TOPICS IN PHARMACEUTICAL SCIENCES 1987

D.D. BREIMER AND P. SPEISER EDITORS

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PREFACE

In 1912 the Fédération Internationale Pharmaceutique (F.I.P.) International Pharmaceutical Federation was founded in The Hague, The Netherlands. Hence in 1987 F.I.P. celebrated its 75th anniversary and it convened in the capital of its country of origin, Amsterdam. Here the 47th International Congress of Pharmaceutical Sciences of F.I.P. took place from 31 August – 4 September 1987, with a programme that offered more than ever before at F.I.P. congresses. There were 12 symposia and 3 update lectures with more than 50 invited speakers, and 325 posters and oral scientific communications were presented. The total number of participants at the congress was over 2000.

This volume, entitled Topics in Pharmaceutical Sciences 1987, represents the continuation of the series as published every other year since 1981. It contains the invited papers presented in 11 symposia. The topics of the symposia and lectures were selected by the Board of Pharmaceutical Sciences of F.I.P. in close association with coordinators in the different areas of interest (names mentioned with the symposia in this publication). These topics all represent important subjects of current interest in the pharmaceutical sciences, in which substantial recent development has taken place and progress is being made.

We are grateful to the invited speakers for conforming to the deadline of delivering their manuscripts so promptly. This made it possible to publish these Proceedings shortly after the Congress.

D.D. Breimer and P. Speiser

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Coordinator/chairman: C.F. Lerk

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POTENTIAL DEVELOPMENTS IN HYDROGEL GASTROINTESTINAL DELIVERY SYSTEMS

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INTRODUCTION

During the past decades there has been an increasing interest in optimizing the efficacy of existing drugs through the use of better designed delivery systems. Intensive interdisciplinary research efforts have led to a variety of advanced dosage forms. The majority of these systems are based on polymers that differ in their permeability, degree of swelling, rate of dissolution and erodibility. An important class of polymer materials that are applied in advanced drug delivery systems are the hydrogels. They are defined as network polymers which can absorb a considerable amount of water and swell without dissolving. Since their introduction in 1960 by Wichterle and Lim (1) synthetic hydrogels have gained a rapidly expanding popularity and their use for a wide range of biomedical applications has been described (2-4). In addition to good biocompatibility their ability to release entrapped solutes when in contact with water and the ease of regulating such release by controlling the swelling, chemical composition and geometry make hydrogels suitable materials for controlled drug delivery systems.

The objective of this paper is to discuss the potential of hydrogels for oral and rectal drug administration. In order to appreciate the application possibilities of hydrogels in drug delivery some fundamental aspects will be briefly reviewed.

MATERIALS AND METHODS FOR HYDROGEL PREPARATION

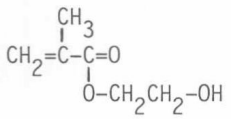
Network formation in hydrogels can be due to covalent, ionic or physical crosslinkage. Most hydrogels developed for biomedical purposes are covalently crosslinked. They can be prepared a) by simultaneous polymerization of hydrophilic monomers, comonomers and a small amount of a suitable polyfunctional monomer acting as crosslinker (monomer approach), b) by chain extension and crosslinkage of hydrophilic prepolymers (prepolymer approach) or by chemical crosslinking of hydrophilic polymers (polymer approach).

Monomer approach

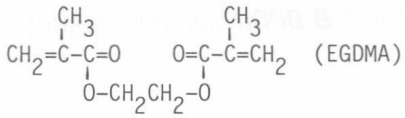
To date the majority of hydrogels have been prepared by radical copolymerization of hydrophilic vinyl monomers, any suitable hydrophobic comonomers and a crosslinker.

Monomers and crosslinkers. The most important classes of neutral hydrophilic monomers are : hydroxyalkyl methacrylates, monomethacrylates of oligo(ethylene

glycols) and their mono-ethers, acrylamide and N-substituted acrylamides and N-vinyl pyrrolidone. The monomer that has received far most attention is 2-hydroxyethyl methacrylate (HEMA).



