DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(7), 1239-1251 (1994)

IN-VITRO RELEASE OF ACETAMINOPHEN FROM SODIUM ALGINATE CONTROLLED RELEASE PELLETS

M.R. Rubio and E.S. Ghaly[1].
School of Pharmacy, Medical Sciences Campus, University of Puerto Rico, G. P. O. Box 5067, San Juan, PR 00936.

ABSTRACT

The production of spheres loaded with acetaminophen by the cross linking technique was achieved. The hydrophilic polymer sodium alginate which gels in presence of a cross linking ion was used as a matrix for the spheres production. Two processing variables were studied. The drug load in the formula which varied from 5% w/v to 20% w/v, and the cross linking agents used; calcium chloride, calcium acetate, and aluminum sulfate. Also the effects of the dissolution medium and the rotational speed of the dissolution apparatus on drug release were investigated. Spheres were compacted into 450 mg tablets without the aid of excipients. The drug release from spheres containing 20% w/v drug was 90% after 6 hours, while the drug release from compacts of these spheres was 90% after 12 hours. The mechanism of drug release from spheres and compacts containing 20% w/v drug and prepared with 5% w/v cross linking material

---

[1]To whom correspondence should be addressed.

followed the diffusion controlled model for inert porous matrix.

INTRODUCTION

Improvement of powder properties has always been a major concern for the tablet formulator. The wet and dry granulation are processes for the densification of powders that will produce a formulation with better characteristics for compression[1]. Besides dealing with the compressional problems, the formulator may want to have a control over the drug release from the tablet, and to achieve this additional treatments of the granules, spheres, or even the compacted tablet are necessary. The use of the cross linking method for spheronization will be of interest for both: conventional dosage forms, and controlled release systems[2-6].

Therefore in this research study spheres of acetaminophen were prepared by cross linking technique using the naturally occuring hydrocolloid sodium alginate and different cross linking agents. The effect of formulation variables on the release rates of acetaminophen from various systems has been investigated.

EXPERIMENTAL

Materials

The naturally occurring hydrophilic polymer used was sodium alginate (Fisher Scientific). The cross linking agents evaluated include: calcium chloride (Spectrum Chemical Mfg. Corp.); calcium acetate (Spectrum Chemical Mfg. Corp.); and aluminum sulfate (Fisher Scientific). The drug used was acetaminophen supplied by Warner Lambert Company.

TABLE 1

Composition of the Various Formulations Prepared

Batch No.	Polymer Level %	Drug Level %	Cross Linking Agent / Level
1	2	5	$CaCl_2$ / 5%
2	2	10	$CaCl_2$ / 5%
3	2	15	$CaCl_2$ / 5%
4	2	20	$CaCl_2$ / 5%
5	2	20	$Ca(CH_3COO)_2$ / 5%
6	2	20	$Al_2(SO_4)_3$ / 5%

Preparation of the Beads

Six formulations were prepared (Table 1). Batches size were of a total volume of 500 ml. The drug dispersion was made by heating 200 ml of distilled water to a constant temperature of 60° C, then 10 g of sodium alginate (2% w/v) was added over 1 minute to the heated stirred distilled water and the mixture was stirred until all the sodium alginate dissolved. Different levels of acetaminophen (100, 75, 50, or 25 g) were added to the sodium alginate solution and completed to volume (500 ml) with distilled water. With the aid of a simple device composed of 4 syringes each filled with 20 ml of the uniform dispersion, it was possible to drop the dispersion at an average rate of 4.5 ml/min from each syringe into a beaker Placed on a magnetic stirrer. The beaker contained 100 ml of a 5% w/v solution of the cross linking agent ($CaCl_2$, $Ca(CH_3COO)_2$ or $Al_2(SO_4)_3$). The agglomeration occurred instantaneously and every drop

turned into a sphere, strong enough to withstand the handling. The residence time of the sphere in the cross linking solution was 15 minutes for all batches. The beads were separated from the cross linking solution and dried in a conventional oven at 35° ± 2 °C.

Compaction of Beads

Beads were compacted into tablets using a Manesty B3B tablet rotary machine equipped with 12/32 inches flat faced tooling. Target hardness was 7-9 Kp and target tablet weight was 450 mg.

