Gradient-IPN-Modified Hydrogel Beads: Their Synthesis by Diffusion–Polycondensation and Function as Controlled Drug Delivery Agents

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Synopsis

Interpenetrating polymer network (IPN) membranes and gradient–IPN polymers were synthesized by immersing crosslinked, 2-hydroxyethylmethacrylate copolymer beads which were swollen in polyol in solutions of diisocyanates. Diffusion of reactants and polycondensation take place simultaneously, and the polymer beads are modified by a polyurethane–IPN layer whose thickness and compositional gradient are a function of reaction rate and diffusion rate. When the reaction is fast relative to diffusion, the reaction zone is narrow and the IPN boundary layer is sharp, whereas when diffusion dominates, the reaction zone and the IPN-modified region becomes broader and more diffuse. A water-soluble drug imbibed into such gradient–IPN-modified hydrogel beads is released over a prolonged time period due to the less permeable IPN barrier and because of a drug-distribution gradient in the polymer, which follows the polyurethane gradient. Diffusion polycondensation can be considered a special case of interfacial polycondensation, one in which the interface area is expanded into and stabilized by a preformed polymer matrix, which serves as reaction medium.

INTRODUCTION

This article describes the synthesis of polymer beads modified by interpenetrating polymer networks (IPN) and the effect of these IPN's on the release of a water-soluble drug from hydrogel beads into an aqueous environment.

Conventional oral dosage forms of water-soluble drugs consist of coated tablets which after dissolution of the coating disintegrate more or less rapidly in the stomach. As a result, drug concentrations in the blood quickly reach a sharp peak and then decrease at a rate determined by their metabolic half-life in the body. The desire to eliminate this initial peak in blood level and thereby toxic or other unwanted side effects, while at the same time maintaining drug concentrations in the blood within the therapeutic range for an extended time period without an increase in overall dose size, has led to the development of more sophisticated oral drug-delivery systems. Examples are injection molded drug containing hydrophilic polymer beads[1] or drug-containing, microporous polystyrene beads.[2] In this laboratory we have developed a family of hydrogels[3] which can, after purification, be imbibed with a drug whose release is diffusion-controlled and dependent on polymer composition and water solubility of the drug. For use as an oral dosage form, these hydrogels are manufactured in the form of round beads by suspension polymerization. As monolithic hydrogel beads uniform in composition, swelling behavior, and drug concentration, they release the drug by a concentration dependent first-order mechanism. This diffusion controlled-release rate is fast at the beginning followed by a gradual and reproducible drop whose slope is determined by the water solubility of the

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drug, the hydrophilicity of the polymer, and the diameter of the bead. If the release is stretched out in this manner over 3–4 h it is a sufficient improvement over coated tablets of most orally administered drugs, provided the half-life of the drug in the body is long enough to keep its concentration within the therapeutic range for several hours. However, if the drug half-life is short, a nearly constant release rate over 6–10 h may be necessary to keep blood levels sufficiently elevated. This kind of release pattern has been achieved by dosage forms which are based on the "osmotic pump" principle.[4]

Our objective was to transform monolithic, that is, uniform hydrogel beads, into membrane covered hydrogels, thereby retarding the release of imbibed water soluble drugs. Since several drying and swelling steps are involved in preparing drug-loaded bead, one major condition this membrane had to meet was that it could expand and contract with the core polymer without cracking or peeling off. It would also have to withstand the osmotic pressure created by the dissolution of the imbibed highly water soluble active ingredients.

Sequentially synthesized interpenetrating polymer networks (IPN's), because of their inherent intimate entanglement and because of their reported high strength and density,[5] seemed therefore a logical choice for this investigation. If the IPN could be obtained in the form of a membrane around the polymer bead and if this bead could still be loaded with drug, a drug-release retarding effect was to be expected.

Interpenetrating polymer networks (IPN's) have been described extensively in the literature,[5–8] including synthesis, morphology, and physical properties.

In an interpenetrating polymer network, a preformed crosslinked polymer matrix is randomly penetrated by a second polymer without being covalently bound to it; a polymer mixture like this differs from a conventional polymer blend by the constraints the original crosslinked polymer puts upon the second polymer, thereby limiting phase separation. IPN's are prepared either by sequential or simultaneous synthesis; for sequential synthesis, a preformed crosslinked polymer is imbibed with a monomer which is then polymerized to form another crosslinked polymer within the original network; in simultaneous synthesis linear polymers or prepolymers are combined with their respective crosslinking agents in melt or solution, followed by simultaneous polymerization and crosslinking of both phases. The simultaneous method allows only the synthesis of macroscopically homogeneous IPN's, whereas the sequential method allows one to polymerize the second monomer before it has come to a concentration equilibrium in the preformed polymer matrix.

This concept has been used to prepare what some authors[9,10] have called "gradient polymers" and which consist of crosslinked polyacrylonitrile interpenetrating a preformed polystyrene or poly(methyl methacrylate) matrix; they are made by irradiation of polymer sheets partially swollen with acrylonitrile. A similar process has been employed in making sequential IPN's of crosslinked hydrophilic acrylic polymers in a polyether–urethane–urea substrate[11] and in making gradient polymers by UV-activated polymerization of 2-chloroethylacrylate in poly(methyl methacrylate).[12,13] An UV-polymerized poly(ethyleneglycol–dimethacrylate) network in the surface of progesterone-filled hydrogel sheets is another example of a sequentially formed IPN which has the characteristic of a membrane and leads to a constant release of progesterone over a prolonged time period.[14]

While sequential synthesis of IPN's allows a wide choice of polymer matrices for the first polymer, the second polymer has for practical reasons been restricted to systems in which the polymerization can be delayed until the matrix is swollen to the desired depth. Free-radical initiated polymerization of vinyl monomers has therefore been the preferred choice for making the second polymer of a sequential IPN. To make the second polymer network of a uniform sequential IPN by a conventional polycondensation seems at first quite impractical; reaction can occur during swelling, and at least two reactants have to be used which after equilibrating in the matrix would have to be present in roughly equimolar amounts in order to form a high molecular weight polycondensate.

Polycondensation seemed to us however ideally suited to prepare nonuniform gradient IPN's; if one reactant is first imbibed into the polymer and the swollen polymer is then immersed in the second reactant or in a solution of the second reactant, simultaneous diffusion and condensation between both compounds should occur. The result would be a diffusion-controlled polycondensation, occurring within the original polymer matrix in a region where both reactants mix.

The special case of a diffusion polycondensation, which is described in this report is the formation of a polyurethane within a preformed water-swellable copolymer matrix: crosslinked polymers based on 2-hydroxyethylmethacrylate and *N*-vinylpyrrolidone are swollen with a diol or triol and a polyurethane containing IPN is formed by reaction with 2,4,4(2,2,4)-trimethylhexane-1,6-diisocyanate (TMDI). We have investigated the effect of polymer composition, solvent, reactant concentration, catalyst concentration, temperature, and reaction time on overall reaction rates and reaction depth. The IPN-modified polymers were analyzed in cross sections by optical microscopy, scanning electron electron microscope (SEM) X-ray line scan, by swelling measurements with ethanol and diffusion measurements using a water-soluble drug.

