

POLYMERIC FILMS AS TOPICAL DRUG DELIVERY SYSTEM FOR ANTIBIOTICS AND LOCAL ANAESTHETICS

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ABSTRACT

The utilization of cellulose acetate butyrate films as a topical drug delivery system for chloramphenicol and lignocaine hydrochloride was investigated. The effect of plasticizers and drug concentration on the In-Vitro release of drug as well as on the physico-mechanical properties of the films have been examined. The drug release data were kinetically studied and were found to follow the diffusion controlled release model. The incorporation of either dimethyl phthalate or diethyl phthalate afforded the optimum rates of release and optimum water vapor transmission rates and exhibited acceptable mechanical properties. The release rate of chloramphenicol was found markedly higher than that of lignocaine hydrochloride.

The effect of plasticizers on drug release is more pronounced in case of water insoluble drug than the water soluble one.

INTRODUCTION

Numerous drug-polymer delivery systems have been proposed for the purpose of releasing biological active agents into the surrounding medium at a constant release rate¹. Many of these preparations, have been available as catheters coated with antibiotic-impregnated polymers², long-acting implants^{3,4} and preparations for dermatological applications^{5,6}.

The potential uses of polymeric films of ethyl cellulose and polyamide resins for aerosol dosage form⁷, prolongation of the release of medicaments in eye administration⁸, management of wounds and surgical practice have been studied. Drug release from inert matrices play an important role in percutaneous absorption especially when solubility of the drug in the matrix is very low^{10,11}. The drug release rate from drug-polymer delivery system was significantly affected by altering the polymer type, amount of drug in the matrix and additives^{12.13.14}. Plasticizers are often added to polymeric films to reduce brittleness, improve flow, impart flexibility and increase toughness.

The efficiency of plasticizers, its compatibility with the polymer and performance can be evaluated by different means. One of these means, is the measurement of the physico-mechanical properties of the plasticized free unmedicated film samples¹⁵⁻¹⁷. Concerning the effect of plasticizers on the water vapor permeation through polymeric films. Crawford and Esmerian¹⁸ found that the addition of plasticizers generally lowered the water vapor transmission rate moisture absorption and water permeation through cellulose acetate phthalate films. Sciarra and Patel¹⁹ showed that the film forming agent as well as plasticizers affected drug release from polymeric films. Okor²⁰ studied the influence of concentration of the hydrophilic plasticizers on permeability of two acrylatemethacrylate copolymers films. He said that permeability is dependent on the hydrophilicity of both the plasticizer and polymer together.

Only a limited amount of work has been reported concerning the effect of plasticizers on cellulose acetate butyrate films in presence of drugs.

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This study was designed to : (a) obtain information on the effect of various plasticizers on some properties of cellulose acetate butyrate drug-free films, and (b) develop a suitable drug delivery system for the topical application of antibiotic and local anaesthetics. Four plasticizers were selected for this study : dimethyl phthalate, diethyl phthalate, propylene glycol 2000 and castor oil.

EXPERIMENTAL

Materials :

Cellulose acetate butyrate; 17% butyrate, 29.5% acetyl, 1.5% hydroxyl, cat # 077 (scientific polymer products, Inc., Ontario, New York), Chloramphenicol grade supplied by CID Co., Egypt), Lignocaine hydrochloride (Pharmaceutical grade supplied by the Nile Co., for Pharmaceuticals and Chemical Industries, Egypt). All other chemicals were analytical reagent grade and were used as received.

Film Preparation :

Solutions were prepared in chloroform to contain 4% w/v total solids. Five ml of the prepared solutions were poured into circular Teflon mould (7.3 cm in diameter, and 1 mm in depth). The mould was covered with an inverted funnel to control solvent vaporization. Solvent was permitted to evaporate for 24 hours at room temperature. The dried films were then transferred to a desiccator containing silica gel for further 24 hours before test. Polymeric films containing 5,10,15 and 20% w/w of each of the aforementioned plasticizers were prepared. Medicated films were prepared at 2% w/w drug level.

Determination of Film Thickness :

Film thickness was measured at 10 random points on the film, by means of a micrometer, and the mean thickness was calculated.

Water Vapor Transmission :

Screw capped glass cups with a circular hole (7.3 cm in diameter) were uniformly filled with sufficient amount of dry anhydrous calcium chloride. A circular piece of the film was sealed to the hole of the cup and fixed with a glass ring. The cups were then placed in a desiccator containing water saturated with ammonium chloride at 25°C (R.H. 79 mm Hg). The cups were periodically weighed and the increase in weight was calculated.

Mechanical Properties of the Films :

The load deformation behaviour of cellulose acetate butyrate free films was determined by clamping a film strip (2 x 4 cm) between two jaws of tensile-testing or dynamometer²¹ machine. Weights were added gradually to the movable lower jaw and the corresponding elongation in the film was automatically recorded in the machine chart until the break point of the film. The load-deformation curves were plotted. Modulus of elasticity, elongation at break and the tensile strength were calculated.

Drug Release from Medicated Films :

Release studies were carried out at 37°C using 300 ml of isotonic phosphate buffer (pH 6.8) as the release medium. The USP basket method was employed at 50 rpm. The medicated film was cut into 4 equal parts and placed in the basket. Aliquots (5 ml) were withdrawn at time intervals and replaced by equal volumes of the fresh medium. The released amount of drug was determined spectrophotometrically at 278 nm for chloramphenicol or 262 nm for lignocaine hydrochloride using fresh medium as a blank.