Characterization of the Beads

Loss on drying for spheres was performed by the Infrared Balance (Van-Kel Industries, Inc.) and particle size distribution was done by selecting a sample of 30 spheres per batch and measuring the diameter by a portable Dial Hand Gauge.

Acetaminophen Content Determination

The drug content was determined by powdering the obtained beads with mortar and pestle and the drug was extracted with distilled water. The absorbance was measured at a wavelength of 242 nm using a Beckman Spectrophotometer (Model DU 40).

In-Vitro Dissolution Testing

The release of acetaminophen from beads was measured by using the USP XX dissolution apparatus. The basket was rotated at 50 rpm at 37° C. The dissolution medium used was 900 ml of distilled water. Beads (200 mg) or tablets (450 mg) were placed in the basket and tested for dissolution over 6 hours (beads) or 24 hours (tablets). Samples were withdrawn at different time intervals and

drug concentration in each sample was determined by measuring the absorbance at the wavelength of 242 nm.

One batch was selected and tested for dissolution also in 900 ml of 0.1 N HCl or phosphate buffer (pH 7.4), and also tested at a rotational speed of 100 rpm or 150 rpm.

RESULTS and DISCUSSION

Beads were succesfully prepared from all formulations and were fairly round spheres. As shown in Table 2 their size ranges between 1.829-2.825 mm with an average diameter of 2.332 mm (Batches 1-4). The surface area of the beads varied from 453.2-578.0 mm^2 with an average of 508.7 mm^2 (Batches 1-4).

The higher the drug level, the higher the average size of the beads and the lower the surface area. The range of loss weight on drying was 2.6-7.4% and the drug content per batch are shown in Table 2.

The dissolution data showed that formula containing 5% w/v drug gave the highest drug release. Fifty percent of drug was released in 60 minutes, while formula with 20% w/v drug level released 50% of drug over 120 minutes, as shown in Figure 1. The increase in drug release from beads containing low drug level may be due to the increase in surface area, since constant weight of spheres (200 mg) was used for testing dissolution for all batches.

A similar behavior was observed when tablets compacted from beads were tested for dissolution (Figure 2). In this condition the surface area was constant for all batches. However spheres containing low level of drug (5% w/v) were difficult to compact and produced tablets of only 4 Kp hardness and during dissolution

TABLE 2

Characteristics of the Produced Spheres

Batch No.	Diameter in mm ± SD	Number of Spheres in 200 mg Sample	Surface Area of the Sample	Loss on Drying %	Amount of Drug mg/g ± SD
1	1.829 ± 0.173	55	578.0	5	464.9 ± 4.1
2	2.239 ± 0.142	33	519.7	7.4	663.3 ± 5.5
3	2.434 ± 0.248	26	483.9	5	776.8 ± 9.5
4	2.825 ± 0.099	18	453.2	3	853.9 ± 5.2
5	2.818 ± 0.228	18	449.1	2.6	834.3 ± 3.2
6	2.804 ± 0.150	18	446.6	3.3	816.6 ± 0.9

testing the tablet disintegrated into individual spheres and gave high drug release compared to other formulations.

Figure 3 shows the release profiles of spheres containing 20% w/v drug level and prepared by the use of different cross linking agents. No significant difference was observed among the different formulas and the same results were true for tablets compacted from those spheres.

Figure 4 shows the effect of the hydrogen ion concentration of the dissolution medium on drug release from spheres containing 20% w/v (Batch 1). The drug release in 0.1 N HCl or distilled water was similar,