For practical reasons our work had to be done with hydroxy-substituted crosslinked polymers and therefore a certain amount of covalent bonding between both polymers of the IPN is to be expected. However, it was found that in the absence of polyols grafting of TMDI under the reaction conditions employed by us was negligible.

EXPERIMENTAL

Materials

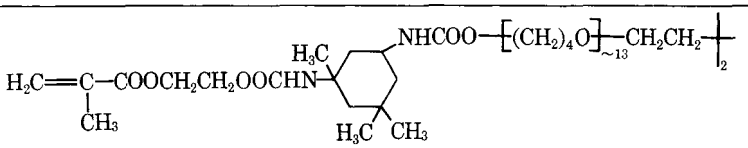
The Polymer Substrates

The polymer bead substrates consisted of copolymers of 2-hydroxyethylmethacrylate and *N*-vinylpyrrolidone (HEMA, NVP, respectively) with a polymeric crosslinking agent (PX), which is derived from poly-*n*-butyleneoxide (MW = 2000) by capping with isophoronediioscyanate followed by reaction with excess HEMA[3] (Table I). The polymer beads were synthesized by free-radical initiated polymerization in aqueous suspension.[15] The filtered beads were rinsed, extracted in a Soxhlet with ethanol for 24 h, dried, and classified into standard mesh sizes, and their degree of swelling in water and ethanol was determined. Unless otherwise indicated, the −16 +18 mesh fractions with an average diameter of 1.1 ± 0.1 mm were used for the experiments. As block co-

TABLE I
Polymer Substrates: Composition and Swelling Properties

Polymer no.	Composition (%)			Equilibrium swelling	
	Hema	NVP	PX[a]	Water (%)	Ethanol (%)
1	60	—	40	18	42
2	70	—	30	25	49
3	80	—	20	30	52
4	70	10	20	40	51
5	45	35	20	46	60
6	35	45	20	50	66
7	20	50	30	49	67
8	10	75	15	68	79

[a]



polymers they are often slightly opaque due to phase separation, with the hydrophobic and rubbery poly-*n*-butyleneoxide phase dispersed in the hydrophilic and glassy vinyl polymer phase.

Chemicals for IPN Synthesis and Abbreviations

TMP	trimethylolpropane
HD	1,6-hexanediol
BD	1,4-butanediol
TMHD	2,2,4(2,4,4)-trimethylhexane-1,6-diol
DBNG	dibromoneopentylglycol
DBBG	2,3-dibromobutenediol (GAF Corp.)
TDI	2,4-toluene-diisocyanate
ISONATE-143L	partially dimerized 4,4′-diisocyanato diphenylmethane (Upjohn Chem. Co.)
TMDI	2,2,4(2,4,4)-trimethylhexane-1,6-diisocyanate (Veba Chemie)
DBTL	dibutyltin dilaurate
TEA	triethylamine
MEK	methylethylketone, urethane grade
PU	polyurethane

All reactants were obtained from commercial sources and were used as supplied; the liquid polyols and MEK were stored over 4A molecular sieves. Oxprenolol·HCl: 1-[*o*-(allyloxy)phenoxyl]-3-(isopropylamino)-2-propanolhydrochloride (Ox) was supplied by CIBA-GEIGY Corp.

Analytical Methods

The amounts of all materials X which were imbibed into or synthesized in the polymer (ethanol; water, reactants; drug; polyurethane) are expressed in percent of total compositions, defined as:

$$X\ (\%\ w/w \text{ or } \%\ v/v) = \frac{(\text{polymer} + X) - \text{polymer}}{\text{polymer} + X} \times 100 \qquad (1)$$

(w/w) denotes weight percentages (applies to water swelling; reactant and drug loading and to polyurethane formation), (v/v) volume percentage (ethanol swelling).

Percent ethanol and rate of ethanol swelling was determined by measuring the volume expansion of approximately 2 g (−18 + 20) mesh beads with a modified dilatometer; this consisted of a 10-mL burette, closed off at one end with a known volume and attached at the other end by a joint to a 50-cc Erlenmeyer flask containing sample and solvent; for each measurement the apparatus was inverted and the volume of beads measured.

Optical microscopy of ethanol-swollen cross sections was used to evaluate the IPN distribution within the polymer and to estimate average % polyurethane (PU) in the IPN itself from % IPN (v/v) and % PU (w/w), assuming equilibrium ethanol swelling of the original polymer matrix. SEM X-ray microprobe line scans of cross-sectioned beads were used to estimate the distribution of a bromine containing polyurethane in the substrate and the distribution of oxprenolol·HCl in drug-loaded beads.

Drug release measurements were carried out by stirring approximately 1 g of drug-loaded beads at 37.5°C in 1-L distilled water which continuously circulated through the cell of an UV spectrophotometer. Automatic readings of UV absorption were taken every 3 min.

Synthesis

Synthesis of Polyurethane IPN's in Hydrogel Beads

Thoroughly dried polymer beads prepared by suspension polymerization[15] with an average diameter of 1.1 mm (−16 + 18 mesh) were immersed in either 100% polyol or a solution of polyol in a solvent (MEK or methanol) until swelling equilibrium was established. The beads were then filtered, rinsed with dry MEK, dried *in vacuo* (0.1 mm Hg) at 50°C for 10 h and stored in a desiccator. The concentration of polyol in the bead was determined gravimetrically.

In a screw-cap vial with a magnetic stirrer, 3 g of polyol-swollen beads were immersed and stirred in 10 g of liquid reaction medium consisting of either 100% diisocyanate or a solution of diisocyanate in dry MEK. Temperature was controlled within ±0.5°C by a glycol bath. As catalyst, dibutyltin–dilaurate (DBTL) or triethylamine (TEA) were used. After a given reaction time the beads were filtered off, rinsed with MEK, and extracted in a Soxhlet with MEK for 18 h. Finally they were dried, and their polyurethane (PU) weight gain was determined. Cross sections of ethanol-swollen beads were viewed under the light microscope and compared to control beads. With some samples ethanol swelling rate measurements were carried out.

Loading Oxprenolol·HCl

Oxprenolol·HCl (Ox), a highly water soluble (73% solubility at 25°C) and ethanol-soluble (22% solubility at 25°C) drug, was used as a model compound. It was loaded into the beads by equilibrating a weighed amount of dried beads in a saturated (55%) solution of oxprenolol·HCl in a mixture of 80% ethanol and 20% water for 24 h. After filtration the beads were rinsed with ethanol and dried at 0.1 mm Hg at 50°C for 16 h. Percent loading was determined gravimetrically.