RESULTS AND DISCUSSION

Drug-free as well as medicated cellulose acetate butyrate films with thickness of about 50 μm were prepared. Water vapor transmission (W.V.T.) in mg/cm^2 , hour through the free films was studied adopting the following equation :

$$(\text{W.V.T.}) = \frac{\text{gm}/\text{a}}{t} = \frac{\text{slope of linear plot of gm versus t.}}{(a)}$$

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where, gm = weigh change in grams, t = time in hours during which change occurred, and a = area of the film exposed to W.V.T. in cm^2 . Figure 1 showed the effect of various plasticizers at different levels (5-20% w/w) on W.V.T. through the free films. Propylene glycol had essentially no effect on the water vapor transmission rate but the use of either diethyl phthalate or castor oil resulted in a rate more than that of unplasticized film. Maximum W.V.T. rates were found at a 5% plasticizer level. The highest levels of plasticizer (15 and 20%) were found to have considerably less effect on the rate. This result may be attributed to the maximum saturation effect for the polymer chains to hold more than 15-20% plasticizer concentration.

The effect of plasticizers at different level on the mechanical properties of cellulose acetate butyrate free films was investigated. The following mechanical characteristics were determined from the load-deformation curves and presented in Table 1 : the elongation at break (rupture) in cm%, ultimate tensile strength (maximum load applied on the film per area) and the modulus of elasticity (from the slope of the curves.)

The results summarized in Table 1 and Fig. 2 show that the addition of either castor oil or diethyl phthalate at most levels gave higher percent elongation values of the films than the other plasticizers comparing with the control films. It is worthy to note that less applied loads were required to produce the same effect with diethyl phthalate. The use of dimethyl phthalate at 20% level exhibited the highest elongation value compared to the various plasticizers or the different tested levels. Generally, the selection of plasticizer was more important than the level to affect the film mechanical properties. The use of dimethyl phthalate at 20% level was the only exception of this statement. The tested plasticizers can be arranged according to their abilities to increase the elasticity of

cellulose acetate butyrate films as diethyl phthalate > castor oil > dimethyl phthalate > propylene glycol. The previous arrangement was based on the increase in elongation as well as the decrease in modulus of elasticity.

Abdel-Bary et al²² studied the effect of the nature of the vehicle and pH on the rate of drug release from ethylcellulose, carboset 525, Eudragit RS.PM and polymethylmethacrylate polymeric films. They used salicylic acid and sodium salicylate as model drugs.

Nouh et al²³ studied the release rate of nystatin from casted film of amphotericin-B. Also, they investigated the role of surfactants in enhancing the drug release.

Drug release kinetics from cellulose acetate butyrate medicated films were studied according to zero order, first order and diffusion-controlled mechanism²⁴. The high correlation coefficients obtained from the linear regression analysis of the amount released (mg/cm^2) versus the square root of time attest the diffusion-controlled mechanism²⁵. In this work, the amount of drug released from the medicated polymeric films per unit area (mg/cm^2) was plotted against the square root of time (hours).

The incorporation of plasticizers (5-20%) was found to increase chloramphenicol release from its medicated films (Figs. 3-6). There is a direct correlation between the plasticizer concentrations and drug release. The tested plasticizers can be arranged according to their effects as follows : dimethyl phthalate > diethyl phthalate > propylene glycol > castor oil > unplasticized films. The differences in release rates among the different plasticizers can be attributed to the hydrophobicity and molecular weight of the added plasticizer as well as to the drug solubility in this plasticizer.

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In this respect, castor oil acts as aqueous release medium repellent and hence, retard the drug release. Propylene glycol due to its high molecular weight will be too difficult to interpose itself between the polymer the polymer chains. Thus, propylene glycol did not significantly affect the film plasticity or permeability. In addition, chloramphenicol is soluble in castor oil and the latter interpose itself between the polymer chain hence chloramphenicol is to difficult to be released from the polymer matrix. Water insoluble plasticizers, although not capable of increasing porosity, of the film, have been found to play a role as solubility modifiers²⁶. A result which confirms the exclusion of kinetic first order dependence of drug release profile. This result may be attributed to the fact that the permeation rate of the release medium through the polymer matrix is the major determinant step in the release process. Fig. 7 shows the effect of drug concentrations (5-15%) on the diffusion controlled release. It was found that 5% of the drug increase initially, then 10% and 15% concentrations increased the release much more than 5% concentration of the drug.

Lignocaine hydrochloride was incorporated in cellulose acetate butyrate containing dimethyl phthalate; diethyl phthalate; propylene glycol and castor oil as plasticizers at 5-20% levels. The drug release from its medicated films was found to be increased as the plasticizer level increases (dimethyl phthalate and diethyl phthalate) (Fig. 8,9). Drug release rate was maximum at 20% plasticizer level.

The release rate of lignocaine hydrochloride from cellulose acetate phthalate films in presence of propylene and castor oil as plasticizers at (5-20%) levels (Fig. 10,11) was found slower than the release from unplasticized films. Fig. 12 showed that as the concentration of the drug increased, its release also, increased.

