another. In the free-volume model the flux from high to low concentrations reflects the fact that fewer holes are occupied in the less concentrated regions and the penetrant has a higher probability of jumping to an unoccupied hole in the low concentration regions. The model predicts a linear relationship between \( \ln P \) and \( 1/H \), where \( P \) is the permeability coefficient in the hydrogel and \( H \) is the degree of hydration. It also predicts that permeability decreases exponentially with increasing solute size and that the permselectivity of solutes increases as the degree of membrane hydration decreases.

According to Yasuda et al.\(^{39}\) the free-volume theory predicts a linear relationship between the hydraulic permeability, \( K_w \), and degree of hydration, \( H \), (above about \( H = 0.4 \)) of the form:

\[
K_w/H = A.\exp(-BHV_{fw})
\]  

(1.3)

where \( A \) and \( B \) are constants and \( V_{fw} \) is the free-volume function of water in the membrane.

However, Kojima et al.\(^{40}\) did not find such a relationship for poly (vinyl alcohol) membranes. They found that data obtained from various hydrogels studied by other authors also did not fit equation 1.3. Instead, Kojima et al. obtained a linear relationship using

\[
\ln(K_w/H) = A + BH
\]  

(1.4)

where, again, \( A \) and \( B \) are constants.
Linearity was satisfied in a range of \( H \) from 0.4 to 0.9. Using the Ogston's Relationship 41, which is a mathematical model for the diffusion of spheres through a random suspension of fibrils, the above authors expanded equation 1.4 into:

\[
K_{W/H} = K_{RW} \cdot \exp[-(1 - H)(1 + r/R_f^2)] \quad (1.5)
\]

where, \( r \) = radius of the solute; \( R_f \) = radius of a fibril in the membrane; and \( K_{RW} \) is a reduced permeability of water in the hydrogel.

Later studies carried out by Kojima et al. 31 found that the Ogston's relationship also applied to the diffusive permeability of solutes such as NaCl, Congo Red and Sunset Yellow dye, in poly (vinyl alcohol) membranes, where its prediction of a linear relationship between \( (1 - H) \) and the logarithm of \( P \) or \( D \) (the permeability and diffusion coefficients respectively) gives the best fit to the experimental results.

More recently, Peppas and Moynihan have proposed a theoretical model for the diffusion of solutes through moderately swollen hydrogels which makes use of topological features as well as free-volume characteristics of the network 42. It yields a general expression which shows the dependence of the normalised diffusion coefficient on factors such as the degree of swelling, the radius of the solute, the number average molecular weight between crosslinks and a function related to the mesh size which takes into account the effects of barriers such as those due to crosslinks and entanglements.

By choice of monomer composition or polymerisation technique the amount of water, porosity and consequent permeability characteristics can be controlled, that is, heterogeneous hydrogels with a fixed macroporous structure can be generated as well as
the homogeneous type mentioned above. This allows hydrogels to be permeable not only to small molecular weight species but also to macromolecules such as the protein hormones.

Davies \(^{43}\) in one of the early studies on the use of hydrogels for the controlled release of high molecular weight species, such as bovine pancreatic insulin, found the diffusion coefficient of the hydrogel, \(D\), to be governed by the molecular weight of the penetrant and the degree of hydration of the polymer. Expressed mathematically by the following empirical equation:

\[
D = D_0 \exp[-(0.05 + 10^{-6}M)P_C]
\]

where \(D_0\) is the diffusion coefficient of the penetrant in aqueous solution; \(M\), the molecular weight of the solute; and \(P_C\), the polymer concentration of the gel.

The polymers were based on polyacrylamide (PA) and polyvinylpyrrolidone (PVP). Langer and Folkman \(^{44}\) studied the release of the macromolecular species, soybean trypsin inhibitor (molecular weight 21,000), from poly HEMA, polyvinylalcohol and ethylene-vinyl acetate copolymer based systems. They found that the release mechanism of such high molecular weight species could not be determined, and in the case of the ethylene-vinyl acetate copolymer, simple diffusion could not explain the release behaviour. Such species that were studied do not diffuse through a homogeneous film of the pure polymer. This may be indicative that these macromolecular species permeate out through heterogeneities (flaws and cracks) that are formed during the manufacture of the polymer devices. Indeed, this concept of a heterogeneous "drug-modified polymer" was used by Brook and van Noort \(^{45}\) to explain the release characteristics of hydrocortisone sodium succinate from acrylic gels. Contrary to the expectations of the free-volume model of Yasuda \(^{30}\) which would predict an increase in the rate of release with an increase in the degree of hydration of the polymer, the opposite was found. The authors concluded that
diffusion of the drug through the polymer matrix was, therefore, insignificant but occurred, instead, by surface release and with dissolution into and diffusion through cracks and channels that were formed due to the presence of the drug within the polymer system.

1.2 Applications of Permselective Membranes.

In recent years synthetic polymeric membranes have been found to be of increasing commercial importance in industrial and biomedical applications. In industry membranes are exploited in separation processes where they act as a selective barrier, separation being achieved by exploiting factors such as size exclusion phenomenon or differential transport rates through the membrane. In biomedical applications the permeability characteristics of membranes find use not only in separation processes but also in the controlled release of drugs, in gas permeable contact lenses, and in sensor devices. Some of the membrane processes that are used in aqueous media have already been discussed section 1.5. It is pertinent now to illustrate these general concepts with some specific examples.

The "precursor" to the study of permselective membranes was the early work carried out on reverse osmosis. The classic case of this would be for the desalination of sea and brackish water using cellulose acetate membranes. The membrane has a stronger affinity for the water than it has for the solute. This results in the existence of essentially pure water on the surface and within the membrane. The water is subsequently transported through the membrane under a pressure gradient in the reverse osmosis process. Reverse osmosis is also employed in the food and dairy industries where it can be used to concentrate solutions such as milk, juices, syrup and coffee. Ultrafiltration is also used by the food and dairy industries where it finds application in areas such as the recovery of products from fermentation or in biomedical work such as the preparation of plasma from whole blood which it achieves by removing all cellular and particulate matter.
One of the major biomedical applications of membranes is in hemodialysis for the removal of waste materials such as urea, creatinine, and uric acid by dialysis of blood through a semipermeable membrane \(^2\). Originally hemodialysis used cellophane tubing as the membrane through which the blood flowed. The tubing was in contact with the dialysate so that the waste material could permeate through the membrane from the blood side to the dialysate side according to its own concentration gradient. Later developments led to a cupra-ammonium cellophane, "cuprophan," being employed. Another type uses amine-modified polyacrylonitile hollow fibres that can be ionically coupled with heparin to provide a non-thrombogenic membrane \(^2\).

The 1980's has seen a considerable increase in interest in clinically relevant electrochemical sensors \(^{50-52}\). This interest is based upon the ability of chemical sensors to be miniturised and to provide valuable real-time information about medical treatment, environmental contamination and chemical production. This gives them the advantage over the slower more traditional analytical techniques.

There are, however, many problems in the design and performance of sensors that have yet to be resolved \(^{50,53}\). Many present devices can only monitor a single variable whereas for a sensor to be commercially viable it is considered that it must have the capability to measure several analytes \(^{50}\). One of the major problems concerning clinical sensors for in vivo monitoring is rejection by the body: that is, encapsulation by body tissues and, perhaps most seriously of all, the pro-ocation of life threatening responses such as potentially fatal blood clots forming around the implanted device.
The term "biosensors" used to refer to any device that measured an analyte that occurred in a biological system. More recently a "biosensor" has come to mean a device based on a biologically selective material such as enzymes, cells or monoclonal antibodies immobilised on or near a transducer (a device for relaying electrical signals or converting a non-electrical parameter into an electrical signal). This distinguishes them from chemical sensors whose selectivity, for example, in the case of ion-selective electrodes is most commonly based on a specific chelating agent dissolved in a polymer matrix (usually plasticised poly (vinyl chloride)). Sensor research has concentrated on a number of electronic configurations such as:

(1) **potentiometric or amperometric electrodes**, in which a reaction produces a potential difference or a current;

(2) **enzyme thermistors**, devices whose electrical response is a function of reaction temperature changes;

(3) **optoelectrical devices**, in which a controlled chemical or biological reaction evokes a change in light transmission and a consequent voltage change: essentially a mini-spectrophotometer; and

(4) **electrochemical-sensitive transistors**, whose signals depend on the potential developed by electrochemical or enzymatic reactions.

Since this work is concerned with membranes for use in electrochemical sensors, these devices will now be discussed more fully.
One of the earliest and perhaps still the most successful is the conventional potentiometric ion-selective electrode. This is based on cell assemblies of the type:

external reference electrode || sample solution || membrane || internal reference system

The membranes used in such systems are typically plasticised PVC containing a selective chelating agent. Over the years a number of ionophores have been tested and developed for a range of ionic species. The classic example is one which is not synthesised but is found in nature: the antibiotic valinomycin. This exhibits a high selectivity towards the potassium ion and as such is used in potassium ion-selective electrodes.

A simpler device was designed by Freiser which he termed coated-wire ion-selective electrodes. Here, the detection part of the electrode is simply a copper, silver or platinum wire with a coating of an ion-selective membrane. For example, the level of potassium in blood has been determined using a coated-wire electrode which employed a membrane of valinomycin in solvent impregnated poly (vinyl chloride). This type of electrode differs with its earlier counterparts in that it has no internal reference.

Some devices are based on semiconductor technology; specifically, field-effect transistors. These sensors can be easily miniturised via current semiconductor production methods. Charge movement in a metal oxide semiconductor field-effect transistor (MOSFET) is controlled by an electrical field between a metal oxide "gate" and a channel made of an n- or p-type semiconductor. The field controls current between the source and the drain and very small inputs can be amplified or can cause large currents to be switched.
The construction of an ion-selective FET (ISFET) is similar to that of the MOSFET, but the gate is replaced by an ion-selective membrane that is in contact with the solution being measured. The effect of the electrical field in the MOSFET metal oxide is replaced by the ion-selective effect of the electrical double layer at the membrane/test solution interface.

ISFETs can be used to measure various electrolytes in body fluids or industrial waste streams. Other membranes may be designed to pass relatively large organic molecules into the gate region for detection. Permselective membranes used in ISFETs have, so far, tended to be either liquid membranes or the solvent impregnated poly(vinyl chloride) type mentioned above, using ionophores as mobile charge carriers. For example, a micro-ISFET for intracellular potassium measurements has been developed which uses a liquid membrane in contact with the test medium via a glass capillary. Another potassium ion ISFET used the polymer membrane previously described of valinomycin in plasticised PVC.

Many models of ISFETs respond in less than thirty seconds and some in only a few seconds. They are also highly sensitive to many ionic species being typically able to detect concentration as low as about 10^{-6} M. However, a problem exists with research into ISFETs in that they are currently difficult to obtain and only a few universities have the integrated circuit fabrication facilities for their manufacture.

Although the electronic configurations of the electrodes may differ, the types of sensing membranes used are the same. In the case of ion-selective electrodes these membranes tend to be hydrophobic in nature. Such electrodes when used to monitor some component in blood are vulnerable to membrane fouling by blood proteins, platelets and other materials. This has lead some workers to employ dialysis membranes in conjunction
with ion-selective electrodes as an overlay membrane for the electrode. From what was discussed in section 1.7, this suggests that one of the roles of hydrogels in ion-selective electrodes may be as blood compatible overlays for conventional hydrophobic sensing membranes.

**1.10 Scope and Aims of This Project.**

The permeability of hydrogels in aqueous systems has been a feature of great importance in setting these materials apart from other polymers. The fact that water exists as an intimate and essential part of the polymer matrix implies that it might have the ability to modulate transport behaviour of water soluble species. This is a feature that may be exploited for use in chemical sensors and related devices.

To date, permeability studies involving hydrogels have been far from systematic. Although interest in desalination stimulated work on sodium chloride transport through hydrogels in the late 1960's, for example, little work on other ionic permeants has been reported. In extending this work to enable a more complete understanding of ionic transport processes in hydrogels to be achieved, it is important to study two distinct aspects of the phenomenon. The first is the variation in transport rate of different cations in the presence of a common anion and the second, the effect of the nature of the anion on the transport of a given cation. It is of further importance that any model or mechanism is capable of accounting for differences that are produced by changes in the backbone structure of the polymer, its equilibrium water content and distribution of binding states.

The first part of this work is concerned with the effect of solute/water interactions on the transport of ions through hydrogel membranes of poly(2-hydroxyethyl methacrylate). The study then progresses to give a more complete understanding of transport phenomena by
studying the effect of variations in water-structuring that may be produced by variations in the polymer, and thus membrane structure. This involved copolymerising 2-hydroxyethyl methacrylate (HEMA), with hydrophobic monomers such as methyl methacrylate (MMA) and styrene.

Another approach to achieve the modulation of transport behaviour of a hydrogel membrane was to incorporate a selective chelating agent or ionophore into the polymer matrix. The ionophores chosen were crown ethers because of their selectivity in the chelation of permeating species and their ready availability. They were incorporated by encapsulation, that is, not bound to the polymer but trapped within the polymer matrix. The technique of encapsulation was used because it was the quickest and simplest way of getting the ionophore into the membranes.

Although this work is mainly concerned with elucidating the various factors surrounding ion transport through hydrogels using a permeability rig, some work was carried out on coated wire ion-selective electrodes. These employed conventional sensing membranes of valinomycin dissolved in plasticised PVC, and the effect of hydrogels as overlay membranes was investigated. The transport conditions for the ions through the hydrogel overlay are somewhat different from those carried out on the permeability cell employed in the general transport studies. With the permeability cell, sink conditions apply, such that solute transport is steady state in nature. With the hydrogel overlay on the sensor, the final steady output of the device reflects the equilibrium state for the test ion partitioning in the membrane. Transport in the pre-equilibrium state is seen in the response time of the device.

This particular investigation relied predominately on HEMA based hydrogel systems, but there exists a vast synthetic potential in this area, both in the type of hydrogel and the type
of ionophore. Dr Tighe's research group possesses a large body of information on hydrogels such as the work carried out by Ng 64, Pedley 65, Atherton 66 and Corkhill 67. There is also a large amount of literature on ionophores but their use in hydrogels to modify permeation is a new application of them.
CHAPTER TWO

MATERIALS AND METHODS.
2.1 Introduction.

This chapter deals with the preparation of the membranes studied and lists the reagents involved. It mentions the techniques used to characterise the membranes and describes the design and operation of the apparatus for both the transport and the ion-selective electrode studies. It also includes brief discussions as to why the particular designs of the permeability cell and sensing electrodes were chosen for this work.

2.2 Reagents.

2.2.1 Monomers.

All monomers used (table 2.1, figure 2.1) were purified by conventional reduced pressure distillation with the exception of methoxy (polyethylene glycol) monomethacrylate, which was used as supplied and 2-hydroxyethyl methacrylate, (HEMA), which was obtained in an already pure form (optical grade). This is because HEMA is a very difficult monomer to purify since it readily undergoes disproportionation to ethylene glycol dimethacrylate and methacrylic acid. The purified monomers were then stored in a refrigerator until required.

**Table 2.1 Monomers Used.**

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Molecular Weight</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-hydroxyethyl methacrylate</td>
<td>130</td>
<td>HEMA</td>
<td>Ubichem Ltd.</td>
</tr>
<tr>
<td>2-hydroxypropyl acrylate</td>
<td>130</td>
<td>HPA</td>
<td>B.D.H.</td>
</tr>
<tr>
<td>2-hydroxypropyl methacrylate</td>
<td>144</td>
<td>HPMA</td>
<td>B.D.H.</td>
</tr>
<tr>
<td>hexyl methacrylate</td>
<td>170</td>
<td>HMA</td>
<td>B.D.H.</td>
</tr>
<tr>
<td>lauryl methacrylate</td>
<td>254</td>
<td>LMA</td>
<td>B.D.H.</td>
</tr>
</tbody>
</table>
2.2.2 Crosslinking Agent.

The crosslinking agent employed in this research (table 2.2, figure 2.2) was used as supplied without further purification. It was stored in a refrigerator until required.

<table>
<thead>
<tr>
<th>Crosslinker</th>
<th>Molecular Weight</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethylene glycol dimethacrylate</td>
<td>198</td>
<td>EGDM</td>
<td>B.D.H</td>
</tr>
</tbody>
</table>
2.2.3 Initiator.

The free-radical initiator was used as supplied without further purification. It was stored in a refrigerator until required (table 2.3, figure 2.3).

<table>
<thead>
<tr>
<th>Initiator</th>
<th>Molecular Weight</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-azo-bis isobutyronitrile</td>
<td>164</td>
<td>AZBN</td>
<td>B.D.H</td>
</tr>
</tbody>
</table>

Figure 2.3 Structure of Initiator.

Azo-bis-isobutyronitrile
2.2.4 Ionophores.

The ionophores were used as supplied and stored in a refrigerator until required (table 2.4, figure 2.4).

Table 2.4 Ionophores Used.

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>Molecular Weight</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-crown-6</td>
<td>264</td>
<td>-------------</td>
<td>Lancaster Synthesis Ltd.</td>
</tr>
<tr>
<td>valinomycin</td>
<td>1111</td>
<td>val</td>
<td>Aldrich</td>
</tr>
</tbody>
</table>

2.2.5 Polymers.

All commercially obtained polymers were used as supplied (table 2.5).

Table 2.5 Commercial Polymers.

<table>
<thead>
<tr>
<th>Commercial Polymer</th>
<th>Comment</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>poly (vinyl chloride)</td>
<td>low molecular weight</td>
<td>PVC</td>
<td>B.D.H.</td>
</tr>
<tr>
<td></td>
<td>MW ~ 100,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2.6 Plasticisers.

The plasticisers were used as supplied (table 2.6, figure 2.5).

Table 2.6 Plasticisers.

<table>
<thead>
<tr>
<th>Plasticiser</th>
<th>Weight</th>
<th>Abbreviation</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>dioctyl phthalate</td>
<td>390</td>
<td>DOP</td>
<td>Fluka</td>
</tr>
<tr>
<td>dioctyl sebacate</td>
<td>426</td>
<td>DOS</td>
<td>Fluka</td>
</tr>
</tbody>
</table>
Figure 2.4 Structure of Ionophores.

dicyclohexano-18-crown-6

18-crown-6

valinomycin
Figure 2.5 Structure of Plasticisers.

diocyl phthalate

\[
\begin{align*}
\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-O-C-C-O-CH}_2\text{-CH-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{-CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{-CH}_3
\end{align*}
\]

diocyl sebacate

\[
\begin{align*}
\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-O-C-(CH}_2\text{)}_8\text{-C-O-CH}_2\text{-CH-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{-CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{-CH}_3
\end{align*}
\]
2.2.7 Salts.

All salts were of analytical grade and purchased from Fisons or B.D.H. and used without further purification. Salt solutions were prepared with deionised water of ionic conductivity \(1.5 \pm 0.5 \, \mu\text{Siemens.cm}^{-1}\).

2.3 Membrane Preparation.

2.3.1 Preparation of Hydrogel Membranes.

Membranes were prepared by the bulk polymerisation of the monomer reaction mixture in a membrane mould consisting of one or two polyethylene gaskets (0.2 mm thick, with rectangular hole \((6 \times 11 \, \text{cm})\)) sandwiched between two glass plates \((8 \times 13 \, \text{cm})\)\(^{14}\). The gaskets were separated from the plates by two sheets of melinex (poly(ethylene terephthalate)) that were present to aid the release of the membrane and give it a smooth finish (figure 2.6). With the assembly being held together by bulldclips, the reaction mixture was transferred into the mould cavity via the needle of a syringe inserted between the melinex sheets - the gasket being split at one corner to facilitate the entry of the needle. With the mould held sideways, thus allowing air to escape through the gap created by the needle and gasket slit, the mixture was slowly injected into the mould until the cavity was almost full. On withdrawing the needle the space between the two mould halves was reduced and the mixture thus filled the mould, with any excess being squeezed out of the sides. The mould assembly was then placed vertically in an air oven at 60°C for three days to allow polymerisation to take place. This was followed by two hours post-curing at 90°C. On removal from the oven the clips were removed and the glass plates prized off. The gasket was removed and the melinex sheets carefully peeled from the membrane which was then placed in distilled water to hydrate. On the few occasions when only one melinex sheet would come off, the membrane and the remaining melinex sheet were placed in...
Figure 2.6 Membrane Mould.

- syringe needle
- polyethylene gasket
- melinex sheets
- spring clip
distilled water for at least a day before being transferred to a beaker of boiling distilled water. The membrane could then be readily peeled from the melinex. Membranes were allowed to fully hydrate in distilled water for at least three weeks, with frequent changes of water to remove any water soluble residue, before being used for study.

2.3.2 Production of Linear Hydrophilic Polymer by Solution Polymerisation.

The reaction mixture consisting of monomer (100g) and initiator (AZBN, 0.5g) was degassed by bubbling N₂ through before being added dropwise, over 30 minutes, to a 2 litre reaction vessel containing 1 litre of ethanol, which itself had been similarly degassed. The system was immersed in a water bath at 60°C and allowed to polymerise under a nitrogen atmosphere for 9 hours with constant stirring. The vessel was then lifted out of the bath and the solution left to cool overnight. If any polymer precipitated out it was redisolved by reheating with stirring. The solution was filtered by pressure filtration. The polymer was precipitated by adding the solution dropwise to diethylether which had been cooled with solid CO₂. The precipitated granules were then filtered out and washed again with diethylether. The polymer was dried under vacuum and stored in a refrigerator until required.

2.4 Properties of Hydrogels.

2.4.1 Determination of the Degree of Leaching

In some membranes that contained ionophore or diluent, the degree of leaching of the additive was determined in the following manner:

On the removal of the membrane from its mould the complete membrane was weighed.
This was carried out quickly in order to minimise any weight gain through absorption of water vapour. The membrane was then placed in distilled water to hydrate and left for some weeks with regular changes of water to allow any water soluble material to leach out. The membrane was then dried by placing it in a 60°C oven for 24 hours; followed by several hours in a vac-oven at 80°C. The degree of leaching was calculated as a % weight loss using:

\[
\text{dry weight} - \text{dry weight}
\]

% weight loss = \( \frac{\text{pre-soaking} - \text{post-soaking}}{\text{pre-soaking}} \times 100 \) \hspace{1cm} (2.1)

2.4.2 Determination of the Equilibrium Water Content.

A disc of 5cm diameter was cut from the hydrated polymer sheet under study (alternatively three discs of 1.1cm in diameter were used), the membrane having been soaked in distilled water for at least three weeks. The disc then had its surface water removed by careful blotting on filter paper. The sample was placed in a preweighed weighing bottle and its hydrated weight, \( W_h \), recorded. The disc was dried; first in an air oven at 60°C overnight and then in a vacuum oven at 80°C until a constant dehydrated weight, \( W_d \), was achieved (at least 5 hours). The Equilibrium Water Content, EWC, is defined as:

\[
\text{EWC} = \frac{\text{weight of hydrated sample} - \text{weight of dehydrated sample}}{\text{weight of hydrated sample}} \times 100
\]

\[= \frac{W_h - W_d}{W_h} \times 100 \] \hspace{1cm} (2.2)
2.4.3 Determination of the Partition Coefficients.

The partition coefficient of a particular salt in a particular membrane is defined as the ratio of the concentration of the salt in the membrane to that of its concentration in solution (equation 2.3). This was determined in the following manner:

A disc, 5cm in diameter, was cut from the hydrated polymer sheet under study. The membrane having been soaked in distilled water for at least three weeks prior to use. The disc was then transferred to a 250mM solution of the test salt and allowed to equilibrate over several days at 37°C. The disc was then removed and, after carefully drying its surface, it was weighed. It was then placed in 40ml of deionised water and left for a few days to allow any salt that was dissolved in the matrix to leach out. The concentration of this solution was measured by flame photometry. Since the volume of water added was known, the amount of salt present in the membrane sample could thus be discovered. The partition coefficient, $S_m$, was then calculated using the following equation:

$$S_m = \frac{\text{concentration of salt in membrane} \text{ / (mMole/g)}}{\text{concentration of salt in equilibrating solution} \text{ / (mMole/g)}}$$

(2.3)

2.5 Permeation Studies.

2.5.1 Permeation Cell: Introduction.

In the study of membrane transport many different kinds of permeability cells have been constructed. For equicompartment systems the various cell designs are usually categorised by membrane placement: that is, whether the membrane is placed horizontally or vertically68.
In horizontal placement the membrane is sandwiched between the two cell halves that are stacked on top of one another. This arrangement leads to certain problems: for example, you can get a hydrostatic head produced; stirring the fluid layers at the membrane is difficult and there is the problem that bubbles may collect on the underside of the membrane.