RESULTS AND DISCUSSION

Gradient IPN's by Diffusion-Polycondensation

Synthesis with Aromatic Diisocyanates

Initial work was done with toluene–diisocyanate and ISONATE 143-L, using beads swollen with trimethylol propane. The reaction was difficult to control because of the high reactivity of aromatic isocyanates and their associated tendency to graft onto the OH groups of the polymer. Yet, as Table II shows, with the larger molecule ISONATE 143-L less weight gain is obtained than with toluene–diisocyanate, which is smaller and diffuses faster; dilution of TDI with heptane alone, which is a poor solvent for the polymer substrate and the TMP, reduces conversion rate; addition of MEK, which is a good solvent for reactants and polymer, leads to a drastic increase in reaction rates due to faster permeation.

That much of the observed weight gain is not due to polyurethane formation but to grafting is obvious from the results obtained with substrate beads free of trimethylol propane (Table II).

Synthesis with Aliphatic Diisocyanate (TMDI)

With less reactive aliphatic diisocyanates the reaction became much easier to control. We choose 2,4,4(2,2,4)trimethylhexane–1,6-diisocyanate (TMDI) for further study. This diisocyanate, because of its high boiling point, is also a safer and more convenient compound to work with. With none of the polymers could any weight gain be measured as a result of grafting when the reaction was carried out in the absence of polyol in 100% TMDI and with 0.1% DBTL at 50°C for 5 h.

TABLE II
Modification of Polymer 5 Beads with Aromatic Diisocyanates at 50°C (No Catalysts)

Substrate	Reactant	% Solvent	Time (h)	Product [% (w/w)] of final polymer
Polymer 5 + 37% TMP	TDI	—	0.25	5
	ISONATE	—	4.0	1
	TDI	33% MEK	0.25	37
	ISONATE	14% MEK	1.0	18
	TDI	50% heptane	4.3	9
	TDI	25% heptane +25% MEK	4.3	59
Polymer 5, without polyol	TDI	50% MEK	0.5	42
	ISONATE	50% MEK	0.5	17
	ISONATE	—	0.5	0

TABLE III
Polyurethane (PU) Formation as a Function of Catalyst Concentration (a) Temperature (b), and Reaction Time (c)[a]

(a) Effect of catalyst (5 h/50°C)		(b) Effect of temperature (5 h/0.1% cat)		(c) Effect of reaction time (0.1% cat/50°C)	
% cat	PU %	°C	PU %	h	PU %
0.035	12	30	5	3	33
0.058	28	40	19	5	41
0.115	44	50	41	7	45

[a] Substrate: polymer 6 + 56% TMP; reaction medium: TMDI + 50% MEK; catalyst: DBTL.

Effect of Solvent on Conversion Rates

Reaction time, catalyst concentration, and temperature influence total polyurethane formation in a predictable and reproducible manner (Tables III and IV). However, the effect of added solvent on reaction rate is contrary to what one would expect for a reaction taking place in homogeneous solution (Table V), and the results confirm the data obtained with TDI and ISONATE. Dilution of TMDI with MEK led to an overall increase in polyurethane–IPN formation, due solely to better mixing between both reactant phases. Up to about 60% MEK as a diluent, the increased diffusion and miscibility between both reactants and catalyst override the rate-reducing effect of greater dilution. In Table V and throughout this article, reactant concentration is deliberately expressed in percent solvent in order to emphasize this positive effect on overall reaction rates.

Beyond some critical dilution the reaction rate necessarily drops to zero; with increasing dilution, more and more of the polyol is probably also leached out of the substrate polymer before any reaction can occur, and much of the product which is formed is of such low molecular weight that it too diffuses out of the polymer.

Effect of Polymer Substrate on Distribution and Morphology of IPN

Microscopy, especially of ethanol-swollen cross sections, is a useful tool to judge depth and distribution of the IPN in the modified beads. Differences in degree of ethanol swelling between both phases of the phase-separated IPN probably

TABLE IV
Polyurethane Formation in Polymer 6 by Diffusion–Polycondensation of Brominated Diols with TMDI at Two Catalyst Concentrations[a]

Substrate: polymer 6 + % polyol	DBTL (%)	IPN Depth (mm) (in ethanol)	Polyurethane % of total polymer	Polyurethane % of IPN only (calcd)
+58% DBNG	0.05	0.25	17	23
	0.10	0.30	25	31
+55% DBBG	0.05	0.30	24	34
	0.10	0.60	28	29

[a] Reaction conditions: 3 h/50°C; 50% MEK in reaction medium.

TABLE V
Formation of Polyurethane (in % of Final Polymer) as Function of MEK Concentration of Reaction Medium[a]

% MEK in reaction medium	% Polyurethane and (in parentheses) IPN thickness (mm)							
	Substrate: polymer 3		Substrate: polymer 6		Substrate: polymer 5			
	+ 37% HD	+ 32% HD	+ 56% TMP	+ 65% TMP	+ 50% BD	+ 50% BD[b]	+ 50% HD	+ 57% TMHD
0	17 (0.08)	16	9			28	30 (0.10)	28 (0.10)
10	24 (0.11)	22	21			26	35 (0.13)	36 (0.15)
20	29 (0.17)	25	29	34		30	40 (0.25)	41 (0.20)
30	31 (0.17)	20	34	42	44	35	42 (0.35)	44 (0.20)
40	32 (0.17)	26	33	43		36	41 (0.30)	42 (0.20)
50	29 (0.20)	25	27	39	43	35	40 (0.30)	42 (0.25)
60	30 (0.10)	26	19	28		30	38 (0.35)	37 (0.25)
70	30	22	12		19	13	31 (0.30)	8 (0.40)
80	26	14	6	7		7	8 —	8 —
90	5	6				3	2 —	5 —

[a] Three polymer substrates loaded as indicated with various polyols and reacted at 50°C for 5 h (unless otherwise indicated); 0.1% DBTL as catalyst. Numbers in parentheses are depth of IPN phase (mm) measured on ethanol-swollen cross sections.

[b] 2-h reaction time.

enhance refractive-index differences and thereby opacity. Also, all gradient-IPN-modified beads show stress-induced birefringence patterns when viewed with crossed polars. This effect is most pronounced in swollen samples which are otherwise optically clear (Fig. 1). The intensity and location of birefringence patterns seems related to the steepness and the location of the compositional gradient. Despite substantial IPN formation homogeneously modified beads with no IPN gradient show no birefringence at equilibrium swelling.

Figures 1 and 2 show typical photomicrographs of an ethanol-swollen cross section of IPN-modified beads. Since the slices were not all of the same thickness, information obtained by microscopy is largely qualitative. All samples show a nonuniform IPN distribution; most noticeable are differences in surface morphology and in the boundary between core and IPN.

The convoluted surfaces of swollen polymer 3 and 4 IPN's (Figs. 1 and 2) indicate a resistance to expansion with the swollen core. This may in part be due to the fact that the polymer 3 substrate was less expanded during IPN synthesis, containing only 37% hexanediol vs. 50% hexanediol in polymer 6; the modified bead may not be able to expand easily beyond the volume it occupied during IPN synthesis.