The release rate of lignocaine hydrochloride (water soluble drug) from unplasticized cellulose acetate butyrate films was higher and uniform than release rate of chloramphenicol (water insoluble drug) Tables 2 and 3. It was found from Tables 2,3 that the additions of plasticizers within the polymeric casted films, increased the release rate of lignocaine hydrochloride (water soluble drug) in case of using dimethyl phthalate and dimethyl phthalate only. But on the other hand the addition of castor oil/and propylene glycol as plasticizers did not increase the release rate inspite of increasing the concentration of the plasticizers from 5% to 20% w/w. in comparison of the release rate of lignocaine hydrochloride in presence of (5-20%) plasticizer level with chloramphenicol release rate in presence of the same plasticizers level; it was found that lignocaine hydrochloride had the slower release rate than that of chloramphenicol (Tables 2,3).

In conclusion, the release characteristics of a drug from cellulose acetate butyrate casted films, was dependent on the solubility of the drug and the addition of plasticizer might not increase the release rate from the medicated casted films whatever it was hydrophilic or hydrophobic in nature.

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Table 1 - Mechanical Properties of Plasticised Cellulose Acetate Butyrate Free Films .

Plasticizer Used	Plasticizer Level % w/w	Modulus of Elasticity Kg/cm ²	Elongation %	Ultimate Tensile Strength Kg/cm ² . 10 ⁻³
Control	---	0.960	6.25	3.488
Dimethyl	5	1.088	6.250	4.501
Phthalate	10	1.000	5.000	3.848
	15	0.880	5.830	3.856
	20	0.857	10.000	3.573
Diethyl	5	0.880	4,580	3.264
Phthalate	10	1.020	8.130	4.245
	15	0.928	9.150	3.556
	20	0.864	8.130	3.436
Propylene	5	0.992	4.580	3.680
glycol	10	1.088	4.580	3.856
	15	1.120	5.830	3.127
	20	1.133	4.530	3.367
Castor	5	0.914	8.130	3.556
Oil	10	1.056	5.000	4.398
	15	0.880	6.900	3.625
	20	0.928	7.500	3.797

Table 2: Effect of Plasticizers on the Release Characteristics of Chloramphenicol from Cellulose Acetate Butyrate Films.

Plasticizers Used	0%	5%	10%	15%	20%
Control	r*	0.9457	-	-	-
	k**	0.3017	-	-	-
	Inter.***	0.0689	-	-	-
Dimethyl phthalate	r*	0.9990	0.9775	0.9967	0.9705
	k**	1.8119	2.6964	2.1119	8.5690
	Inter.***	0.5355	0.5370	0.6305	1.4086
Diethyl phthalate	r*	0.9646	0.9823	0.9757	0.9756
	k**	0.4012	2.2101	1.5333	4.5137
	Inter.***	0.8882	0.0115	0.2383	0.1705
Propylene glycol	r*	0.9924	0.9905	0.9866	0.9653
	k**	0.2985	0.5375	0.6601	2.1589
	Inter.***	0.2071	0.0654	0.3032	0.7367
Castor oil	r*	0.8977	0.9327	0.9782	0.9814
	k**	0.3315	0.5244	0.9583	0.9393
	Inter.***	0.0677	0.0701	0.5742	0.5689

r* : Correlation coefficient
k** : Release rate constant.hr.⁻¹
Inter.*** : Intercept.

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Table 3: Effect of Plasticizers on the Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Films.

Plasticizers Used	0%		5%		10%		15%		20%	
	r**	k***	r**	k***	r**	k***	r**	k***	r**	k***
Control	0.9853	0.4038	-	-	-	-	-	-	-	-
	Inter. 0.2053									
Dimethyl phthalate	0.9825	0.7047	0.9825	1.6779	0.9828	1.1019	0.9814	2.5762	0.9822	3.3494
	Inter. 0.4375		Inter. 1.1019		Inter. 1.7176		Inter. 2.2091			
Diethyl phthalate	0.9642	0.2380	0.9798	0.6310	0.9726	0.6461	0.9676	0.7013	0.9676	0.7013
	Inter. 0.1637		Inter. 0.4558		Inter. 0.4839		Inter. 0.5374			
Propylene glycol	0.9809	0.1508	0.9939	0.2207	0.9793	0.2018	0.9931	0.4004	0.9931	0.4004
	Inter. 0.0968		Inter. 0.1022		Inter. 0.1115		Inter. 0.1992			
Castor oil	0.9361	0.1425	0.9666	0.2108	0.9755	0.2242	0.9762	0.2882	0.9762	0.2882
	Inter. 0.0789		Inter. 0.1262		Inter. 0.1359		Inter. 0.1653			

* : Correlation coefficient
 ** : Release rate constant hr.⁻¹
 *** : Intercept.

