Hydrogel Capsules for Sustained Drug Release

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SYNOPSIS

Interpenetrating polymer networks (IPNs) based on polyacrylamide and poly(vinyl alcohol) for hydrogel capsules were synthesized. These polymer networks were evaluated as drug-delivery devices using Crystal Violet and Bromothymol Blue as model drugs. The observed drug release is higher for semi-II-IPN than full-IPN. The drug-release behaviors from these capsules were analyzed by the exponent relation $Mt/M\alpha = Kt^n$, where "K" and "n" are constants and $Mt/M\alpha$ is the fraction of the drug released until time "t." The constant "n" was found to be above 0.5, which suggests that the release of drug from the capsules follows the non-Fickian diffusional model. The mechanical behavior of hydrogel disks were also analyzed. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Hydrogels are polymeric materials that exhibit the ability to swell in water or biological fluids and retain a significant fraction of water within their structures. The biocompatibility of hydrogels is attributed to their ability to stimulate the natural tissue due to their higher water content and special surface properties. Their low interfacial tension and higher permeability to small molecules and soft and rubbery nature make hydrogels well-suited biomaterials. In spite of the increasing importance of hydrogels, their poor mechanical strength, especially when a large amount of water is absorbed, limits the applications. Many attempts have been made to improve the mechanical behavior of the hydrogels by modifying the method of synthesis[1-5] or reinforcing polymer networks with suitable particles[6] or by blending.[7] Water content is a factor that affects the mechanical strength and can be controlled by making morphological changes in the form of interpenetrating polymer networks (IPNs). An IPN is an intimate combination of two polymers in the network form, at least one of which is synthesized or cross-linked in the immediate presence of the other.[8-11] Such IPN systems can be used to develop drug-delivery devices.

Controlled-release systems represent a relatively new development that evolved out of a continuing need for prolonged and better-controlled drug administration. Each drug has a therapeutic range above which it is toxic and below which it is ineffective. The aim of the controlled-release system is to ensure that the drug concentration remains in the therapeutic range for a prolonged time using a single-dosage form.

The importance of the controlled-delivery systems that release the drug at a constant rate is well recognized.[12] Although the matrix system offers a major advantage in the ease of fabrication and manufacture on a large scale, it suffers from the limitation that the release of the drug from the matrix devices follows first-order kinetics.[13] Generally, the matrix devices exhibit a continuously diminishing rate with time.[14,15] This is a consequence of increasing diffusional distance and decreasing area at the penetrating diffusion front. Consequently, an innovative approach is made here to achieve zero-order release from capsule-type drug-delivery systems. When such a devi̧ce comes in contact with water, the polymer swells and the loaded drug is released by countercurrent diffusion.

The prominent materials used for the preparation of cross-linked hydrogels include poly(2-hydroxyethyl methacrylate),[16] poly(*N*-vinyl-2-pyrrolidone),[17] poly(acryl amide),[18-20] and poly(vinyl alcohol).[21,22] Ritger and Peppas[23] showed that the exponential relation

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Table I Composition of Hydrogel Capsules

Code	Sample	% Composition*					Gelation
		PVA	AAm	GLA	BIS	H_2O	
A	Blend	4.0	20	—	—	76.00	No
B	Semi-I-IPN	4.0	20	0.2	—	75.80	Not good
C	Semi-II-IPN	4.0	20	—	0.2	75.80	Good
D	Full-IPN	4.0	20	0.2	0.2	75.60	Good
E	Semi-II-IPN	2.0	20	—	0.2	77.80	Good
F	Full-IPN	2.0	20	0.2	0.2	77.60	Good

* See Table II for definitions of abbreviations.

$$\frac{Mt}{M\alpha} = Kt^n \quad (1)$$

could be used to describe the Fickian and non-Fickian release behavior of the rubbery release system.

In this article, we report the synthesis of transparent hydrogel capsules in the form of interpenetrating polymer networks (IPNs) from polyacrylamide and poly(vinyl alcohol). The drug-release pattern and mechanical behavior were studied in detail.

EXPERIMENTAL

Materials

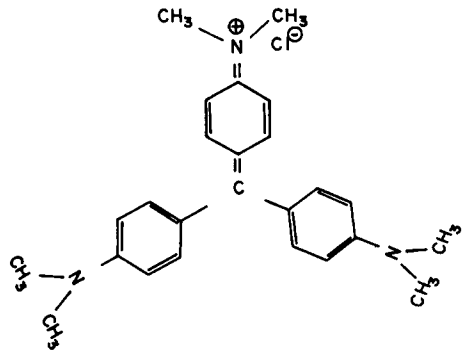
The raw materials used have been described in Table I. Crystal Violet (CV) and Bromothymol Blue (BTB) were used as model drugs and their chemical structures and properties are shown in Figure 1 and Table II, respectively. Disodium hydrogen orthophosphate and citric acid were used to prepare a 0.1 *M* phosphate buffer solution.