The different morphology could also be a result of a grafting and crosslinking side reaction. Although no grafting was observed in the absence of polyol, in the highly expanded polyol-swollen network some grafting may indeed occur; if it does, then the HEMA content of the substrate would determine at what average degree of polymerization the polyurethane chain is stopped by reaction

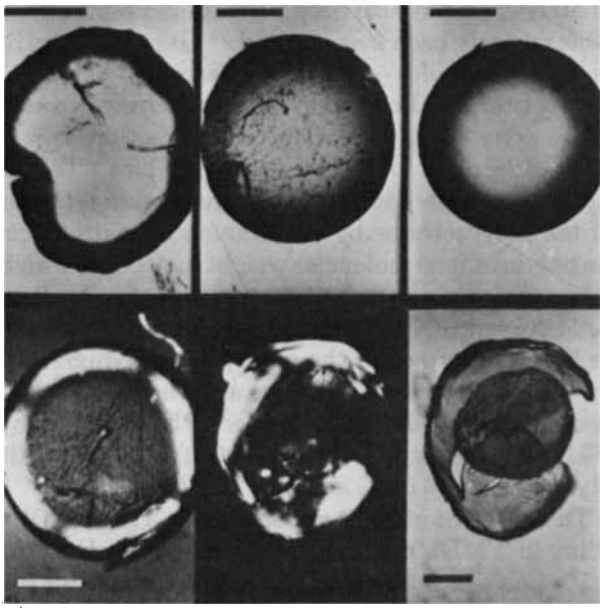


Fig. 1. Photomicrograph. Upper row: cross sections of IPN-modified beads in ethanol (see Table V, 20% MEK in reaction medium). Left to right: polymer 3 + 29% PU (HD + TMDI); polymer 5 + 40% PU (HD + TMDI); polymer 5 + 41% PU (TMHD + TMDI). Lower row: left: polymer 8 + 66% PU (TMP + TMDI), cross section in ethanol, viewed with crossed polars (see Table VI); middle and right: polymer 6 + 28.5% PU (TMP + TMDI) in ethanol, with IPN shell split off during swelling; viewed with (middle) and without crossed polars (synthesis: polymer 6 + 54% TMP, 100% TMDI, 1% triethylamine, 24 h at 50°C). Bars represent 0.5 mm.

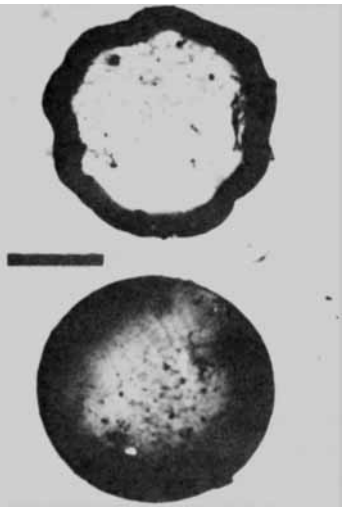


Fig. 2. Photomicrograph of cross-sectioned IPN-modified beads in ethanol. Top: polymer 4 + 25% PU; bottom: polymer 5 + 28% PU; bar represents 0.5 mm. (See also Fig. 12 for release rate data and Fig. 13 for SEM X-ray line scan.)

with a poly-HEMA hydroxyl group of the matrix polymer. If this covalent bonding occurs at both ends of the growing molecule, the polyurethane forms a crosslink, whose average chain length would be shorter and whose ability to expand would therefore be more restricted with the highly hydroxylated polymers 3 and 4 than with polymers 5 and 6. The effect of crosslinking between the two components of an IPN on physical properties, phase separation, domain structure, and size has recently been investigated.[16] It is possible that these effects also contribute to the behavior of the IPN's described here.

One would expect that all linear polyurethane formed from diols and diisocyanates be easily extractible, yet exhaustive extraction with MEK, dichloromethane, or ethanol resulted in little or no extractibles. This supports the assumption that either some interpolymer crosslinking through grafting or crosslinking of the polyurethane by allophanate formation occurred. On the other hand, the polyurethane molecular weight may be very high and its entanglement with the substrate polymer phase too intensive for it to be extracted.

The boundary between IPN-modified surface regions and the unmodified core of the polymer bead is sharpest in the most polar polymers which have a high HEMA and low NVP content and therefore a low affinity for TMDI. Note, for instance, in Figures 1 and 2 the sharply defined IPN boundary in polymers 3 and 4 (80% and 70% HEMA, respectively) in contrast to the more diffuse boundary of IPN's in polymers 5 and 6 (45% and 35% HEMA).

Likewise, in Table VI, the affinity of polymers 1–3 for TMDI, judged by their degree of swelling in TMDI, decreases with increasing HEMA content in the order polymer 1 > polymer 2 > polymer 3 (20.0%, 13.1%, 7.9% swelling in TMDI at equilibrium, respectively). Polyurethane formation decreases in the same order and the deepest and most diffuse IPN is obtained with polymer 1. Although more TMP than HD is imbibed in all three polymers, more IPN is formed with HD, which is better miscible with the TMDI–MEK solution. TMP with its higher functionality, on the other hand, gives a more dense IPN with higher polyurethane content.

TABLE VI
Synthesis and Distribution of Polyurethane (PU) in Five Polymers[a]

Substrate polymer + polyol	IPN depth (mm) and gradient structure	Polyurethane % of total polymer	Polyurethane % of IPN only (calcd)
Polymer 1 + 25% HD	0.35 Diffuse	25	27
+ 31% TMP	0.15 Diffuse	16	34
Polymer 2 + 32% HD	0.25 Sharp	23	36
+ 40% TMP	0.07 Sharp	14	57
Polymer 3 + 35% HD	0.15 Sharp	19	34
+ 39% TMP	Very thin	12	—
Polymer 7 + 56% HD[b]	0.85 Complete penetration; no gradient	30	30
+ 65% TMP[b]	0.85 Complete penetration; no gradient	32	32
Polymer 8 + 65% HD[b]	0.85 Complete penetration; no gradient	23	23
+ 66% TMP[b]	0.25 Diffuse	60	77

[a] Synthesis conditions: 50°C/5 h; 50% MEK in TMDI; 0.05% DBTL (for TMP samples), 0.1% DBTL (for HD samples). IPN depth and % IPN (v/v) calculated from ethanol-swollen cross sections.

[b] These samples are optically clear and were viewed with crossed polars. Both unmodified control beads and IPN-modified beads show with crossed polars stress-induced birefringence patterns during swelling in ethanol or other solvents; only the gradient–IPN beads (polymer 8 + TMP), however, retain this pattern even after swelling is completed (Fig. 1; low row, left).

The most diffuse IPN's are obtained with polymers 7 and 8, which contain the lowest amounts of HEMA (20%, 10%) and are highly swollen with polyol (Table VI). We assume that diffusion between both reactants occurs relatively fast with much of the polyol leaching out and reacting in the liquid medium. Unless the faster diffusion is balanced by an increased reaction rate as in the case of polymer 8 + TMP, the IPN will extend deep into the polymer and have only a flat or no compositional gradient.

When brominated diols were used as reactants (Table IV), the nonuniform polyurethane distribution in the modified bead could be demonstrated by SEM X-ray Microprobe Br line scan (Fig. 3).