In those designs where the membrane is placed vertically, the problem of a hydrostatic head and air bubbles is resolved but this still leaves the problems of stirring. Some workers solved this by mechanical means using gears and shafts that penetrate the permeability cell, such as that of Flynn and Smith 68. Misra et al. used completely internal stirrers mounted on shafts which were magnetically coupled to external stirrer motors 69.

It was a permeability cell similar to that of Misra et al. that was used in this work. The original cell was obtained from D.C. Sammon of A.E.R.E., Harwell, and first used by Nigel Atherton 66. Copies of it were later made, thus allowing for more than one permeability study to be carried out at the same time.

2.5.2 The Design and Set-Up of the Ion Permeability Apparatus

The permeability cell (figure 2.7) was constructed mainly of perspex and was cylindrical in shape with a diameter of 9cm and about 14cm long. The cell consisted of two chambers (each of diameter 3.8cm by about 5.7cm) separated by a membrane barrier. This test membrane was held in place by two silicone rubber gaskets (9cm outer diameter, 4cm inner diameter). The two compartments were clamped together by six bolts. This had to be done carefully since if it was too loose then leakage between the chambers may occur and if too tight then the membrane may be damaged. Each chamber had an inlet and an outlet to
Figure 2.7: Diagrammatic Representation of the Permeability Cell
allow the continuous circulation of fluid. The fluid outlet was directly above the fluid inlet to facilitate the removal of air bubbles. The solutions on each side of the membrane were stirred by paddles positioned close to the membrane. They were driven, via magnetic couples, by stirrer motors external to the system. The completed cell assembly was immersed in a specially constructed water bath of the right dimensions to allow the proper functioning of the magnetically coupled stirrers. As well as regulating the temperature within the cell, the bath also prevented the edges of the membrane from becoming dehydrated. Each chamber was connected to a 250ml separating funnel that acted as a reservoir through which the system could be filled. The chambers were also attached to sampling tubes that allowed samples to be taken by inserting a needle through the supaseal. Alternatively, the low concentration side was connected to a flow through conductivity cell, thus allowing the concentration to be monitored conductometrically. The closed fluid loops of each side of the permeability cell were circulated by a peristaltic pump with a flow rate of 30ml.min⁻¹. The stirring rate was in the region of 150 rev.min⁻¹ (figure 2.8).

2.5.3 Operation of the Ion Permeability Apparatus.

A disc, of at least 5cm in diameter, was cut from the membrane to be studied and sandwiched between the silicone rubber gaskets. The permeation cell was then assembled and immersed in the water bath. Each cell half was filled from its respective reservoir, a process which took a few minutes to fill the cell and eliminate all the bubbles from the system. The low concentration chamber was filled with deionised water while the high concentration chamber was filled with a 250mM solution of the test salt. A stop clock was started as soon as the cell began to fill, this point being taken as the zero time. To prevent a pressure gradient across the membrane, the hydrostatic pressure in each chamber was equalised by moving a sampling reservoir up or down until the membrane no longer bulged
to one side. Unequal pressures would have distorted the fragile hydrogel membrane and affected the permeability characteristics of the system. Finally, the stirrer motors were switched on and set at their minimum speed (approximately 150rpm). The solution to be assayed was removed, in 1ml portions, from the low concentration sampling reservoir at set time intervals: either hourly or every 45 minutes. Alternatively, the solution was assayed conductometrically by having a flow-through conductivity cell attached to the circulatory system of the low concentration side.

2.5.4 Use of Flame Photometer.

Ion concentrations of the samples taken from the permeability cell were assayed by flame photometry using a Model A EEL Flame photometer (Evans Electro-Selenium Ltd.). The species studied were K⁺, Na⁺, Li⁺ and Ca²⁺. Calibration curves, covering a number of ranges up to 10 mM, were constructed by preparing a series of standard solutions of their chloride salts. The appropriate filter for each salt was chosen and the flame photometer adjusted to read "0" for distilled water and "100" for the top concentration of the particular calibration curve range (either 0.1, 1 or 10 mM) of the salt under study. The readings of the intermediate concentrations could then be noted and a graph of photometer reading against concentration plotted. The reading obtained from an assay could thus be read off as a concentration using the relevant calibration curve.

2.5.5 Calibration of the Conductivity Cell.

As has been mentioned, as well as flame photometry, some permeation runs were monitored conductometrically. A flow-through conductivity cell (cell constant k = 1) was employed with an Alpha 800 conductivity meter (CP Instruments Company Ltd.). The relatively small concentration changes occurring in the low concentration chamber (always
Figure 2.8 Permeability Apparatus: Solution Flow Path.
within 0-10 mM) meant that conductivity changed linearly with concentration. This meant that only one standard solution was required to convert the conductivity readings to concentrations. The conductivity cell was calibrated by selecting a standard solution of the test salt that lay within the range of measured conductivities (either 0.1, 1 or 10 mM). This allowed a simple conversion factor to be calculated to translate μsiemens to mM. The conductivity of standard solutions was determined by placing the ATC probe in a beaker containing 150ml of the solution and the dipping and removing the flow-trough cell into this solution to rinse the solution through the cell (the cell having been previously flushed through with deionised water). This was repeated a few times, ensuring no bubbles appeared in the cell, until a constant reading was obtained.

2.6 Coated Wire Ion-Selective Electrode Studies.

2.6.1 The Coated Wire Ion-Selective Electrode: Introduction.

The relatively simple construction of coated wire ion-selective electrodes, CWISE's, as well as the ease with which different membrane coatings can be changed, makes these devices a useful test-bed for studying new sensing membrane formulations that are also suitable for more sophisticated devices such as ISFETs. The design and construction of both the CWISE and the electrochemical cell are now described, in addition to the techniques employed to determine some important parameters of the sensing electrode.

2.6.2 Preparation of Membrane Coating Solutions.

A typical preparation was as follows:

Poly (vinyl chloride), PVC, (0.4g, 40% by weight); the plasticiser, dioctyl sebacate, DOS, (0.6g, 60%) and the ionophore valinomycin (0.01g, 1%). The membrane components were weighed out and dissolved in unstabilised THF to yield a 10% by weight membrane
coating solution. The other hydrophobic membrane formulations were prepared in a similar manner. For the hydrogel membranes, 10% by weight of the linear polymer dissolved in methanol was found to create a suitable coating solution.

2.6.3 Coated Wire Ion-Selective Electrode Construction.

The electrode socket was removed from a Corning BNC electrode lead, exposing the coaxial cable. About 2cm of the outer insulation was removed from the exposed end and the braided outer copper conductor cut away. 0.5cm of the inner insulation was removed and the exposed copper wire was twisted tightly together. Onto this was soldered 2cm of platinum wire (Aldrich, Gold Label, 0.25mm diameter). The Pt-wire was washed with detergent and water; thoroughly rinsed with deionised water; and dried with acetone. The wire was then rinsed with chloroform and allowed to dry.

The cable was clamped vertically and the membrane deposited by dipping the wire in the coating solution, to a depth of 1cm, five times quickly. The coating was allowed to dry for one minute before repeating the dipping process. This was continued until a bead of approximately 2mm in diameter had been built up at the Pt-tip. The membrane was left to dry over-night before wrapping the coated-wire tip in Nescofilm, from about 1cm above where the outer insulation was cut, up to 2mm from the end, thus leaving only the deposited membrane bead exposed (figure 2.9a).

An alternative and more convenient assembly was the detachable-tip CWISE (figure 2.9b). In this case, instead of soldering the Pt-wire to the electrode lead, a sliding terminal blade (250 blade, R.S. Components Ltd. 0.25") was crimped onto the inner copper wire. The blade was filed down to a width of 0.11 inches to allow it to fit a 110-in-line receptacle (R.S. Components Ltd.). A 2cm piece of Pt-wire was crimped into this receptacle, having
Figure 2.9 Coated Wire Ion-Selective Electrode.

Figure 2.9a Conventional CWISE.

Figure 2.9b Detachable-Tip CWISE.
first folded over 0.5cm of the end of the wire that was being crimped to ensure a secure attachment. A small piece of 1.6mm heat shrinkable sleeving was slid over the Pt-wire leaving 1cm of the wire exposed. 2.4cm diameter sleeving was placed over both the smaller sleeving and the crimped part of the receptacle. Using a hot air blower the sleeving was shrunk to achieve a tight fit. Only the parts of the receptacle that receives the blade at one end and the Pt-tip at the other, were left uncovered. The membrane was dip-coated onto the Pt-wire and the tip wrapped in Nescofilm as before. In the case of layered membranes, each layer was allowed to dry for 24 hours before the next membrane formulation was deposited.

The blade that was attached to the electrode lead was covered by 2.5cm piece of 3.2mm diameter heat-shrinkable sleeving that extended about 1cm beyond the end of the blade such that when the blade was inserted into the in-line receptacle, the sleeving covered the point of attachment thus protecting the assembly from any possible splashes from the test solution.

When testing a particular membrane formulation was completed the membrane was readily changed by carefully cutting off the Nescofilm and scrapping off the old membrane. The Pt-wire was then cleaned and the new membrane attached as previously described.

2.6.4 The Design and Set-Up of the Electrochemical Cell.

The coated-wire ion-selective electrodes were tested on the following electrochemical cell (figure 2.11):

\[
\text{Ag} \mid \text{AgCl}_2 \mid 4.0\text{M KCl} \mid 0.1\text{M NH}_4\text{NO}_3 \mid \text{CMKCl} \mid \text{test membrane} \mid \text{Pt}
\]

The indicator electrode is shown schematically in figures (2.9a and 2.9b) and its
construction is detailed above (2.6.3). In the choice of reference electrode there is the possibility that the electrolyte in the salt bridge may interfere with the test ion determination. This was resolved by use of a flowing double junction Ag/AgCl reference electrode that employed AgCl saturated 4M KCl as the internal reference solution with 0.1M NH$_4$NO$_3$ as the outer reference solution.

The reference/CWISE electrode pair were placed close together in a 100ml beaker and the solution was stirred magnetically by using a teflon-coated stirring bar. The potential produced was measured with the aid of a WPA CP460 pH/mV meter.

2.6.5 Calibration of the Coated Wire Ion-Selective Electrode.

The CWISE was calibrated by measuring the potential produced by the electrode when placed in a series of potassium salt solutions. The calibration curve was constructed by plotting the electromotive force, EMF, in mV against minus the log $K^+$ ion activity. The slope could thus be determined for the linear portion of the curve. Activities were calculated from an extended form of the Debye-Huckel equation $^{70}$:

$$\text{-log } a_j = \frac{0.511 Z^2 m^{0.5}}{1 + 3.3 \times 10^7 i m^{0.5}} \quad (2.4)$$

where $a_j$ is the activity; $i$ is the ion size parameter; $Z$, the ionic charge$^-$ and $m$, the ionic strength of the test solution.

A series of KCl solutions from $10^{-1}$M to $10^{-6}$M were prepared from a $10^{-1}$M KCl stock
solution. The CWISE was conditioned overnight in 10^{-3}M KCl followed by 10 to 20 minutes in deionised water, prior to use. The CWISE / reference electrode pair was then immersed in the solution of lowest concentration, the solution being stirred by a magnetic follower. Typically at intervals from 1 to 5, or 5 to 20 minutes, depending on the test membrane. On attaining a steady reading the electrode pair was transferred to the next test solution and the measuring procedure repeated. From this data the calibration curve, and hence the slope, could be determined.

2.6.6 Determination of Selectivity Coefficients.

The potential of an ion-selective electrode is not wholly dependent upon a single ion activity but other interferent species may also elicit a response. This is quantitatively described by the selectivity coefficient, \( k_{j,K} \). Of the various techniques developed to determine this parameter, the two most important are the mixed solution and the separate solution methods\(^7\). Both were employed in this study for the sake of comparison but the former is regarded as the preferred technique.

**Mixed Solution Method.**

The technique was the same as employed in 2.6.5. In this case, however, the \( E_{\text{cell}} \) values measured for a series of concentrations of the determinand, KCl, were performed in the presence of a constant interferent concentration (typically 10^{-1}M NaCl). Again the EMF of the cell was plotted against minus the log \( K^+ \) ion activity (log \( a_j \)). The value of \( a_j \) at the intercepts of the asymptotes of this curve was used to calculate the selectivity coefficient, which is defined

\[
k_{j,K} = \frac{a_j}{a_K Z_j Z_K} \tag{2.5}
\]
where $a_K$ is the activity of the interferent, and $Z_J$ and $Z_K$ are the charges on the determinand and the interferent ions respectively.

**Separate Solution Method.**

In this technique the EMF of the cell is measured in a solution of the determinand (such as 10⁻¹M KCl) in the absence of the interferent. Likewise, the EMF of the cell is determined for the interferent (10⁻¹M NaCl) in the absence of the determinand. If these values are $E_1$ and $E_2$ respectively, then assuming that $E_{cell}$ for both species is described by the simple Nernst equation, the selectivity coefficient can be calculated from the following equation:

$$\log k_{J,K} = \frac{E_2 - E_1}{2.303 \, RT/(Z_J \, F)} + \frac{Z}{Z_K} \left(1 + \frac{J_-}{a_J}\right) \log a_J$$  \hspace{1cm} (2.6)

**2.6.7 Measurement of CWISE Response Times.**

The CWISE was conditioned overnight in a 10⁻³ M solution of KCl before being connected to the electrochemical cell. The CWISE/reference electrode pair were placed in deionised water which was magnetically stirred with the aid of a Teflon stirring bar. The electrode pair were left until a stable EMF of the cell ($E_1$) was obtained. The electrodes were quickly transferred to either a 10⁻¹ M or 10⁻³ M KCl solution and the response time, $\tau_{90}$, was defined as being the time required to reach 90% of the total change of the final EMF value ($E_2$). That is:

$$\tau_{90} = E_1 + 0.9 \, (E_2 - E_1)$$  \hspace{1cm} (2.7)
CHAPTER THREE

CHARACTERISATION OF HYDROGEL MEMBRANES.
3.1 Introduction.

This chapter is intimately related to chapters 4 and 5 which will deal with transport studies of salts through hydrogel membranes. It is, however, important to be aware of parameters such as the equilibrium water content, EWC, (a measure of the amount of water held in the polymer matrix) and the partition coefficient, Sm, (the solubility of a salt in a membrane). This chapter is concerned with these parameters but the implication of the results for the permeability of salts through hydrogels necessitates that some questions are left open in anticipation of being dealt with in the subsequent chapters. It should however be stated that EWC and Sm are important in their own right, giving useful information in the study of water swollen polymer networks.

3.2 Discussion of Hydrogel Synthesis.

The membranes were, almost exclusively, all based on either the hydrophilic monomer, 2-hydroxyethyl methacrylate, HEMA, or comonomers of HEMA with a hydrophobic monomer such as methyl methacrylate, MMA or styrene (figure 2.1). Polymerisation occurred by free radical addition initiated by α-azo-bisisobutyronitrile, AZBN, (figure 2.3), which readily undergoes thermodegradation into free radicals at 60°C. Crosslinking of the membrane was achieved by the addition of 1% by weight ethylene glycol dimethacrylate, EGDM, (figure 2.2). The amounts of EGDM and AZBN employed were added with respect to the quantity of monomer used which was 3g for a single gasket and 6g for a double gasket membrane, since this provided sufficient volume to fill the mould cavity. It was mainly double gasket membranes that were employed in this study since their additional thickness relative to single gasket membranes (0.04cm compared with 0.02cm) meant that they were easier to remove from the mould and were more robust, being less likely to tear in the permeability cell.
3.3 Equilibrium Water Contents.

These were determined by the technique described in section 2.4.2. All EWC measurements were carried out in distilled water at 37°C unless otherwise stated. All membranes contained 1% of the crosslinker EGDM unless otherwise indicated.

3.3.1 Effect of the amount of crosslinker on EWC.

The EWC's for a series of poly HEMA membranes containing differing amounts of the crosslinker ethylene glycol dimethacrylate, EGDM (figure 2.2), were determined. It can be seen from table 3.1 and figure 3.1 that as the amount of EGDM is increased, the EWC decreases. However, the change with EGDM content is far less than for other more water swollen networks that have been studied by other authors, such as HPMA-vinyl pyrrolidone (50:50) \(^{64}\). This may be explained by the fact that water is a rather poor solvent for HEMA \(^{72}\). Consequently, this thermodynamic factor affecting the swelling of poly HEMA in water may tend to over-shadow the effect of the amount of crosslinker added. It is important to note that the amount of EGDM only gives the nominal degree of crosslinking, since the actual degree will be dependent on other factors such as chain entanglements leading to physical crosslinking, and the tendency for HEMA to self-crosslink due to chain transfer \(^{72}\).

<table>
<thead>
<tr>
<th>Amount of EGDM (% by weight)</th>
<th>EWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>37.3</td>
</tr>
<tr>
<td>1.0</td>
<td>36.1</td>
</tr>
<tr>
<td>4.6</td>
<td>31.5</td>
</tr>
<tr>
<td>7.6</td>
<td>28.2</td>
</tr>
<tr>
<td>10.0</td>
<td>24.3</td>
</tr>
</tbody>
</table>
Figure 3.1: Effect of the amount of crosslinker on the EWC.
3.3.2 Effect of chemical composition on EWC.

A series of copolymer membranes were prepared containing HEMA and varying proportions of either styrene or methyl methacrylate. These copolymers are essentially random in structure due to the similarities in the reactivity ratios of their respective comonomers. Thus in the HEMA-St copolymer the reactivity ratios are 0.56 and 0.41, respectively, and for the HEMA-MMA copolymer the values are 1.25 and 0.79 respectively\textsuperscript{15}. There is almost 100% conversion in the polymerisation system with the resultant membranes possessing only a trace of leachable material. These random copolymers produce rigid and brittle films over the whole compositional range in the dehydrated state. When hydrated they give rise to flexible transport gels, flexibility being dependent on the amount of water absorbed, which in turn depends upon the interaction between water molecules and the polar chains of the copolymers.

The copolymers of HEMA-St and HEMA-MMA consist of a hydrophilic and a hydrophobic component: namely, the hydrophilic 2-hydroxyethyl methacrylate and the hydrophobic styrene or methyl methacrylate. The equilibrium water contents of these copolymers were plotted against the proportion used of the hydrophobic monomer (figure 3.2, tables 3.2 and 3.3). It can be seen that the EWC falls as the proportion of the hydrophobic component is increased - the HEMA-St series falling off faster than that of HEMA - MMA. This greater hydrophobicity of styrene can be explained as being due to the dominating nature of its bulky and hydrophobic phenyl sidegroup. The side chain on methyl methacrylate, by contrast, is smaller and the presence of the carboxylate group will lead to this monomer being less hydrophobic than styrene.
Table 3.2 Effect of the proportion of MMA on EWC of HEMA-MMA copolymers.

<table>
<thead>
<tr>
<th>Proportion by Weight of MMA (%)</th>
<th>EWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>36.1</td>
</tr>
<tr>
<td>2.5</td>
<td>34.0</td>
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<tr>
<td>5.0</td>
<td>32.1</td>
</tr>
<tr>
<td>7.5</td>
<td>30.8</td>
</tr>
<tr>
<td>10.0</td>
<td>29.1</td>
</tr>
<tr>
<td>12.5</td>
<td>27.2</td>
</tr>
<tr>
<td>15.0</td>
<td>26.2</td>
</tr>
<tr>
<td>20.0</td>
<td>23.5</td>
</tr>
<tr>
<td>25.0</td>
<td>20.8</td>
</tr>
<tr>
<td>30.0</td>
<td>19.3</td>
</tr>
<tr>
<td>35.0</td>
<td>16.6</td>
</tr>
<tr>
<td>40.0</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Table 3.3 Effect of proportion of styrene on EWC of HEMA-St copolymers.

<table>
<thead>
<tr>
<th>Proportion by Weight of styrene (%)</th>
<th>EWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>36.1</td>
</tr>
<tr>
<td>1.0</td>
<td>34.5</td>
</tr>
<tr>
<td>2.5</td>
<td>32.0</td>
</tr>
<tr>
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<td>28.0</td>
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<td>7.5</td>
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</tr>
<tr>
<td>10.0</td>
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</tr>
<tr>
<td>12.5</td>
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<tr>
<td>15.0</td>
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<td>14.8</td>
</tr>
<tr>
<td>30.0</td>
<td>10.9</td>
</tr>
</tbody>
</table>

It is observed that poly HPMA has a smaller EWC than poly HEMA (table 3.4). This can be explained by the additional methylene group in the side chain of HPMA (figure 2.1) which makes the resultant polymer more hydrophobic in nature thus decreasing the EWC of the system relative to poly HEMA.
Figure 3.2: EWC as a function of the % weight of comonomer in HEMA:MMA and HEMA:St copolymers.
Poly HPA, however, has a higher EWC than both poly HEMA and poly HPMA. Poly
HPA is a much more flexible polymer since it lacks the steric hindrance of the \( \alpha \)-methyl
group that the other two possess, being flexible in both the dehydrated and hydrated state.
This lack of the sterically hindering and hydrophobic \( \alpha \)-methyl groups in the polymer
backbone results in poly HPA being more hydrophilic than poly HPMA.

Comparison of the EWC's of the monomer isomers of HPA and HEMA (see figure 2.1)
shows the greater hydrophobicity created by methylene insertion into the backbone as
opposed to its introduction in the side chain.

Another interesting feature was that HEMA-HPA (50:50) was found to have a higher EWC
than either of its component homopolymers. As has been stated, water is a relatively poor
solvent for poly HEMA \(^2\) and consequently the hydrophobic interactions play an important
role in determining the overall degree of hydration. It may be that the random copolymer
having a less sterically organised structure has less hydrophobic interactions than the
homopolymers, particularly between the \( \alpha \)-methyl groups of the HEMA component in the
backbone, thus producing a greater EWC than may have been anticipated.

This varying interaction of water with the polymers can also be monitored, in terms of the
freezing and non-freezing water states, by differential scanning calorimetry \(^{15,66}\), D.S.C..
Although the overall EWC is the dominant parameter in understanding transport properties,
the nature of water binding has important consequences for the permeability and
permselectivity of the polymers. This will be discussed in subsequent chapters.
Table 3.4 EWC of various hydrogels.

<table>
<thead>
<tr>
<th>Hydrogel</th>
<th>EWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMA</td>
<td>20.4</td>
</tr>
<tr>
<td>HPA</td>
<td>39.3</td>
</tr>
<tr>
<td>HPA-HEMA (50:50)</td>
<td>40.8</td>
</tr>
<tr>
<td>PEM-400:MMA (55:45)</td>
<td>39.4</td>
</tr>
</tbody>
</table>

3.3.3 Effect of salts on EWC.

3.3.3.1 Effect of chloride salts on poly HEMA.

It can be seen from the first row of figures on table 3.6 that all the chloride salts had the effect of lowering the EWC for poly HEMA in comparison with the EWC in pure water (figure 3.3a). KCl, NaCl and LiCl were found to influence membrane hydration by the same extent but the salt of the divalent Ca\(^{2+}\) ion seemed to exert a greater deswelling effect on poly HEMA. Other authors have also observed this reduction in the EWC of poly HEMA when the hydrogel was transferred from pure water and placed in a solution of NaCl \(^{30,^{64}}\). It was suggested that the deswelling may be attributed to the water structuring effects of NaCl which may enhance the hydrophobic bonding within the polymer matrix \(^{64}\). The divalent calcium ion has the greater of the interactions with water as is evident from its enthalpy of hydration being higher than those of the other ions \(^{73}\). This greater ion/water interaction for Ca\(^{2+}\) may help explain the slightly lower value for the EWC of poly HEMA when placed in a solution of CaCl\(_2\) but any differences in EWC in solutions of the monovalent cation salts seems to have been subsumed by the influence exerted by the chloride ion. If the EWC's of a hydrogel in salt solutions of different cations in the presence of a common anion are dominated by the influence of that anion, the logical corollary would be to expect to see a wider variation in the EWC of poly HEMA in the presence of salt solutions of different anions in the presence of a common cation.
Figure 3.3a: The influence of chloride salts on the EWC of poly HEMA.