Bulk Polymerization and Preparation of Hydrogel Capsules

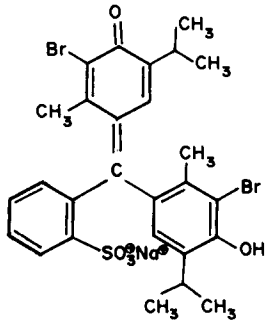
Two milliliters of 50% (w/w) aqueous acrylamide solution containing 10 mg *N,N'*-methylenebisacrylamide was bulk-polymerized in the presence of 10% (w/w) aq. poly(vinyl alcohol) and glutaraldehyde using potassium persulfate (10 mg) as initiator and sodium metabisulfite (10 mg) as accelerator. *N,N'*-Methylenebisacrylamide (BIS) and glutaraldehyde were used as cross-linking agents for polyacrylamide and poly(vinyl alcohol), respectively. The polymerization was carried out at 32°C for 30 min and subsequently placed in a water bath at 10°C for about 30 min for easy removal of the hydrogel capsule from the mold. These transparent hydrogel capsules were of 6.9 cm length, 1.1 cm diameter, and 0.2 cm thickness, released from a 5 mL capacity glass mold. The polyacrylamide hydrogels could not be removed from the mold under identical conditions without rupture. This prompted the authors to go for incorporation of poly(vinyl alcohol), which is very soft in the swollen state and will incorporate elasticity into the structure for facile handling of hydrogel capsules.

Table II Raw Materials and Source

Abbreviation	Name and Description	Source
CV	Crystal Violet	Aldrich Chemical Co.
BTB	Bromothymol Blue	Aldrich Chemical Co.
AAm	Acryl amide	J. T. Baker Chemical Co.
PVA	Poly(vinyl alcohol)	BDH Chemical Co., England
BIS	*N,N'*-Methylene bisacrylamide	Eastman Kodak Co., USA
GLA	Glutaraldehyde (25% solution)	S. D. Fine Pvt Ltd., India
PPS	Potassium persulfate	E. Merck (India) Ltd.
SMB	Sodium metabisulfite	E. Merck (India) Ltd.
CA	Citric acid	S. D. Fine Pvt Ltd., India
SHP	Disodium hydrogen orthophosphate	S. D. Fine Pvt. Ltd., India



CRYSTALL VIOLET (**CV**)



BROMOTHYMOL BLUE (**BTB**)

Figure 1 Chemical structures of CV and BTB.

Characterization

In Vitro Release Studies

The drug-release experiments were carried out in 100 mL of 0.1 *M* phosphate buffer solution (PBS) (pH 7.4) at 37°C. Ten milligrams of the drug was loaded at the bottom of the capsule to which 1 mL of buffer was added and the whole capsule kept in 100 mL buffer solution under constant stirring. The quantity of the drug released with time was followed by monitoring the absorbance of the release medium at λ_{max} = 590 nm for CV and at λ_{max} = 616 nm for BTB on a Shimadzu 160A UV spectrophotometer. The amount of drug released at time "t" was taken as Mt and the total amount of drug released from the capsule after keeping it in solution for prolonged periods ($M\alpha$) was taken as the total amount of drug loaded.

Mechanical Properties

The hydrogel samples corresponding to C, D, E, and F compositions (Table III) were subjected to 50% compression and decompression using an Instron (Model 4301) universal testing machine (with a 10 kg load cell) interfaced with an Apple IIe computer. The compressional tests were carried out on 2.8 cm diameter and 1 cm thickness cylindrical disks using a crosshead speed of 10 mm/min.

Swelling Analysis

Cylindrical disks were cut from a hydrated sheet of the hydrogel equilibrated in 0.1 *M* PBS at 37°C. The equilibrium swelling ratio in percent (Seq.) was calculated from the equation

$$\text{Seq.} = \frac{\text{Wt of wet sample} - \text{Wt of dry sample}}{\text{Wt of dry sample}} \times 100 \qquad (2)$$

The weight of the wet sample was determined after removing the surface water by blotting with tissue paper and the dry weight was determined after dehydrating under vacuum at room temperature to constant weight.

RESULTS AND DISCUSSION

Currently, there is a keen interest to develop polymeric hydrogels with enhanced mechanical strength that could be used in the biomedical field as drug-delivery systems. Polyacrylamide and poly(vinyl alcohol) are polymers capable of retaining a large amount of water within their structures. Therefore, these polymers have very extensive biomedical applications.[18-22] However, these polymers lose their mechanical strength when they absorb large amounts of water, thereby limiting the range of applications. This problem could be rectified by cross-linking the polymer chains by suitable cross-linkers. This precisely is the possibility that we envisaged to obtain interpenetrating hydrogel networks based on these macromolecules.

From Table III, it is seen that the addition of 2% cross-linker allows the samples to gel. However, in case of semi-I-IPN(B), the gelation is not good,

Table III Properties of Drugs

Drug	T_m (°C)	Solubility in PBS[a]	Absorbance in PBS[b]	
			λ_{max} (nm)[a]	E
CV	214–216	2.0	590	9.11×10^4
BTB	200–202	[c]	616	4.83×10^4

[a] g/100 mL PBS at room temperature.
[b] Measured by UV spectrophotometer.
[c] Freely soluble.

which may be due to insufficient cross-linking or the side-chain cross-linking. On the other hand, when polyacrylamide is cross-linked by BIS, it shows good gelation and enhanced rigidity.