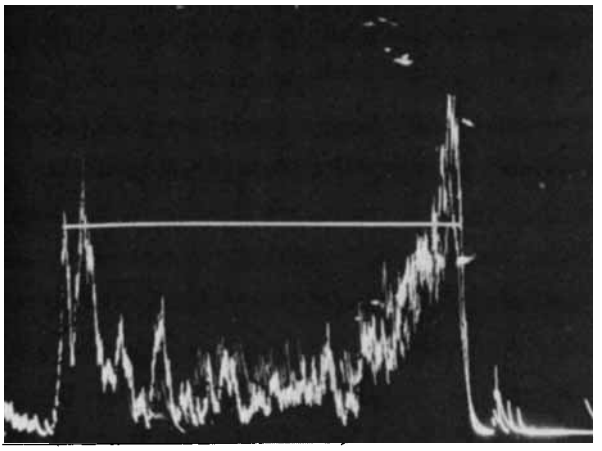


Fig. 3. SEM X-ray linescan for bromine of cross-sectioned polymer 6 bead, IPN-modified with 25% dibromoneopentylglycol/TMDI polyurethane (see Table IV). The bar indicates the diameter (1.1 mm) of the bead, whose outline is barely visible.

TABLE VII
IPN Formation in Presence of MEK as Function of Reaction Time[a]

Reaction time (h)	0.28	1.0	2.0	3.0	4.0	5.0	7.0	16	24
PU (%)	5.3	22	31	38	40	41	43	47	47
IPN thickness[b] (mm)	0.04	0.16	0.20	0.20	0.24	0.5	0.75[c]	0.75[c]	0.75[c]

[a] Substrate: Polymer 6 + 50% HD; reaction conditions: 50% MEK in TMDI; 0.1% DBTL; 50°C.
[b] Of ethanol-swollen cross sections.
[c] Bead completely penetrated by IPN.

Effect of Reaction Time on IPN Distribution

Tables VII and VIII show the results obtained when the reaction is carried out for a long time under conditions of either fast or slow diffusion. Under conditions which favor diffusion, the IPN eventually penetrates the whole bead (Table VII); when TMDI was diluted to 50% with MEK, after 24 h a total polyurethane yield based on polyol of 38% was obtained; the remaining 62% polyol was either leached out of the bead before the reaction or after conversion to low-molecular-weight polyurethane. However, when the reaction is carried out under conditions which slow down diffusion, but favor high initial reaction rates such as in 100% TMDI (Table VIII), the polyurethane-IPN layer becomes a barrier to further diffusion and reaction. Overall rates of polyurethane formation are therefore lower and the IPN remains restricted to an outside layer.

Resistance to Cracking

Although some of the formed polyurethane may cover the polymer surface as a continuous film, all of it is well anchored through the IPN to the substrate polymer. As a result of the more or less gradual compositional change between IPN-modified region and core the modified beads are able to withstand several cycles of deswelling (drying) and reswelling without cracking. This is especially important when the beads are extracted with solvents and are then used to be imbibed with active ingredients for later release into an aqueous environment; any physical disintegration of the IPN due to osmotic pressure would lead to a very rapid release of solute. Cracking and peeling of the surface IPN layer is regularly observed only when the IPN was formed under conditions which favor high reaction rates, such as high TMDI and high catalyst concentrations (Fig. 1). Cracking as a result of sharp differences in swelling behavior between core and modified surface has also been observed in poly(ethyleneglycol–dimethacrylate) network membranes, interpenetrating hydrogel surfaces,[14] and in our own work with plasma treated hydrogels.

The product can be called a double-layer polymer (a double-layer hydrogel in the case of a water swellable polymer substrate like ours) or a gradient polymer, depending on which aspect is most pronounced: the layer of IPN surrounding the original polymer and connected to it by a very narrow, although quite steep

TABLE VIII
IPN Formation in Absence of MEK as Function of Reaction Time[a]

Substrate	Time (h)	PU (%)	IPN depth (mm) (in ethanol)
Polymer 3 + 50% TMP	5	7	0.05
	24	11	0.05
Polymer 6 + 54% TMP	5	11	0.05
	24	13	0.10
Polymer 6 + 53% HD	24	24	0.10
	96	46	0.25

[a] Reaction conditions: 0.25% DBTL, 50°C; 100% TMDI.

gradient, or the broad compositional gradient from outside into the core of the polymer.

The Reaction Mechanism

The observed results fit well with the model of a diffusion-controlled polycondensation. The reaction occurs in an interfacial region within a preformed polymer matrix where both reactants mix. Thus the process resembles a conventional interfacial polycondensation, one in which the contact between reactants is diffusion controlled and retarded by a polymer matrix. Conventional interfacial polycondensation in low viscosity liquids is usually restricted to systems with very high reaction rates because otherwise complete mixing of reactants would occur; with diffusion polycondensation much slower reactions are practical.

The depth of the mixing and reaction zone during diffusion polycondensation and the compositional gradient of the IPN depend on reaction time and the experimental conditions which affect (a) the rate of reaction and (b) the rate of mixing between both reactants.

The reaction rate depends primarily on reactant concentration and reactivity of the reactants, on catalyst concentration, and on temperature. The mixing rate depends primarily on miscibility between both reactants, on the affinity of the polymer substrate for the reactant diffusing in from the outside, and on any solvent which may be present. A good solvent for both reactants as well as the polymer, such as MEK, aids diffusion; a poor solvent like heptane has no effect. Thus, qualitatively at least, one can predict that conditions which favor mixing and diffusion will increase the depth of the mixing zone and thereby that of the IPN and that conditions which speed up reaction rates will prevent the establishment of a broad mixing zone and result in a thinner and denser IPN region. We assume that the molecular weight of linear polyurethanes formed from TMDI and hexanediol is quite high since a concentration equilibrium between OH— and NCO— groups is maintained and constantly reestablished by the competing and self-regulating processes of diffusion and reaction, one supplying, the other removing reactants from the reaction zone.

Contrary to conventional polycondensations in homogeneous solutions where the mol ratios of reactants can accurately be determined before and during the reaction, this system has concentration and therefore reaction gradients which are difficult to quantify. Independent rate measurements of the separate diffusion processes involved (diffusion of diisocyanates and catalyst into the polymer swollen by polyols; of polyols into the outside solution of diisocyanates) and of the reaction rate might allow a more precise prediction of IPN depth and gradient; however, the continuously changing nature of the polymer substrate itself has to be taken into account.

In our specific case the process is further complicated by the round geometry of the substrate, dictated by its end use as an oral drug-delivery system, which made it necessary to preswell it with one reactant. A later paper will deal with the more simple case of a diffusion polycondensation, where a flat, nonreactive polymer film separates both reactants which diffuse against each other and react within the film.