Figure 3.3b: The influence of potassium salts on the EWC of poly HEMA.
3.3.3.2 Effect of potassium salts on poly HEMA.

To study the influence of the anion on the EWC of poly HEMA a series of salt solutions with a range of anions but with a common cation were prepared. The important cation, potassium was the chosen common cation. The EWC's of poly HEMA in these solutions were determined and the results are tabulated in table 3.5 (figure 3.3b). The importance of the nature of the anion on the EWC can clearly be seen, ranging from the significant swelling effect of the thiocyanate ion to the deswelling effect of the sulphate ion. This variation in the degrees of hydration is due to the nature of the solute/water interactions of these anions. It is intimately related to other parameters such as the partition coefficients of the salts in the hydrogel and the permeabilities of the salts through the hydrated polymer membranes. It will be more pertinent to discuss in some detail the nature of ion/water interactions in chapter 4 when all these parameters come together to elucidate the factors effecting the transport of salts through poly HEMA membranes. It is sufficient for now to highlight the importance of the anion and to bear in mind that the solute will have an effect on the water held within the hydrated polymer matrix which in turn will influence the transport properties of the membrane.

<table>
<thead>
<tr>
<th>Salt</th>
<th>Concentration (mM)</th>
<th>EWC (%)</th>
<th>EWC(salt) - EWC(H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF</td>
<td>250</td>
<td>33.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>KCl</td>
<td>250</td>
<td>33.5</td>
<td>-2.6</td>
</tr>
<tr>
<td>KBr</td>
<td>250</td>
<td>34.9</td>
<td>-1.2</td>
</tr>
<tr>
<td>KI</td>
<td>250</td>
<td>39.9</td>
<td>+3.8</td>
</tr>
<tr>
<td>KSCN</td>
<td>250</td>
<td>44.1</td>
<td>+8.0</td>
</tr>
<tr>
<td>KHCO₃</td>
<td>250</td>
<td>34.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>125</td>
<td>33.9</td>
<td>-2.2</td>
</tr>
<tr>
<td>KNO₃</td>
<td>250</td>
<td>35.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>K₂SO₄</td>
<td>125</td>
<td>31.6</td>
<td>-4.5</td>
</tr>
</tbody>
</table>
3.3.3.3 Effect of salt solutions in HEMA-MMA copolymers.

So far the influence of salt solutions on a single polymer matrix has been examined. It is now appropriate to study the effect that salt solutions have on hydrogels of various chemical compositions: namely, the effect of different salt solutions on a range of HEMA-MMA hydrogels.

Table 3.6 and figure 3.4 shows the influence of chloride salts with different cations on HEMA-MMA copolymers. In section 3.3.3.1 it was stated that KCl, NaCl and LiCl cause a similar depression of the EWC of poly HEMA in comparison to its value in pure water, the same depression effect is found to occur throughout the copolymer range, with CaCl₂ having a slightly greater influence than the other salts.

<table>
<thead>
<tr>
<th>%MMA</th>
<th>KCl</th>
<th>NaCl</th>
<th>LiCl</th>
<th>CaCl₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>33.5</td>
<td>33.4</td>
<td>33.5</td>
<td>32.7</td>
</tr>
<tr>
<td>2.5</td>
<td>-----</td>
<td>32.7</td>
<td>33.0</td>
<td>31.6</td>
</tr>
<tr>
<td>5.0</td>
<td>30.7</td>
<td>30.9</td>
<td>30.9</td>
<td>29.5</td>
</tr>
<tr>
<td>7.5</td>
<td>29.6</td>
<td>29.6</td>
<td>29.8</td>
<td>28.6</td>
</tr>
<tr>
<td>10.0</td>
<td>26.7</td>
<td>27.9</td>
<td>27.9</td>
<td>26.2</td>
</tr>
<tr>
<td>12.5</td>
<td>25.7</td>
<td>26.2</td>
<td>26.7</td>
<td>24.5</td>
</tr>
<tr>
<td>15.0</td>
<td>24.9</td>
<td>25.3</td>
<td>25.4</td>
<td>23.1</td>
</tr>
<tr>
<td>20.0</td>
<td>21.5</td>
<td>22.7</td>
<td>22.6</td>
<td>20.9</td>
</tr>
<tr>
<td>25.0</td>
<td>19.3</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>30.0</td>
<td>-----</td>
<td>19.8</td>
<td>18.1</td>
<td>16.9</td>
</tr>
<tr>
<td>35.0</td>
<td>16.2</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

Table 3.6 EWC of HEMA: MMA copolymer membranes in salt solutions with fixed anion.

When the cation is fixed and the anion varied the greater influence of the anion over the cation is observed (table 3.7, figure 3.5). The potassium salts of SCN⁻ and SO₄²⁻ are chosen here since they represent the extremes of swelling and deswelling effects of the anions originally observed in poly HEMA. The ability of the anions to either swell or
Figure 3.4: The EWC of HEMA: MMA copolymers in different chloride salt solutions.

% MMA

% EWC

CaCl₂
NaCl
KCl
H₂O
Figure 3.5: The EWC of HEMA-MMA copolymers in different potassium salt solutions.
deswell the hydrogel is seen throughout the compositional range. However, it can be seen that their influence on the final equilibrium water content diminishes as the overall EWC decreases - that is as the hydrophobic component of the copolymer is increased the EWC values of the salt solutions tend to that of the copolymer in pure water. This can be more clearly illustrated when the EWC of the hydrogels in the salt solutions are normalised by being divided by their respective values for that of pure water. Table 3.4 shows these values tending towards unity as the EWC of the polymer system decreases.

<table>
<thead>
<tr>
<th>%MMA</th>
<th>EWC(KSCN) (250mM)</th>
<th>EWC(K₂SO₄) (125mM)</th>
<th>EWC(KSCN) (H₂O)</th>
<th>EWC(K₂SO₄) (H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>44.1</td>
<td>31.6</td>
<td>1.22</td>
<td>0.88</td>
</tr>
<tr>
<td>10.0</td>
<td>33.3</td>
<td>26.2</td>
<td>1.14</td>
<td>0.90</td>
</tr>
<tr>
<td>20.0</td>
<td>26.2</td>
<td>21.5</td>
<td>1.11</td>
<td>0.91</td>
</tr>
<tr>
<td>35.0</td>
<td>17.8</td>
<td>15.9</td>
<td>1.07</td>
<td>0.96</td>
</tr>
</tbody>
</table>

3.3.4 Effect of diluent on EWC.

The addition of ethylene glycol in the quantities used in the reaction mixtures (20%), seems to have no significant effect on the final EWC, (table 3.8). This lack of deviation from the EWC of the diluent free analogues may be due to the same reason for the small changes of EWC in poly HEMA with EGDM content: that is, the poor solvation of these polymer systems by water is the dominant factor in determining the degree of hydration and not the initial reaction conditions.
### Table 3.8 Effect of diluent on final EWC.

<table>
<thead>
<tr>
<th>Polymerisation Mixture (+ 20% ethylene glycol)</th>
<th>EWC(%)</th>
<th>EWC(%) (no diluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMA-MMA (80:20)</td>
<td>23.5</td>
<td>23.5</td>
</tr>
<tr>
<td>HEMA-MMA (65:35)</td>
<td>16.6</td>
<td>16.6</td>
</tr>
<tr>
<td>HEMA-MMA (60:40)</td>
<td>15.1</td>
<td>14.8</td>
</tr>
</tbody>
</table>

#### 3.3.5 Effect of temperature on EWC.

As the temperature of a hydrogel is increased it should be expected that the polymer matrix would undergo entropic expansion causing an increased capacity for water absorption. An increase in the hydrophilic interaction by way of an increase in the formation of hydrogen bonding with the polar groups of the polymer chains might also be expected to induce an increase EWC for the hydrogel.

Hydrophobic bonding, which is brought about by the Van der Waal’s interactions between non-polar groups, plays an important rôle in determining the degree of hydration of poly HEMA. The formation of these bonds being an endothermic process. Hydrophobic hydration, which is the solvation of a non-polar group by water, is entropically unfavorable because water is capable of structuring in the vicinity of such groups. An increase in temperature reduces the hydrophobic interaction with a resultant increase in the formation of hydrophobic bonds. Such bonds effectively act as crosslinks and reduce the EWC.

With hydrogels, therefore, the temperature hydration curve is determined by the processes mentioned above, which compete with one an other. There is very little change observed in the EWC of poly HEMA as temperature is increased, either in pure water or in salt solution (table 3.9). The maximum change for poly HEMA in this study is only 2.2% and 2.4% for pure water and 250mM KCl respectively. The nature of constituent monomers is known to be very important and not all hydrogels are so insensitive to temperature as poly HEMA.
For example, one group of workers found that the EWC of a copolymer of HPA-St (80:20) went from about 27% to over 50% as the temperature changed from 25 to 60°C. They argued that the greater sensitivity of acrylates as opposed to methacrylates was due to the presence of a hydrogen atom in the backbone as opposed to the hydrophobic α-methyl group found in the methacrylates.

The competition between the various factors effecting the hydration/temperature profile frequently leads to a minima in the curve. Previous work indicated that for poly HEMA this minima should occur between 50 and 80°C. The results shown in table 3.9 show a slight dip at about 37°C. The fact that this dip is observed for poly HEMA in both water and the KCl solution indicates that this may be an actual phenomenon and not just scatter due to experimental error. It should, however, again be emphasised that such changes are very small for poly HEMA and, in fact, for any copolymer employing HEMA as its hydrophilic component (table 3.10).

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>H₂O</th>
<th>KCl (250 mM)</th>
<th>K₂SO₄ (125 mM)</th>
<th>KSCN (250 mM)</th>
<th>CaCl₂ (250 mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>38.3</td>
<td>35.9</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>37</td>
<td>36.1</td>
<td>33.5</td>
<td>31.6</td>
<td>44.1</td>
<td>32.7</td>
</tr>
<tr>
<td>45</td>
<td>36.9</td>
<td>34.1</td>
<td>32.3</td>
<td>42.0</td>
<td>32.7</td>
</tr>
<tr>
<td>60</td>
<td>36.8</td>
<td>33.4</td>
<td>31.6</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hydrogel</th>
<th>EWC(%) at 22°C</th>
<th>EWC(%) at 37°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMA (0.1% EGDM)</td>
<td>38.6</td>
<td>37.3</td>
</tr>
<tr>
<td>HEMA-MMA (87.5:12.5)</td>
<td>27.9</td>
<td>27.2</td>
</tr>
<tr>
<td>HEMA-MMA (65:35)</td>
<td>17.5</td>
<td>16.6</td>
</tr>
<tr>
<td>HEMA-St (97.5:2.5)</td>
<td>31.7</td>
<td>31.4</td>
</tr>
<tr>
<td>HEMA-St (95:5)</td>
<td>28.8</td>
<td>28.0</td>
</tr>
<tr>
<td>HEMA-St (90:10)</td>
<td>23.1</td>
<td>22.1</td>
</tr>
</tbody>
</table>
3.3.6 Accuracy of EWC determination.

The important polymer, poly HEMA was chosen for a careful examination as to the accuracy of the technique for EWC determination. Using two hydrated poly HEMA sheets, ninety nine discs (1.1cm diameter) were cut and using three discs for each determination thirty three EWC's were calculated and subjected to statistical analysis, (see appendix 1). This was found to give a mean EWC of 36.1% at 37°C with $\sigma_{n-1} = 0.42$.

3.4 Partition coefficients of salts in hydrogel membranes.

The partition coefficient, Sm, is a measure of a solute's ability to dissolve in the membrane matrix; the method of determination was outlined in section 2.4.3. This is an important parameter that affects properties such as the transport of permeants through the membrane. At equilibrium the chemical potential of the salt in the membrane phase must be equal to the chemical potential of the salt in the equilibrating solution. It is reasonable to suppose that most salts would have minimal direct interaction with the polymer component of the hydrated membrane but would, instead, be solvated by the water held within the hydrogel matrix. The partition coefficient, therefore, should be expected to be related to the equilibrium water content of the membrane. It should be stressed, however, that this relationship to EWC does not mean that the concentration of the salt in membrane water is equal to the concentration of the equilibrating solution; this is because interactions between the membrane water and the polymer will exert an effect on the chemical potential of the partitioned salt, even when there are negligible, or even no polymer/salt interactions.

Following a similar outline to that on the study of equilibrium water contents, the partition coefficients of a series in a single polymer matrix will be examined and then the effect of changing the polymer backbone will be looked at.
3.4.1 Partition coefficients in poly HEMA membranes.

From table 3.11 it can be seen that the chloride salts have comparatively similar values for the partition coefficient (figure 3.6a). This recalls the study on EWC's where the chloride salts were found to exert a similar degree of depression of the EWC of poly HEMA (figure 3.3a). Again we see the dominating influence of the anion which seems to overshadow any effect of cation variation.

In a likewise manner, when the cation was fixed and the anion varied (table 3.11, figure 3.6b) a large variation in the partition coefficients is found. This ability of the anion to greatly alter the solubility of a salt in a membrane has major implications for the transport of salts through hydrogel membranes. This will be discussed more fully in chapter 4.

### Table 3.11 Partition coefficients in poly HEMA.

<table>
<thead>
<tr>
<th>Salt</th>
<th>Concentration of Equilibrating Solution (mM)</th>
<th>Partition Coefficient (Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiCl</td>
<td>250</td>
<td>0.179</td>
</tr>
<tr>
<td>NaCl</td>
<td>250</td>
<td>0.157</td>
</tr>
<tr>
<td>KCl</td>
<td>250</td>
<td>0.174</td>
</tr>
<tr>
<td>CaCl₂</td>
<td>250</td>
<td>0.157</td>
</tr>
<tr>
<td>KF</td>
<td>250</td>
<td>0.117</td>
</tr>
<tr>
<td>KBr</td>
<td>250</td>
<td>0.226</td>
</tr>
<tr>
<td>KI</td>
<td>250</td>
<td>0.390</td>
</tr>
<tr>
<td>KSCN</td>
<td>250</td>
<td>0.533</td>
</tr>
<tr>
<td>KHCO₃</td>
<td>250</td>
<td>0.116</td>
</tr>
<tr>
<td>K₂SO₄</td>
<td>125</td>
<td>0.044</td>
</tr>
<tr>
<td>KNO₃</td>
<td>250</td>
<td>0.278</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>125</td>
<td>0.045</td>
</tr>
</tbody>
</table>

3.4.2 Partition coefficients of salts in hydrogel membranes of varied composition.

The change in the partition coefficient, Sm, for KCl in a series of HEMA:MMA copolymers is shown in table 3.12. This change is plotted as a function of the corresponding equilibrium water contents for the copolymer range in figure 3.7. The
Figure 3.6a: The partition coefficients of chloride salts in poly HEMA.

Figure 3.6b: The partition coefficients of potassium salts in poly HEMA.
Figure 3.7: The partition coefficients of KCl in a series of HEMA:MMA copolymers.
dependency of Sm upon EWC can be seen in this figure but as was mentioned in the introduction of section 3.4, this relationship is not a simple one. A more complete picture can be gained by looking at a range of salts (table 3.13, figure 3.8). It was found that KCl and CaCl₂ solutions exerted a similar effect on the EWC's of HEMA:MMA copolymers (table 3.6, figure 3.4) but the partition coefficient seems a more sensitive parameter to cation variation. The Sm value of CaCl₂ is found to fall off more rapidly than that of KCl and does not seem to partition on the HEMA:MMA (65:35) copolymer: its value of 0.003 for this copolymer could readily be explained as being due to contamination from the original equilibrating solution. The EWC's of the polymers in a CaCl₂ solution were even closer to those for K₂SO₄ than the KCl values but the divalent anion exhibits an even lower solubility in the copolymer hydrogels than the divalent cation, Ca²⁺. Both divalent species finally confer insolubility on their salts in the HEMA:MMA (65:35) membrane at a water content of 16%.

Table 3.12 Partition coefficients of KCl in HEMA-MMA copolymers.

<table>
<thead>
<tr>
<th>%MMA</th>
<th>Sm</th>
<th>%MMA</th>
<th>Sm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.174</td>
<td>15.0</td>
<td>0.086</td>
</tr>
<tr>
<td>7.5</td>
<td>0.119</td>
<td>20.0</td>
<td>0.065</td>
</tr>
<tr>
<td>10.0</td>
<td>0.109</td>
<td>25.0</td>
<td>0.055</td>
</tr>
<tr>
<td>12.5</td>
<td>0.094</td>
<td>35.0</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Table 3.13 Partition coefficients of various salts in HEMA-MMA copolymers.

<table>
<thead>
<tr>
<th>% MMA</th>
<th>Sm (250mM)</th>
<th>Sm (250mM)</th>
<th>Sm (250mM)</th>
<th>Sm (125mM)</th>
<th>Sm (250mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KCl</td>
<td>CaCl₂</td>
<td>KSCN</td>
<td>K₂SO₄</td>
<td>KI</td>
</tr>
<tr>
<td>0.0</td>
<td>0.174</td>
<td>0.157</td>
<td>0.533</td>
<td>0.044</td>
<td>0.390</td>
</tr>
<tr>
<td>10.0</td>
<td>0.109</td>
<td>0.077</td>
<td>0.447</td>
<td>0.021</td>
<td>0.282</td>
</tr>
<tr>
<td>20.0</td>
<td>0.065</td>
<td>0.022</td>
<td>0.323</td>
<td>0.013</td>
<td>0.205</td>
</tr>
<tr>
<td>25.0</td>
<td>0.055</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>0.172</td>
</tr>
<tr>
<td>35.0</td>
<td>0.022</td>
<td>0.003</td>
<td>0.136</td>
<td>0.004</td>
<td>------</td>
</tr>
</tbody>
</table>
Figure 3.8: The partition coefficients of various salts in HEMA/MA copolymers.
The partition coefficients of all the salts are seen to fall with decreasing EWC (figure 3.8). In the study of the partition coefficients in hydrogels a more informative parameter is that of $\text{Sm/H}$, where $H$ is the degree of hydration ($H = \text{EWC/100}$). If the salt did not directly interact with the polymer but was equally soluble in both the membrane water and the equilibrating solution, then $\text{Sm/H} = 1$. It can be expected that $\text{Sm/H}$ will tend to unity as the degree of hydration approaches a value of 1 (i.e. a purely aqueous solution).

In real systems, water interactions with the polymer results in the concentration of the salt in the imbibed water being less than that of the equilibrating solution, in other words, $\text{Sm/H}$ is less than 1. A plot of $\text{Sm/H}$ against $H$ (figure 3.9) shows that for $\text{KCl}$, $\text{K}_2\text{SO}_4$ and $\text{CaCl}_2$, the value of $\text{Sm/H}$ falls with decreasing water content of the membrane. This means that as the overall degree of hydration decreases the membrane water becomes proportionately less accessible to the test salt. As was mentioned in chapter 1, water in a hydrogel exists in a continuum of states from that which is bound to the polymer through to the water which is bulk like in its properties. In differential scanning calorimetry, D.S.C., the membrane water is shown to be either freezing (the bulk and interfacial phases) or non-freezing (the bound phase). As the overall EWC of a hydrogel system decreases there is a proportionately greater amount of non-freezing water. The fall of $\text{Sm/H}$ with decreasing $H$ for $\text{KCl}$, $\text{CaCl}_2$ and $\text{K}_2\text{SO}_4$ suggests that these salts do not partition in the non-freezing water as readily as in the freezing component.

The picture for KSCN and KI is somewhat more complex. Particularly KSCN which for part of the copolymer range exhibited values of $\text{Sm/H}$ of greater than 1. This suggests that $\text{I}^-$ and $\text{SCN}^-$ anions, and especially the latter, are capable of partitioning in both the water and polymer phases. Again the importance of the anion is illustrated in its influence on the properties of the salt.
Figure 3.9: Plot of SmH against EWG for salts in HEMA:MA copolymers.
3.4.3 Effect of temperature on the partition coefficient.

Increasing the temperature of a hydrated sample of poly HEMA was shown to have only a small effect on the equilibrium water content (see 3.3.5). EWC seemed to show a minimum at about 37°C. This is not reflected in the partition coefficients shown in table 3.14. KCl shows a steady decrease in its value of Sm as the temperature is increased (figure 3.10). K₂SO₄ also seems to show this trend but its transition looks less smooth than that for KCl. This is probably due to experimental error being more significant for K₂SO₄ due to the relatively low values of Sm for this salt. There is insufficient data for KSCN and CaCl₂ to discern any clear trend for these salts but there does seem to be a lowering in the partition coefficient with temperature for KSCN.

Any change in the overall water content of the system with temperature could be expected to produce a concomitant change in the partition coefficient. But EWC alone seems an insufficient parameter to explain the changes in Sm. Although the changes in EWC may be small it is possible that temperature will have an influence in the relative proportions of the different states of water, such as "bound" and "bulk like", held within the polymer matrix. If proportionately more water is interacting with the polymer as the temperature is increased then this may reduce the ability of the membrane water to partition the salt.

Table 3.14 Effect of temperature on the partition coefficient of salt solutions in poly HEMA.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Sm KCl (250mM)</th>
<th>Sm K₂SO₄ (125mM)</th>
<th>Sm KSCN (250mM)</th>
<th>Sm CaCl₂ (250mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.199</td>
<td>0.041</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>37</td>
<td>0.174</td>
<td>0.044</td>
<td>0.533</td>
<td>0.157</td>
</tr>
<tr>
<td>45</td>
<td>0.154</td>
<td>0.032</td>
<td>0.494</td>
<td>0.158</td>
</tr>
<tr>
<td>60</td>
<td>0.145</td>
<td>0.031</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>
Figure 3.10: The effect of temperature on the Sm of two potassium salts.

Temperature (°C)
3.4.4 Errors in the determination of partition coefficients.

The main difficulty with this procedure is the possibility of contamination of the sample discs when transferring them from the equilibrating salt solution to the deionised water. If the discs are not sufficiently wiped then traces of salt solution will lead to erroneously high values of the partition coefficient. This could be solved by dipping the discs in water before transferring to the deionised water where the salt is to be leached out. This, however, may lead to erroneously low values of Sm since there is the risk of salt leaching out during the washing process. And so care was taken to remove the surface salt solution by careful wiping only. This produced errors in the third decimal place, for example the Sm for KCl in poly HEMA at 37°C was calculated to be 0.179, 0.170 and 0.173 on three different determinations. This led to a value of 0.174 being taken with a degree of accuracy to within 0.005.

3.5 Concluding comments.

To summarise then, this chapter showed how varying the degree of crosslinking and/or the monomer composition has an effect on the overall equilibrium water content of the hydrogel. The importance of the solute as a modulator of EWC was also revealed - especially the nature of the anion, which mostly subsumes any influence by the cation. The partition coefficient is seen to be a more sensitive parameter for the water/solute interactions within the hydrated polymer matrix than EWC. This is shown in temperature effects where Sm changes to a slightly greater degree than EWC.

As was stated at the beginning of this chapter, the results shown here are related to the transport studies dealt with in chapters 4 and 5. Consequently, this chapter has been essentially factual in nature, with the implications from the results and the discussion concerning them being retained for the next two chapters.
CHAPTER FOUR

TRANSPORT BEHAVIOUR OF

POLY(2-HYDROXYETHYL METHACRYLATE) MEMBRANES.
4.1 Introduction.

The permeability of hydrogels in aqueous systems has been a feature of great importance in setting these materials apart from other polymers. The fact that water exists as an intimate and essential part of the polymer matrix implies that it might have the ability to modulate transport behaviour of water soluble species. Indeed, it is the link between oxygen permeability and water content that enabled contact lenses to be developed that are sufficiently permeable to be worn during sleep. The transport properties of hydrogels are important in reverse osmosis (particularly desalination) processes and controlled drug delivery systems. More recently, the potential applications of hydrogels as membranes for sensors have been recognised.