Release of CV in Phosphate Buffer Solution (PBS)

Drug-release vs. time curves are shown in Figures 2 and 3 for samples C, D, E, and F. These data were analyzed by eq. (1), where "K" is a constant related to the hydrogel matrix, and "n," a diffusional exponent. Figure 2 shows the drug-release pattern from the hydrogel capsules corresponding to the compositions C and D, where C corresponds to semi-II-IPN (with only polyacrylamide cross-linked). This composition shows a faster drug-release rate compared to sample D (full-IPN), which has additional cross-links by glutaraldehyde. The hydrogel capsules were subjected to drug-release studies without equilibration in water. In this case, the drug-release process involves molecular relaxation in addition to diffusion. Molecular relaxation is less in full-IPN than in semi-IPNs due to the additional cross-linking. Therefore, the drug release is less for full-IPN than for the semi-IPNs. In the case of semi-II-IPN (sample C), the drug release starts after 5 h time, because of the time required for the permeation of the drug to reach the medium from the inside cavity of the capsule, whereas in case of full-IPN (sample D), it takes 14 h for the drug to reach the medium. This is because additional cross-linking reduces the degree of molecular relaxation, which delays the permeation of the drug very extensively. It makes

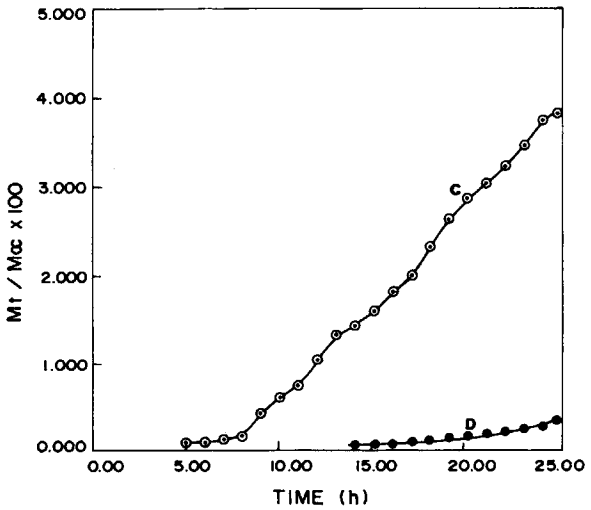


Figure 2 Drug-release vs. time curves for CV-loaded capsules.

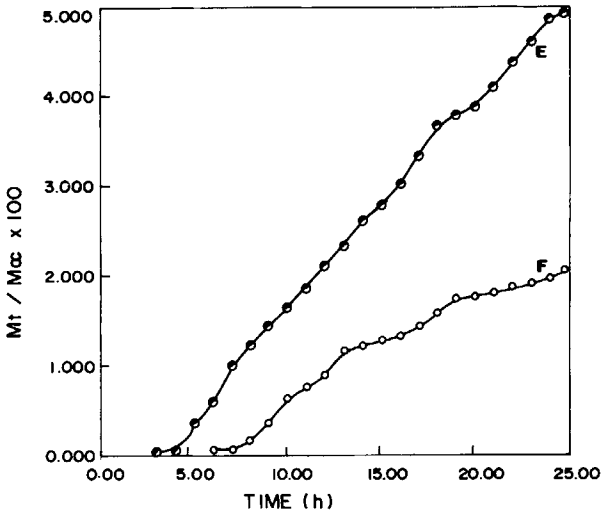


Figure 3 Drug-release vs. time curves for CV-loaded capsules.

clear that the synthesis of IPNs can change the drug-release timing and rate.

The drug-release kinetics of CV for different hydrogel compositions (samples E and F) is shown in Figure 3, illustrating the enhanced drug-release rate compared to samples C and D. This is because of the increased water content in the composition, which increases the free volume of the hydrogel capsule. Sample F has a slow drug release compared to sample E, because of additional cross-linking of poly(vinyl alcohol) by glutaraldehyde. Using the natural logarithm of eq. (1),

$$\ln(Mt/M\alpha) = n \ln(t) + \ln(k) \qquad (3)$$

"n" and "k" were calculated from the slope and intercept of the plot of $\ln(Mt/M\alpha)$ against $\ln(t)$ (Fig. 4). The results of these analysis are shown in Table IV. The diffusional exponent "n" can be used to obtain important information about the release mechanism of a drug in a polymeric device.[23] The value of "n" for all samples (C, D, E, F) for CV drug release were all above 0.5, which indicates that the release of the drug obeys the non-Fickian diffusional model.[24] This is a three-dimensional polymer network system formed by cross-linking the water-soluble polymers. Therefore, it is essentially a diffusion-controlled release system. Since the hydrogel is subjected to drug-release studies without equilibration in water, the drug-release process involves molecular relaxation in addition to diffusion, which is believed to be the reason for the observed non-Fickian behavior. From Table IV, it is clear that