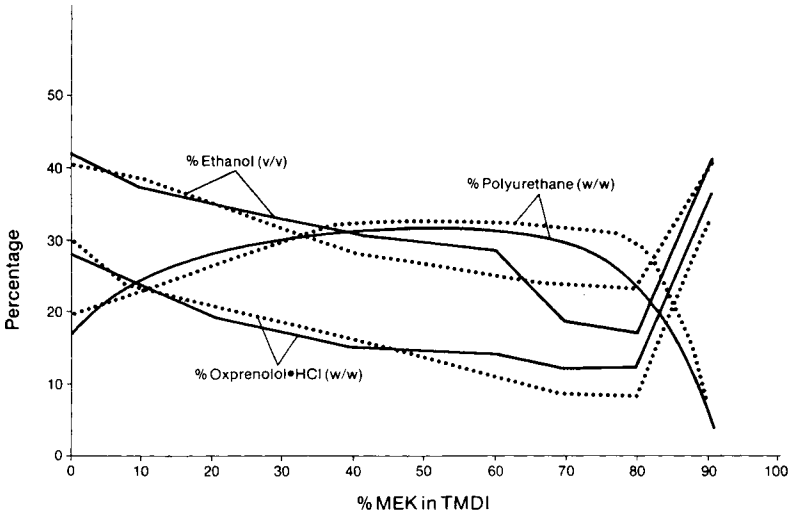


Fig. 4. Percent polyurethane (w/w), ethanol at equilibrium (v/v), and imbibed oxprenolol·HCl (w/w) of polymer 3 beads modified by diffusion polycondensation in presence of varying amounts of MEK. (—) 16 + 18 mesh polymer 3 + 37% HD as substrate (see Table V); (- - -) 20 + 25 mesh polymer 3 + 34% HD as substrate (same reaction conditions).

Swelling and Drug Release Behavior of IPN Modified Hydrogel Beads

Ethanol Swelling

The final degree of swelling in ethanol of the modified beads is inversely proportional to the amount of polyurethane which has been formed (Fig. 4). Since the IPN concentration is not uniform throughout the bead, it is reasonable to assume that the equilibrium ethanol concentration follows a similar gradient.

Volumetric ethanol swelling-rate measurements typically show a delay in swelling and as a result an inflection point in the rate curve. The length of the delay is a function of the amount and density of the IPN (Fig. 5).

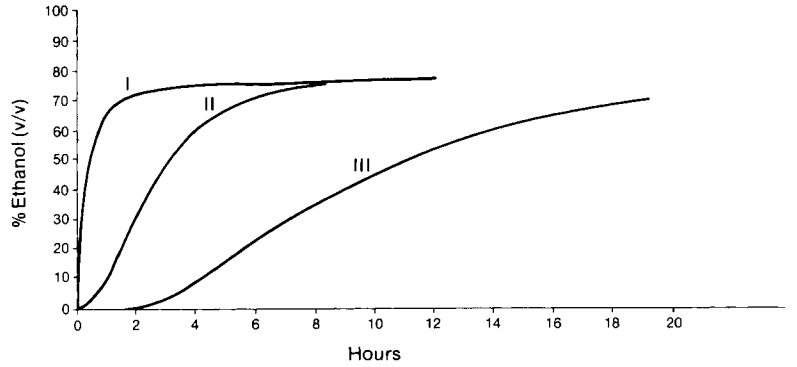


Fig. 5. Ethanol swelling by dilatometry of polymer 6 monolith and two polymer 6 IPN-modified samples (see Table IIIa; 0.035% and 0.058% DBTL as catalyst). (I) Polymer 6 monolith; (II) polymer 6 + 12% PU; (III) polymer 6 + 28% PU.

Ethanol swelling of unmodified control beads occurs with a sharp solvent front (Fig. 6), moving at constant speed, slowing down only close to the beads center (Fig. 7); this is characteristic of a Case II diffusion, which is controlled by chain relaxation of the glassy phase.[17,18] Complete equilibrium ethanol concentration of the swollen gel portion of the polymer (Fig. 7, dotted line) is more slowly established by Fickian diffusion.

IPN-modified polymers, when they were transparent enough to be measured, also show a sharp solvent front (Fig. 6), but one which moves slowly initially, then at slightly increased speed through 90% of the beads radius, followed by a rather sharp increase toward the end (Fig. 7). Final equilibrium is established only a considerable time after the solvent front has penetrated the bead.

Drug Release Measurements

Ethanol was chosen for swelling measurements because all our polymers swell much more in ethanol than in water. Ethanol or an ethanol–water mixture is therefore also a better solvent to imbibe the polymers with oxprenolol·HCl or other highly ethanol soluble drugs.[19]

Depending on their composition, the solubility parameters of the polymer substrates fall somewhere in between that of water and ethanol and therefore maximal degrees of swelling are obtained not with the pure solvent but with mixtures.[3] Although these mixtures are slightly different and specific for each

Fig. 6. Photomicrographs of whole beads during swelling in ethanol. Left: polymer 6 monolith; right: polymer 6 IPN-modified with 40% PU (HD + TMDI). Top: after 34 min swelling time; bottom: after 61 min. Bar represents 0.5 mm.

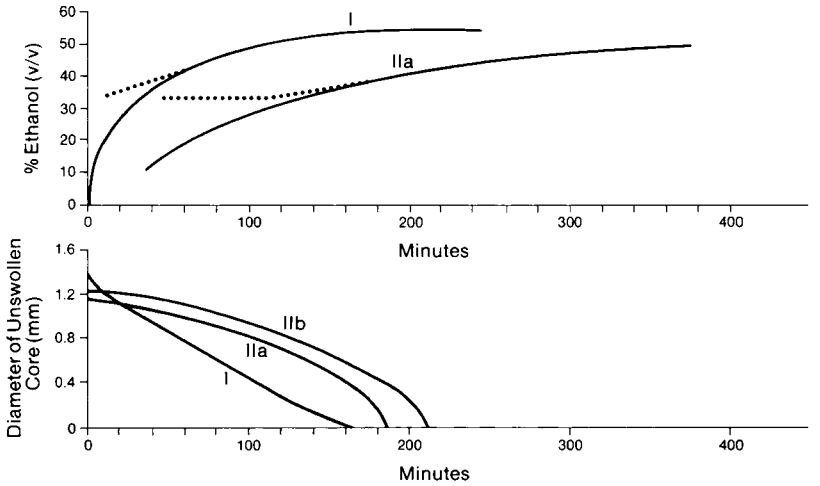


Fig. 7. Ethanol swelling of single beads, by microscopy. Polymer 5 monolith (I) and polymer 5 IPN-modified with 42% PU (IIa, b) (TMHD + TMDI; see Table IV, 50% MEK in reaction medium). Top: cumulative volume swelling of whole beads and (dotted line) % ethanol of swollen fraction only. Bottom: linear swelling by observation of solvent front.

polymer, 80% ethanol/20% water was used as drug-loading solvent. This mixture dissolves up to 55% oxprenolol·HCl. Percent ethanol at equilibrium proved to be an excellent indicator for the degree to which a given polymer could be loaded with a drug from ethanol–water solutions (Fig. 4).

Drug release curves are shown in Figures 8–11 and 12. With all unmodified control beads drug release follows a first-order mechanism, typical for drug release from monolithic hydrogels and characterized by a rapidly decreasing release rate.