In the late 1960's interest in desalination stimulated work on sodium chloride transport through hydrogels but little work on other ionic permeants has been reported. The interest in sodium chloride transport lay primarily in the computation of salt rejection factors for the membrane, these being derived from the relative values of water permeability to that of sodium. A great deal of published work involving neutral molecules such as amides, steroids, sugars and water itself exists and models for the permeability process through hydrogels have been suggested. Despite this, permeability studies involving hydrogels have been far from systematic.

In the previous chapter it was shown that the type of salt in solution and above all the nature of anion, will affect important parameters of the hydrogel such as the degree of hydration and the solutes ability to partition in the water swollen matrix. It was mentioned that these would have an influence on other parameters - the one that we are concerned with here is that of the permeability coefficient of the salt in the membrane. To understand more fully ionic transport processes in hydrogels, it is essential to consider ion-water, ion-
polymer and ion-water-polymer interactions. The permeation of anions and cations does not appear to be directly related to any single physical characteristic, but rather a complex interaction of competing processes. It is evident from the literature that some of the fundamentals regarding the physico-chemical interactions concerning ions in solution are not generally appreciated by polymer scientists interested in the transport phenomena of water-swollen polymer matrices. It is therefore appropriate at this point to highlight various factors relating to water structuring and to such concepts as hydrodynamic radii and the Hofmeister series in relation to ion permeation in water swollen hydrogels.

A comprehensive study of water has been compiled by Franks. The structure of bulk water can be considered to consist of long range, tetrahedrally coordinated hydrogen bonds. Electrolytes perturb this steady state equilibrium giving rise to three essentially different water phases. The primary water phase around the electrolyte can be considered to be strongly associated and ordered by the electrolyte. The secondary water phase is considered to be less ordered than the primary phase, although it is still influenced by the electrolyte. Finally, there is the tertiary phase which is unperturbed bulk water.

The ratio of primary phase ordering to secondary phase disordering is dependent on the nature of the electrolyte. Relatively small ions and multivalent ions such as Li\(^+\), Na\(^+\), H\(_3\)O\(^+\), Ca\(^{2+}\), OH\(^-\), F\(^-\) are said to be structure-making ions. That is to say, they order and electrostrict near-neighbour water molecules to form a primary water shell and have a tendency to induce order beyond that to form a long-range hydration shell thus reducing the effect of the secondary disordered phase. Such structuring would increase the relative viscosity of water (quantitatively expressed as the viscosity β-coefficient 84, 85) and decrease the rate of ion permeation compared to that of a non-water-structuring species.
Large, monovalent ions are generally thought of as net structure-breakers. Ions such as K⁺, Cl⁻, Br⁻, I⁻, NO₃⁻, C₁₀₄⁻ generate a relatively weak electrostatic field capable of perturbing only near-neighbour water molecules. The secondary disordered phase is extensive and the fluidity of this phase is greater than that of bulk water itself, therefore, permeation of these structure-breakers appears greater than expected from size predictions alone.

Another important concept in ion permeation is that of the hydrodynamic size of the permeating species. Stokes law of motion characterises the movement of a spherical particle through a continuous medium, in terms of the particles mobility, radius and the solvent viscosity. The Stokes radius, therefore, describes the effective size of the hydrated ion in water and, as such, has been of interest in the examination of the ion permeation through a water containing membrane ⁵, ⁷⁹, ⁸⁶. It has, however, been noted that the application of Stokes law to simple electrolytes yields inappropriately low values for the radius ⁸⁴, ⁸⁷. The Stokes assumption of continuous viscous flow of the solvent medium is not valid since the water molecule, is of comparable size to the hydrated ions ⁸⁷.

This chapter presents results relating to the transport of a series of cations through, principally poly(2-hydroxyethyl methacrylate) hydrogel. The effects of counter ion variation are described and the results used as a basis for a discussion of the available models for transport phenomena in hydrogels.

4.2 Calculation of permeability coefficients.

Permeability is a measure of the ease of transmission of a penetrant (gas, vapour, liquid or solute) through a resisting material without consideration of the actual mechanism involved. In the study of permeation through hydrogel membranes it is observed that as the salt is
transported through the membrane, the concentration, \( C_2 \), of the donor side of the permeability cell will decrease with time causing a concomitant increase in the concentration, \( C_1 \), in the receptor side with both concentrations tending to equilibrium. Authors have, in such cases, obtained the permeability coefficient by plotting \( \log[(C_2 - C_1)/C_0] \) versus time (or related forms of this plot), where \( C_0 \) is the initial donor solution concentration 16, 19, 29, 30. In some cases the change in the concentration of each side is very small, and consequently steady state conditions are achieved. In such situations the permeability coefficient can be derived from the far simpler plot of concentration versus time 31, 88. Such was the case in this work, the equation used to describe the permeation process being derived as follows:

recalling equation (1.2) we can express the steady state flow inside a membrane using Fick's first law as:

\[
F = DS \frac{\Gamma_2 - \Gamma_1}{L} \tag{1.2}
\]

where, \( F = \) total flow rate; \( D = \) diffusivity; \( S = \) cross-sectional area of membrane; \( L = \) membrane thickness and \( \Gamma_2, \Gamma_1 \) are the concentration of solute just inside the membrane surface at the high and low concentration sides respectively.

If a linear isotherm (Henry's Law) is applicable then:

\[
\Gamma_1 = Sm.C_1 \tag{4.1}
\]
\[
\Gamma_2 = Sm.C_2 \tag{4.2}
\]
where, Sm is the partition coefficient and C₂, C₁ are the concentration terms of bulk solution in the high and low concentration sides of a permeability cell.

Also,

\[ P = \text{Sm.D} \quad (4.3) \]

where, P = the permeability coefficient.

Substituting equations (4.1), (4.2) and (4.3) we can write:

\[ F = \text{PS} \cdot \frac{C₂ - C₁}{L} \quad (4.4) \]

Rearranging this to express it in terms of P we have:

\[ P = F \times \frac{L}{S(C₂ - C₁)} \quad (4.5) \]

Relating this to the work undertaken, the term C₁ relates to the concentration on the low concentration side of the permeability cell which was originally zero and never more than a few mM at the end of the run. Since the donor concentration was 250mM this means that C₁ can effectively be ignored and sink conditions can be assumed. The final form of the equation used was:

\[ P = F \times \frac{L}{S.C₂} \quad (4.6) \]

where the flow rate, F was obtained from:

\[ F = G \times V \quad (4.7) \]
G is the slope of concentration with time in the low concentration side and V is the volume of the permeability cell half.

4.3 Characterisation studies.

4.3.1 Reproducibility between permeation runs.

The effects of experimental parameters upon permeation rates were investigated to eliminate any effects from subsequent studies. Early permeability studies on systems of a similar design suggested that the stirring rate at the surface of the membrane was not critical at 30 rpm or above 68. Subsequent work has shown, in particular, that it is essential to stir the high concentration side of the membrane to prevent any surface layer effects 66, 89. Studies with the experimental system used in this work showed that there is a decrease in permeation of 3% if the high concentration side only is stirred and a decrease in 10 ± 1% if the low concentration side only or neither sides are stirred. Forward and reverse solution flow appear to have no significant effect. Similarly, changes in flow rate between 30 ml/min and 90 ml/min did not appear to be critical 33.

The question of reproducibility was examined by carrying out repeat runs on a single membrane system - namely, the permeability of KCl through poly HEMA. Under identical conditions three permeation runs yielded permeability coefficients of 24.9, 24.3 and 23.7 cm²s⁻¹. This gives an average of 24.3 ± 0.6 cm²s⁻¹, which is a reproducibility of ± 2.5%. Typical primary results are shown in Figure 4.1.

4.3.2 The effect of membrane thickness.

In chapter three it was shown that the salt solution had an influence on various hydrogel parameters. It is important to appreciate the swelling/deswelling effects on a hydrogel by
the solute used - particularly so in the case of anion variation. This means that even for the same test membrane, its thickness, L, will vary for different salt solutions and will differ from its value in distilled water. This can be seen in table 4.1 where the thickness of a single poly HEMA membrane in a series of salt solutions is recorded. Thus in the calculation of the permeability coefficient, the value of L was determined separately for each solute at the end of each run of the permeability cell.

Table 4.1 Effect of salt on thickness of poly HEMA membranes.

<table>
<thead>
<tr>
<th>Salt</th>
<th>Thickness, L (cm)</th>
<th>Salt</th>
<th>Thickness, L (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>0.0435</td>
<td>KSCN</td>
<td>0.0459</td>
</tr>
<tr>
<td>KCl</td>
<td>0.0435</td>
<td>KHCO₃</td>
<td>0.0435</td>
</tr>
<tr>
<td>KF</td>
<td>0.0433</td>
<td>K₂SO₄</td>
<td>0.0424</td>
</tr>
<tr>
<td>KBr</td>
<td>0.0435</td>
<td>KNO₃</td>
<td>0.0441</td>
</tr>
<tr>
<td>KI</td>
<td>0.0435</td>
<td>K₂CO₃</td>
<td>0.0435</td>
</tr>
</tbody>
</table>

4.3.3 Flame photometry versus conductimetry.

The concentration of salt in the receptor half of the permeability cell was originally monitored by withdrawing 1ml samples every hour or forty five minutes and measuring the concentration by flame photometry. This, however, limited the range of test salts to those that contained K⁺, Na⁺, Ca²⁺ and Li⁺. It has the additional disadvantage of causing a reduction in the solution volume in the low concentration side of the cell. Monitoring concentration by conductimetry causes no such volume reduction and allows a wider range of salts to be examined. Test runs using both conductimetry and flame photometry showed good correlation between the two types of analysis. This is illustrated in table 4.2 which shows the primary data for the transport of KCl through a poly HEMA membrane.
Table 4.2 Comparison of primary permeability data from flame photometry and conductivity

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>KCl Concentration (mM), as determined by:</th>
<th>Conductivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flame Photometry</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.31</td>
<td>0.34</td>
</tr>
<tr>
<td>3</td>
<td>0.77</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>1.47</td>
<td>1.45</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>1.73</td>
</tr>
<tr>
<td>7</td>
<td>2.03</td>
<td>2.02</td>
</tr>
<tr>
<td>8</td>
<td>2.30</td>
<td>2.29</td>
</tr>
</tbody>
</table>

4.4 Transport through poly HEMA

4.4.1 Transport behaviour of salts with a common anion.

Various experiments were carried out to establish the relative effects of cation and anion on permeation. The permeability of poly HEMA membranes to a variety of monovalent and divalent cations was first investigated, at 37°C using 0.25M cation solutions in the form of the chloride on the donor side of the cell. Primary transport data, of the form shown in figures 4.1 and 4.2, was used to determine the respective permeation coefficients for the cations, which are listed in Table 4.3. An initial examination of the results shows that the highly water-structuring divalent cations have significantly lower permeability than the monovalent species.

Table 4.3 Permeation and diffusion coefficients of salts with a common anion.

<table>
<thead>
<tr>
<th>Salt</th>
<th>P x 10^8 (cm^2 s^-1)</th>
<th>D x 10^7 (cm^2 s^-1)</th>
<th>D₀ x 10^5 (cm^2 s^-1)</th>
<th>ln(D/D₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiCl</td>
<td>16.7</td>
<td>9.3</td>
<td>1.267</td>
<td>-2.61</td>
</tr>
<tr>
<td>NaCl</td>
<td>17.9</td>
<td>11.4</td>
<td>1.475</td>
<td>-2.56</td>
</tr>
<tr>
<td>KCl</td>
<td>23.9</td>
<td>13.7</td>
<td>1.838</td>
<td>-2.60</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>28.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaCl₂</td>
<td>4.3</td>
<td>2.7</td>
<td>1.107</td>
<td>-3.71</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>3.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BaCl₂</td>
<td>3.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4.1: Effect of Monovalent Cation Variation on Transport through PolyHEMA.
Figure 4.2: Effect of divalent cation variation on transport through polyHEMA.
P is the permeability coefficient of the solute; D, its diffusion coefficient in the membrane,
and $D_0$ the diffusion coefficient in water.

4.4.2 Transport behaviour of salts with a common cation.

In a subsequent set of experiments the effect of the counter ion on potassium ion transport
across poly HEMA was investigated under similar conditions (37°C, donor solution 0.25M
with respect to cation concentration). Primary transport data is illustrated in figure 4.3, and
the resultant potassium ion permeation coefficients listed in Table 4.4. A significant
difference between the permeability coefficients of the various anions investigated was
found. Thus, the thiocyanate ion produces permeability coefficients some three times
greater than that of the chloride which in turn is some fifteen times faster than that of the
sulphate ion. Yet again the importance of the anion in having the dominant influence in
physical parameters is demonstrated.

<table>
<thead>
<tr>
<th>Salt</th>
<th>$P \times 10^8$ (cm$^2$·s$^{-1}$)</th>
<th>$D \times 10^7$ (cm$^2$·s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF</td>
<td>12.2</td>
<td>10.4</td>
</tr>
<tr>
<td>KCl</td>
<td>23.9</td>
<td>13.7</td>
</tr>
<tr>
<td>KBr</td>
<td>32.0</td>
<td>14.2</td>
</tr>
<tr>
<td>KI</td>
<td>61.0</td>
<td>15.6</td>
</tr>
<tr>
<td>KSCN</td>
<td>86.8</td>
<td>16.2</td>
</tr>
<tr>
<td>KHCO$_3$</td>
<td>9.4</td>
<td>8.1</td>
</tr>
<tr>
<td>K$_2$SO$_4$</td>
<td>1.8</td>
<td>4.1</td>
</tr>
<tr>
<td>KNO$_3$</td>
<td>41.8</td>
<td>15.0</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>3.6</td>
<td>8.0</td>
</tr>
</tbody>
</table>

4.4.3 Discussion of transport studies.

Permeability correlation with the Stokes or hydrodynamic radii of the permeating species
has been previously inferred 4, 5, 79, 86, 90. Whilst the crystallographic radii increase in the
Figure 4.3: Effect of anion variation on transport through polyHEMA
order $Na^+ < Ca^{2+} < K^+$, the Stokes or hydrodynamic radii increase in the order $K^+ < Na^+ < Ca^{2+}$, which is the same order as the relative ion permeation through both water and water-swollen poly HEMA: a point reflected in the results shown in Table 4.4. However, in previous work, the examination of a limited range of permeating species and the extent and quality of the data presented, was insufficient for the correctness of the correlation to be assessed. The work was restricted to cation variation in the presence of the chloride ion, which exerts a relatively modest effect on the transport process. Even when a simple correlation of cation permeability with hydrodynamic radii for the metal chlorides is attempted, an obvious anomaly arises in the case of lithium. This is even more evident when the ratio of the diffusion of the ion through the membrane (D), and through water ($D_0$), is used as the basis of correlation. Treatment of the results in this way is particularly interesting in that it enables comparisons to be made with the transport of neutral solutes of various sizes across poly HEMA membranes. Figure 4.4 shows a plot of $\log D / D_0$ against the square of the radius of the diffusing cationic species using data from Tables 4.3 and 4.5. In addition a solid line showing the position of the diffusion coefficient ratios obtained by Kim 79 for a series of hydrophilic solutes of various sizes is included. It is immediately apparent that even if the abnormality of the lithium value is ignored the diffusion rates for the cations are much lower than would be expected from the results on neutral hydrophilic solutes of similar size. The difference may be associated with the validity of the respective values used for the hydrodynamic radii and the size of the non-ionic solutes, a point which must be considered further.
Figure 4.4: Comparison of Cation Transport Data
Table 4.5 Ionic radii: crystallographic ($r_c$) and Stokes hydrodynamic ($r_s$)

<table>
<thead>
<tr>
<th>Ion</th>
<th>$r_c$ 87 (Å)</th>
<th>$r_s$ 87 (Å)</th>
<th>Ion</th>
<th>$r_c$ 84,87 (Å)</th>
<th>$r_s$ (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li$^+$</td>
<td>0.60</td>
<td>2.38</td>
<td>F$^-$</td>
<td>1.36</td>
<td>1.49</td>
</tr>
<tr>
<td>Na$^+$</td>
<td>0.95</td>
<td>1.84</td>
<td>Cl$^-$</td>
<td>1.81</td>
<td>1.07</td>
</tr>
<tr>
<td>K$^+$</td>
<td>1.33</td>
<td>1.25</td>
<td>Br$^-$</td>
<td>1.95</td>
<td>1.05</td>
</tr>
<tr>
<td>NH$_4^+$</td>
<td>1.48</td>
<td>1.25</td>
<td>I$^-$</td>
<td>2.16</td>
<td>1.07</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>0.99</td>
<td>3.10</td>
<td>SCN$^-$</td>
<td>-----</td>
<td>1.23</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>0.65</td>
<td>3.47</td>
<td>HCO$_3^-$</td>
<td>-----</td>
<td>1.84</td>
</tr>
<tr>
<td>Ba$^{2+}$</td>
<td>1.35</td>
<td>2.90</td>
<td>SO$_4^{2-}$</td>
<td>1.44</td>
<td>2.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NO$_3^-$</td>
<td>2.64</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CO$_3^{2-}$</td>
<td>2.66</td>
<td>2.66</td>
</tr>
</tbody>
</table>

It is apparent from figure 4.3 and Table 4.4 that the effect of the anion on cation permeability is dramatic and that any transport model must take this into account. Furthermore, the fact that co-anions have relatively small effects on the water diffusion ($D_o$) values for individual cations indicates that it is the transport process within the membrane that must be addressed. As a basis for discussion, data can be referred to relating to the size, transport and partition behaviour of the anions (Tables 4.4, 4.5 and 3.11). Two attempted correlations are shown in figures 4.5 and 4.6. Figure 4.5 presents the variation in permeability coefficients of potassium as a function of hydrodynamic radius of its co-anion. Clearly no correlation exists. Figure 4.6, on the other hand, is more promising and indicates that the diffusion component of the transport process is probably size dominated.

This still leaves several questions unanswered. Even if diffusion coefficients of a cation can be related to the hydrodynamic radius of the counter-anion, on what basis can the important partition or solubility components be structurally correlated? Will the anion always dominate the transport process or will the larger of the two (anion or cation) exert the controlling influence? Does the lack of correlation between $D / D_o$ values for hydrophilic
Figure 4.5: The permeability of potassium as a function of the hydrodynamic radius of its co-anion.
Figure 4.6: The diffusivity of potassium as a function of the hydrodynamic radius of its co-ion.
solute and for ionic species reflect fundamentally different behaviour, or merely a failure to recognise the effective dimensional correlation for a pair of transported ions? Clearly some molecular model is needed to enable both the size permeability effects and the structural relationship of the diffusing species and the hydrogel matrix to be established.

Qualitatively, cation permeation is observed to fall into the two categories. On the one hand there are the highly mobile structure-breakers, for example K⁺, and on the other, the less mobile structure-makers, such as Li⁺, Na⁺ and Ca²⁺. The anions can also be classified as structure-makers or breakers, and it is interesting to compare this division of the ions with observed permeation rates. Anion structure-breakers like SCN⁻, I⁻, Br⁻, Cl⁻ are observed to permeate more rapidly than structure-makers such as F⁻ and SO₄²⁻. Polyatomic ions are not easily classified, other than by experimentation, and the hydrogen carbonate anion does not fit into this simple qualitative scheme. From size and valency HCO₃⁻ is predicted to be a structure-breaker but in order of ion permeation it is sandwiched between two structure-making ions. However, it is worth remembering that the pH of the water in the hydrogel is slightly acidic, pH 6. Under this condition it is possible that the hydrogen carbonate partially dissociates to give the carbonate anion (CO₃²⁻) which, due to its greater charge density, is more likely to structure its aqueous environment. For the purpose of illustration the diffusivities of both the CO₃²⁻ and the HCO₃⁻ anions are included in Table 4.4.

The order of permeability of the salts (Tables 4.3 and 4.4) is found to be consistent with the changing influence of ionic structure on behaviour found in the lyotropic (Hofmeister) series. It is significant that this series has been interpreted by Luck ⁹¹ as one in which water binding changes. Measurements were made of the structure temperature (Tₛₚₚ) which is defined by Luck as the temperature to which pure water is raised or lowered in order that it
should have the same extinction coefficient, in the region of free or weakly-bound OH, as the electrolyte solution. The structure temperature corresponding to 1M anion concentrations of various salts at 20°C gave a series:

\[
\text{NaClO}_3 > \text{NaClO}_4 > \text{KSCN} = \text{KNO}_3 > \text{NaI} > \text{KBr} > \text{KCl} > \text{NaCl} > \text{BaCl}_2 > \text{MgCl}_2 > \text{Na}_2\text{SO}_4 (T_{str} = 20°C) > \text{Na}_2\text{CO}_3 > \text{MgSO}_4
\]

This spectroscopic series is obviously similar to the Hofmeister series. In commenting upon his experiences with the concept Luck makes the point that the anions play the dominant, and cations a secondary, ordering role in the series. This point emerged in earlier studies of the swelling of poly HEMA hydrogel.\(^{92, 93}\) The dominant effect of the anion over the cation is thought to arise from the fundamental difference between the water-ion interaction. Anions are considered to react strongly with water to form partial covalent bonds with the primary hydration shell. Whereas cations interact with water in a less intense and probably electrostatic manner. Furthermore, there is a reasonably good correlation with the structure-making and structure-breaking concepts discussed above. Despite the obvious general relevance of hydrodynamic radii to transport processes involving hydrated ions they do not provide an adequate basis for understanding the behaviour of ionic species in water-swollen membranes. This may be illustrated in several ways. On comparing results based on hydrodynamic radii and on Nightingales "corrected" radii\(^{87}\) with the Kim's results (figure 4.5) that relate the diffusion of neutral species with their radii, it is apparent that no satisfactory correlation is obtained. In addition, this approach does not take into account the discontinuous nature of water held within a polymer matrix, nor can it allow for any interaction of the permeating species with the polymer itself. Not even refinements to the Stokes radii can explain (figure 4.1) why lithium ions appear to migrate through water-swollen poly HEMA much faster than
anticipated on the basis of the hydrodynamic radii. It is apparent that any satisfactory permeation model must take additional factors into account.

The simple permeation of a solute which requires a solvent in order to permeate through an otherwise impermeable membrane is well documented\textsuperscript{4, 30}. In the case of a simple salt such as NaCl it is indisputable that the ions permeate through a membrane such as water-swollen poly HEMA in the water phase. This is extended in theoretical models such as the "free volume theory"\textsuperscript{30}, or mathematical models relating permeation to pore size\textsuperscript{94}, to take into account the size of the hydrated solute. Additionally, some fundamental relationships between solutes and polymer partition coefficients have been investigated. The partition coefficient is defined as the concentration of the solute in the membrane phase. For simple electrolytes, such as the alkyl halides, the partition coefficient in the water-swollen polymer, Sm, should be not more than one, and Sm will increase with an increase in polymer hydration\textsuperscript{30, 31}. However, this is not necessarily the case for non-electrolytes. Previous workers have demonstrated that the diffusion of non-electrolytes through water-swollen polymers can be influenced by the interaction of the solute and the polymer chain\textsuperscript{31, 79}. Kim, describes the diffusion of macromolecules through polyHEMA membranes, swollen to various degrees, as either hydrophilic or hydrophobic solute diffusion\textsuperscript{79}. Hydrophilic macromolecules are described as permeating through the bulk-water phase of the membrane via the "pore" mechanism. Hydrophobic macromolecules are described as diffusing either by the "pore" or "partition" mechanism.

