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CHANGES IN THE INTERNAL STRUCTURE OF HYDROGELS

W.E.ROORDA*,J.A.BOUWSTRA,M.A.de VRIES,C.KOSHO,H.E.JUNGINGER

Center for Bio-Pharmaceutical Science,Gorlaeus Laboratories,P.O.Box 9502,
2300 RA Leiden,The Netherlands

*To whom correspondance should be addressed.

SUMMARY

A hypothesis is presented that explains the swelling behaviour of pHEMA hydrogels in the presence of solutes. Essence of the hypothesis is that in a swollen pHEMA gel almost no bulk water is present, and that solute absorption by the gel is possible only if the solutes can disrupt the integral structure, formed by water and the polymer in the gel. The hypothesis is supported by swelling experiments and differential thermal analysis.

INTRODUCTION

Hydrogels can be defined as systems, consisting of two completely interpenetrating components, one of which is a non-soluble, hydrophilic network polymer, and the other water. Drug molecules can be incorporated into these gels, and after subsequent administration to a patient they are released at a predeterminable rate. This property, and the good biocompatibility in a number of applications, have made hydrogels promising materials for the development of sustained release drug dosage forms (ref.1).

An important parameter for the rate of release of a drug from a hydrogel is the swelling behaviour of this gel in the presence of the drug molecules. Since it is known that this behaviour is strongly influenced by the presence of solutes in the surrounding medium (ref.2,3), we want to study this swelling behaviour in more detail.

For hydrogels based on poly(hydroxyethylmethacrylate), pHEMA, a number of peculiar properties has been described in literature :

1. The water content of these gels in equilibrium with pure water is about 40% by weight, and is almost independent of cross-linker contents up to 5% (ref.4).
2. The presence of several classes of water has been described, among which bound water, which is so strongly bound to the polymer that it does not freeze upon cooling, and bulk water, which behaves like normal "free" water (ref.5).
3. Based on thermodynamical and light scattering experiments it was proposed that in pHEMA a specific, water-induced macromolecular

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ordering of the polymer chains exists (ref.6)

4. The presence of solutes in the surrounding aqueous medium has a profound influence upon the swelling behaviour of the gels (ref.2,3)

We have formulated a hypothesis, based upon these and other data, that may account for the observed influence of solutes upon the swelling behaviour of pHEMA hydrogels :

The water and the polymer in the gel form a coherent, integral structure, in which there is essentially no place for solute compounds. Absorption of solutes is possible as far as the solutes can disrupt the integral structure of the gel. Disruption of the structure allows further relaxation of the macromolecular chains, which leads to increased water sorption and swelling of the gels.

If the solutes cannot enter the gel significantly, their presence in the surrounding medium causes a disturbance in the swelling equilibrium, due to the increased osmotic value of the outside medium. This leads to a decrease in water content, so to deswelling of the gel.

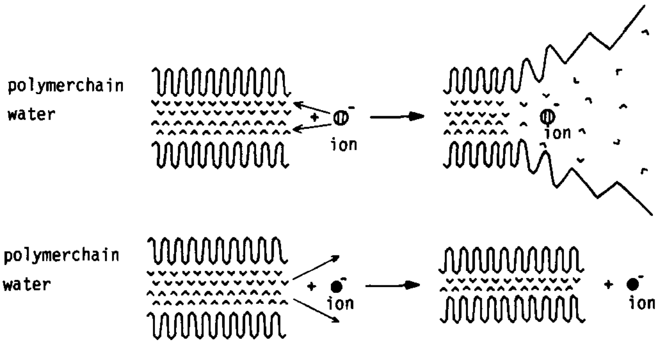


Fig.1 Schematic representation of the swelling, resp. deswelling behaviour of a hydrogel under influence of an ionic solute.

To test the validity of this hypothesis, we have performed two types of experiments :

1. Swelling experiments
2. Differential Thermal Analysis (DTA)

The gels used in these experiments were polymerized in solution containing 65% (w/w) of monomer and 35% of an aqueous solution of 0.5%(w/w) $(NH_4)_2S_2O_8$. The monomer was carefully purified from traces of methacrylic acid by chromatography over a basic Al_2O_3 column. For DTA experiments on the hydrogels the monomer contained 0.2% (w/w) ethyldimethacrylate (EDMA), for the swelling experiments this was raised to 1.2%, since in this way the swelling behaviour was found to be better reversible.

During the polymerization the temperature was raised from 20 to 70 °C at 1°/min. and kept at 70 °C for 5 hours.

The gels were washed with frequently refreshed demineralized water, until no more traces of residual monomer were detectable.