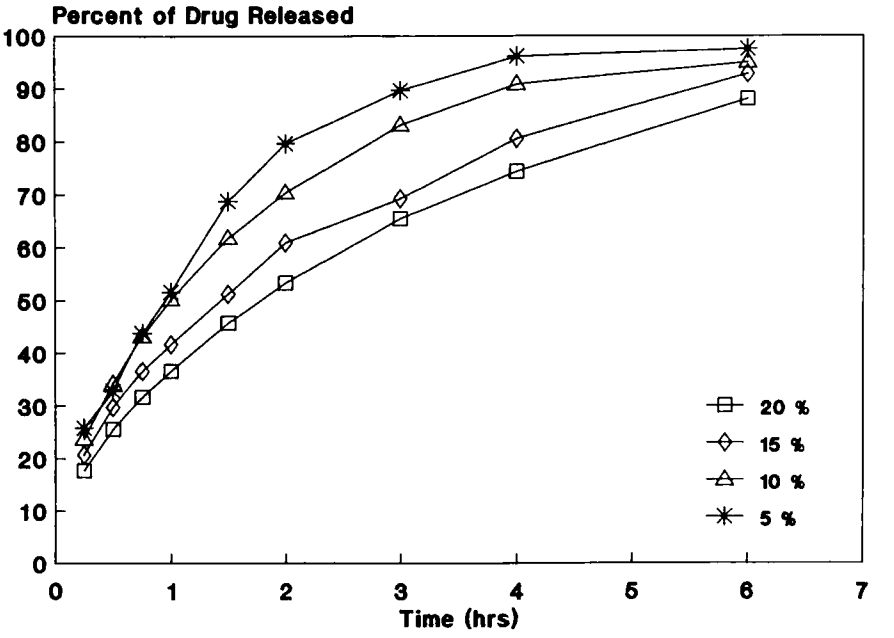

FIGURE 1

Percent of Drug Released versus Time for Spheres Prepared with 5% w/v Calcium Chloride Cross Linking Material and Containing : 20% w/v Drug, 15% w/v Drug, 10% w/v Drug, and 5% w/v Drug.

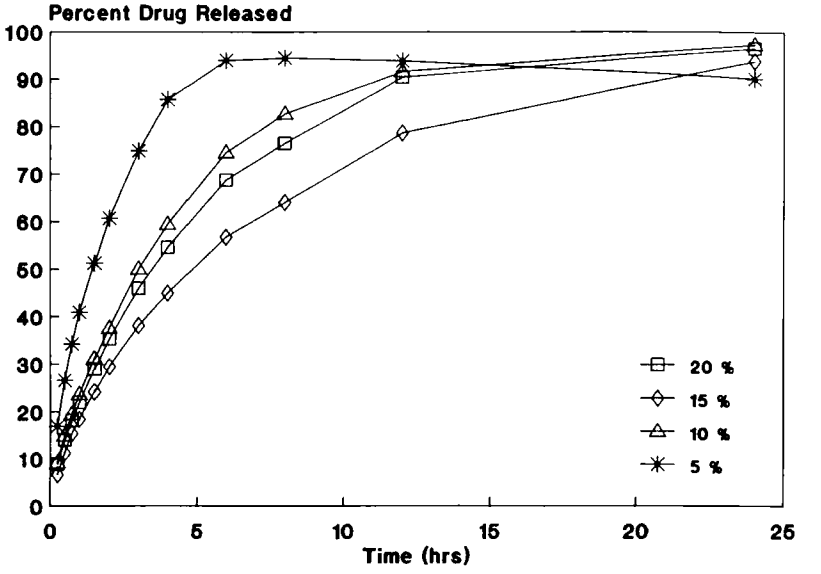

FIGURE 2

Percent of Drug Released versus Time for Tablets Compacted from Spheres Prepared with 5% w/v Calcium Chloride Cross Linking Material and Containing : 20% w/v, 15% w/v, 10% w/v, or 5% w/v Acetaminophen.