An examination of the effect that the partition coefficient has upon cation transport (for various cations with common co-ions) shows little correlation. This implies that the diffusion of these cations does not occur by a partition effect but by transport through the water phase only. A similar conclusion was reached by other authors from studies of
diffusion through hydrated membranes of electrolytes, and, in the case of NaCl, from the associated activation energy. However, an interesting trend may be observed in the effect of the counter-ion on cation permeation. The permeation of potassium appears directly related to the partition coefficients of the particular salts involved (Table 4.4, figure 4.5). This point is highlighted by the structure breaking halides Cl⁻, Br⁻ and I⁻ which have similar diffusion coefficients and whose differences in permeability can be explained in terms of the partition coefficient alone (Tables 3.11, 4.4). It is recognised that a certain degree of membrane expansion or contraction is observed in different salt solutions (Table 4.1). The relative volume change in the membrane does not, however, absolutely parallel the relative changes in potassium permeation in the presence of different co-anions. Some comparison of partition and structuring effects is relevant. The membrane partition coefficients increase in the order \( \text{SO}_4^{2-} < \text{HCO}_3^- < \text{F}^- < \text{Cl}^- \). These particular anions are all water-structuring ions, Cl⁻ being a borderline case. These ions are also classed as hard bases. Partition coefficients increase further in the order \( \text{Br}^- < \text{I}^- < \text{SCN}^- \). These ions are all classed as structure-breakers in water. They are also classed as soft bases, Br⁻ being a borderline case.

It is useful to consider the "interfacial zone" of water between the polymer and the ions. The greater the water structuring ability and the harder the ion, the greater the requirement of aqueous "pores" or domains for the ion to permeate through. As the water-structuring ability decreases, however, so the hydration requirement decreases. For the particular anions under investigation this trend is accompanied by a greater ability for the ion to approach the lipophilic backbone. Thus, as this trend is extrapolated, permeation through the membrane becomes possible, not only through the mobile hydration shell but also, to a lesser extent, via the polymer. Whereas it is accepted that the permeation of KSCN would not be possible in the absence of water, it is arguable that the ease of SCN⁻ approach to the
backbone influences the rate of ion permeation to a secondary extent. This would explain the relatively large values for its partition coefficient (Table 3.11) and permeability through the hydrated membrane (figure 4.3). It should be noted, that like all studies involving water structuring, that the results are concentration dependent. At infinite dilution it can be expected that the solvent cospheres around an ion are complete. As concentrations increase, then the probability of the cospheres overlapping increases, to a point where contact-ion pairs may be formed.

In summary it is apparent that both size and water structuring effects are important in determining the transport properties of an ion in a hydrated matrix. The effect of the ion on the hydrated matrix itself and the resultant nature of the "interfacial zone" is more difficult to measure, but an interesting and informative reflection of this behaviour is found in the melting endotherms obtained using differential scanning calorimetry (D.S.C.). The rôle of this technique in characterising water structuring phenomena in hydrogels is discussed in a paper by Corkhill et al. Although a well established technique, D.S.C. has not previously been used in the study of water structuring effects for different salt solutions in hydrated polymer matrices. Figure 4.7 shows the melting endotherm obtained for polyHEMA hydrogels hydrated in water and in solutions of potassium iodide, potassium chloride and potassium sulphate. Figure 4.7 includes, for convenience, the ionic concentrations of the hydrated solutions, the overall EWC's and the equilibrium freezing and non-freezing water contents. It is apparent that both the structure-making ions (Cl⁻ and SO₄²⁻) reduce the free or freezing water content and increases the non-freezing (sometimes called "bound") water content relative to hydration in deionised water. Similarly the structure-breaking ion (I⁻) has the opposite effect in that it increases the freezing and decreases the non-freezing water contents. The fine structure of the endotherm and in particular the position of the depressed water peak is also characteristically different with
Figure 4.7 Melting endotherms of poly HEMA in water and potassium salt solutions.

(a) KI (250 mM)
- EWC = 39.9%
- Freezing Water = 18.3%
- Non-Freezing Water = 21.6%

(b) K_2SO_4 (125 mM)
- EWC = 32.7%
- Freezing Water = 5.4%
- Non-Freezing Water = 27.3%

(c) KCl (250 mM)
- EWC = 34.9%
- Freezing Water = 7.1%
- Non-Freezing Water = 28.8%

(d) H_2O
- EWC = 37.6%
- Freezing Water = 13.2%
- Non-Freezing Water = 24.4%
the two classes of ions.

4.5 The effect of temperature on transport through poly HEMA.

The transport studies that have been discussed so far were all performed at the physiologically important temperature of 37°C. It is known that diffusing species have an associated "activation energy" of diffusion 29, 32, 96. It was therefore decided to determine the diffusion coefficients (Table 4.6) in poly HEMA over a series of temperatures for the strongly structure making K₂SO₄ and the mildly structure breaking KCl. From this, Arrhenius type plots could be constructed and their respective activation energies obtained.

<table>
<thead>
<tr>
<th>Temperature (centigrade)</th>
<th>P x 10⁸ (cm²·s⁻¹)</th>
<th></th>
<th>D x 10⁸ (cm²·s⁻¹)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KCl</td>
<td>K₂SO₄</td>
<td>KCl</td>
<td>K₂SO₄</td>
</tr>
<tr>
<td>25</td>
<td>20.9</td>
<td>1.0</td>
<td>10.5</td>
<td>2.4</td>
</tr>
<tr>
<td>37</td>
<td>23.9</td>
<td>1.8</td>
<td>13.7</td>
<td>4.1</td>
</tr>
<tr>
<td>45</td>
<td>28.0</td>
<td>1.6</td>
<td>18.2</td>
<td>5.0</td>
</tr>
<tr>
<td>60</td>
<td>42.4</td>
<td>2.1</td>
<td>29.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

From figure 4.8 an increase of permeability for both KCl and K₂SO₄ with temperature is clearly discernable - although the transition is less smooth in the case of K₂SO₄. Increasing the temperature from 25°C to 60°C has the effect of approximately doubling the permeability coefficients of both salts (Table 4.6). When their partition coefficients are allowed for and their diffusivities calculated then an Arrhenius plot of lnD against 1/T can be plotted, where T is the temperature in degrees Kelvin (figures 4.9a and 4.9b). For diffusion processes the Arrhenius equation can be written as 32:
Figure 4.9a: Arrhenius plot for the diffusion of potassium chloride through poly HEMA.

Figure 4.9b: Arrhenius plot for the diffusion of potassium sulphate through poly HEMA.
\[ \ln D = \kappa - \frac{E_D}{RT} \]  (4.8)

Where \( D \) is the diffusion coefficient of the solute in the membrane; \( \kappa \) is the preexponential factor; \( E_D \) is the associated activation energy of diffusion; \( R \) is the universal gas constant and \( T \) is temperature.

The slope of \( \ln D \) versus \( 1/T \) is, therefore, equal to \( E_D/R \). If this is calculated for KCl and \( K_2SO_4 \) then \( E_D \) is found to be 24.5 kJ.mole\(^{-1}\) for KCl and 24.0 kJ.mole\(^{-1}\) for \( K_2SO_4 \). In other words, these two different salts seem to possess the same value for \( E_D \), the activation energy of diffusion. This is, at first examination, less marked than expected from analogous studies of gas transport through polymer membranes where penetrant size is generally regarded as influencing the activation energy of the diffusion process\(^96\). Yasuda argued in his free-volume theory for the transport of solutes through hydrogels, that \( E_D \) was not only proportional to the cross-sectional area of the diffusing species but that the dependence of the free-volume of the total system on temperature would also have an influence on the experimentally determined value of \( E_D \)\(^4\). This latter influence might not be so pronounced in the case of transport through water swollen poly HEMA, since any increase in free-volume due to thermal expansion may be counteracted by the slight decrease in the EWC of the system with increasing temperature (see 3.3.5).

It is interesting to compare these results with those of Higuchi and Iijima\(^32\) who determined the activation energies for the diffusion of NaCl through a series poly (vinyl alcohol-co-itaconic acid) membranes. The \( E_D \) of sodium chloride through the membrane with the nearest equilibrium water content (34%) to that of the poly HEMA membranes studied here, was found to be 28.5 kJ.mole\(^{-1}\) (6.8 kcal.mole\(^{-1}\)). Spacek and Kubin\(^29\)
found a $E_D$ value of 38.6 kJ.mole$^{-1}$ (9.2 kcal.mole$^{-1}$) for the diffusion of KCl through a membrane of composition 93.8% 2-hydroxyethyl methacrylate (glycol methacrylate), 5% diethylene glycol methacrylate and 1.2% ethylene glycol dimethacrylate. The authors fail to mention the value of its equilibrium water content but the membrane is compositionally close to the test membrane employed here. These values can be compared with the $E_D$ of KCl in water, 15.7 kJ.mole$^{-1}$ \cite{29}. Spacek and Kubin observed that the $E_D$ of KCl through a series of hydrogel membranes tended to the $E_D$ of KCl in water as the EWC of the test membrane increased. Higuchi and Iijima in their study of NaCl transport found a similar relationship to $E_D$ with the degree of hydration of the membrane \cite{32}. From differential scanning calorimetry Higuchi and Iijima noted that the proportion of non-freezing water increased with decreasing EWC. The increase in the activation energy with decreasing EWC was interpreted to be due to the diffusion in non-freezing water needing a higher activation energy than in freezing or bulklike water. A reflection of this is found in the work by Uragami et al \cite{18}. From differential scanning calorimetry studies of NaCl solutions in cellulose acetate and poly (vinyl alcohol) membranes, these workers concluded that NaCl finds it more difficult to partition into the non-freezing (or stable) water relative to the freezing (or free) water.

In the D.S.C work performed for this study, the K$_2$SO$_4$ solution was found to produce proportionately more non-freezing water than KCl - yet both are observed to possess the same activation energy for the diffusion process. In addition, there is still the problem to resolve of the apparent insensitivity to the size of the hydrated ion within the membrane matrix. Using the Stokes radii, in the case of KCl, the K$^+$ ion should be the size dominating species with a radius of 1.25Å and in the case of K$_2$SO$_4$, it is the SO$_4^{2-}$ anion which is the larger with a radius of 2.06Å. Clearly then, one would expect K$_2$SO$_4$ to possess a higher value of $E_D$ than KCl - this is not observed.
It is perhaps relevant here to recall the criticisms of the Stokes radii mentioned in the introduction to this chapter where it was pointed out that the assumptions inherent in the Stokes radii yielded values that are best described as apparent as opposed to actual. Although the Stokes radius of an ion may be a useful parameter in helping to explain its rate of diffusion relative to other ionic species, it may be less useful as a guideline for the kinetics of the transport process. After all, the Stokes radii is derived from the measured mobility of an ion. The nature of the hydration shell of the ions may also have an influence - that is, it could be expected that there is a constant exchange of water molecules between states such as bound to the ion, bound to other water molecules only, and bound to the polymer. The rate of exchange of water molecules between sites may be expected to increase with increasing temperature, therefore the membrane may not see a "fixed size species". The interactions between ion, water and polymer is such that the classical ways of thinking about transport that were originally developed for gas transport through non-solvent swollen membranes may not be appropriate for the diffusion of salts in hydrogels.

This chapter dealt with a single polymer composition which was used to examine the effect that the nature of the permeant has on water structuring and transport in hydrated membranes. Such work provides an essential basis for the study of ion transport and water structuring in various hydrated membranes, in which the modulation of the water binding properties of the polymer itself, and its consequent influence on ion transport is examined. This involves keeping the anion constant and producing variations in water binding by changing polymer structures. The results of these studies are dealt with in the following chapter.
CHAPTER FIVE

TRANSPORT PROCESSES IN 2-HYDROXYETHYL METHACRYLATE COPOLYMERS.
5.1 Introduction.

From the solute-water interactions discussed in the previous chapter, it is clear that water-structuring phenomena are of fundamental importance in transport processes through hydrogel membranes. In seeking a more complete understanding of these phenomena, and the development of an acceptable model, it is logical to study variations in water-structuring that may be produced by variations in polymer, and thus membrane structure. In addition to the importance of this underlying understanding of the molecular aspects of transport processes, great interest centres around the ability to design permselective membranes by achieving a degree of discrimination against the transport of specific individual ions. In this chapter the results of ion permeation studies are described (various cations in the presence of a common anion) through a series of hydrogel membranes in which both the gross water content and the water binding (or structuring) processes are varied. The results are discussed in terms of models that seek to relate the transport process to the quantity and nature of water in the membrane.

A series of hydrogel membranes based on copolymers of 2-hydroxyethyl methacrylate (HEMA) with styrene and with methyl methacrylate were prepared. Membrane thicknesses were chosen to enable a reasonable compromise of strength (and thus ease of handling) and transport properties (minimum equilibration, lag time and duration of experiments) to be achieved. Styrene and methyl methacrylate were known, from previous experiments 15, to yield homogeneous hydrogels whose water binding properties vary regularly between those of the respective comonomers (figure 3.2). In the present study it was necessary to achieve, by change in membrane structure, variations in the membrane that in some way reflect the water structure-making and structure-breaking properties previously observed. The analogous behaviour in hydrogel membranes is frequently characterised by the terms freezing and non-freezing water. These are obtained by analysis of the melting endotherms
obtained with differential scanning calorimetry 14, 15, 98. Briefly, water that is strongly associated with polar groups in the polymer matrix is unable to freeze and does not, therefore, contribute to the melting endotherm. In this way the relative proportions of freezing and non-freezing water in the polymer can be determined.

Referring back to chapter 3, figure 3.2 showed the relative effect of styrene and of methyl methacrylate comonomers on the equilibrium water content (EWC) of 2-hydroxyethyl methacrylate copolymers where the greater hydrophobicity of the styrene over methyl methacrylate caused a sharper decrease in the overall EWC as the proportion of comonomer was increased. Perhaps more significant, in the present context, are the relative proportions of freezing and non-freezing water that make up the EWC values. These proportions are shown in figure 5.1 for methyl methacrylate-HEMA. The effects of three salts (whose transport behaviour was studied in the previous chapter) on the water binding properties of poly HEMA are included in figure 5.2 for comparison. From these figures it can be seen that an interesting parallel exists between the effect of ions and of monomer structure on water binding processes in polymer membranes.

5.2 Transport of salts through HEMA/MMA copolymers.

The permeability of these membranes to a range of cations in the presence of a fixed anion (chloride) was studied at 37°C. Examples of the changes in ion concentration in the receptor compartment as a function of time are shown in figure 5.3. This illustrates both the form of the primary data and the transport properties of a (HEMA:MMA)(80:20) copolymer relative to those of poly HEMA. The conversion of primary results, obtained in this form, to permeability coefficients is straightforward (see 4.2) and enables experimental changes arising in membranes, such as membrane thickness, to be eliminated. The permeability coefficients thus obtained provide the first basis upon which variations in membrane
polyHEMA in a series of potassium salt solutions

Figure 5.2: The amount of freezing and non-freezing water for...
Concentration (mM)

Figure 5.3: Typical results for salt transport through gels.

- KC(HEMA)
- NaCl(HEMA)
- LiCl(HEMA)
- CaCl(HEMA)
- KCl(H-M(80:20))

Time (hours)
structure can usefully be correlated. Figure 5.4 summarises the results for HEMA-MMA copolymers. Here, the permeability coefficients for potassium, sodium, lithium and calcium (in the form of their chlorides) are shown as a function of the fractional hydration \((H = EWC/100)\) of the membranes.

5.3 Transport of KCl through HEMA/Styrene copolymers.

The proposition that permeation is linked to the water content rather than the polymeric structure of the membrane is well known in the literature and is based on studies with ions \(^{30, 31}\) and with neutral molecules \(^{17, 99}\). Such studies have, however, been carried out on a limited range of membranes and permeants in each case. It is both necessary and appropriate to examine the validity of the proposition as a basis for interpreting the rather wider range of variations that are achievable. In broad terms the use of fractional hydration does seem to provide a reasonable basis for correlating results. Thus figure 5.5 shows the variation in permeability coefficients of potassium (chloride) as a function of fractional hydration for the HEMA-styrene copolymers. The results are strikingly similar to those obtained with HEMA-methyl methacrylate copolymers of corresponding water contents. Changes in equilibrium water contents may similarly be achieved, without modification of the backbone structure, by use of variations for a series of HEMA membranes in which the proportion of ethylene glycol dimethacrylate cross-linking agent has been varied. Changes in EWC, freezing and non-freezing water contents are shown together with their effect on calcium, sodium and potassium permeability coefficients (Table 5.1). It is apparent that the same broad dependence of transport on the state of hydration of the membrane is exhibited here.
Figure 5.4: Effect of degree of hydration on the permeability of salts through HEMA:MA copolymers.

Legend:
- CaCl₂
- MgCl₂
- NaCl
- KCl

P X 10⁻⁸ (cm² s⁻¹)
Table 5.1  Effect of cross-linking agent on the freezing and non-freezing water contents and permeation coefficients of HEMA hydrogels at 21°C.

<table>
<thead>
<tr>
<th>EGDM/EWC (%)</th>
<th>FWC 67 (%)</th>
<th>NFWC 67 (%)</th>
<th>Permeability x 10^8 (cm²-s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>38.5</td>
<td>14.4</td>
<td>24.1</td>
</tr>
<tr>
<td>1.00</td>
<td>37.6</td>
<td>13.2</td>
<td>24.4</td>
</tr>
<tr>
<td>2.00</td>
<td>36.0</td>
<td>11.2</td>
<td>24.8</td>
</tr>
<tr>
<td>4.60</td>
<td>31.5</td>
<td>7.6</td>
<td>23.9</td>
</tr>
<tr>
<td>7.60</td>
<td>28.2</td>
<td>4.9</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
</tr>
</tbody>
</table>

5.4 Correlation of results with transport models.

It is relevant at this point to compare techniques for handling permeation data through membranes of varying water contents. There are two major aspects to this point. The first relates to those correlations which is equivalent and which differ in form of mathematical presentation 15, 30, 31; the second relates to differences of behaviour that might be attributed to the two (or more) water binding states in the polymer 11, 13. The latter point is more closely related to the detail of a transport model for hydrated membranes and will be discussed in that context.

There are two major types of relationships between hydration and permeation coefficient, the first of these has been most usually associated with the name of Yasuda 17, 30 but is in fact based on much earlier work of Cohen and Turnbull 100. It is based on the concept that the major rôle of water is to provide a "free volume" from which the permeant is to be transported, and involves a plot of ln(permeability coefficient) (logarithm P) against the reciprocal of fractional hydration (1/H). The second, proposed by Refojo 90 relates ln P to 1/(H-1), and is based on Poiseuille-type flow through the membrane. These methods of presentation of our results are compared with a direct plot of ln P versus H in figures 5.6a, 5.6b and 5.6c. It should be noted that the values of EWC and thus H upon which these
plots are based are determined in deionised water. The effect of individual salt solutions is reserved for later discussion.

The simple plot of \( \ln P \) against \( H \) (Figure 5.6a) is, perhaps surprisingly, reasonably linear. This empirical relationship has been found to give the best fit for results of oxygen transport measurements through hydrogel membranes \(^{35}\). Although this is obviously not the case here, given that the plot does not take into account any effect of transported ions on water content, it does provide a yardstick against which to judge the other approaches. Such a comparison has the advantage that it engenders caution in the acceptance of the transport models that such approaches imply. A fairly marked change in slope (or onset of curvature) is found in Figure 5.6a at an equilibrium water content of around 25%. A similar phenomenon is observed in the more complex presentation (figure 5.6b) of \( \ln P \) versus \( 1/(H-1) \). This latter function has been found, in water flux experiments, to correlate directly with the effective mean pore radius of the gel \(^{4}\). Here again considerable doubt must centre on the meaning and validity of the model, but it does provide a conceptual basis for discussion.

In the absence of other information it would be reasonable to suggest that the significance of departure from linearity in figure 5.6a and 5.6b is found in the change in water binding behaviour reflected in figure 5.1. Thus, the more marked decrease in permeability might be supposed to correspond with the point at which "freezing" water (as determined by D.S.C) disappears from the hydrogel. Such a view would certainly not conflict with the important part that water-structuring plays in these transport processes - a point discussed and demonstrated in papers by Tighe et al \(^{14, 15}\). The pore radius to which this change in
Figure 5.6a: Plot of ln P vs. H for chloride salts through HEMA:MA copolymers.
Figure 5.6b: Plot of ln p vs. 1/[H(I-I)] for chloroform-salt透过

HEMA:MA copolymers

I(H-I)

ln p

-1.2  -1.3  -1.4  -1.5  -1.6

0  1  2  3

Irp of CACl²
Irp of LiCl
Irp of NaCl
Irp of KCl
Figure 5: Ge: Plot of In P vs. H/H for chloride salts through

HEMA:HEMA copolymers.
behaviour corresponds (2.4 Å) is obviously too large to provide the basis for a size exclusion model. Because this value is derived from water flux measurements on higher water content gels, however, it does not take into account any rôle that water which is strongly associated with the polymer might play in reducing available pore size for hydrated ion transport. Even when some notional account is made, it is clear that no specific size exclusion effect can be operating at this point. On the other hand the results (figures 5.6a and 5.6b) could be taken to sustain a model that interpret the observed effect in terms of a progressive decrease in effective pore volume combined with a more marked change in water binding properties.

Against this must be offset the information derived from figure 5.6c. Here, the relatively undisturbed linearity of ln P versus 1/H suggests that the permeation process is governed solely by the free volume associated with the aqueous polymer. Before accepting this view however, it is essential to address some important questions. These relate to the apparent absence in figure 5.6c of any effect relating to water binding processes, size exclusion phenomena or changing glass transition temperature in the membrane. The first point that must be made is that it is a consequence of extrapolating ln P and 1/H to low values of both P and H, that errors and deviations in the values of P and H are progressively more difficult to detect in the plot. To this must be added the effect, already alluded to but not included in the H values used, that the salt solutions have on values of equilibrium water contents. It is relevant to point out here that there will be a salt concentration gradient across the membrane (from donor cell to receptor cell) and that the only unambiguously measured value of EWC is that obtained under standard hydration (distilled water, controlled pH) conditions. The effect of salt solution on EWC is likely to increase progressively as EWC, and thus H, increases. For this reason it may be anticipated that a superimposed correction should be overlaid on figure 5.6a, b and c that make any assessment of their linearity in
their present form, suspect. A useful comparison may be made, in this respect, by plotting ln P against 1/H using the values of H in distilled water (the effective receptor cell concentration of zero) and the values of H in 250mM solutions of the test salt (the effective donor cell concentration). These are shown in Figures 5.7a-d where both H[water] and H[salt] plots appear to obey the free-volume prediction of linearity. The use, therefore, of standard hydration (ie. distilled water) values in the analysis of transport behaviour seems valid. However, from the studies of the effect of salts on hydrogels discussed in chapter 3 caution must be recommended if using standard hydration values on transport studies of salts of a common cation but different anion, due to the greater impact of anion variation on water structuring than the cation variation dealt with here.

The question of water binding as it relates to the conditions used in the permeation experiments is complex. It was a deliberate decision to minimise structural variations in the polymers studied by using 2-hydroxyethyl methacrylate as the hydrophilic monomer. Additional experiments with hydroxypropyl acrylate and hydroxypropyl methacrylate were also carried out, the results corresponding with those of hydroxyethyl methacrylate copolymers of corresponding water contents. Thus, we observe that despite modifications to the network structure (by use of a non-hydrophilic comonomer as a crosslinking agent rather than a backbone component, Table 5.1) and despite the use of hydrophilic centres in different local environments (hydroxypropyl acrylate and methacrylate) the water content, rather than the polymer structure is the dominating feature in transport control. In figure 5.8 the permeability results for the transport of KCl through HEMA:Styrene copolymer membranes is superimposed on the parallel results with HEMA:MMA membranes. Despite possessing different hydrophobic components both sets of ln P versus 1/H data appear to overlap. The important consequence of the way in which all these structural variations have been made, however, is that the same hydrophilic centre is at work. This in turn produces a
Figure 5.7a: Comparison of ln P vs. 1/H plots for H[water] and H[KCl].

Figure 5.7b: Comparison of ln P vs. 1/H plots for H[water] and H[NaCl].
Figure 5.7c: Comparison of $\ln P$ vs. $1/H$ plots for $H[\text{water}]$ and $H[\text{LiCl}]$.