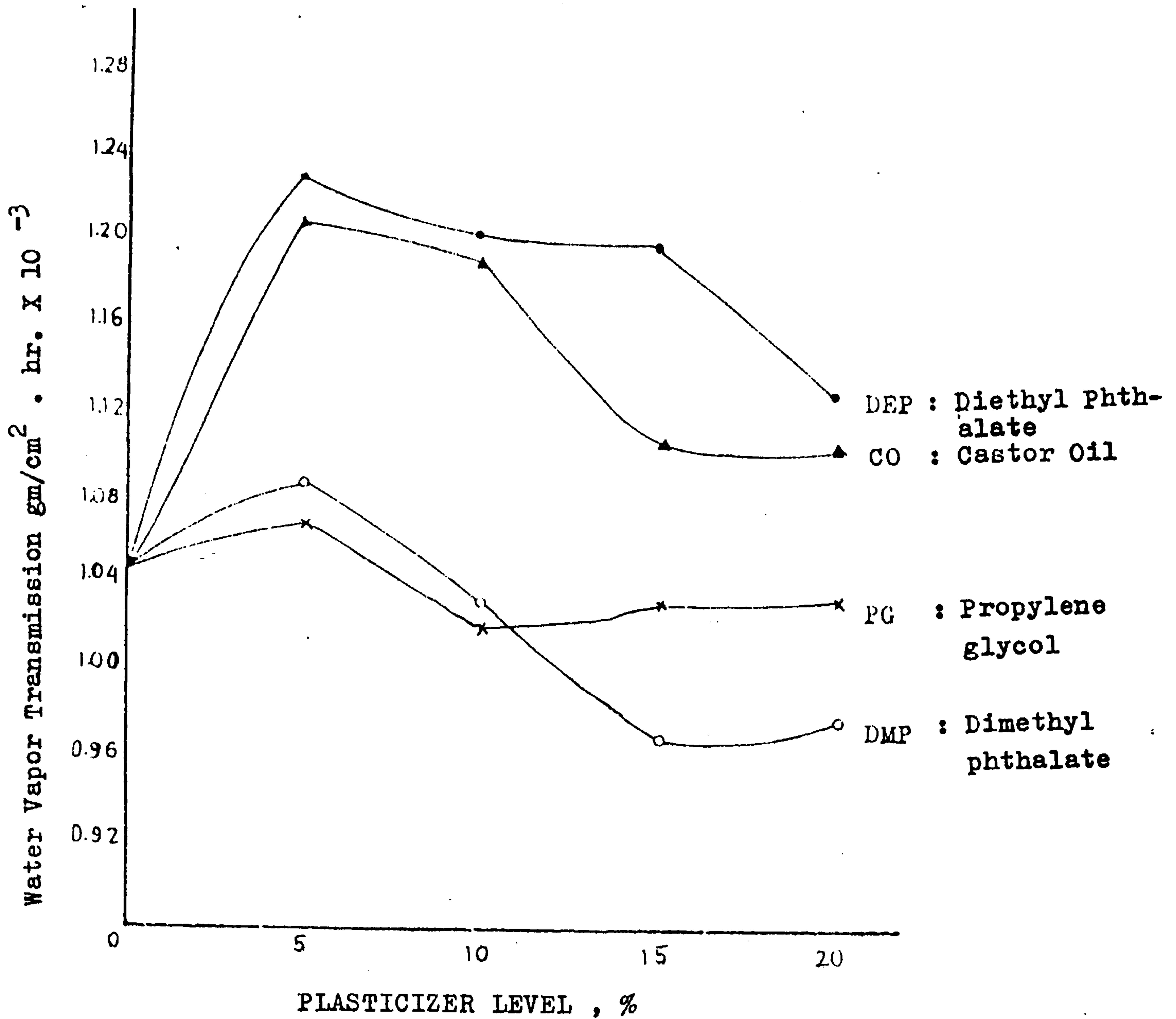


Figure 1- Water Vapor Transmission Characteristics of Plasticized Cellulose Acetate Butyrate Drug-Free Films.

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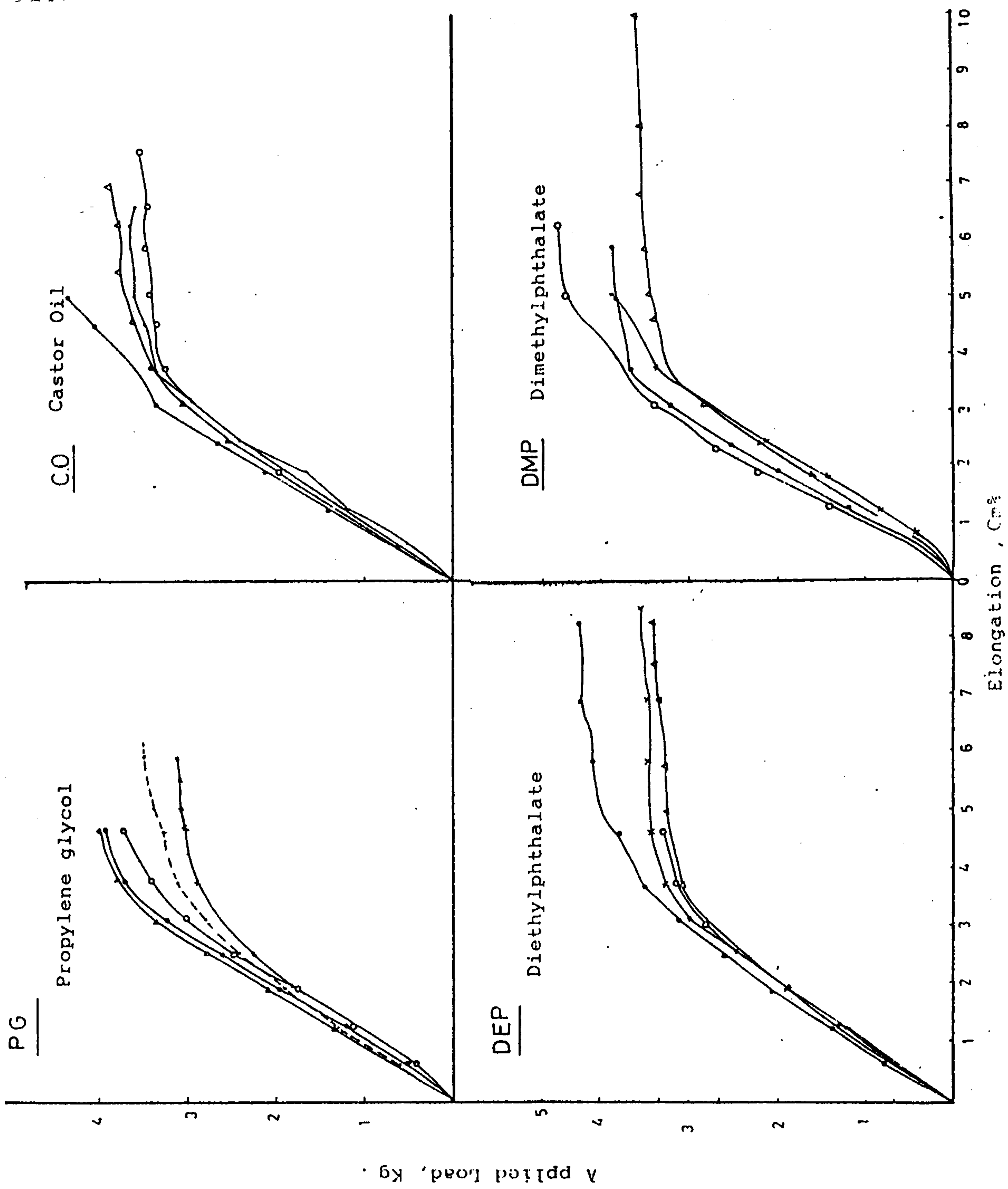