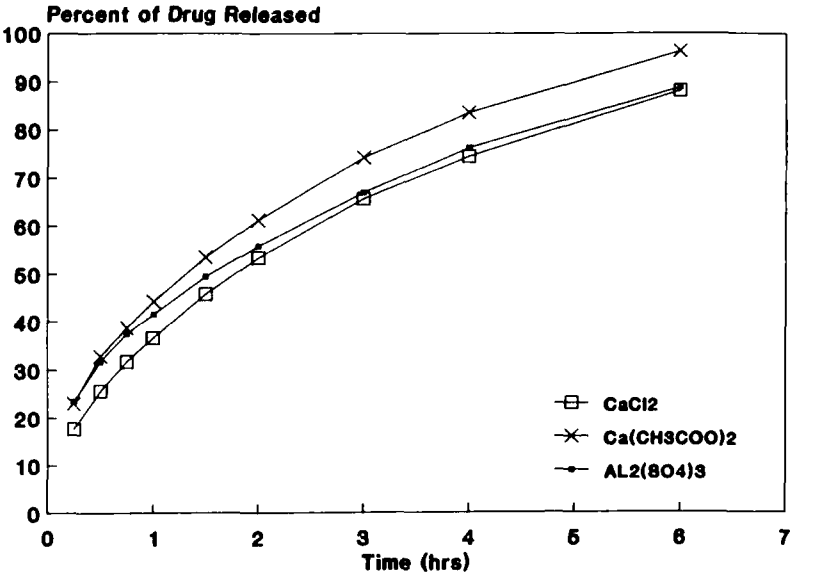

FIGURE 3

Effect of Cross Linking Material on Drug Release from Spheres Containing 20% w/v Acetaminophen and Prepared with 5% w/v Cross Linking Materials: Calcium Chloride; Calcium Acetate; Aluminum Sulfate.

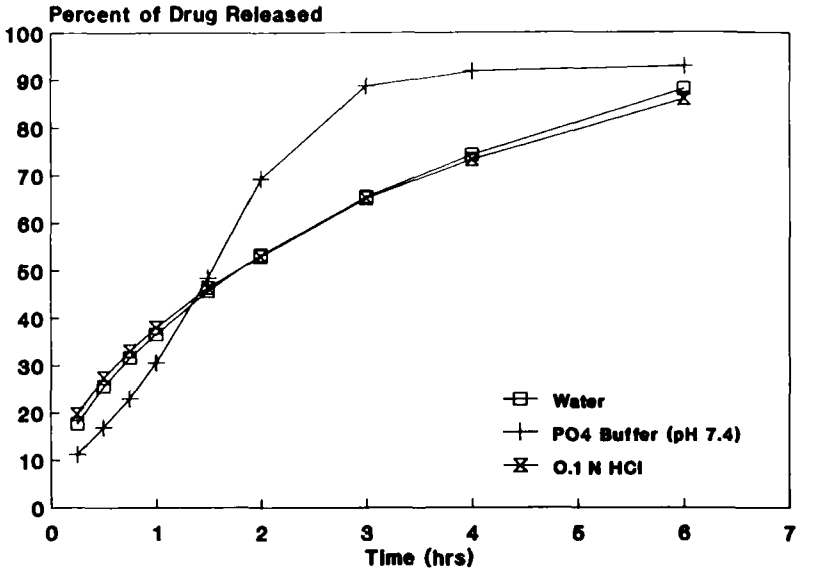

FIGURE 4

Effect of Hydrogen Ion Concentration of Dissolution Medium on Acetaminophen Release from Spheres Containing 20% w/v Drug and Prepared with 5% w/v Calcium Chloride Cross Linking Material: Distilled Water; Phosphate Buffer pH 7.4; 0.1 N HCl.

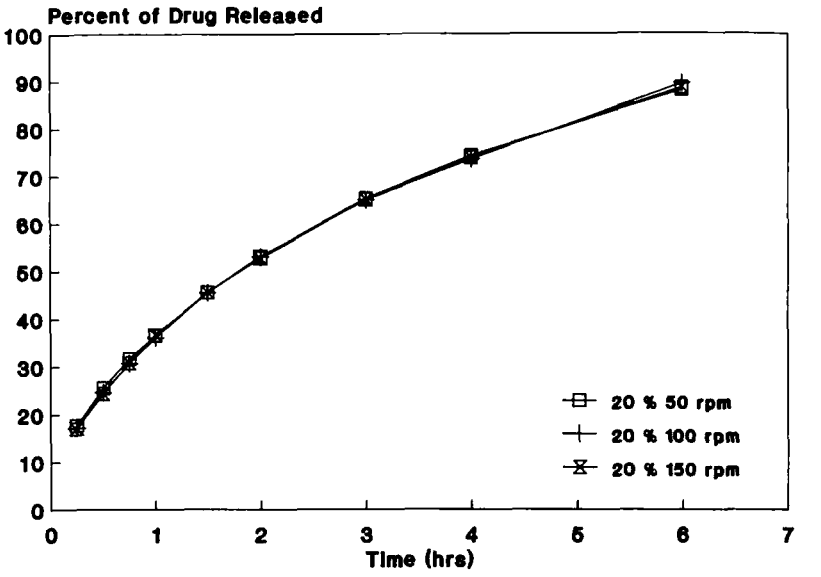

FIGURE 5

Effect of Rotational Speed on Drug Release from Spheres Containing 20% w/v Acetaminophen and Prepared with 5% w/v Calcium Chloride Cross Linking Material: 50 rpm; 100 rpm; 150 rpm.

while in phosphate buffer pH 7.4 the drug release behavior was completely different. The drug release was slow in the early time of testing dissolution, however after 90 minutes all the drug was liberated at a very fast rate. The same results were true also for tablets compacted from the same spheres.