(HEMA)



(EGDMA)

Addition of cationic or anionic comonomers to the monomer feed will lead to ionogenic hydrogels. Acidic or anionic monomers include acrylic and methacrylic acid, vinyl and styryl sulphonate and phosphorylated hydroxyalkyl methacrylates. As basic monomers have been used aminoalkyl methacrylates and vinyl pyridine. Protonation or alkylation of these monomers gives cationic derivatives. Increasing the content of charged groups in the hydrogel will ultimately lead to a material that can be categorized as an ion exchange resin.

Examples of polyfunctional monomers acting as crosslinkers are diacrylates and dimethacrylates of diols (e.g. ethyleneglycol dimethacrylate, EGDMA), diacrylamides and reactive methacrylate esters (glycidyl methacrylate, allyl methacrylate).

The properties of hydrogels can be easily varied by adjusting the composition of the polymerization mixture : type of monomer(s), amount and nature of the crosslinker, type and amount of diluent.

Residual monomer. Hydrogels prepared as described above will contain residual monomer, crosslinker and initiator or initiator fragments. These contaminants can be removed by exhaustive extraction with water or an appropriate volatile organic solvent.

For a given monomer feed the residual monomer content depends on the polymerization time and temperature, the initiator and the type and amount of diluent (5,6). The data shown in table I was obtained in the author's laboratory and demonstrates the influence of the diluent.

The drastic decrease in residual monomer with increasing diluent concentration in the polymerization mixture can be explained in terms of the aggregation state of the polymerizing mixture. In absence of diluent a glassy material is formed. Addition of a diluent that can solvate the polymer chains leads to the formation of a rubbery material. The increased mobility of the monomer in the system favours the conversion. The observed dependence of monomer residue on the nature of the solvent can be due to differences in polymer-solvent interaction and to interference of the diluent in the radical polymerization process.

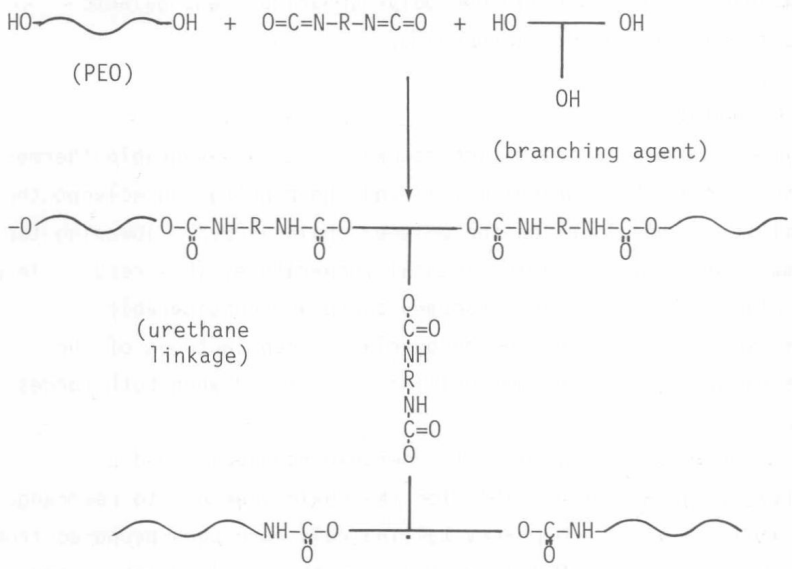
TABLE I
EFFECT OF DILUENT ON THE RESIDUAL MONOMER[1] IN P-HEMA HYDROGELS[2]

vol%	none	glycol	ethanol	DMF	water
0	22,370				
5		4,640	5,920	6,590	208
10		58	203	5,913	26
20		23	55	1,594	25
		(3.6[3])			

1 Monomer residue expressed in ul per ml initial monomer.
2 Prepared from HEMA, 0.5 mol% EGDMA, 0.5 mol% t-BuOOH; 60°C, 48 hours.
3 Polymerization conditions: 46 hr at 60°C and 4 hr at 90°C.