Figure 2 - Load- Deformation Curves of Plasticized cellulose Acetate Butyrate Free Films .

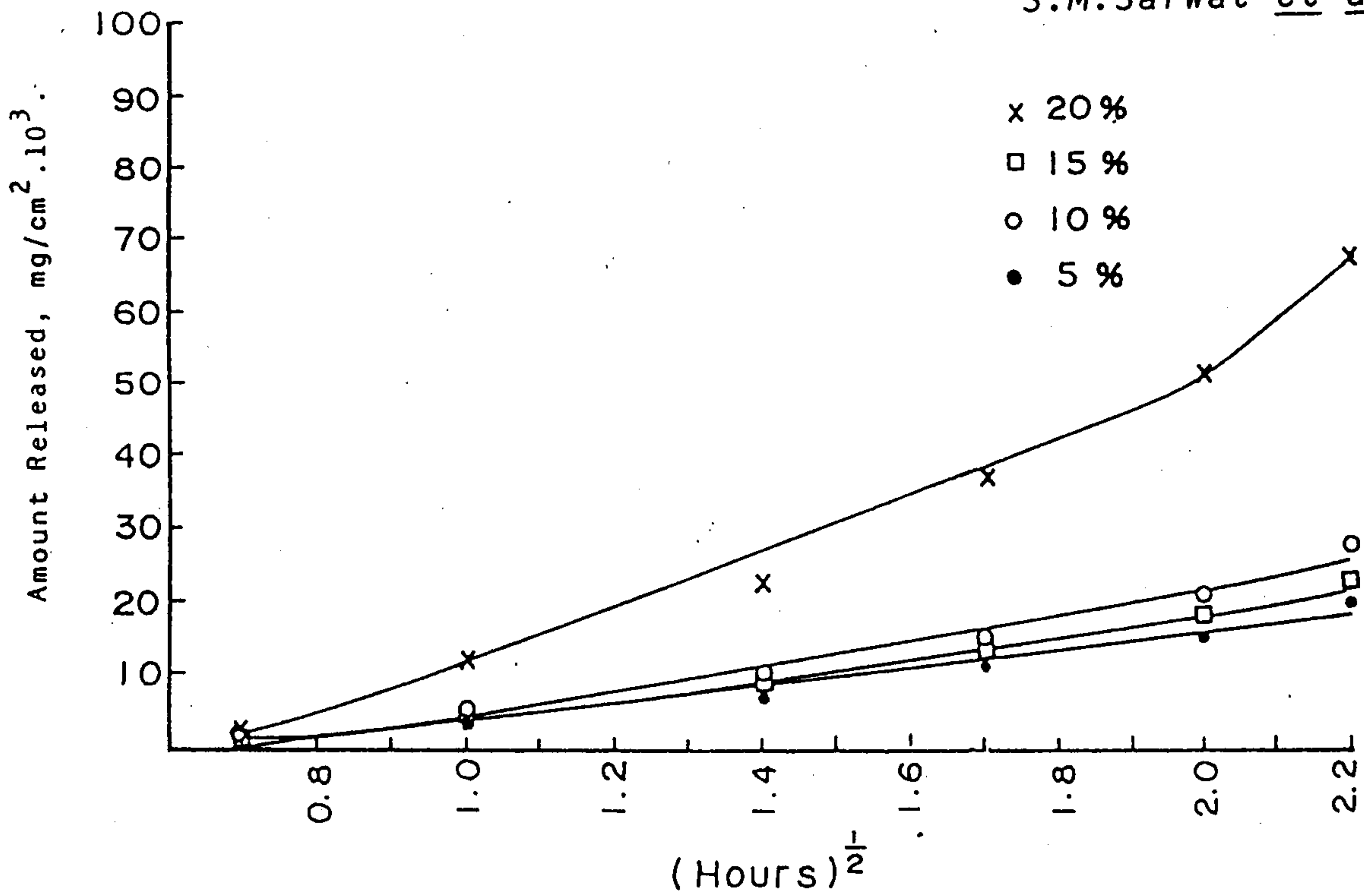


Figure 3- Effect of Dimethylphthalate Concentration on the Diffusion-Controlled Release Characteristics of Chloramphenicol from Cellulose Acetate Butyrate Medicated Films.