In general the drug release from spheres was higher than from compacts containing the same spehres. The drug release from spheres containing 20% w/v acetaminophen and prepared with 5% w/v $CaCl_2$ as cross linking agent was 90% after 6 hours of testing dissolution, while the drug release from compacts of the same spheres was 90% after 12 hours of testing dissolution.

Figure 5 shows the dissolution profiles of acetaminophen from spheres containing 20% w/v drug, 2% w/v

sodium alginate, and 5% w/v calcium chloride as a cross linking agent, tested for dissolution at different rotational speed (50, 100, and 150 rpm). The drug release profile was coinciding under the different test conditions, indicating that the rotational speed of the dissolution apparatus has no effect on drug release since the spheres formed matrix and the drug is embedded in it.

The drug release from an inert matrix is described by Higuchi's equation[7]

$$Q = [D\epsilon/\tau\ (2A-\epsilon C_s)\ C_s t]^{1/2} \quad (1)$$

in which Q is the amount of drug released per unit area of exposed surface of the matrix, D is the diffusion coefficient of the drug in the matrix, τ is the tortuosity, ϵ is the total porosity of the matrix after the drug has been extracted, A is the amount of drug in the matrix, C_s is the solubility of the drug in the polymeric matrix, and t is the time. An approximation of Higuchi's equation can be obtained by plotting the percent of drug released versus the square root of time as expresed by equation (2).

$$Q = Kt^{1/2} \quad (2)$$

By taking the logarithm of both sides of equation (2), one obtains

$$\log Q = \log K + \tfrac{1}{2} \log t \quad (3)$$

A plot of log Q versus log t must give a straight line with a slope of 0.5, if the drug release followed the square root of time plot of Higuchi.

Figure 6 shows the plot of cumulative percent drug released versus square root of time for tablets compacted of spheres and containing different levels of drug. A linear relationship was obtained over 12 hours from tablets containing 20% w/v drug, whereas tablets containing 5% w/v drug gave a linear only over 4 hours, after which the tablets disintegrated into beads and

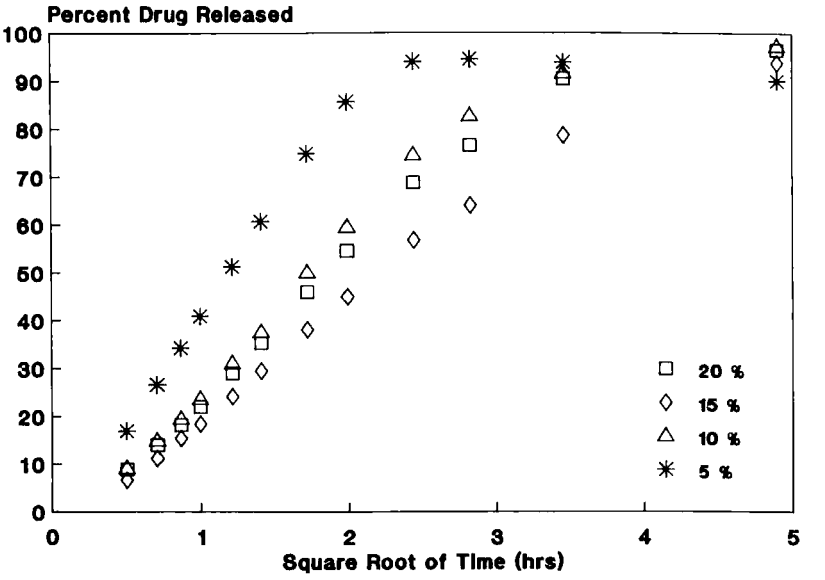

FIGURE 6

Square Root of Time Plots for Spheres Prepared with 5% w/v Calcium Chloride Cross Linking Material and Containing Different Levels of Drug: 20% w/v; 15% w/v; 10% w/v; 5% w/v.

exposed larger surface area to dissolution medium and the drug release was increased.