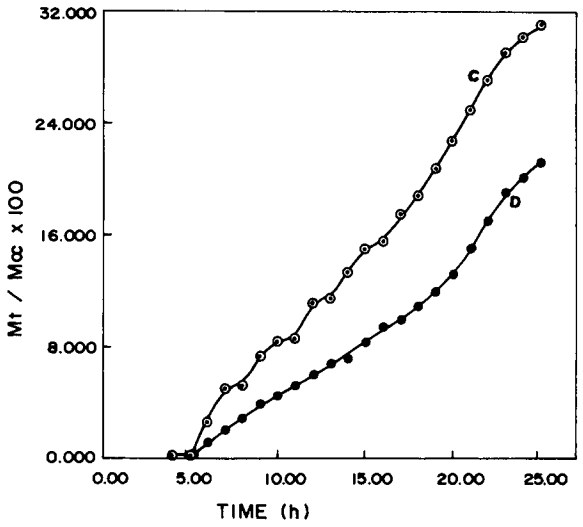


Figure 4 Plots of $\ln(Mt/M\alpha)$ against $\ln(t)$ in CV system.

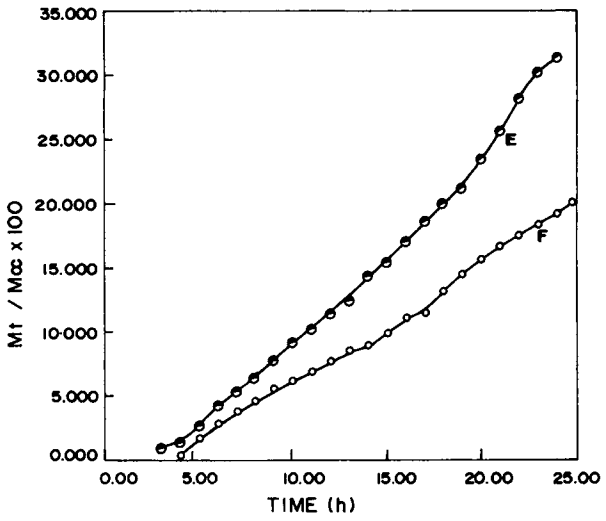


Figure 5 Drug-release vs. time curves for BTB-loaded capsules.

the drug-release constant k is directly proportional to the equilibrium swelling Seq., where sample C has larger k value than that of sample D, and sample E has a larger k value than that of sample F. This is due to an increased cross-link density; thereby, the space between each cross-link decreases with decrease of the release rate.

Release of BTB in Phosphate Buffer Solution (PBS)

The release of BTB also follows the same pattern as that of CV in all compositions (Figs. 5 and 6 and Table IV). But the comparative release rate in case of BTB is more than that of CV. This may be because of the higher permeability of BTB, due to its more hydrophilic nature, through the hydrogel matrix than that of CV. The higher solubility of BTB in PBS than that of CV may also be a constituting factor. Fully cross-linked sample D exhibits a slow drug release compared to partially cross-linked sample C, because of the difference in molecular relaxation and the free volume of the network. The same kind of difference is observed between samples E and F. But these samples show relatively higher release rates compared to C and D, because of the increase in water content in the synthetic composition itself. The values of n and k were obtained from the plot of $\ln(Mt/M\alpha)$ against $\ln(t)$ (Fig. 7) and are given in Table IV. The dimensional changes of the hydrogel capsules are given in Table V. The dimensional changes will influence the molecular relaxation and shrinkage, thereby controlling the drug-release behavior.

Mechanical Properties

The mechanical properties of polyacrylamide and poly(vinyl alcohol)-based hydrogels (semi-II-IPN and full-IPN) are shown in Figures 8–11 in the form

Table IV Results of Drug Release Test for Hydrogel IPNs

Sample Code	$K \times 10^7$		n		Total Drug Release Period (Days)		
	CV	BTB	CV	BTB	CV	BTB	Seq.
C	1174	16,610	0.92	0.84	289	37	1186
D	6	7,101	1.33	0.85	6900	63	826
E	9118	31,827	0.63	0.73	214	35	1020
F	3354	19,300	0.63	0.70	474	53	778