Prepolymer approach

A typical example of the preparation of hydrogels from hydrophilic prepolymers was described by Graham (7). Hydrophilic polyurethane network were prepared by reaction of poly(ethylene oxide) (PEO) with aliphatic or aromatic diisocyanates in presence of a small amount of a compatible triol.



Amphiphilic hydrogels were prepared analogously by Gander (8,9) and Van Bos (10,11) starting from poloxamers which are hydroxyl terminated ethylene oxide (EO, A) - propylene oxide (PO, B) A-B-A blockcopolymers.

PEO hydrogels have alternatively been prepared by water induced crosslinkage of isocyanate-terminated trifunctional PEO (Hypol^{R} resin) (12), by chain extending PEO with bis(dihydro pyrans) (13) or by radiation or radical curing of PEO (14).

Polymer approach

A number of hydrogels have been prepared by chemical crosslinkage of natural and synthetic hydrophilic polymers like polysaccharides, proteines, unsaturated polyesters, poly(vinyl alcohol). Their preparation and applications have been reviewed recently (15,16) and will not be discussed here.

Ionic crosslinked hydrogels

Polymers containing considerable amounts of ionic groups can be crosslinked by salt formation with polyvalent counterions. The gelation of sodium alginate with Ca^{2+}-ions is a well known example (17).

If the polyvalent counterions are polymeric in nature the result is a polyelectrolyte complex. A commercial example that received biomedical evaluation is the complex formed by poly(vinylbenzyltrimethyl ammonium chloride) and sodium poly(styrene sulphonate) refered to as Ioplex 101 (18).

Compression molded hydrogels

Hydrogels can also be prepared by compression of hydrophilic polymers (19). This fabrication method is generally simple, reproducible and allows high drug loads. Polymers used for compression include cellulose derivatives (hydroxypropyl methyl cellulose, methyl cellulose,..), non-cellulose polysaccharides (eg. galactomannans) and acrylic acid polymers (eg. Carbopol^{R}).

SWELLING PROPERTIES OF HYDROGELS

Dry hydrogels are mostly glassy at room temperature. Given a favourable thermodynamic compatibility between the hydrogel matrix and the penetrating solvent the latter will have a plasticizing effect on the polymer chains (20,21) lowering the glass transition temperature below the experimental temperature. This results in a change from a rigid glassy state to a soft rubbery state and considerable swelling. The volume expansion is counteracted by elastic contractions of the stretched polymer network. The equilibrium swelling is achieved when both forces are balanced (22).

For some hydrogels the polymer chains exhibit a certain regularity and a sufficient flexibility as to make it possible for the chain segments to rearrange in ordered patterns and crystallize. Semi-crystalline gels have been prepared from PEO of molecular weigth exceeding 1000 daltons (7). For these gels which in the dry state contain crystalline and amorphous regions the swelling process will be additionally complicated (23).

For moderately crosslinked p-HEMA hydrogels the equilibrium water content (EWC, weight percentage of water in the equilibrium swollen gel) is about 40%. If more than 40% water is present during polymerization phase separation will occur and the resulting gel will be opaque and even microporous (24).

Copolymerization of HEMA with monomers of varying hydrophilicity will give gels with a water content ranging from almost 0 to over 90% (25,26). This is illustrated in table I with results obtained by Van Bos. Substituting part of the HEMA by the more hydrophobic HPMA or DEAEMA resulted in a decreased EWC value. Hydrogels with an increased water uptake were obtained by incorporation of the hydrophilic AAM or by protonation or alkylation of the DEAEMA monomer residues.