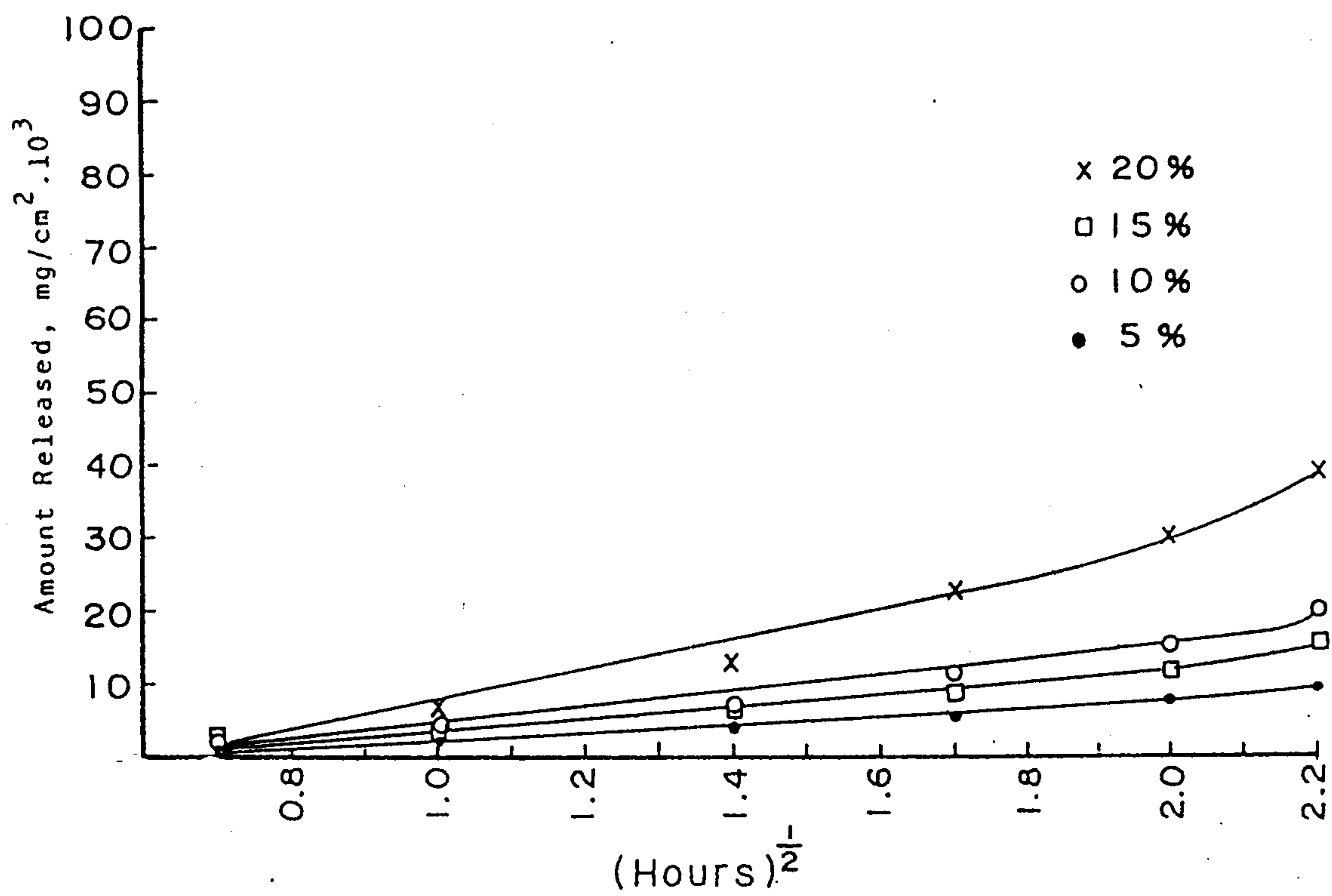


Figure 4 - Effect of Diethylphthalate Concentration on the Diffusion-Controlled Release Characteristics of Chloramphenicol from Cellulose Acetate Butyrate Medicated Films .