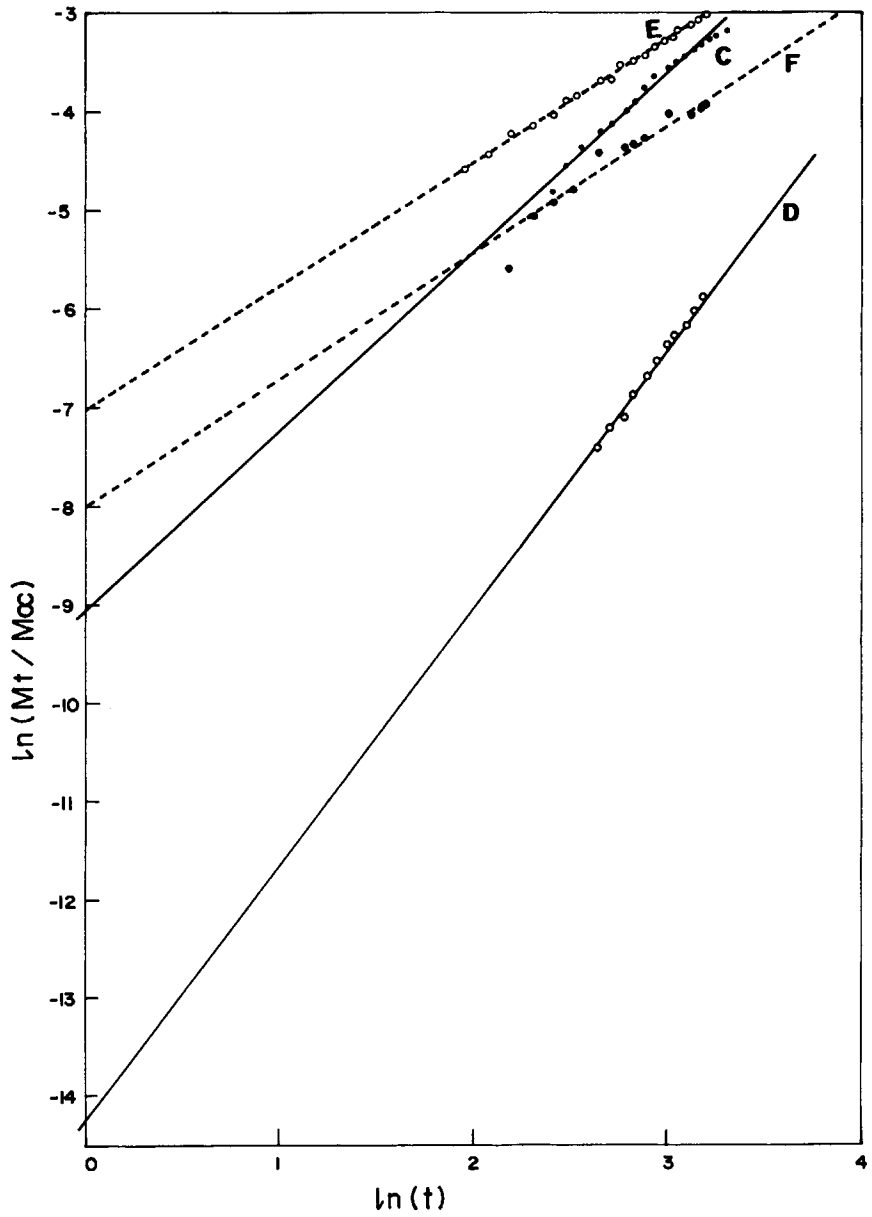


Figure 6 Drug-release vs. time curves for BTB-loaded capsules.

of compression–decompression curves. When the semi-IPN (sample C Figure 8) is subjected to compression, it takes 1883 g of load for 50% compression and is decompressed without rupture of the structure. This is indicative of the elasticity of the hydrogel sample. Figure 9 corresponds to sample D (full-IPN), which takes more load (2929 gm) for 50% compression. This indicates the enhanced mechanical strength for the full-IPN. A certain minimum number of cross-links is essential to impart and safeguard the properties of elasticity, with an increase in cross-link density (full-IPN). This introduces an element of rigidity into the network.

The compression and decompression curves corresponding to samples E and F are shown in Figures 10 and 11. From these figures, it is clear that the 50% compressional load of sample E is 1250 g less than for sample F (1750 g) because of the lower cross-link density. But the overall compressional load for samples E and F are less than for samples C and D, because of the increased spacing between cross-links with increased water content.

CONCLUSION

Interpenetrating polymer network (IPN) hydrogel capsules synthesized from polyacrylamide and

Table V Dimensional Changes of Hydrogel Capsules (cm)

	Actual Dimension			After Drying			After Swelling		
Sample	L	D	W	L	D	W	L	D	W
C	6.9	1.1	0.2	4.4	0.5	0.15	10.7	1.6	0.4
D	6.9	1.1	0.2	3.9	0.5	0.15	9.5	1.4	0.4
E	6.9	1.1	0.2	4.4	0.5	0.15	10.2	1.5	0.4
F	6.9	1.1	0.2	4.1	0.45	0.10	9.0	1.3	0.3

L = length; D = diameter; W = wall thickness of the capsules.

poly(vinyl alcohol) were found to have prolonged drug release. Semi-IPNs were found to exhibit a faster drug-release rate than that of the full-IPNs. Hydrogel disks synthesized by the present methods have significant mechanical strength and elasticity. Full-IPNs are found to have higher compressional