Figure 5.7d: Comparison of $\ln P$ vs. $1/H$ plots for $H[\text{water}]$ for $H[\text{CaCl}_2]$. 
Figure 5.8: Combined plot of In P vs. 1/H for HEMA copolymers.
uniform variation of "freezing : non-freezing" water content ratio with equilibrium water content. A further, and most important consequence of this, is that the plot of ln(freezing water content) versus 1/H using data presented here is linear, with no more scatter than that found in figure 5.6c. These comments, taken together, offer some explanation of the uniformity of transport variation with equilibrium water content in the polymers studied, but also demand caution in interpreting the uniformity of particular forms of data presentation in terms of a universally applied transport model. In the light of this, the permeabilities of salts through a PEM-400:MMA(55:45) membrane were performed. In this case a different hydrophilic centre is involved, namely the poly (ethylene glycol) side chain of the PEM-400 moiety. It is interesting to note that for a membrane with an equilibrium water content of 39.4% the permeabilities of KCl, LiCl and CaCl₂ were 90.7 x 10⁻⁸, 62.3 x 10⁻⁸ and 41.4 x 10⁻⁸ cm².s⁻¹ respectively. The permeabilities of these salts in the same order as above are 23.9 x 10⁻⁸, 16.7 x 10⁻⁸ and 4.3 x 10⁻⁸ cm².s⁻¹ through a poly HEMA membrane with an EWC of 36.1%. The permeabilities of the PEM-400:MMA membrane are considerably greater than would be predicted by simple extrapolation of the HEMA:MMA series. This may indicate that care must be taken not to over generalise and over emphasise the rôle of the water content alone in the determination of transport characteristics of hydrogel membranes.

It has previously been mentioned that the permeability, P, is the product of two separate parameters: namely, the partition coefficient, Sm and the diffusivity, D.

\[
\text{If } P = \text{Sm}. \text{D} ,
\]

\[
\text{then, } \ln P = \ln \text{Sm} + \ln \text{D} .
\]
Plots of $\ln S_m$ versus $1/H$, and $\ln D$ versus $1/H$ are found in figures 5.9 and 5.10, respectively. Strictly speaking, the free-volume model addresses itself to the relationship between the diffusivity (or diffusion coefficient) to the degree of hydration. It is a result of the partition coefficient showing the same linear dependence on $1/H$ that causes the consequent straight line relationship of the permeability coefficient. This is a point more fully discussed by Yasuda et al in their paper on the transport of NaCl through hydrated polymer membranes$^{30}$.

The central point in the use of figure 5.6c to derive a universal model centres around the proposition that EWC alone (and thus free, or non-polymer volume) is the determining factor in the transportation process. This must be set against the possibility that one or more other factors will induce a discontinuity in this relationship. Such factors might be expected to include water-structuring (eg the ratio of "freezing" to "non-freezing" water); effective mean pore size of the matrix; the partitioning of the ion between different available environments (which in turn will depend upon water binding behaviour in the matrix) and rate of diffusion of the ion (which may be related to size exclusion effects in the polymer). Some support for the expectation that discontinuities will occur is found in the data for calcium in figure 5.6c in which no detectable transport is observed at values of $1/H$ above 3.8. Whatever value is taken for the hydrodynamic radius of calcium, a point discussed in chapter four, its value must be regarded as something in excess of twice that of potassium. Since there is little reason to expect the nature of the requirements of the hydrated calcium ion (in terms of water-structuring of the matrix) to be greatly different from those of potassium it is a reasonable assumption that the difference in behaviour is related to size exclusion phenomena.
Figure 5.9: Plot of In Sm vs. UH for KCl in HEMA-MMA copolymers.
Figure S.10: Plot of In D vs. 1/H for KCl through HEMA:MMA copolymers.
A similar danger exists in the assumption that the linearity of figure 5.6c demonstrates that the equilibrium water content and thus free volume is more important than water-structuring phenomena in controlling permeability. The correspondence of decline in freezing water content with decline in equilibrium water content on a regular basis in the polymers studied here has been previously commented on. Results with different polymer structures of similar water contents to those used here demonstrate that EWC alone does not control water flux and salt rejection in membranes. Although we find differential scanning calorimetry to be the most convenient method for water-structuring studies, the nature of water in membranes at 37°C (the temperature used here for transport measurements) will not be identical with that existing at or near the melting point of water. Thus D.S.C provides a useful technique for the study of variations within a series but is not necessarily a good predictor of water-structuring behaviour under different environmental conditions. It would be expected, in general, that under the conditions used for permeation studies, polymers will contain somewhat more "freezable" water than under the conditions of D.S.C measurements. As a result, predicted permeation discontinuities resulting from water-structuring phenomena would be expected to occur at slightly lower water contents that those predicted directly by D.S.C measurements. A secondary effect which may be expected to affect pore-size mobility within membranes is that the glass transition temperatures are progressive and none of the polymers studied are substantially below their glass transition temperature at the temperature used for transport measurements.

One general principle that emerges from results presented in this and the preceding chapter is the effect of the counter-anion on the transport of potassium salts through poly HEMA. Both the size and the water structuring effect of the anion were found to be important in influencing the overall permeability of the salt. It was found that the anion had a marked influence on the equilibrium water content of the hydrogel membrane. Permeability data
for the potassium salts and their respective water contents can be superimposed on the data for KCl through different HEMA:MMA copolymer membranes, (figure 5.11). It is observed that those salts that produced a greater EWC for poly HEMA than does KCl fit the slope of lnP versus 1/H, while those with comparatively lower EWC's are seen to substantially deviate from the straight line relationship. Like the chloride ion, the anions that fit the slope all have hydrodynamic or Stoke's radii smaller than that of potassium. In these cases the cation will exhibit the size controlling influence on the permeability. On the other hand, those salts that deviate from the slope have anions with larger effective radii than their potassium counterion.

Both size and water structuring phenomena contribute to the transport process and situations exist where either can play the dominant rôle. The free volume model accounts reasonably well for cation permeation controlled by diffusional size effects. It cannot, however, account for water structuring effects whether produced by the transported ionic species, or the polymer matrix. Water structuring phenomena within the membrane are controlled by the combined effects of dissolved cation, anion and the polymer itself. Thus in the potassium dominated cases described here, the overall degree of hydration is observed to have the controlling influence on permeability, irrespective of whether the water content is modulated by the anion or polymer backbone.
Figure 5.11: Free-volume rearrangement to compete influence on H/I by action and polymer and their effect on permeability.
CHAPTER SIX

THE EFFECT OF IONOPHORES ON THE TRANSPORT BEHAVIOUR OF HYDROGEL MEMBRANES.
6.1 Introduction.

6.1.1 The nature of ionophores.

The selective permeability of ions is a phenomenon that occurs frequently in biological membranes but is rarely exploited in artificial ones. One of its major applications in synthetic polymer membranes is in the field of ion-selective electrodes. One possible way to achieve permselectivity in a polymer membrane is to use neutral chelating agents (ionophores) \(^{101, 102}\) that specifically bind to particular ions, usually alkali and alkaline earth metal cations, and thus affect the relative flux of these species through the membrane.

In general, ionophores for cations act as chelating agents by possessing an electron rich cavity into which an ion can enter and bind through electrostatic interactions with donor atoms such as oxygen. For an ionophore to work efficiently requires a balance between the binding energy of an ion in its cavity and the ion's hydration energy in solution. In cases where the hydration energy of the cation greatly exceeds that of its binding energy to the ionophore, the ion would be unable to escape from its hydration shell. The hydration energies for alkali and alkaline earth metal cations are in the order of about 100 kcal/mol, thus molecules of water are quite tightly bound \(^{103}\). If, however, the hydration energy is much less than the binding energy, the ion would have no tendency to go back into solution, thus "killing off" the ionophoric sites. The stability of a given ionophore/cation complex depends, therefore, on the difference between the hydration and the ligand binding energies and this difference may well be a maximum for a particular cation. Thus, the selectivity of ionophores is ultimately a consequence of a complicated interplay between hydration and chelation. However, the dominant influence on selectivity are the diameters of the cation and ionophore cavity, with the greatest selectivity being displayed in cases of best fit between ion and cavity.
In considering a choice of a suitable ionophore the kinetics, as well as the thermodynamics of the chelation process, are also important since the ion must be able to enter or leave its cage at a reasonably fast rate if the ionophore is to act effectively. The mechanism of complexation can be regarded as being concerted in the sense that the loss of solvation is compensated by the formation of new interactions to the ionophores in a stepwise fashion \(^{103}\). This requires that the ionophore molecule be flexible enough to undergo rapid conformational rearrangements.

One of the ways and, up till now virtually the only way, that ionophores have been used in permselective membranes is to use them as mobile sites (ion-selective carrier ligands) incorporated into a lipophilic liquid membrane or a solvent impregnated poly (vinyl chloride) membrane \(^{55}\). Such membranes are used commercially in ion-selective electrodes \(^{104}\). In theory, extremely high selectivities can be achieved by using neutral ion specific ligands. Some commercially available ion-selective electrodes use the dodecadepsipetide valinomycin as a carrier for the potassium ion in solvent impregnated poly (vinyl chloride) \(^{104}\), although a great many synthetic ionophores have also been studied \(^{55}\).

The first multidentate macrocyclic compound synthesised with a proven ability to form stable complexes with the alkali and alkaline earth metal cations were the crown ethers \(^{105}\). These are macrocyclic polyethers which contain repeating (-O-CH\(_2\)-CH\(_2\))\(_n\) units. The first crown ether synthesised was 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacycloocta-2,11-diene \(^{106}\). Charles Pedersen, who first made this macrocyclic compound, devised the descriptive name of dibenzo-18-crown-6 for brevity and ease. From this beginning a nomenclature of crown names developed \(^{106}\). The names consist of in order:
(a) the name and kind of hydrocarbon rings;
(b) the total number of atoms in the polyether rings;
(c) the class, crown; and
(d) the number of oxygen atoms in the polyether ring.

Subsequent work has led to many types of crown compounds being synthesised including those in which some of the O-atoms have been replaced by other substituents, for example azacrown ethers contain NH or NR groups in place of O, and in the thiacrown ethers S-atoms are used in an analogous manner 105, 107, 108.

Other types of ionophores include cage-type bicyclic crown compounds called cryptands, first synthesised by Lehn and his coworkers 109. Relative to Pederson's crown ethers, these were found to exhibit both a higher ion selectivity and a greater stability of the complexes formed. More recently, interest has grown in macrocyclic condensation products of phenol-formaldehyde called calixarenes 110-112. They bear a structural similarity to some of the crown ethers in that they posses a central cavity containing electron-donor groups capable of binding cations. Initially, they were only efficient chelating agents for metal hydroxides, which allowed them to form neutral complexes with cations through the loss of a phenolic proton 110. The addition of functionalised groups, such as esters, to the convergent phenolic groups has resulted in calixarene derivatives capable of binding a greater range of salts 111-112.

6.1.2 Ionophores in polymers.

The degree of ion selectivity shown by these ionophores has resulted in attempts to incorporate them into polymer films to yield a permselective membrane. One of the first attempts at this was the polyether-polyamide PC-6 101, (figure 6.1). Membranes based on
PC-6 are much more permeable to water than to salts because of the low mobility of absorbed salts. The measured permeabilities are about $10^{-7}$ cm$^2$.s$^{-1}$ for water and $10^{-10}$ to $10^{-11}$ for the sodium salt. This implies strong cation binding to the dibenzo-18-crown-6 ligand. However, the permeability characteristics of PC-6 are strongly affected by their storage and history.

![Figure 6.1: PC-6](image)

The problem of low permeability is alleviated in part by using alloys of the poly (crown amide) with poly (vinyl pyrrolidone), PVP. Some alloys are reported to have water diffusion coefficients only fifty times below that of pure water. Salt diffusion coefficients also increase, for example, $0.44 \times 10^{-11}$ cm$^2$.s$^{-1}$ for the poly (crown amide) to $7.0 \times 10^{-11}$ cm$^2$.s$^{-1}$ for an alloy containing 70% poly (vinyl pyrrolidone).

The apparent "activation energy of diffusion" of the sodium ion in such membranes is found to be essentially identical (~12 kcal) with the activation energy of the decomplexation of the sodium/crown complex. Crown ethers can also be incorporated into phenol-formaldehyde type resins. This is achieved by reacting a dibenzo-crown ether and formaldehyde in the presence of formic acid. One such resin, containing dibenzo-21-crown-7 has been used to separate a mixture of lithium, sodium and potassium thiocyanate.
One of the problems of having crown ethers incorporated into the backbone of the polymer chain is the resulting brittleness of the membrane. Attempts to reduce this problem have led to interest in the synthesis of polymers containing crown ether moieties as pendant side groups. Such polymers can be prepared by either polymerisation reactions with ionophoric monomers \(^{114-117}\) or by using functional groups on a polymer to attach the crown ether \(^{102,118}\). An example of the latter are the polymers synthesised by Kimura et al containing crown ether moieties at the side chains which are capable of forming rather tough films. These are prepared by the polymer reaction of poly (vinyl alcohol) with formyl derivatives of aliphatic crown ethers such as 12-crown-4, 15-crown-5 and 18-crown-6 \(^{102}\). Permeability studies showed that the passive transport of alkali metal picrates across the poly (crown ether) membranes differed significantly from those of poly (vinyl alcohol). The workers concluded that the cation sandwiches intramolecularly between two adjacent crown ether moieties in a polymer chain, that is, the poly (crown ether)s form 2:1 crown ether ring-to-cation complexes with certain cations that are slightly larger than the crown ether cavity. The tacticity of the poly (crown ether)s was also found to affect their cation-binding abilities. The selectivity ratio of two alkali cations was found to be dependent upon the crown ether content and cavity size.
Oue, Ishigaki *et al* synthesised thiacrown ether polymers where the benzo-crown ether sidechain moiety has some of its oxygen atoms replaced by sulphurs\(^{114}\) (figure 6.3). Such replacement causes both a decrease in cavity size of the crown ethers and an increase in its affinity for softer metal ions than the alkali and alkaline earth cations. Studying the extractability of the poly (thiacrown ether) for various cations they were found to be selective for the transition and heavy metal cations of \(\text{Ag}^+\) and \(\text{Hg}^{2+}\) over \(\text{Na}^+\), \(\text{K}^+\) and \(\text{Ca}^{2+}\) as well as over the transition and heavy metals \(\text{Cd}^{2+}\), \(\text{Co}^{2+}\), \(\text{Pd}^{2+}\) and \(\text{Fe}^{3+}\).

**Figure 6.3: Generalised structure of the thiacrown ether polymers.**

\[
\begin{align*}
\text{\(\text{X} = \text{-S-}\)} \\
\text{or \(\text{-S-(CH}_2\text{)}_3\text{S-}\)}
\end{align*}
\]

Crown ether containing polymers are not only effective in their selective complexation of spherical cations, in addition they also interact with organic cations such as primary ammonium, diazonium ions, and even with neutral molecules such as urea and acetonitrile\(^{119}\). Polymers carrying crown ether ligands can often exhibit selective cation binding different from that of their monomeric crown analogues. Such differences may arise from cooperative effects involving neighbouring ligands or comonomer substituents and from effects due to charge accumulation in the polymer matrix \(^{113,114,119}\). The effect
of substituent groups on ionophores may also be important. Studies on mono-benzene
crown ethers showed that substituents on the 4'-position had a considerable influence on
complexation \(^{120, 121}\). In a similar manner, the functional group that attaches the ionophore
to the polymer may also have an influence on cation binding, particularly in the case of
crown ethers possessing a benzene ring moiety.

6.1.3 Applications of ionophores.

From the early work by Pederson on crown ethers there has been a continuous growth in
both the number of new ionophores and in their applications in various scientific
disciplines. For example, ionophores such as the macrocyclic polyethers are used in
organic synthesis both in homogeneous organic solution and in phase transfer catalysis,
where they act as complexing agents that can solubilise alkali metal ions in non-polar
solvents as well as complex alkaline earth cations, transition metal cations and ammonium
cations \(^{122, 123}\). They have use in the separation of ions by extraction and in ion exchange
resins \(^{124}\). Recent work in colorimetric crown compounds has led to their use in
chromogenic membranes for optical sensors \(^{125-128}\). More pertinent to this study is their
application as the sensing component in ion-selective electrodes \(^{129, 130}\). The ability of
ionophores to selectively chelate to a specific species, coupled with the ability to modify
structural parameters such as cavity diameter with the consequent effect on selectivity
means that these compounds possess a clear potential as possible modulators of the
permeability characteristics of membranes. Such work, however, has almost exclusively
involved the use of ionophores in the organic phase. There seems to have been relatively
little work carried out on the effect of ionophores on the transport of salts through a water
swollen polymer matrix. From chapters 3 to 5, the importance of the nature of the solute
and the chemical composition of the polymer on water binding and consequently
permeation behaviour was discussed. The selective chelating ability of ionophores seems a
potentially useful way of influencing the transport characteristics of a membrane. It was to this end that attempts were made to incorporate crown ether compounds into hydrogel membranes.

6.2 The incorporation of ionophores in hydrogels.

It is apparent from the examples of ionophore containing polymers mentioned in the above introduction that the main emphasis has been on comparatively hydrophobic membranes. Of the small number of papers on water containing membranes, the influence of the ionophore has not been studied with the background of knowledge of water binding and other phenomena that are so important in controlling transport. It is in the light of information from chapters 3 to 5 that the incorporation of ionophores into hydrogel membranes will now be discussed.

6.2.1 Discussion of the synthesis of ionophore containing membranes.

Although ionophores such as crown ethers have been used as mobile carrier ligands for the transport of ions through hydrophobic liquid membranes and plasticised poly (vinyl chloride) membranes, there seems to have been little attempt to use their selective chelating ability in hydrogels.

18-crown-6 and subsequently dicyclohexano-18-crown-6 (figure 2.4) were the ionophores used. The crown ethers were added to the reaction monomer mixture in the hope that they would become trapped within the polymer matrix on polymerisation. Both dicyclohexano-18-crown-6 and 18-crown-6 were found to be readily soluble in the reaction mixture. The membranes produced were clear, indicating that no phase separation had occurred between the polymer and ionophore during the polymerisation process. On hydration, the membranes remained transparent, which is consistent with the membranes retaining their
homogeneity in the water swollen state.

6.2.2 Discussion of leaching studies.

The concept of physically immobilising species in hydrogel matrices is well known. Hydrogels are sometimes regarded as having an associated mean pore size with a concomitant cut off point for any species larger than this. Early attempts in this study at ionophore encapsulation in hydrogels used 18-crown-6 as their selective chelating agent. A range of water contents of decreasing pore size were used to investigate the possibility of physically immobilising this simple ionophore. However, no observable changes were found in the properties of such nominally ionophore containing membranes, either in terms of EWC or transport behaviour. Figure 6.4 shows permeability runs of KCl through two poly HEMA membranes, one of which contained 20% 18-crown-6 in its original reaction mixture. Within the experimental error of the permeability determination technique, there is no significant difference between the membrane transport properties.

Table 6.1 Leaching studies.

<table>
<thead>
<tr>
<th>original composition</th>
<th>% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMA:MMA(65:35) + 20.7% 18-crown-6</td>
<td>19.6</td>
</tr>
<tr>
<td>HEMA:MMA(60:40) + 20.6% 18-crown-6</td>
<td>20.7</td>
</tr>
<tr>
<td>HEMA:MMA(65:35) + 20% ethanediol</td>
<td>20.6</td>
</tr>
<tr>
<td>HEMA:MMA(60:40) + 20% ethanediol</td>
<td>20.7</td>
</tr>
</tbody>
</table>

It was suspected that the ionophore might be leaching out of the polymer matrix during hydration. To test this, two low water content membranes were prepared containing 18-crown-6 in their reaction monomer mixtures. These were chosen since if ionophore
immobilisation was going to succeed then it would most likely occur with the lower water content membranes as these would possess the smallest effective average pore radius \(^90\). Analogues of these membranes were prepared for comparison using ethanediol, a sterically smaller, water soluble organic species that is frequently used as a diluent in the preparation of hydrogels. From the results of % weight loss, (Table 6.1), it is evident that virtually all of the additive has leached out. The failure of 18-crown-6 to become immobilised in the membrane matrix is probably caused by an ability of the ionophore to interact with, and hence become soluble in, the polymer phase as well as the water phase within the hydrogel. Therefore, unlike simple alkali and alkaline earth metal salts, its ability to diffuse through the membrane is not confined to the water filled pores and channels of the hydrogel matrix. The classic concept of Rechojo's mean pore size \(^90\) is thus rendered invalid, since it assumes that permeants are soluble only in the water phase. The 18-crown-6 may, in effect, see the membrane as nothing more than a rather viscous liquid out of which it can slowly diffuse.

It was determined to try the ionophore dicyclohexano-18-crown-6, since this is lipophilic in nature due to its large cyclohexyl substituents (figure 2.4). This ionophore has been used in plasticised PVC membranes \(^130\) and it was thought that it was less likely to leach out than 18-crown-6 as it should prefer the relative hydrophobicity of the hydrogel membranes to the bulk aqueous phase. The supporting polymer matrix for the ionophore had to be a compromise between having sufficient permeability for transport measurement to be easily made (a property that increases with increasing EWC) and high hydrophobicity (a property that increases with decreasing EWC) to provide a preferable environment for the ionophore relative to the aqueous surroundings. In addition, lowering EWC increases the glass transition temperature, \(T_g\), of the system. The mobility of the ionophore, and consequent rate of loss from the membrane, should decrease with the increasing polymer chain stiffness associated with \(T_g\). In summary then, a membrane was required with easily
observable transport properties, reasonable hydrophobicity and low ionophore mobility. The hydrogel matrix originally chosen was a HEMA:MMA(80:20) copolymer. Leaching studies on such a hydrogel, containing 20% by weight dicyclohexano-18-crown-6, showed a weight loss of 11.1% after one week and 19.1% after two weeks. Although considerably better than 18-crown-6, which completely leached out in a few days, it was decided to try another matrix. The polymer composition finally employed was HEMA:EGDM(90:10), that is, a poly HEMA membrane with 10% crosslinker. This possesses a similar EWC to HEMA:MMA(80:20) membranes (24.3% and 23.5% respectively), but in addition, possesses a high degree of crosslinking which should increase the steric hindrance within the matrix and hopefully reduce the ionophore’s mobility in the membrane.

Ionophore containing membranes discussed in the rest of this chapter have a composition of HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6.

6.2.3 Effect of ionophore on EWC.

In order to minimise the loss of ionophore through leaching, the membranes were stored in their dry state and soaked in water overnight before use. In order to ensure that sufficient time was being allowed for the membranes to fully hydrate, a time course study on water content was performed (figure 6.5). The amount of water absorbed by the hydrogel was observed to reach equilibrium within two hours.

From the information in Table 6.2 it can be seen that the presence of ionophore in the membrane leads to no significant deviation in the value of the EWC. In part, this may be due to the ionophore, like the monomer, containing both hydrophobic and hydrophilic parts, the effect being, that any increase in the hydrophobicity of the membrane due to the cyclohexyl groups on the crown ether will be counteracted by the accompanying
Figure 6.5: Hydration curve of a HEMA-EGDMA(90:10) + 5% DC-18-crown-6 membrane.

(time (mins))

water absorbed (%)
hydrophilicity of the ethylene glycol repeat units in the ring. However, it is possible that the main reason for the lack of any marked change in EWC is that the comparatively small amount of ionophore, at 5% by weight, that has been incorporated into the membrane is insufficient to have a significant impact on EWC.

Table 6.2 Values of EWC at 37°C of HEMA:EGDM(90:10) membranes with and without 5% DC-18-crown-6.

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Equilibrating Solution</th>
<th>EWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMA:EGDM(90:10)</td>
<td>H₂O</td>
<td>24.3</td>
</tr>
<tr>
<td>HEMA:EGDM(90:10) + 5% DC-18-crown-6</td>
<td>H₂O</td>
<td>24.6</td>
</tr>
<tr>
<td>HEMA:EGDM(90:10) + 5% DC-18-crown-6</td>
<td>250mM KCl</td>
<td>23.6</td>
</tr>
<tr>
<td>HEMA:EGDM(90:10) + 5% DC-18-crown-6</td>
<td>250mM LiCl</td>
<td>21.4</td>
</tr>
</tbody>
</table>

The slight deswelling effect seen in both the KCl and LiCl solutions are reminiscent of the results in chapter 3 that dealt with the influence of salt solutions on the EWC of non-ionophore containing hydrogels. The ability of dicyclohexano-18-crown-6 to chelate to cations, especially K⁺, does not seem, therefore, to have an impact on the overall hydration of the water swollen polymer matrix.