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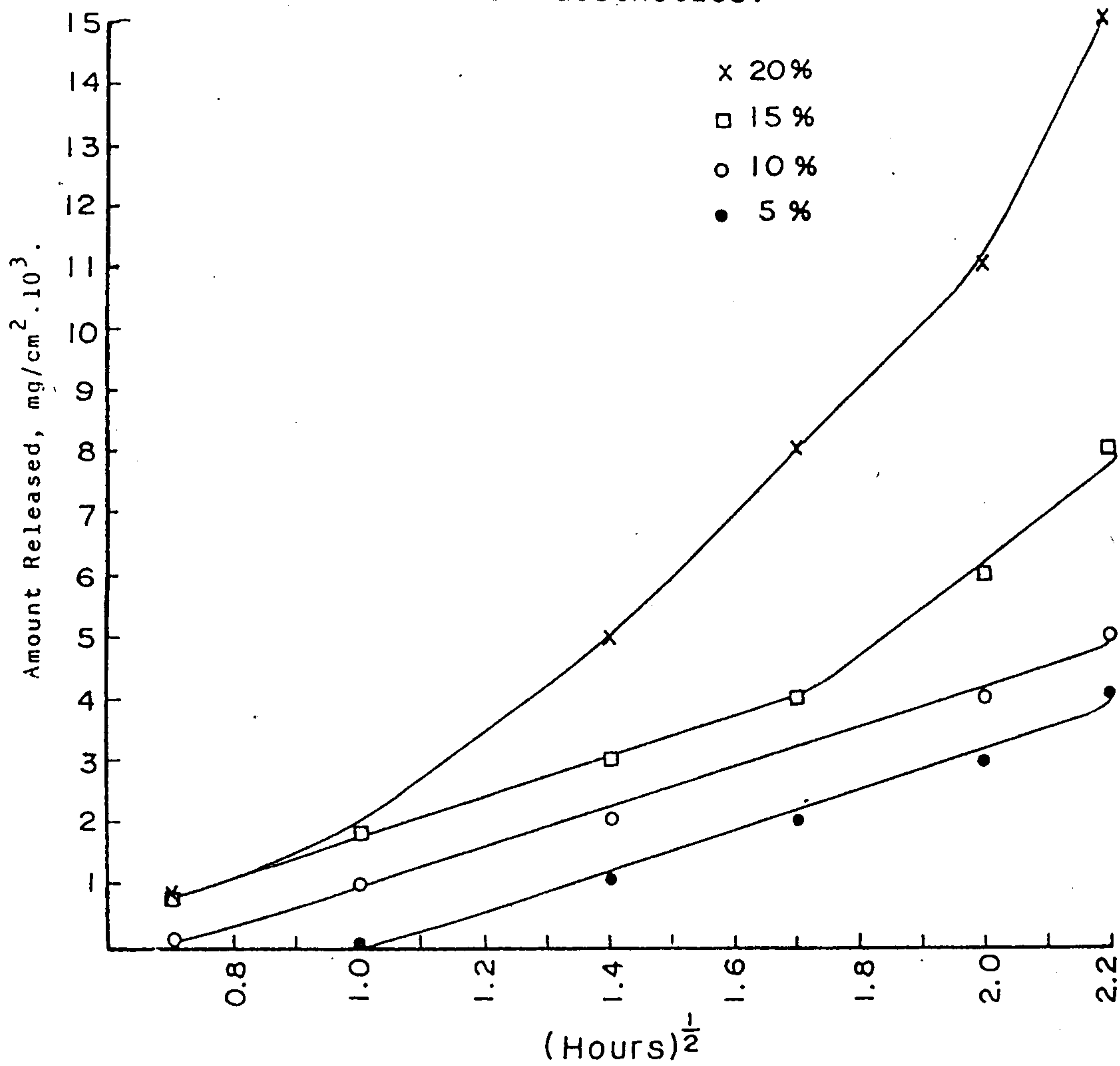


Figure 5- Effect of Propylene Glycol Concentration on the Diffusion-Controlled Release Characteristics of Chloramphenicol from Cellulose Acetate Butyrate Medicated Films.