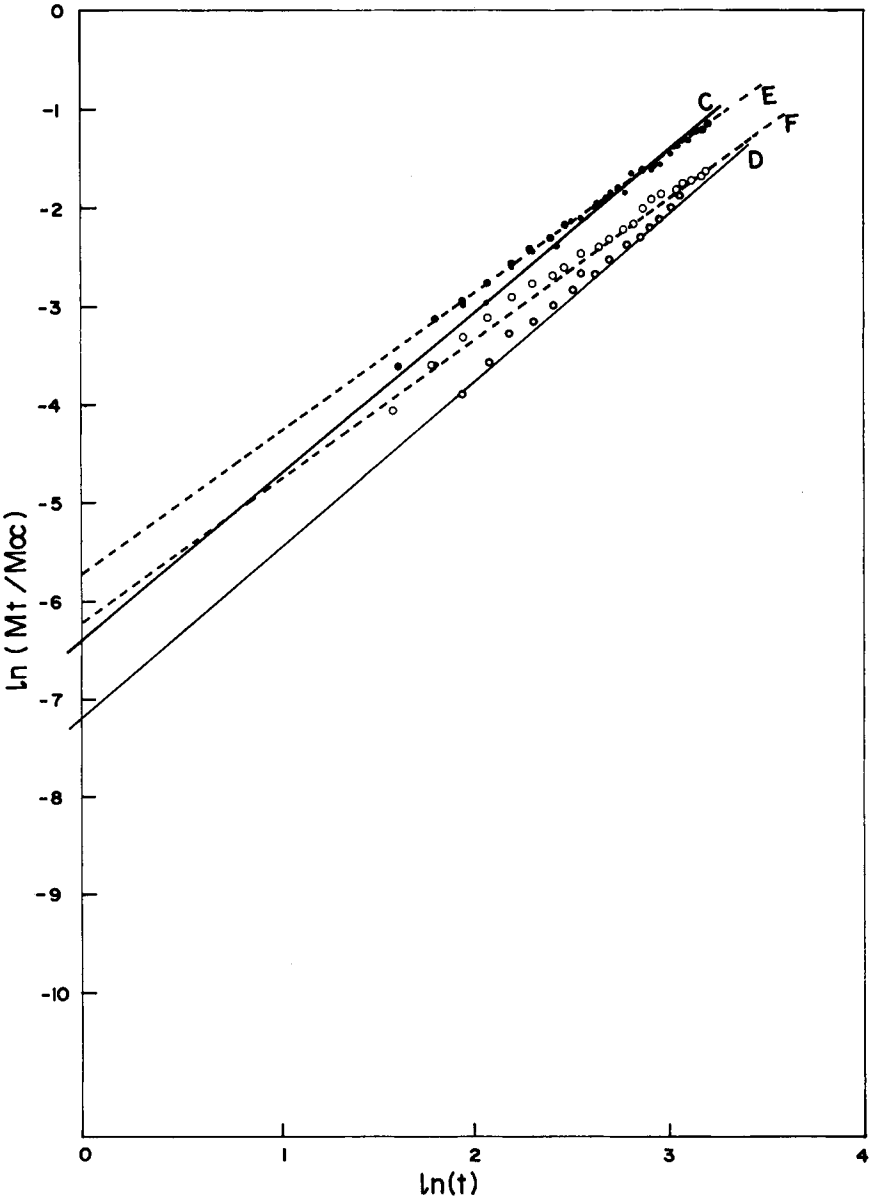


Figure 7 Plots of $\ln(Mt/M\alpha)$ against $\ln(t)$ BTB system.