6.3 Transport studies on a hydrogel containing dicyclohexano-18-crown-6.

6.3.1 Permeation of various salts (through HEMA: EGDM(90:10) + 5% Dicyclohexano-18-crown-6 copolymer membranes.

The ionophore, dicyclohexano-18-crown-6, possesses a central cavity diameter in the range 2.6 - 3.2 Å. From the range of chloride salt which were examined, the K⁺ cation with
an ionic diameter of 2.66 Å would generally be expected to form the stabllest complex with this crown ether \(^{131, 132}\). Therefore, the first point to be established, was whether the presence of ionophore in the hydrogel matrix altered the transport characteristics of the membrane. Figures 6.6a and 6.6b compare results for the transport of KCl and NH\(_4\)Cl through an unmodified HEMA:EGDM(90:10) membrane with one containing 5% by weight of dicyclohexano-18-crown-6. Although this ionophore caused little change in the EWC of the host membrane, its effect on permeability was significant and clearly visible. The ionophore containing membranes possess an increased induction period, or lag-time, relative to the crown free analogues. This is indicative of the solute interacting with the crown ether. The extended lag-time seems greater in the case of KCl than NH\(_4\)Cl - this correlates with the free energy of complexation, \(\Delta G\), in water being greater for K\(^+\) than NH\(_4\)\(^+\) \(^{132}\). It is a general aspect of steady state transport processes through membranes that they have an associated lag-time while the penetrant is dissolving in the membrane up to a constant level, before steady state is achieved. On close examination of the initial part of the concentration versus time curve, the best fit relationship of the observed permeation for ionophore containing membranes is a linear one. That is, the membranes containing the crown ether can effectively be regarded as having two associated permeability rates, an initial one during the induction period, \(P_1\) and a final steady state value, \(P_2\). This contrasts with unmodified hydrogels where the concentration with time plot "curves" into the final steady state value. This is illustrated in figure 6.7a for the permeation of CaCl\(_2\) through poly HEMA, where the induction period, (highlighted in figure 6.7b), is clearly non-linear.

In the comparison of permeation through ionophore-containing and ionophore-free membranes, not only is the lag-time extended by the presence of the ionophore but the final steady state permeation is also effected. These are \(2.36 \times 10^{-8}\) and \(1.36 \times 10^{-8}\) cm\(^2\).s\(^{-1}\) for
Figure 6.6a: Transport of KCl through HEMA:EGDM(90:10) with and without 5% DC-18-crown-6.

concentration (mM)

KCl - no crown
KCl - crown

time (hours)

0.00 0.04 0.08 0.12 0.16 0.20 0.24

Figure 6.6b: Transport of NH4Cl through HEMA:EGDM(90:10) with and without 5% DC-18-crown-6.

concentration (mM)

NH4Cl - no crown
NH4Cl - crown

time (hrs)

0.00 0.10 0.20 0.30 0.40
Figure 6.7a: Complete 7 hour run of transport of CaCl₂ through poly HEMA.

Figure 6.7b: Initial 2 hours of transport of CaCl₂ through poly HEMA.
KCl through unmodified and ionophoric membranes, respectively, and $4.16 \times 10^{-8}$ and $3.06 \times 10^{-8}$ cm$^2$s$^{-1}$ for NH$_4$Cl. Again, the greatest impact is found with KCl permeability which falls by 42% when the ionophore is present, this contrasts with a fall of 26% in the case of NH$_4$Cl. Both reductions, however, are significant and it should be repeated that this fall cannot be accounted for by a drop in EWC of the membrane on the addition of dicyclohexano-18-crown-6 since no fall in the water content is observed to occur (table 6.2). The final steady state permeation, therefore, must involve an interaction between the transported solute and the ionophore within the membrane matrix.

Permeability runs were performed with KCl, NaCl, NH$_4$Cl and LiCl. Their primary concentration versus time curves are shown in figure 6.8. The associated transport data is tabulated in table 6.3 and shown graphically in figures 6.9 and 6.10. There are a number of initial observations that can be made from the the primary data: the final steady state permeability rates, $P_2$, for the salts go in the order of NH$_4$Cl > LiCl > NaCl > KCl. From the permeability studies discussed in chapters 4 and 5, this order is different from what might be predicted. For example, the order for poly HEMA is NH$_4$Cl > KCl > NaCl > LiCl. The extended lag-times range from 4.45 hours for KCl to 0.62 hours for LiCl. The former seems significantly extended in comparison to transport behaviour found in non-ionophoric membranes but the LiCl value falls within the pre-steady state induction period observed in conventional hydrogels. This may indicate that although there clearly is an ionophore effect with KCl, the transport of LiCl is relatively unperturbed by the crown ether. Comparison of the steady state permeabilities, $P_2$, with the apparent permeabilities, $P_1$, associated with the time-lag, shows that the greatest changes occur with KCl and NH$_4$Cl. Taking the ratios of $P_2/P_1$ gives an order of KCl > NH$_4$Cl > NaCl > LiCl. The respective values of $P_2/P_1$ are 4.53, 2.62, 1.59 and 1.52. If the ratios are an indication of the degree of interaction of the cation and crown ether and if it is assumed that
Figure 6.9 Permeability data for the transport of salts through HEMA:EGDM(90:10) + 5% DC-18-crown-6.

$P \times 10^8$ (cm$^2$.s$^{-1}$)

- KCl
- NaCl
- NH$_4$Cl
- LiCl

salt (250mM)

Figure 6.10: Extended lag-times of salts in HEMA:EGDM(90:10) + 5% DC-18-crown-6.

Extended lag-time (hours)

- KCl
- NaCl
- NH$_4$Cl
- LiCl

salt (250mM)
K⁺ strongly interacts and Li⁺ virtually does not, then from the ratios for NH₄Cl and NaCl it may be stated that the NH₄⁺ cation interacts with the crown ether but to a lesser extent than K⁺ while Na⁺ is, perhaps, borderline as to whether it does or does not.

**Table 6.3 Permeability data for the transport of salts through HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6 copolymer membranes.**

<table>
<thead>
<tr>
<th>salt (250mM)</th>
<th>permeabilities (10⁻⁸ cm²·s⁻¹)</th>
<th>extended lag-time (θ (hrs))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P₁</td>
<td>P₂</td>
</tr>
<tr>
<td>KCl</td>
<td>0.30</td>
<td>1.36</td>
</tr>
<tr>
<td>NaCl</td>
<td>1.05</td>
<td>1.67</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>1.17</td>
<td>3.06</td>
</tr>
<tr>
<td>LiCl</td>
<td>1.21</td>
<td>1.84</td>
</tr>
</tbody>
</table>

In chapter 5 it was shown that the EWC was the major parameter for determining the permeability coefficient of a salt in a series of copolymer membranes that shared the same hydrophilic centre. The "free-volume" plot of ln P versus 1/H was shown to be linear, were P is the steady state permeability and H the degree of hydration (H = EWC/100). Where HEMA is the hydrophilic component, it is therefore, possible to predict the permeability coefficient of a salt through a membrane of known EWC (and therefore 1/H value) by reading off the corresponding ln P value on a free-volume plot. Figures 5.7a-c are the ln P versus 1/H plots for KCl, NaCl and LiCl. If the EWC was the sole criteria for predicting the permeability coefficient, then from using these plots, the HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6 membrane, which has an EWC of
24.6%, should have associated permeabilities for KCl, NaCl and LiCl of $2.2 \times 10^{-8}$, $2.0 \times 10^{-8}$ and $1.9 \times 10^{-8} \text{cm}^2\text{s}^{-1}$ respectively. The corresponding measured values are $1.34 \times 10^{-8}$, $1.67 \times 10^{-8}$ and $1.84 \times 10^{-8} \text{cm}^2\text{s}^{-1}$.

The measured permeability for KCl is considerably less than the predicted value again indicating that the presence of ionophore has a strong influence on KCl transport. However, the permeability coefficient of KCl through the HEMA:EGDM(90:10) membrane with no ionophore at $2.36 \times 10^{-8} \text{cm}^2\text{s}^{-1}$, correlates well with the predicted value, thus showing the validity of using the $\ln P$ versus $1/H$ plot to predict permeabilities in cases where the EWC is the only significant parameter. The comparison of predicted permeability coefficient for NaCl with the value actually found indicates that there is some Na$^+$/ionophore interaction. By contrast, in the case of LiCl, the closeness in permeability values seems to show that this salt is indeed uninfluenced by the presence of ionophore in the membrane.

6.3.2 Influence of concentration on the transport of KCl through HEMA: EGDM(90:10) + 5% Dicyclohexano-18-crown-6 copolymer membranes.

It is evident from the above permeability studies that KCl exhibits the greatest modulation of its transport properties through the HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6 membrane. Consequently, it was decided to perform further studies on this salt and examine the effect of concentration on the permeability behaviour. The concentration versus time curves are shown in figure 6.11. The associated transport data is tabulated in table 6.4 and illustrated graphically in figures 6.12 and 6.13.
Figure 6.1: Transport of KCl solutions of different concentrations through HEMA:EGDMA (90:10) + 5% DC-18-Crown-6.
Figure 6.12: Permeability data for the transport of KCl through HEMA:EGDM(90:10) + 5% DC-18-crown-6.

![Permeability data graph](image)

Figure 6.13: Extended lag-times of KCl solutions in HEMA:EGDM(90:10) + 5% DC-crown-6.

![Extended lag-time graph](image)
Table 6.4 Permeability data for the transport of KCl through HEMA:EGDM(90:10)
+ 5\% dicyclohexano-18-crown-6 copolymer membranes.

<table>
<thead>
<tr>
<th>KCl concentration (mM)</th>
<th>permeabilities (10^{-8}\text{cm}^2\text{s}^{-1})</th>
<th>extended lag-time (\Theta) (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>0.60</td>
<td>1.13</td>
</tr>
<tr>
<td>250</td>
<td>0.30</td>
<td>1.36</td>
</tr>
<tr>
<td>500</td>
<td>0.13</td>
<td>1.37</td>
</tr>
</tbody>
</table>

Both the lag-times and associated pseudo-steady state permeability of the induction period are observed to fall with increasing concentration. The final steady state permeabilities, however, remain relatively constant over the range of concentrations studied. The various interpretations and diffusion models discussed in the previous two chapters are clearly insufficient on their own to understand the phenomena in this study. In the light of the observations made on transport through this ionophore containing membrane, it is now appropriate to draw these results together and try and rationalise them in terms of what is already known about membrane transport phenomena in both the liquid and gaseous phase.

6.3.3 General discussion of transport through an ionophore containing membrane.

Various ionophore containing polymers were discussed in section 6.1.2. Although permeability work was carried out on such membranes,\(^ {101, 102}\) it should be emphasised that they were relatively hydrophobic compared to the ionophore containing membrane studied here, being, as they were, considered for such applications as reverse
The permeabilities observed in the HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6 membrane was in the order of \(10^{-8}\) cm\(^2\).s\(^{-1}\): a value considerably higher than the \(10^{-11}\) and \(10^{-12}\) cm\(^2\).s\(^{-1}\) permeabilities observed with the ionophoric polymers studied by Shchori \(^{101}\) and Kimura \(^{102}\). There are problems in making direct comparisons between this work and that of the authors mentioned above, for example, both groups of workers fail to discuss pre-steady state phenomena, and in the case of Kimura et al, fail to say if the zero time of their linear concentration versus time plot of salt flux is at the start of introducing the salt solution or is an arbitrary point selected during the final steady state period.

Perhaps surprisingly, it is from studies in the field of gas transport through polymer membranes that some of the best analogies to this work may be found. It has been observed that in elastomeric polymers, like non-ionophore containing hydrogels, the partitioning of gas into the polymer matrix may be adequately described in terms of Henry's Law. With many glassy polymers, however, a nonlinear sorption isotherm is observed for a number of gases: this led to the "dual sorption" model being proposed which considers that the penetrant exists in two populations within the polymer matrix; namely, a population with a Henry's Law isotherm and the other with a Langmuir isotherm\(^{97}\). The partition coefficient can, therefore, be described by the following equation:

\[
S_T = \frac{C_m}{C} = S_m + C'_H \cdot \frac{b}{(1 + bC)}
\]  

(6.1)

where \(S_T\) is the overall partition coefficient, \(C_m\) is the total concentration of solute in the membrane, \(C\) is the equilibrating concentration; \(S_m\) is the Henry's Law partition coefficient; and for the Langmuir part: \(C'_H\) is the "hole saturation" constant; \(b\) is the "hole affinity" constant and represents the rate constants of solute adsorption and desorption in
the sorption sites.

This behaviour of glassy polymers may be mirrored in the ionophoric hydrogel where salts partitioning in the water phase of the polymer matrix can be described by Henry's Law while the ionophore provides sorption sites that follow Langmuir type behaviour.

In the study of gas transport through glassy polymers, in cases where the dual sorption model is seen to apply, both the lag-time and permeabilities are observed to decrease with increasing feed concentration 133, 134. In the study of concentration effects in this work, the lag-time for KCl through the HEMA:EGDM(90:10) + 5% dicyclohexano-18-crown-6 was found to decrease with increasing feed concentration - a result consistent with a dual-sorption mechanism (table 6.4, figure 6.13). Likewise the apparent steady state permeability of the induction period, P₁, is also observed to fall. This is not so clearly reflected in the final permeability rate, P₂. The latter remains relatively unaffected by concentration. Although the dual-sorption model predicts a decrease in permeability with increasing feed concentration, this is a diminishing effect with the permeabilities tending to a constant value - presumably due to the Langmuir sites reaching saturation level. The feed concentrations used here may have been too high to notice a change in the final permeabilities.

The Langmuir type sorption sites associated with glassy polymers originates from frozen microvoids that occur due to the nonequilibrium nature of glassy polymers 135. A more recent, and perhaps closer analogy to this work, was done on the development of an oxygen selective membrane using 2.5-4.5% by weight of a porphyrin complex as a fixed carrier in a poly (butyl methacrylate) matrix 136, the studies being performed at above the glass transition temperature of the polymer. They reported a reduction in both
permeabilities and induction period with increasing upstream gas pressure: an observation consistent with the dual-sorption model.

In the light of these comparisons with gas transport studies, it seems reasonable to conclude that a dual-sorption mechanism is also in operation in the ionophore containing membrane.

The rôle of ionophores in hydrogel membranes seems to be different from that in organic membranes where, essentially they act by selectively solubilising a species, allowing it to partition in the membrane. The type of behaviour seen here in hydrogels has not been clearly identified in the literature. This chapter, therefore, can best be regarded as a preliminary study into the phenomenon and certain implicit assumptions in the above discussion should be stated:

It was assumed that within the time scale of the ionophore studies (8-11 hours) that none of the crown ether was leaching out. This is a reasonable assumption, since from previous leaching studies on dicyclohexano-18-crown-6, the ionophore can be expected to take some weeks to leach out. The influence of the ion on the solubility of the crown ether in the form of its complex is an important aspect that must be considered but it seems reasonable to assume that the ion will not alter the solubility by several orders of magnitude and, therefore, should not lead to significant loss of ionophore within the time scale of the experiment. These are points that should be further examined as indeed should the leaching of the smaller 18-crown-6. This crown may be coming out of the membrane due to its water solubility but to help clarify the situation transport studies of the crown itself through an unmodified hydrogel membrane would be useful, as would differential scanning calorimetry in the presence and absence of the crown compound. This would help reveal
any changes in structural effects such as gross pore structure caused by the presence of crown ether in the reaction mixture during polymerisation of the polymer matrix. The influence of ionophores in hydrogel membranes seems significant and potentially important for applications requiring permselective membranes - the area is certainly worthy of further investigation.
CHAPTER SEVEN

THE USE OF THE COATED WIRE ION-SELECTIVE ELECTRODE

AS A MEMBRANE TEST-BED:

A PRELIMINARY INVESTIGATION.
7.1 Introduction.

So far, this work has been concerned with steady state transport, where sink conditions effectively apply. The membrane processes involved in sensor applications are quite different in as much as the steady output of a potentiometric device is a reflection of the equilibrium value for the partitioning of the test ion within the membrane matrix. Potentiometric sensors, such as ion-selective electrodes (ISEs), and field effect transistors usually employ hydrophobic membranes, (typically plasticised PVC), as their sensing membranes. These operate by having some electroactive component dissolved in the matrix - an example being neutral chelating agents that selectively bind to the test ion, causing the ion to dissolve in the membrane and produce a transmembrane potential.

The problem with using this type of device to detect some component in complex biological fluids, such as blood, is that the sensing membrane is subject to membrane fouling by proteins, blood platelets and various other dissolved species. One approach to resolving this problem is to "protect" the sensing membrane by overcoating it with a more biotolerant permeable membrane. Attempts have been made at this approach by using conventional dialysis membranes as overlays.

The type of synthetic hydrogels studied here are probably more suitable, not only in terms of their considerably enhanced biocompatibility compared to plasticised PVC, but also in terms of the transport characteristics discussed in chapters 3 to 5 of this work. Important parameters for hydrogels that have been discussed so far and that are of interest for sensor applications are the partition coefficients - since the concentration of the test ion in the hydrogel overlay is the concentration the sensing membrane will effectively see - and the permeability coefficients, since this gives an indication of how rapidly an ion-selective electrode will respond to a change in concentration.
In the light of observations made in the previous chapters of this work, it was decided to see what influence hydrogel membranes would have, as outer coatings, on the response characteristics of ion-selective electrodes that used a conventional plasticised PVC membrane as the actual sensing membrane.

If the hydrogel overlayer did not adversely interfere with the normal operation of such devices, then at the very least they would engender a higher degree of biocompatibility on the electrode, as well as exclude potential interferents such as proteins and other large organic species that may be present in the test solution. At best, they may act as a permselective outerskin that can discriminate between electrolytes and, by tailoring the hydrogel to select its "cut-off" point, may inhibit the transport of potentially interfering species such as Ca\(^{2+}\) ions.

This research group has an interest in sensors - both optical and potentiometric. Of the latter type, the particular interest lies in ion-selective field effect transistors (ISFETs). These devices are described in the introductory chapter of this work. The sensing membranes that are employed in conventional ion-selective electrodes can also be used with ISFETs\(^{101,137}\). This means that membrane studies performed on conventional ISEs are also applicable to ISFETs. This is useful in as much as ISFETs have certain difficulties associated with their construction due to their very small size. Aspects such as encapsulation and membrane deposition can be tedious, time consuming and frequently unsuccessful\(^{51,138}\).

Since we were concerned with a simple membrane test-bed system for bench work and not some sensor device for direct commercial application, it was decided to use the mechanically far simpler coated wire ion-selective electrode, CWISE\(^{139,140}\). The detection
part of this sensor is a wire coated with an electroactive ion-selective membrane dip coated onto it. The wire itself may be simply the exposed end of the inner conductor of the coaxial cable, or a piece of silver or platinum wire soldered onto the end. The device has the advantage over other types of ISEs in that it is comparatively easy to construct, and test membranes can be readily changed by scraping off the old membrane, cleaning the wire and dip coating a new membrane onto the exposed wire tip.

This chapter is, therefore, concerned initially with the design and construction of CWISEs, whose physical form is described in chapter 2. Since this laboratory did not possess one, its design was adapted from original papers by Freiser 57, 58. The chapter then deals with the characterisation of the electrode system, and finally with some preliminary studies on the influence of hydrogels used as membrane overlays on the potentiometric response of conventional plasticised PVC - valinomycin sensing membranes. HEMA based hydrogels were used of the same compositional type characterised in chapters 3 to 5 of this work.

7.2 Characterisation of the coated wire ion-selective electrode system.

The principles of operation and construction of the coated wire ion-selective electrode are outlined in chapter 2. What we are concerned with here is the characterisation of the CWISE system and its development into a practical test-bed for novel membrane formulations.

The two ionophores employed were dicyclohexano-18-crown-6 and the antibiotic valinomycin (see chapter 2, figure 2.4). Both are selective for the potassium ion and both are exploited in commercial potassium ion-selective electrodes. Of the two, valinomycin has the higher specificity for potassium and is the one most frequently used in commercial sensors. Valinomycin is highly hydrophobic and with regards to its solubility it was
considered that dicyclohexano-18-crown-6 was a more suitable candidate for incorporation into the water swollen polymer matrix of a hydrogel (dealt with in chapter 6). Both ionophores were, however, readily soluble in the plasticised poly (vinyl chloride) membranes used as the sensing membranes for the CWISEs studied here.

Figures 7.1 and 7.2 show typical potentiometric responses for CWISEs for a series of potassium chloride solutions - one set of solutions containing the test salt alone, and the other set containing a series of KCl solutions with a constant background concentration of NaCl. The sodium ion is an interferent which competes against potassium for the cavity binding site of the ionophore. The selectivity coefficient of K⁺ over Na⁺ for both ionophores can be calculated from such plots.

The membrane formulation for figure 7.1 was PVC(49.5%), dioctylphthalate, DOP(49.5%) and valinomycin (1%). The resultant potentiometric responses were a slope of 55mV.decade⁻¹ for the KCl solutions and 56mV.decade⁻¹ for the solutions containing 0.01M NaCl with an associated selectivity coefficient, $k_{a,\text{J}}$, of $7 \times 10^{-5}$. The membrane featured in figure 7.2 was PVC(33%), DOP(66%), and DC-18-crown-6(1%). The KCl only slope was 50mV.decade⁻¹, the KCl solution containing 0.01M NaCl yielded a slope of 49mV.decade⁻¹ and a concomitant selectivity coefficient, $k_{a,\text{J}}$, of $4 \times 10^{-3}$.

The two major features to note in the comparison of the valinomycin and DC-18-crown-6 systems are the extent of linearity and the selectivity coefficients. Linearity of the voltage output of the assembly is consistent with a Nernstian type response \(^{141}\). In the CWISE using valinomycin this is evident for the whole range of concentrations examined. It was only the central portion of the DC-18-crown-6 containing membrane that showed such a relationship. But it is perhaps with regards to their selectivity coefficients that the greatest
contrast is seen. In the particular examples shown here, valinomycin comes out as being about sixty times more selective than dicyclohexano-18-crown-6 for potassium over sodium. Caution must be made about putting too much quantitative significance on any single determination of the selectivity coefficient since it is influenced by various factors such as the method of calculation and the activities of the test ion and its interferent. For example, the selectivity coefficient for the valinomycin system was $2 \times 10^{-5}$ when 0.1M NaCl was used as the background interferent, which can be contrasted with $7 \times 10^{-5}$ when 0.01M NaCl is used. However, the significant selectivity for the potassium ion by valinomycin is clearly demonstrated.

In the development of the CWISE design, it was decided to construct a form of the device with a detachable tip which would allow a rapid interchange between tips of different membrane formulations. This meant that instead of the number of CWISEs available being limited to the number of coaxial cable connectors, only one connector was necessary and an array of easily interchangeable tips could be prepared (see chapter 2, section 2.6.3, and figure 2.9). The performance of such a device is shown in figure 7.3 The membrane in this case was PVC(39%), dioctyl sebacate(60%) and 1% valinomycin. The slopes shown here are 58mV.decade$^{-1}$ for the KCl only solution and 63mV.decade$^{-1}$ for the solution containing 0.1M NaCl. The determined selectivity, $K_a$, was about $2 \times 10^{-5}$ - this is of the same order as the earlier determination on valinomycin using the conventional CWISE mentioned above. Other runs showed that the detachable-tip CWISE was as reliable as the more conventional continuous type.

The reproducibility between calibration plots is shown in figure 7.4. The potentiometric plots were recorded with a period of five days in between, with the CWISE having been stored dry in the interim. The slopes are 43mV.decade$^{-1}$ and 42mV.decade$^{-1}$. The shift in
Figure 7.3: Response curves of detachable lip
Figure 2.4: Response curves of CWISE taken within 5 days of each other.
slopes seen here is typical for ISEs in general and is due primarily to the reference electrode - it is the slope and extent of the linear range that are the important parameters.