In contrast, the release rate curves of oxprenolol·HCL from IPN-modified beads in all cases go through an inflection point. Although all release curves look roughly similar, two types of curves can be distinguished and correlated to IPN

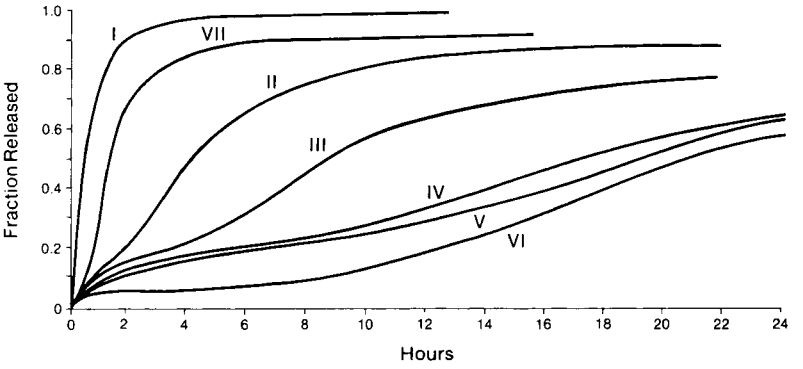


Fig. 8. Cumulative release of oxprenolol·HCl (Ox) from polymer 3 monolith and IPN-modified samples (Table IV: polymer 3 + 37% HD series). (I) polymer 3 monolith, 38% Ox; (II) polymer 3 + 17% PU (no MEK in TMDI), 28% Ox; (III) polymer 3 + 24% PU (10% MEK in TMDI), 24% Ox; (IV) polymer 3 + 29% PU (20% MEK in TMDI), 20% Ox; (V) polymer 3 + 32% PU (40% MEK in TMDI), 15% Ox; (VI) polymer 3 + 26% PU (80% MEK in TMDI), 12% Ox; (VII) pol. 3 + 5% PU (90% MEK in TMDI), 37% Ox.

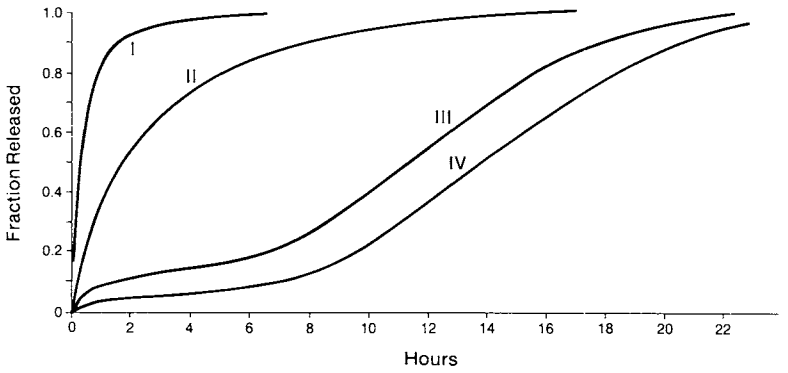


Fig. 9. Cumulative release of oxprenolol·HCl (Ox) from polymer 1 (31% Ox) (I) and polymer 4 monoliths (42% Ox) (II) and IPN-modified samples; reaction conditions: polymer 4 and 44% HD [25% PU (HD + TMDI): 23% Ox] (III) and 49% BD [28% PU (BD + TMDI): 21% Ox] (IV); 50% MEK in TMDI; 0.1% DBTL; 5 h/50°C.

structure: (1) if the IPN layers appear to be dense and sharply defined, as in polymers 3 and 4, the release rates are characterized by a pronounced delay, up to several hours, and only after 10–20% of the drug has diffused out does the release rate reach a maximum (Figs. 8 and 9); (2) if the IPN layers appear to be more diffuse, as in polymers 5 and 6, the initial delay is shorter and the inflection point in the rate curve is less pronounced (Figs. 10 and 11).

Figure 13 shows the SEM X-ray Microprobe chloride line scan of two cross-sectioned drug-loaded beads with very different IPN morphology; their ethanol swollen cross sections are pictured in Figure 2. The scan of the polymer 4 IPN-modified bead shows a core with uniform drug concentration surrounded by a narrow, almost drug-free layer. Also visible in the SEM micrograph is a change in morphology between core and IPN. The thickness of the drug-free IPN region corresponds well to the thickness of the dark ring visible in the Figure 2 photomicrograph. The line scan of the polymer 5 IPN-modified bead shows a smooth drug concentration gradient extending throughout the bead; similarly, the corresponding photomicrograph (Fig. 2), indicates a smooth compositional IPN gradient. In contrast to both IPN-modified beads, the unmodified polymer 5 control bead exhibits a uniform drug concentration profile.

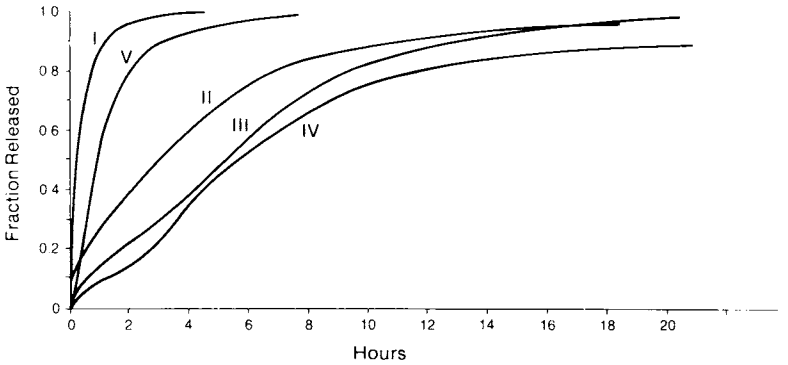


Fig. 10. Cumulative release of oxprenolol·HCl (Ox) from polymer 5 monolith (40% Ox) (I) and IPN-modified samples: (II) polymer 5 + 40% PU: 21% Ox; (III) polymer 5 + 40% PU (16% Ox); (IV) polymer 5 + 31% PU: 17% Ox; (V) polymer 5 + 8% PU: 34% Ox. From Table V, polymer 5 + 50% HD series. % MEK in TMDI: (II) 20%; (III) 50%; (IV) (70%); (V) 80%.

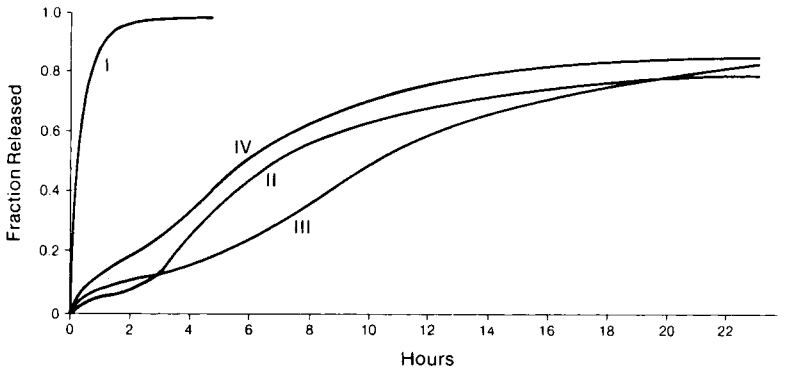


Fig. 11. Cumulative release of oxprenolol·HCl (Ox) from polymer 5 monolith (40% Ox) (I) and IPN-modified samples: (II) polymer 5 + 41% PU: 18% Ox; (III) polymer 5 + 42% PU: 17% Ox; (IV) polymer 5 + 28% PU: 20% Ox. From Table V, polymer 5 + 57% TMHD series. % MEK in TMDI: (II) 20%; (III) 50%; (IV) 70%.