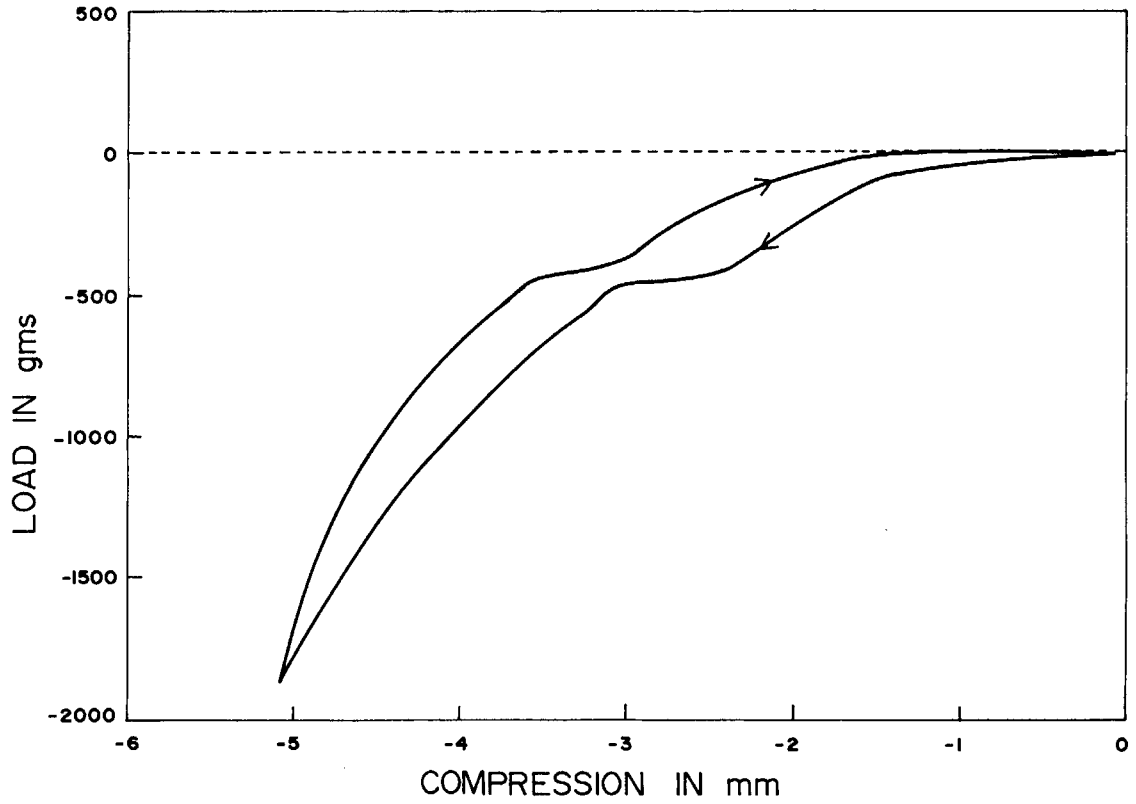


Figure 8 Compression–decompression curve (Sample C).

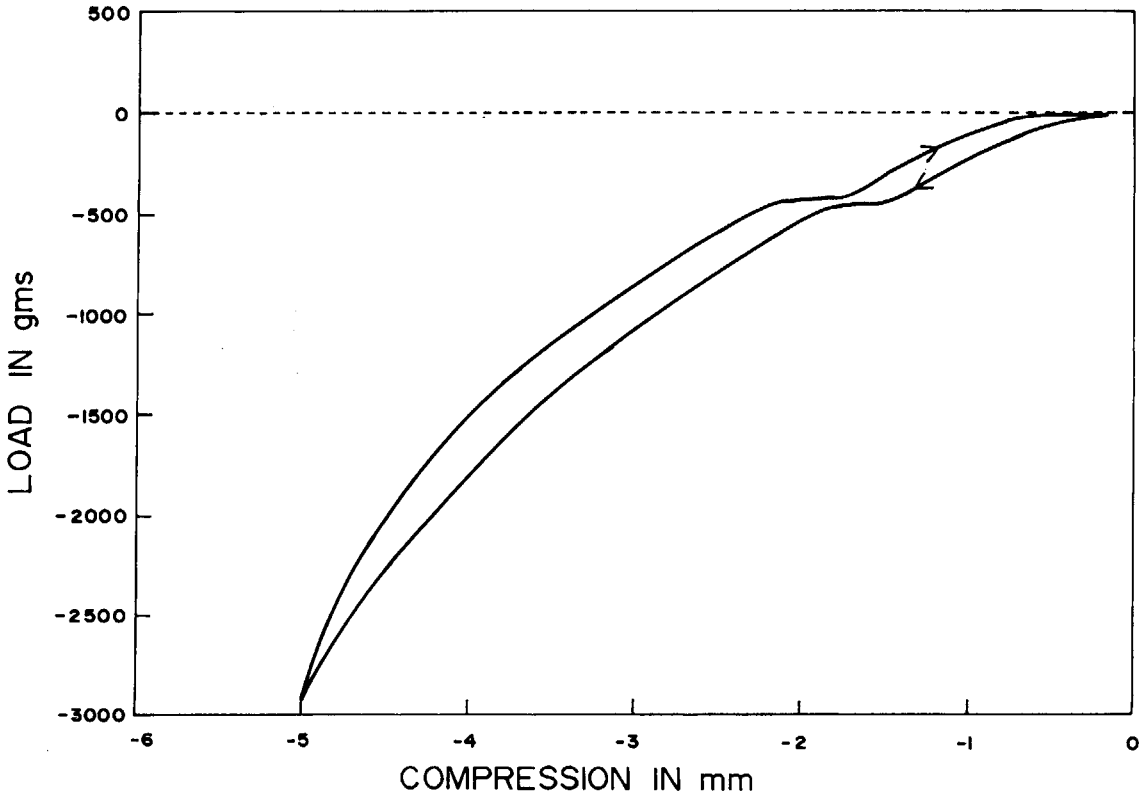


Figure 9 Compression–decompression curve (Sample D).