1.Swelling experiments

If our hypothesis is correct, there should be a correlation between the swelling behaviour of the gels and the amount of absorbed solute. This was checked for the following series of solutes :

1. NaF , NaCl , NaBr , NaI
2. $NaClO_4$, Na_2SO_4
3. Glucose , urea , antipyrine

From each of these compounds solutions were prepared of 0.5 , 1.0 and 2.0 M. (except NaF , Na_2SO_4 and glucose, that do not dissolve upto 2.0 M.).

The gels were cut in cylinders of 500 mg wet weight (in equilibrium with pure water) and placed in 75 ml of the test solutions until their weight was constant for at least one week. The final weight of the gels was determined.

Subsequently they were stirred with 1000ml of demineralized water, and the solute release was recorded conductometrically for the salts and spectrophotometrically for the organic compounds.

When the gels were subject to a second release experiment, a negligible amount of residual solute was recovered. They had also returned to their original weight within limits of ±1%. This was taken as an indication that the solutes were completely released by the gels. The amount of absorbed or released water was calculated from the final and initial weight of the gels and the amount of released solute.

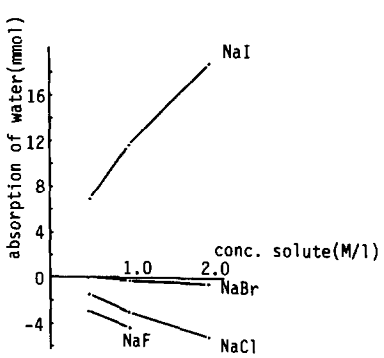


Fig.2^a Swelling behaviour of pHEMA gels, initially containing 300 mg polymer and 200 mg water,in the presence of sodium halogenides.

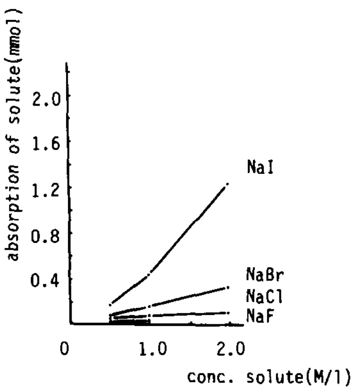


Fig.2^b Solute absorption during the swelling process.

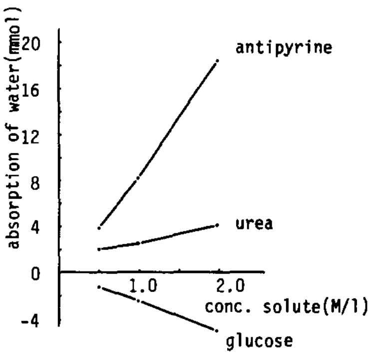


Fig.3^a Swelling behaviour of pHEMA gels in the presence of organic solutes.

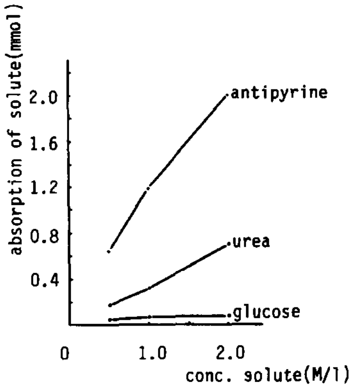


Fig.3^b Solute absorption during the swelling process.

In Fig.2 and 3 the results of these experiments are shown. Similar results were found for $NaClO_4$ and Na_2SO_4, $NaClO_4$ causing a strong increase in swelling and Na_2SO_4 a strong decrease. Although the reasons for the observed behaviour are subject of further study, it is clear that a good correlation exists between the swelling behaviour of the gels and the amount of absorbed solute, which is in agreement with our hypothesis.

2.Differential Thermal Analysis

We have used cooling as well as heating scans, taking into account the effects of undercooling that may occur during the former type of measurements.

In Fig.4 the DTA curves obtained by cooling resp. heating a swollen pHEMA gel are compared.

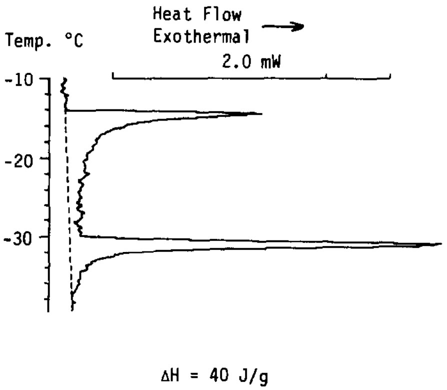


Fig.4^a DTA curve obtained by cooling a pHEMA gel at 1°C/min.