Other aspects that had to be considered in the characterisation of the CWISE system were drift and response times. Figure 7.5 shows the response of a CWISE (with a membrane of PVC(49.5%), DOP(49.5%) and valinomycin(1%). The zero time represents the electrode being transferred from deionised water to a stirred solution of 10^{-3}M KCl. The potential/time plot shows the electrode to be stable enough for drift not to be a problem during the time scale for the construction of a calibration curve. The response time for this particular CWISE can be seen more clearly in figure 7.6. From this plot the response time, τ₉₀, is calculated to be 3.6 minutes. It is known that the response time of a CWISE can be decreased by increasing the level of plasticiser. The membranes of the CWISEs that are discussed in section 7.3 all contained 60% plasticiser and all attained steady readings in under one minute.

As part of the characterisation and development work attempts at finding an alternative matrix to plasticised PVC were made. Different membranes have been used in the study of ion-selective electrodes such as poly (styrene-butadiene), poly methyl methacrylate, epoxy resin and polyurethane. It is, however, a general observation that most ISEs employ plasticised PVC as their sensing membrane. Poly hexyl methacrylate (pHMA) and a copolymer of methyl methacrylate and lauryl methacrylate were prepared. With regards to their consistencies, poly hexyl methacrylate seemed the more suitable as a membrane for the CWISE. A CWISE with a pHMA membrane containing 1% by weight dicyclohexano-18-crown-6 was constructed. When tested, no response to change in KCl concentration was produced. Another CWISE with the same membrane formulation was prepared with.
Figure 7.5: Drift curve of conventional PVC/DOP/valinomycin CWSE.
Figure 7.6: Response curve of conventional PVC/DOPO/vanilomycin/CW3E
similar negative results. It was therefore decided to return to using the plasticised PVC systems.

Another physical variation that was examined was the size of the polymer bead. Studies using the same formulation but different size found that beads with a diameter below 1mm produced wildly inconsistent results. For example, a CWISE with a bead 0.8mm in diameter of the membrane PVC(33%), DOP(66%) and DC-18-crown-6(1%) gave calibration slopes ranging from 12mV.decade⁻¹ to 28mV.decade⁻¹. Likewise, one of the same membrane but 0.5mm in diameter had slopes of 13 to 38mV.decade⁻¹. A diameter of 1mm was found to be the minimum for a CWISE to give a reasonably reproducible response.

Dioctyl phthalate, dioctyl adipate and dioctyl sebacate were all examined as plasticisers for PVC. All were found to be equally suitable. The latter two would probably not have been looked at if this work had existed in isolation, but different studies into electrochemical sensors by other workers in this research group encouraged the use of a plasticiser other than DOP.

In the light of the characterisation studies discussed above, the final CWISE chosen as a suitable test-bed for hydrogel overcoating was one having a polymer bead of 2mm in diameter consisting of PVC(39%), DOS(60%) and valinomycin(1%). As was mentioned earlier, this had a response time of under a minute.

7.3 Effect of hydrogel overcoating on conventional plasticised PVC CWISEs.

Having decided on both the sensing membrane composition and the physical form of the
CWISE the influence of hydrogel over coating on the CWISEs was investigated. The aim was not to make a commercially viable device but to see the effect of the hydrogel, therefore a substantial and coherent hydrogel coating was applied. This was done in the knowledge of permeability behaviour studied in chapters 3 to 5, such that thickness dependent transport would be expected to produce a noticeable time dependent effect on both ion transport and the ion response of the electrode system.

Figures 7.7 and 7.8 show the response curves of CWISEs with outer layers of the order of 50 microns thick of poly HEMA and a copolymer of HEMA:MMA(90:10) respectively. Both used PVC(39%), DOS(60%) and valinomycin(1%) as their inner sensing membranes. The figures show the "before and after" effect of applying the hydrogel. Both coatings produced a reduction in the Nernstian slope of the CWISE response. In the case of poly HEMA (figure 7.7), the slope went from 48mV.decade^-1 to 41mV.decade^-1. The extent of linearity was, however, unaffected by the hydrogel. The slope of the CWISE with the HEMA:MMA(90:10) copolymer coating (figure 7.8) was reduced from 46mV.decade^-1 to 36mV.decade^-1 - a greater reduction than is observed for the poly HEMA coated CWISE. In addition, the response deviates from linearity towards the lower concentration end of the potentiometric response curve. This tailing off effect can be explained in terms of the partition coefficient of the hydrogel. The actual concentration that the plasticised PVC membrane detects is not the concentration of the test solution but the concentration of KCl in the hydrogel matrix. In chapter 3 the partition coefficients, Sm, of a series of salts in HEMA:MMA copolymers were described (table 3.13). The Sm of KCl in a HEMA:MMA(90:10) copolymer is 0.109. This means, in effect, that the sensing membrane sees approximately 10% of the concentration of the test solution. At the lower concentration end of the response curve the sensor is, therefore, being pushed to the limits of its detection range and hence a deviation from linearity is observed.
Figure 7.8: Effect of HEMA on PVC/DOS/Palladium/HCl overlay
The poly HEMA coated CWISE took approximately 10 minutes for each potentiometric response to stabilise, whereas, the HEMA:MMA(90:10) copolymer coated CWISE required about 15 minutes for a constant voltage output to be attained. This longer time is a reflection of the lower water content of the latter - which produces a slower transport rate through its water swollen polymer matrix. The response time curve of a CWISE coated with the even lower water content HEMA:MMA(70:30) copolymer membrane is shown in figure 7.9. The curve shows the effect of the CWISE being transferred from deionised water to 10^{-1}\,\text{M}\,\text{KCl}. The response time, \tau_{90}, of this low water content membrane is 63 minutes. The reader should be reminded that the response times for these CWISEs without the hydrogel overlays is less than one minute. In summary then, it is clear, therefore, that hydrogel effects exist in terms of slope, linear range and response time, but the device still functions as an ion-selective electrode.

The thickness dependence of transport through hydrogels coupled with previous work carried out on the membrane transport system enables analogies to be drawn between gels used here and in permeability techniques based on membrane electrodes \textsuperscript{146}. The response time plot shown in figure 7.9 was redrawn as a plot of \ln(E_2 - E_1) against time where \(E_2\) is the final voltage output and \(E_1\) the response at any time on the response curve (figure 7.10). The linearity of this relationship shows it to be analogous to the oxygen permeability work that uses the slope of \(\ln(P_2 - P_1)\) against time to obtain the permeability coefficient (\(P_2\) being the final oxygen electrode reading and \(P_1\) the reading at any time) \textsuperscript{146}. There is, therefore, an analogy between the use of a membrane in a CWISE described here and techniques used to study membrane transport processes.

It must be clearly stated that the presence of the hydrogel membrane has a noticeable effect on the response time and on the absolute output of the device but, in the case of the higher
Figure 7.10: Presentation of response curve of CWISE with HEMA-MMA (70:30) in form of permeability study.
water content hydrogels, there is only a minimal effect on the efficiency with which the
electrode responds to a range of ion concentrations. Absolute outputs vary anyway, and
this is a test-bed, not a working sensor. The fact that the hydrogel membrane affects the
response without dramatically altering it provides information that they may have a rôle to
play on this type of sensor system.

As the work was done with thick membranes in order to observe an effect, it is clear that
the response versus time curve is going to be directly dependent. The logarithm form of
data presentation shown in figure 7.10 is conventionally used to determine permeability.
Considering that the coating was of the order of 50 microns or so, then at coatings of about
2 microns the response times of transported species will be comparatively unaffected in
plasticised PVC/valinomycin systems. In addition, microprocessor control of sensors is
now common. Many such systems work from response versus time curves as opposed to
equilibrium values. It is clear that in form, time and response, data for different ions might
be of potential value in a device intended to discriminate between such parameters.
Whatever the form of the device it appears that the differences in transport through
hydrogels achieved by controlling the structure and water binding behaviour might be used
as a basis for the construction of a differential ion selective device using membrane
transport technology.

7.4 The Potential Application of Hydrogels in Sensors.

At this stage, following the initial results, it is appropriate to summarise what hydrogel
membranes will and will not do as an overcoating for CWISEs. Because it does not
interfere with or inhibit the broad response of the electrode then, if nothing else, the
hydrogel can provide a biocompatible outer skin for the electrode. The EWC dependence
on transport and the fact the membrane is behaving as a membrane means that ion
selectivity, through cut off effects, may be exploited in this type of sensor. As well as their potential use as overlays in potentiometric sensors, hydrogels have already been used as inert supports for enzymes in enzyme electrodes 147, 148. Enzymes have been bound to polyacrylamide gels to produce sensing membranes in both glucose-sensitive 147 and penicillin-sensitive field effect transistors 148.

The potential applications of hydrogels is not, however, restricted to electrochemical devices. It should be possible to functionalise such polymers with pH-sensitive dyes or chromogenic crown ethers and thus provide a sensing membrane for optical sensors. By altering the monomer composition of the hydrogels it is possible to alter parameters that may be important for optical devices, such as the refractive index of the polymer matrix and the transport characteristics, which may be altered to exclude potential interferences.

With reference to the work carried out in this study it should be emphasised that only a limited range of hydrogels have been investigated here. This hydrogel membrane controlled transport can be exemplified by studying the influence of various other hydrogels of similar thickness. This has been a necessarily brief investigation but has revealed that fundamental understanding of transport through hydrogel membranes has some potential in sensor systems. It may therefore be concluded that the work described here indicates the potential value of a more extensive experimental programme in order to continue and exploit these studies.
CHAPTER EIGHT

DISCUSSION AND CONCLUSIONS.
8.1 Conclusions.

This thesis is concerned with the elucidation of factors surrounding the permeation of alkali and alkaline earth metal salts through synthetic hydrogel membranes. Although of relevance to aqueous separations in general, it was with their potential in sensor applications in mind that this work was carried out.

To date, permeability studies on hydrogels has been both limited in their extent and far from systematic in their approach. The polymer matrices studied have been almost exclusively restricted to cellulose acetate and poly HEMA. As far as solutes are concerned, there is a substantial body of literature on the transport of neutral water soluble organic compounds, such as sugars, amides and steroids. There have, however, been few salts studied: such work mainly concentrating on NaCl transport for desalination membranes. It was clear then that to obtain a greater understanding of transport phenomena through hydrogel membranes, the permeation of a larger range of salts had to be studied through a greater number of polymer matrices.

This research group has studied a variety of hydrogels that extend over a broad range of water contents. It was the more modestly swollen systems that this study dealt with: that is, membranes possessing equilibrium water contents ranging from about 40% to 16% by weight. In such systems, the water does not simply act as a plasticiser but is itself an essential and intimate part of the matrix. The structure of water in these membranes is highly influenced by water structuring functional groups on the polymer. This means that in these lower water content membranes the nature of the polymer plays an important part on associated physical parameters such as its transport properties. If a discrimination in the transport rates between different solutes is to be achieved, then it is to modestly swollen polymer systems that one must look.
As a first step in this work, water structuring in the polymers used was achieved by use of the hydroxyl groups. In order to study the influence of solute variation on transport processes, a single polymer matrix, poly (2-hydroxyethyl methacrylate) was initially employed. On examining the permeation of a series of mono- and divalent cations in the presence of a common anion (chloride), it was discovered that some simple relationship involving the size of the hydrated cation did not provide a sufficient basis for understanding the transport process. This was shown in chapter 4 when the diffusion of some chloride salts were compared with literature values for the diffusion of neutral solutes in a plot relating the diffusion coefficient to the size of the transported species.

When a variety of anions in the presence of a common cation (potassium) were studied, the greater influence of the anion over the cation on the transport process was shown. This was explained in terms of the structure-making and structure-breaking capability of the anion, with respect to its solute/water interactions. These interactions are reflected by parameters such as the amount of water held in the polymer matrix, the EWC; and the solubility of the solute in the hydrogel membrane, the S\text{m}. When the cation variation in the presence of a common anion is studied there is little change in the EWC's and partition coefficients. The influence of the anion (in this case Cl\textsuperscript{−}) seems to subsume any effect exerted by the cation. When the reverse is tried, that is, potassium salts of differing anions, a significant range of both EWC's and S\text{m}'s is seen.

The permeation process consists of essentially two processes, a thermodynamic part and a kinetic one: namely, the ability of the solute to dissolve in the polymer matrix and its ability to be transported through it. These are quantitatively expressed as the partition and diffusion coefficients. When variations in the solubility of salts in the membrane are
allowed for, then diffusional size effects can be demonstrated. The cation is seen to dominate the diffusion process in cases where its calculated hydrodynamic or Stokes radius is greater than that of its co-anion.

The order of both the swelling/deswelling effects and the solubilities of these salts is reflected in the Hofmeister series. This is a long established series and is commonly observed in the physico-chemical behaviour of simple electrolytes. The solute/water interactions with the water swollen polymer matrix of the hydrogel, and their consequent influence on transport processes, is seen to be no exception, a point exemplified by the D.S.C. thermograms for salts in poly HEMA shown in chapter 4.

It is interesting to note that previous work on the transport of salts has almost exclusively involved the chloride anion. This is fairly limited in its water structuring capabilities relative to the highly structure-breaking thiocyanate anion and the highly structure-making sulphate. In previous transport studies on chloride salts (mainly NaCl), the main concern has been reverse osmosis membranes for the desalination of sea and brackish water. For the application of membranes in other aqueous systems, such as in buffers and in plasma, it has to be noted that there is usually a range of anions present in solution. One of the main points to emerge from the work performed for this thesis is the importance of understanding the rôle of the anion on water structuring within the hydrated membrane and the resultant influence on solute permeability.

To obtain a more complete understanding on transport phenomena through hydrogel membranes, it was logical to study the water structuring effects of the polymer composition. As has been previously stated, the membranes that were studied here were
only modestly swollen such that a large proportion of the water held in the polymer matrix was significantly influenced by water structuring groups on the polymer. The imbibed water of a hydrogel exists in a continuum of states which range from water which is tightly bound to the polymer matrix to that which is bulk like in its properties. This is reflected by the amount of "freezing" and "non-freezing" water as determined by differential scanning calorimetry. A series of copolymers based on 2-hydroxyethyl methacrylate as their hydrophilic component was prepared. D.S.C. melting endotherms showed the water binding of the series to vary regularly between those of the respective comonomers.

Of the various techniques for handling permeation data, the free-volume model was found to produce the best fit. This model, however, centres around the proposition that the EWC alone is the determining factor. Although it accounts reasonably well for cation permeation controlled by diffusional size effects, it does not allow for water structuring effects, whether produced by the transported ionic species or the polymer matrix. The superimposed plot of lnP against 1/H for the HEMA:MMA and HEMA:St copolymer series is seen to be linear. It is important to note that in this, as in the few previous studies of this type, water structuring by the polymer was achieved by use of hydroxyl groups. In the case for two copolymer series where different hydrophilic centres are at work the superimposition of their respective lnP versus 1/H relationships may not result in a single linear plot due to the different water structuring behaviour of the hydrophilic moieties. There is in fact a growing amount of information that indicates that the water structuring effects of different functional groups vary considerably.

Previous studies involving the rôle of ionophores in the transport of ions has mainly been concerned with their use in hydrophobic membranes. Their mode of action being to chelate onto the ion and solubilise it in the organic membrane phase. In this study the ionophores
were occluded in a hydrophilic water swollen matrix and, consequently, compliment the water structuring groups of the polymer in their influence of membrane transport.

This thesis showed that the presence of an ionophore in a hydrogel can effect the order of permeability of a series of salts, as well as the final rates of permeation and associated lag-times. Similar transport behaviour has been reported in the literature for the permeation of gases through glassy polymers, where a dual-sorption model was presumed to be in operation.

The synthetic potential of hydrogels is such that there is significant scope to modulate parameters such as permeability and biocompatibility. They, therefore, may be of potential value in sensor applications as non-thrombogenic outer-coatings or as a permselective outer skin that prevents potential interferents from reaching the underlying sensing membrane. The use of hydrogel membranes as overlays for coated wire ion-selective electrodes carried out in this work showed that such materials do not interfere with the broad response of the device. It is the access of the analyte that is affected, not the underlying process of the electrode.

In summary then, this thesis has both revealed and in part resolved the previously incomplete picture on the influence of solute/water, water/polymer and solute/polymer interactions on transport processes through hydrogel membranes. In addition, their potential exploitation in sensors was shown where, for example, they can act as overlays for electrochemical devices without interfering with the electrochemistry.

8.2 Suggestions for further work.

It is evident that the nature of solute, in particular the anion, has a significant water
structuring effect on the membrane water. It is not unreasonable to expect that the nature of the hydrophilic groups on the polymer will also play an important water structuring rôle - not simply in terms of the gross amount of water held with the polymer matrix but also the proportions of "freezing" to "non-freezing" water. The hydrogels studied here all used hydroxyl groups as their hydrophilic component. This is the same water structuring group that is found in other membranes, such as poly (vinyl alcohol) and cellulose acetate, whose transport properties is well documented in the literature. It is not surprising that there has been a limited picture, in the past, of the transport of salts through water swollen polymer systems when the studies have been restricted to the same anion (Cl\(^-\)) and to polymers possessing the same water structuring group. It should be stated that the rôle of the hydroxyl group is not completely understood and is certainly still worthy of further study. It is, however, important for a more complete understanding of transport processes to broaden the area by studying hydrogels with different hydrophilic centres such as polyacrylamides and polyethers.

The D.S.C. thermograms in this study showed the significant effect that the nature of the anion had on the proportion of "freezing" and "non-freezing" water held within a polyHEMA membrane. A more complete picture on the interaction between the solute, water and polymer would be obtained if a greater range of salts and polymer compositions were studied.

The large number of ionophores currently available and the large number of species to which they are selective, indicates the potential importance of ionophores for the selective control of transport through hydrogel membranes. The leaching of 18-crown-6 should be further investigated to more fully understand why it was so readily being lost from the membrane. This could be done by performing a transport study on the permeability rig of
18-crown-6 through an unmodified membrane. In addition, D.S.C. studies could be carried out on membranes containing the 18-crown-6 and membranes from which it has leached out. Such work would help reveal whether this crown ether is both soluble in and readily transportable through a coherent hydrogel membrane, or whether its presence in the reaction monomer mixture during the polymerisation process leads to the formation of a macroporous heterogeneous membrane whose gross pore structure was responsible for the loss of the ionophore.

It was noted that dicyclohexano-18-crown-6 had only a small influence on the EWC of the membrane into which it had been incorporated. It would be interesting to see from D.S.C. studies if this negligible impact in water content is reflected in the type of water held within the matrix. The presence of the crown might be expected to have some effect on the proportion of "freezing" to "non-freezing" water in the membrane. In addition, the partition coefficients in a series of concentration of the same salt should be performed which would help resolve as to whether or not the dual sorption model of Henry's law and Langmuir type sorption are in operation.

From the point of view of polymer synthesis, the problem of ionophore leaching out of the membrane could be resolved by covalently attaching it to the polymer.

It was important to demonstrate that the use of hydrogels as overlays for conventional plasticised-PVC membranes would not adversely influence the operation of the device. This was clearly shown. The rôle of hydrogels in sensors was something only touched upon in this thesis and is an area which should certainly be pursued.

The hydrophobicity of the PVC membrane and the hydrophilicity of the hydrogel outerlayer
should result in a high interfacial tension between the two layers. Better cohesion between the membranes and a reduction in any boundary layer effects may result from the generation of a hydrophilic surface on the PVC membrane. This could be achieved by treatment of the PVC membrane with a glow discharge oxygen plasma.

It is evident from the literature that the understanding of the rôle of the plasticiser is largely empirical and somewhat rudimentary. A more coherent approach would improve matters, as indeed, would a systematic study into alternative polymer matrices, especially ones that were above their glass transition temperature at ambient conditions and did not require the use of a plasticiser.

The use of hydrogel membranes need not be reserved only for electrochemical devices. The ability functionalise the polymer with colorometric agents such as dyes and chromogenic crown ethers would provide an excellent sensing membrane for optical sensors. In addition, the ability to alter the water structuring capability of the polymer by choice of monomer composition should allow such parameters to be altered as refractive index, blood compatibility and transport properties. If a single polymer matrix could not satisfy all the requirements of the system, then layering of different hydrogel membranes could be performed.

This thesis has tried to go some way in resolving the lack of systematic study on the transport of simple inorganic salts through hydrogel membranes. It has shown the need to understand such processes if hydrogel membranes are to be used either in aqueous separations or for sensor devices.
APPENDIX 1

ACCURACY OF THE EWC DETERMINATION TECHNIQUE.
Appendix 1: Statistical treatment of error of EWC determination technique.

The important polymer, poly HEMA was chosen for a careful examination as to the accuracy of the technique for EWC determination. Using two hydrated poly HEMA sheets, ninety nine discs (1.1cm diameter) were cut. Using three discs for each determination thirty three EWC's were calculated at 37°C. The results are listed below.

<table>
<thead>
<tr>
<th>Sample</th>
<th>EWC (%)</th>
<th>Sample</th>
<th>EWC (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
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<td>18</td>
<td>36.3</td>
</tr>
<tr>
<td>2</td>
<td>36.4</td>
<td>19</td>
<td>36.0</td>
</tr>
<tr>
<td>3</td>
<td>36.4</td>
<td>20</td>
<td>35.1</td>
</tr>
<tr>
<td>4</td>
<td>35.8</td>
<td>21</td>
<td>36.1</td>
</tr>
<tr>
<td>5</td>
<td>36.2</td>
<td>22</td>
<td>35.8</td>
</tr>
<tr>
<td>6</td>
<td>36.1</td>
<td>23</td>
<td>35.7</td>
</tr>
<tr>
<td>7</td>
<td>36.1</td>
<td>24</td>
<td>36.4</td>
</tr>
<tr>
<td>8</td>
<td>35.9</td>
<td>25</td>
<td>36.4</td>
</tr>
<tr>
<td>9</td>
<td>36.5</td>
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<td>10</td>
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</tr>
<tr>
<td>12</td>
<td>35.9</td>
<td>29</td>
<td>36.2</td>
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<tr>
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<td>30</td>
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</tr>
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<td>14</td>
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<td>31</td>
<td>37.0</td>
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<td>36.0</td>
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<td>36.2</td>
</tr>
<tr>
<td>17</td>
<td>35.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A statistical treatment of the above results reveals that this sample size of n = 33 yields a mean, \( \bar{x} = 36.1 \) with a standard deviation, \( \sigma_{n-1} = 0.4 \).
APPENDIX 2

PERMEABILITY COEFFICIENTS FOR THE COPOLYMERS OF
2-HYDROXYETHYL METHACRYLATE.
Appendix 2. Permeability coefficients for the copolymers of 2-hydroxyethyl methacrylate.

Permeability coefficients of HEMA:MMA copolymers.

<table>
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<tr>
<th>% MMA</th>
<th>KCl</th>
<th>NaCl</th>
<th>LiCl</th>
<th>CaCl₂</th>
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<tr>
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<td>2.2</td>
</tr>
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<td>5.0</td>
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<td>7.5</td>
<td>9.2</td>
<td>6.9</td>
<td>7.9</td>
<td>0.82</td>
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<td>10.0</td>
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<td>4.9</td>
<td>4.8</td>
<td>0.32</td>
</tr>
<tr>
<td>12.5</td>
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<td>3.4</td>
<td>0.18</td>
</tr>
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<td>15.0</td>
<td>3.2</td>
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<td>3.0</td>
<td>----</td>
</tr>
<tr>
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<td>1.4</td>
<td>1.3</td>
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</tr>
<tr>
<td>25.0</td>
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<td>----</td>
<td>0.4</td>
<td>----</td>
</tr>
<tr>
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<td>0.30</td>
<td>0.41</td>
<td>----</td>
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</tr>
<tr>
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</tr>
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<td>40.0</td>
<td>N.D.</td>
<td>----</td>
<td>----</td>
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</table>

N.D. = non-determinable

Permeability coefficients of KCl through HEMA:St copolymers.

<table>
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<tr>
<th>% Styrene</th>
<th>KCl</th>
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</thead>
<tbody>
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</tr>
<tr>
<td>2.5</td>
<td>13.0</td>
</tr>
<tr>
<td>5.0</td>
<td>5.3</td>
</tr>
<tr>
<td>7.5</td>
<td>2.2</td>
</tr>
<tr>
<td>10.0</td>
<td>0.84</td>
</tr>
<tr>
<td>15.0</td>
<td>0.09</td>
</tr>
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</table>
LIST OF REFERENCES.


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