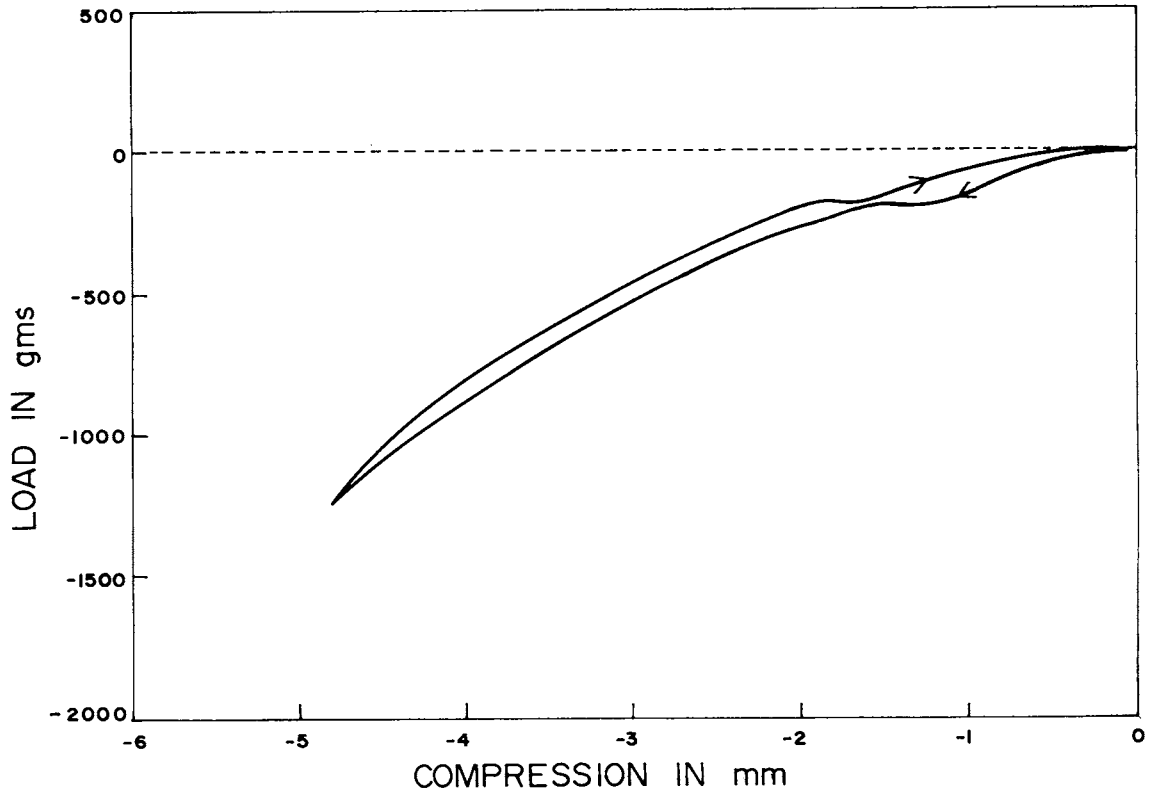


Figure 10 Compression–decompression curve (Sample E).

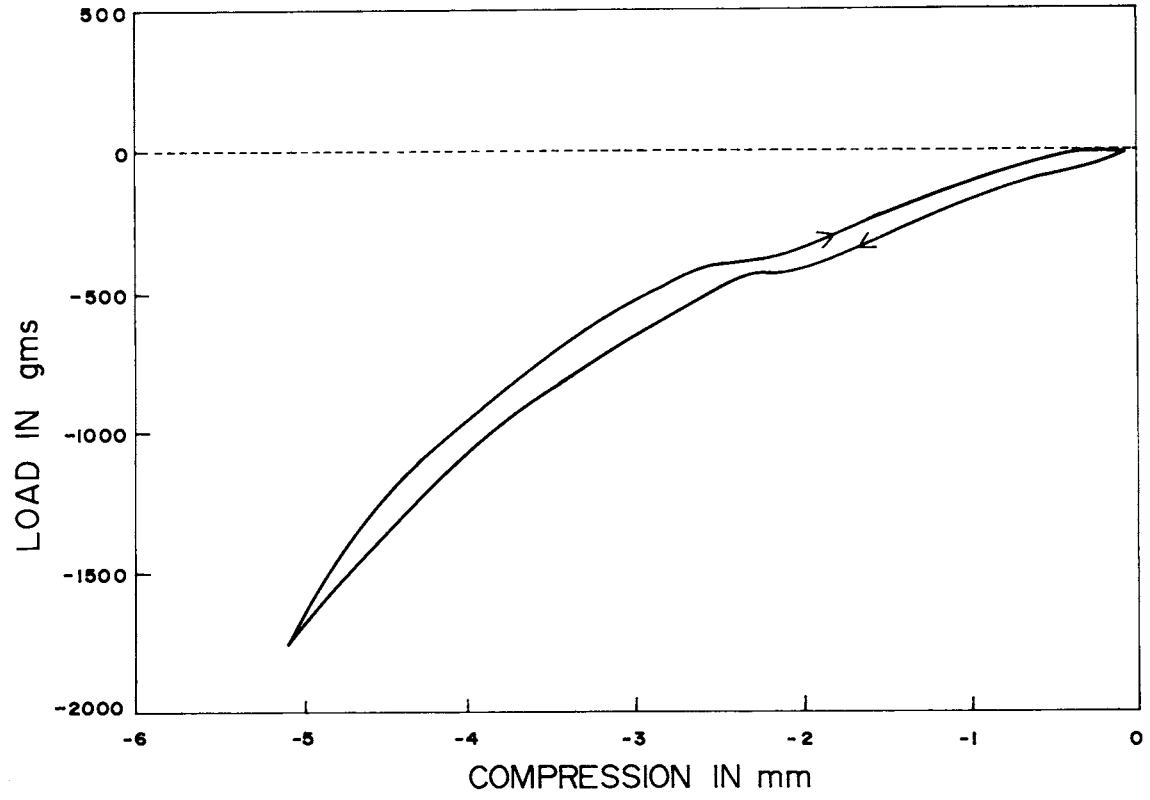


Figure 11 Compression–decompression curve (Sample F).

strength than that of the corresponding semi-II-IPNs. The present systems may find application as hydrogel drug-delivery systems for sustained release.

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