Figure 7 shows the plot of equation (3) for spheres containing 20% w/v drug level and as depicted in it, a straight line with slope of 0.5 was obtained. These data indicated that the drug release from spheres containing 20% w/v acetaminophen followed the diffusion controlled model for inert porous matrix as described by the Higuchi's square root of time equation. The same results were true for the 15% w/v and 10% w/v formulations. However, a plot of log Q versus log t for the 5% w/v preparation gave a curved line.

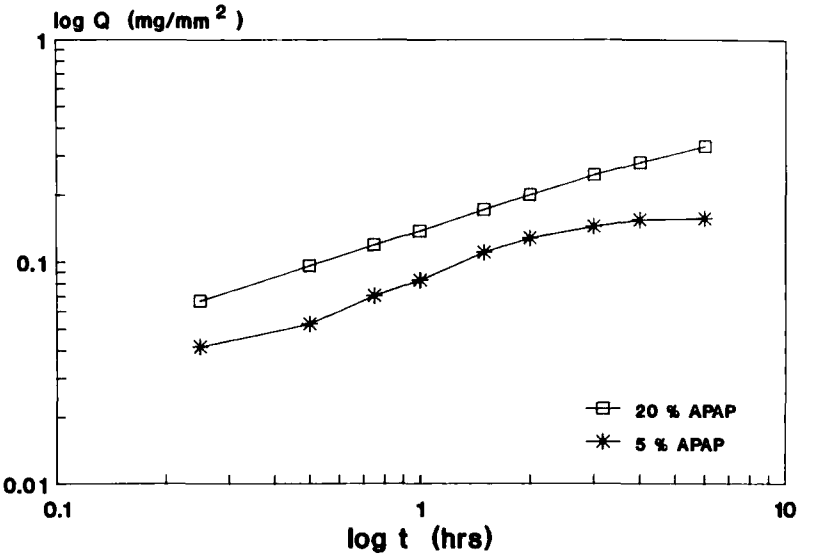

FIGURE 7

Log Cumulative Amount of Acetaminophen Released per Unit Surface Area versus Log Time Plot for Spheres Containing 20% w/v Acetaminophen and Prepared with 5% w/v Calcium Chloride Cross Linking Material.

CONCLUSIONS

1. Beads containing low drug level and prepared with 5% w/v cross linking material were of smallest bead size and largest surface area.
2. Smaller bead size resulted in faster drug release.
3. The cross linking materials tested (calcium chloride, calcium acetate, and aluminum sulfate) had no effect on the properties of beads or the drug release from the beads.
4. Changing the rotational speed of the dissolution apparatus had no effect on the drug release from spheres containing 20% w/v and prepared with 5% w/v cross linking material.

5. The drug release in distilled water or 0.1 N HCl from spheres or compacts from spheres containing 20% w/v drug is similar, the drug release from spheres or compacts in phosphate buffer (pH 7.4) was less than in water or in 0.1 N HCl in the first 90 minutes then became higher than the other two dissolution mediums.
6. The mechanism of drug release from spheres containing 20% w/v acetaminophen and prepared with 5% w/v cross linking materials and compacts of the same spheres followed the diffusion controlled model for inert porous matrix.
7. Spheres were successfully prepared from sodium alginate and cross linking material. Both spheres and compacts of spheres can offer the formulator control over the drug release.

REFERENCES

1. L. Lachman, H.A. Lieberman, and J.L. Kanig, "The Theory and Practice of Industrial Pharmacy", Lea & Febiger, Philadelphia, 1986.
2. H. Tanaka, M. Matsumura, and I.A. Veliky, Biotech. Bioeng., 26, 53 (1984).
3. T.N. Julian, G.W. Radebaugh, and S.J. Wisniewski, J. Controlled Release, 7, 165 (1988).
4. R. Bodmeier and O. Paeratakul, J. Pharm. Sci., 78, 964 (1989).
5. A.A. Badwan, A. Abumalooh, E. Sallam, A. Abukalaf, and O. Jawan, Drug Dev. Ind. Pharm., 11, 239 (1985).
6. A.F. Stockwell, S.S Davis, and S.E. Walker, J. Controlled Release, 3, 167 (1986).
7. A. Martin, J. Swarbrick, and A. Cammarata, "Physycal Pharmacy", Lea & Febiger, Philadelphia, 1983.