TABLE II
EFFECT OF COMONOMER ON THE SWELLING OF HYDROGELS

Hydrogel	Monomer(s)	Crosslinker (0.5%)	EWC (%)
1	HEMA	EGDMA	39.2
2	HEMA/HPMA (80/20)	EGDMA	36.0
3	HEMA/HPMA (50/50)	EGDMA	33.1
4	HPMA	EGDMA	23.0
5	HEMA/DEAEMA (90/10)	EGDMA	35.6
6	HEMA/DEAEMA.HCl (90/10)	EGDMA	87.3
7	HEMA/MDEAEMA (90/10)	EGDMA	84.3
8	HEMA/AAM (80/20)	MBMA	46.6
9	HEMA/AAM (50/50)	MBMA	57.4
10	AAM	MBMA	92.1

HPMA= 2-hydroxypropyl methacrylate, AAM= acrylamido morpholine, DEAEMA= N-diethylamino ethyl methacrylate, MDEAEMA= N-(methyldiethyl) ammonium ethyl methacrylate methyl sulphate (reaction of DEAEMA with dimethyl sulphate), MBMA= methylene bismethacrylamide.
The hydrogels were prepared with 20 vol% glycol as diluent. EWC was determined at 25°C. Comonomer composition is expressed as molar ratios.

Using uncharged comonomers large variations in comonomer composition are required in order to obtain significant changes in swelling. For ionized comonomers small quantities can generally cause a drastic increase in water content. This is attributed to mutual repulsion of charges of the same sign rather than to an influence on chain hydration (21). The ionization of hydrogels containing acid or amino groups is pH dependent and so is the swelling of these gels (cfr.gels 5,6 in table II).

For polyurethane hydrogels prepared from poly(EO-co-PO) the swelling can be adjusted by the hydrophilic/lipophilic balance of the prepolymer. Van Bos (10)

reported EWC values ranging from 6.7 to 86.4% for hydrogels prepared from a series of poloxamers of varying EO-content.

The swelling of hydrogels is also temperature dependent. Hydrogels composed of polymers having a lower critical solution temperature (LCST) lose water as the temperature is raised to the LCST and above (27,28). This process is reversible. Thermally reversible N-isopropyl acrylamide hydrogels with an LCST in the range 30-40°C have been reported (29,30). The swelling of polyurethane hydrogels based on PEO or poloxamers is also thermoreversible (31,32). This is illustrated in figure 1.

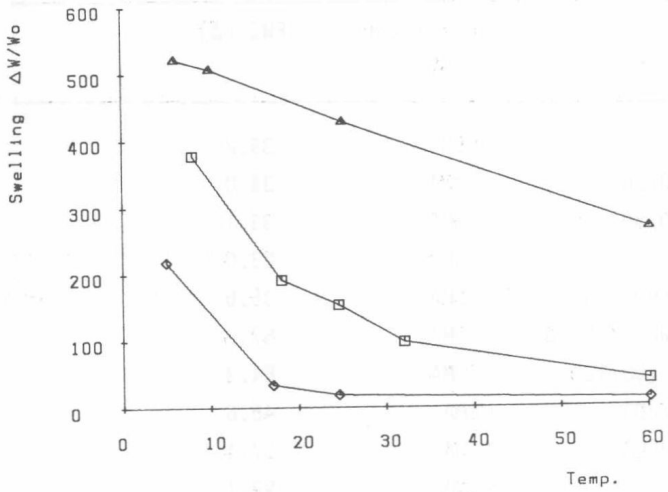


Fig.1. Temperature dependent swelling of polyurethane hydrogels

△ :PEO, MW 4000; ◇ :P(EO-PO), 20 % EO, MW 3650; □ :P(EO-PO), 40 % EO, MW 4600
Hydrogels prepared from polyether, Desmodur W and 1,2,6-hexane triol (cfr.10)

PREPARATION OF DRUG LOADED HYDROGELS

Drug loaded hydrogels can be prepared by a one-step procedure where the drug is added to the polymerization mixture. This method is practical provided the content of residual reactants is below acceptable levels. Since this is difficult to achieve most therapeutic hydrogels for in vivo use are prepared by a two-step procedure. A hydrogel device is fabricated in the desired geometry and tediously purified by repeated extraction. It is then loaded with drug by soaking the dry gel in a drug solution. Drug sorption can occur from solutions in water or a volatile organic solvents.