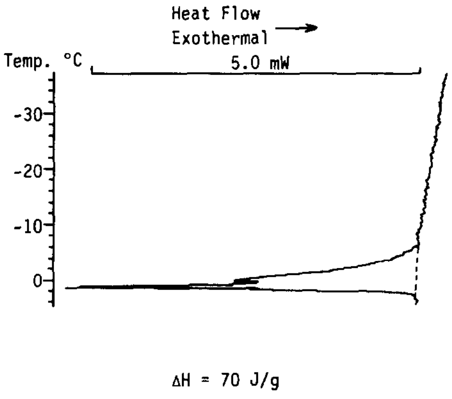
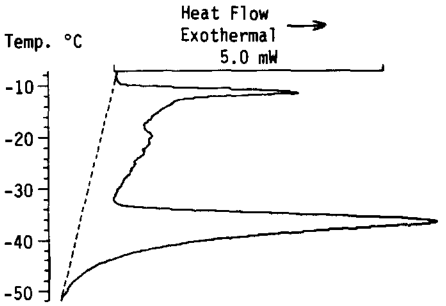


Fig.4^b DTA curve obtained by heating a pHEMA gel at 1°C/min.

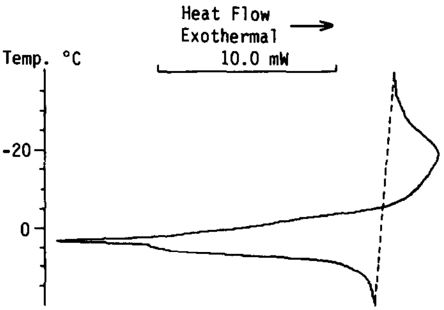
Apart from a difference in shape, there is a large difference in the enthalpy effect involved. This difference is so large, that it can only mean that during the cooling a slow exothermal process takes place, which is so small that it is not distinguishable from the base line at this scanning speed.

In Fig.5 the same experiment is performed at 10°C/min. At this speed the slow process no longer dissappears into the baseline, and the enthalpy effects are in good agreement , if it is considered that the freezing processes takes place at lower temperatures than the melting. The shape of the heating curve can be explained by assuming that at -80°C the gel has turned into a glass before the slow process has gone to completion. At subsequent heating it is completed before the melting occurs, which makes this process very similar to the pre-melting crystallization after observed in glasses.



ΔH = 32 J/g

Fig.5^{a} DTA curve obtained by cooling a pHEMA gel at 10°C/min.



ΔH = 40 J/g

Fig.5^{b} DTA curve obtained by heating a pHEMA gel at 10°C/min.

According to our hypothesis only a very small amount of bulk water, available for the unhindered uptake of solutes from the surroundings may be present.

The peak at about -14°C in the cooling curves coincides with the freezing peak of undercooled bulk water in experiments where gel and bulk water were measured together, and we therefore conclude that this peak is associated with the freezing of bulk water in the gel. The freezing of undercooled water, however, produces a very sharp peak, while the gel peak shows a distinct tail, as is illustrated in the expanded representation in Fig.6.

In our opinion only the shaded part of the curve represents the freezing of bulk water present at one moment in the gel. The tail may be caused by freezing of regions of bulk water that appear due to polymer movements, while at the same time, normally, other regions would disappear.

We have calculated the enthalpy effect involved in the shaded part of the curve, using scanning speeds of 1, 5 and 10°/min.,and starting temperatures of 20, 30 and 40°C. Taking into account that the freezing occurs at -14°C instead of at 0°C, we found effects of 10-15 J/gram of water, which means that no more than 3 to 5% of all the water in the gel is really bulk water. This is considered to be a second support for our hypothesis of the integral hydrogel structure.

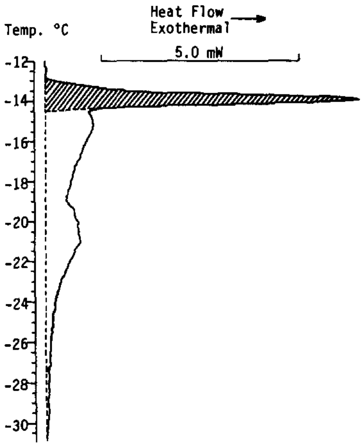


Fig.6 DTA curve obtained by cooling a pHEMA gel at 5°C/min.

CONCLUSION

In conclusion it may be stated that the hypothesis of the integral structure of pHEMA hydrogels does well explain the swelling behaviour of hydrogels in the presence of solutes, and that it is supported by swelling experiments and by differential thermal analysis.

ACKNOWLEDGEMENTS

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