The corresponding drug release curves of modified polymers 4 and 5 are shown in Figure 12; as a monolithic control for the release rate measurements we used oxprenolol loaded polymer 1, because it had a more comparable drug loading.

Drug Release Mechanism

Assuming that the IPN phase of the bead is composed of roughly equal parts vinyl–polymer matrix and polyurethane, the hydrophilicity and rate of swelling of the IPN as well as its permeability for the drug will be highest for the most hydrophilic polymer matrices. This effect is reinforced by the presence of oxprenolol·HCl, a highly water-soluble compound, which contributes heavily to the overall hydrophilicity of the drug polymer composite. Since the drug is loaded from ethanol–water solutions, its distribution in the bead closely follows the ethanol–water concentration gradient, which in turn probably follows the compositional gradient. Therefore, more drug is imbibed into the higher swelling and more hydrophilic IPN's of polymers 5 and 6 than into the IPN layers of polymers 3 or 4.

The drug-release curve of IPN-modified polymer 4 can thus be interpreted as follows: diffusion of water into the IPN-modified polymer 4 beads is initially

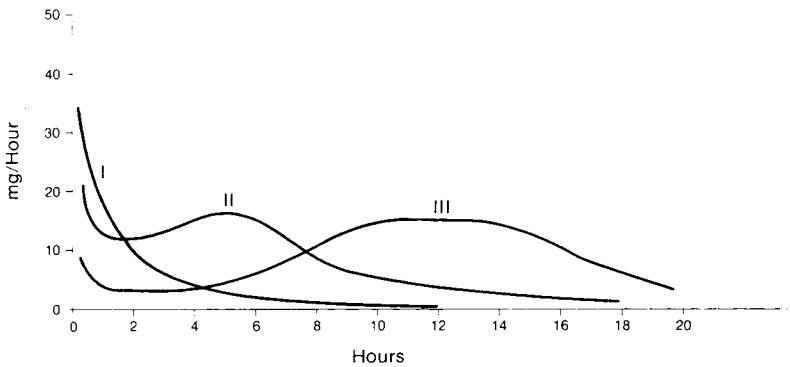


Fig. 12. Oxprenolol release rates for polymer 1 monolith (19% Ox) (I) and IPN-modified polymer 5 (+28% PU: 20% Ox) (II) and polymer 4 (+25% PU: 23% Ox) (III), based on a 100-mg dose.

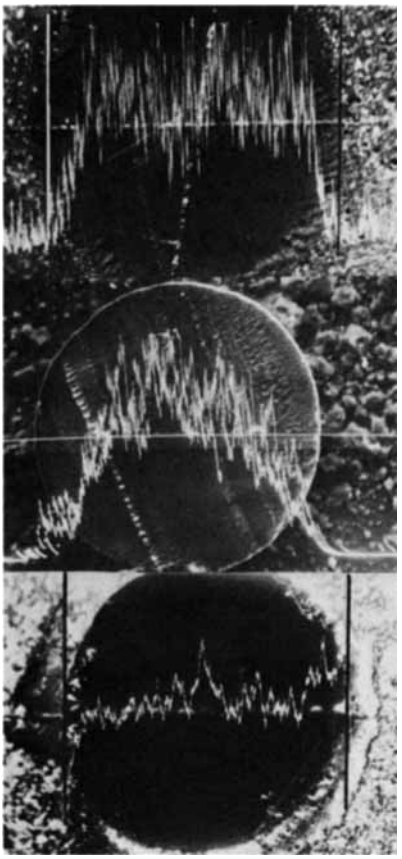


Fig. 13. SEM X-ray line scans for chloride of oxprenolol·HCl-loaded, cross-sectioned beads. Top: polymer 4 + 25% PU; middle: polymer 5 + 28% PU; bottom: unmodified monolith control, polymer 5. Vertical lines mark bead diameter. (See also optical photomicrograph of unloaded beads, Fig. 2, and release rates in Fig. 12.)

very slow due to the presence of a relatively hydrophobic and dense polyurethane IPN layer which swells little in water and ethanol and also contains little drug; thus, except for an initial burst due to drug absorbed at the surface, only small amounts of active ingredients are very slowly released during this initial phase, whose length is determined by the density and depth of the IPN layer. After the diffusing water front comes in contact with the water-soluble drug in the core, osmotic pressure accelerates water diffusion and the expanding IPN layer becomes more permeable. At that time release rates increase dramatically, dependent on overall drug concentration in the core polymer. Toward the end the drug release rate falls off in a concentration-dependent first-order fashion determined by the permeability of the IPN layer (Fig. 12, III).

On the other hand, the polymer 5 IPN is more hydrophilic and as a result contains more drug. Therefore, swelling and drug release are not delayed to the same extent. Since the IPN and therefore the drug concentration gradient extends far into the bead, the spherical geometry is compensated for by the higher concentration of drug toward the center and a prolonged period of fairly constant release rate is obtained (Fig. 12, II).

CONCLUSIONS

Gradient interpenetrating polymer networks have been synthesized by a new process termed diffusion polycondensation. During diffusion polycondensation two initially separated reactants diffuse against each other within a polymer matrix and react in a mixing zone whose width is controlled by reaction conditions. In this the process resembles an interfacial polycondensation, but one in which the interface is expanded and supported by a preformed polymer. The product is a sequentially formed IPN, bonded to the original polymer through a compositional gradient zone. The thickness of the IPN and the width and steepness of the compositional gradient depends on reaction time and on the relative rates of reaction and diffusion; high reaction rates result in narrow IPN layers and steep gradients, whereas high diffusion rates produce deep IPN's with flat gradients. The flatter the compositional gradient is between unmodified polymer phase and IPN phase, the stronger is the bond between both layered phases.

Thin IPN's synthesized by polyurethane formation in the surface of water-swellable beads act as membranes and retard the release of imbibed, water-soluble drugs from a monolithic hydrogel core.

If these IPN's penetrate into such water-swellable polymer beads with a smooth and deep compositional gradient, they themselves act as drug reservoirs and the release of an imbibed drug is partially a function of a drug-concentration gradient which follows the compositional gradient.

Diffusion polycondensations and diffusion reactions in general promise to be useful tools to synthesize IPN membranes of defined thicknesses and specific structure in existing polymeric surfaces, films, and membranes, especially if one considers the great variety of available reactant pairs and polymeric substrates.

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