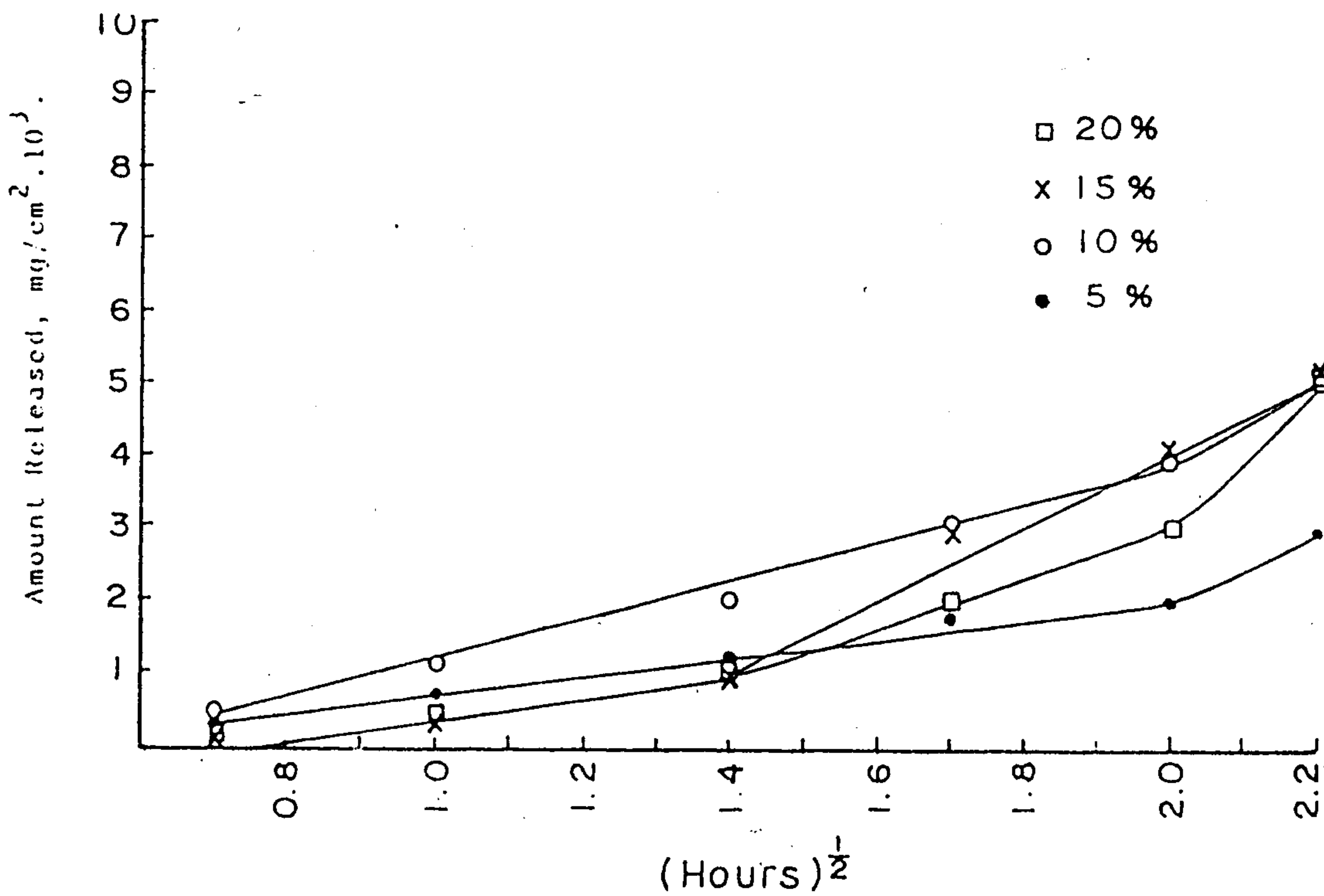


Figure 6- Effect of Castor Oil Concentration on the Diffusion-Controlled Release Characteristics of Chloramphenicol from Cellulose Acetate Butyrate Medicated Films.

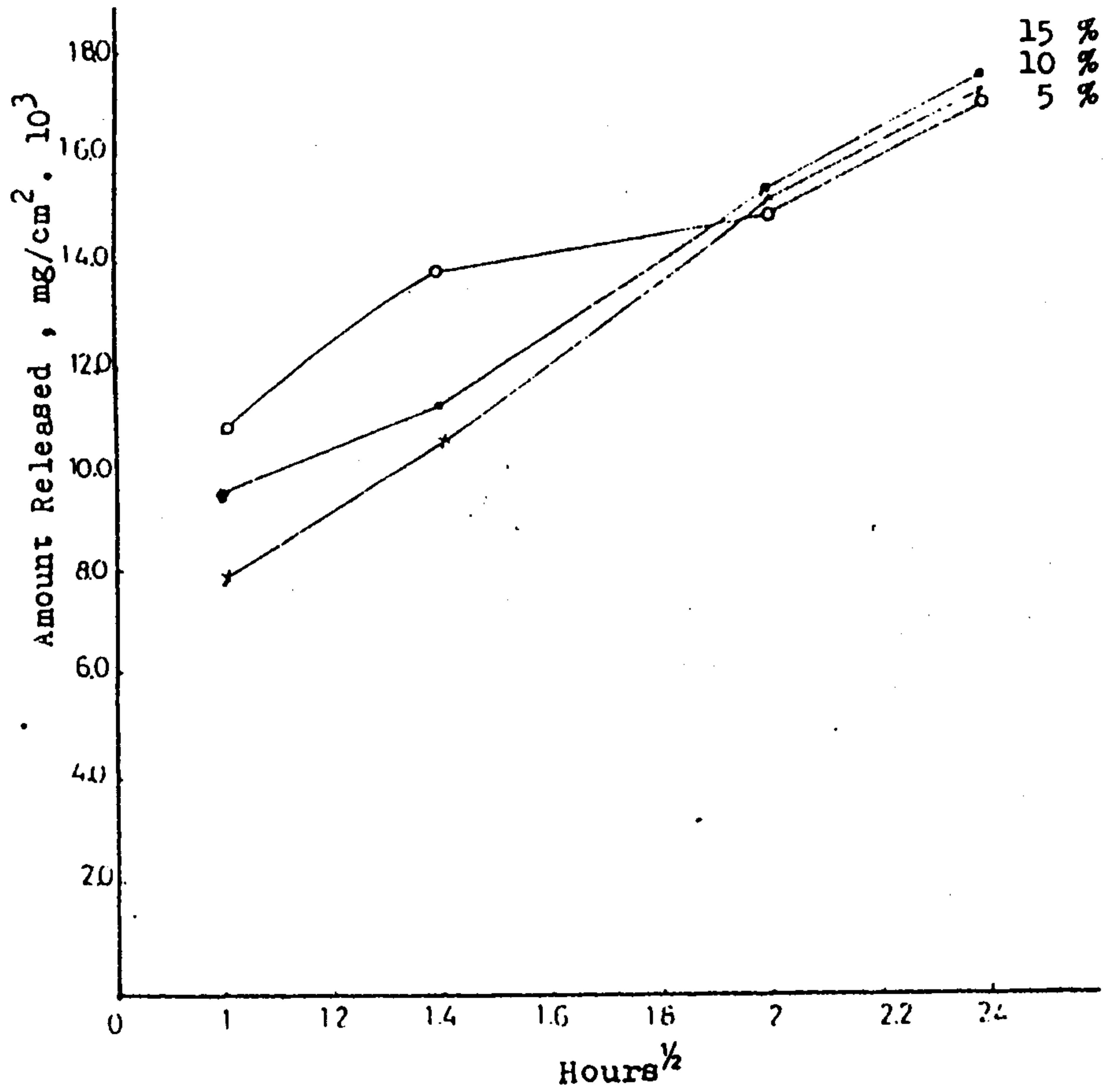


Figure 7- Effect of Drug Concentration on the Diffusion Controlled Release Characteristics of Chloramphenicol Cellulose Acetate Butyrate Medicated Films.

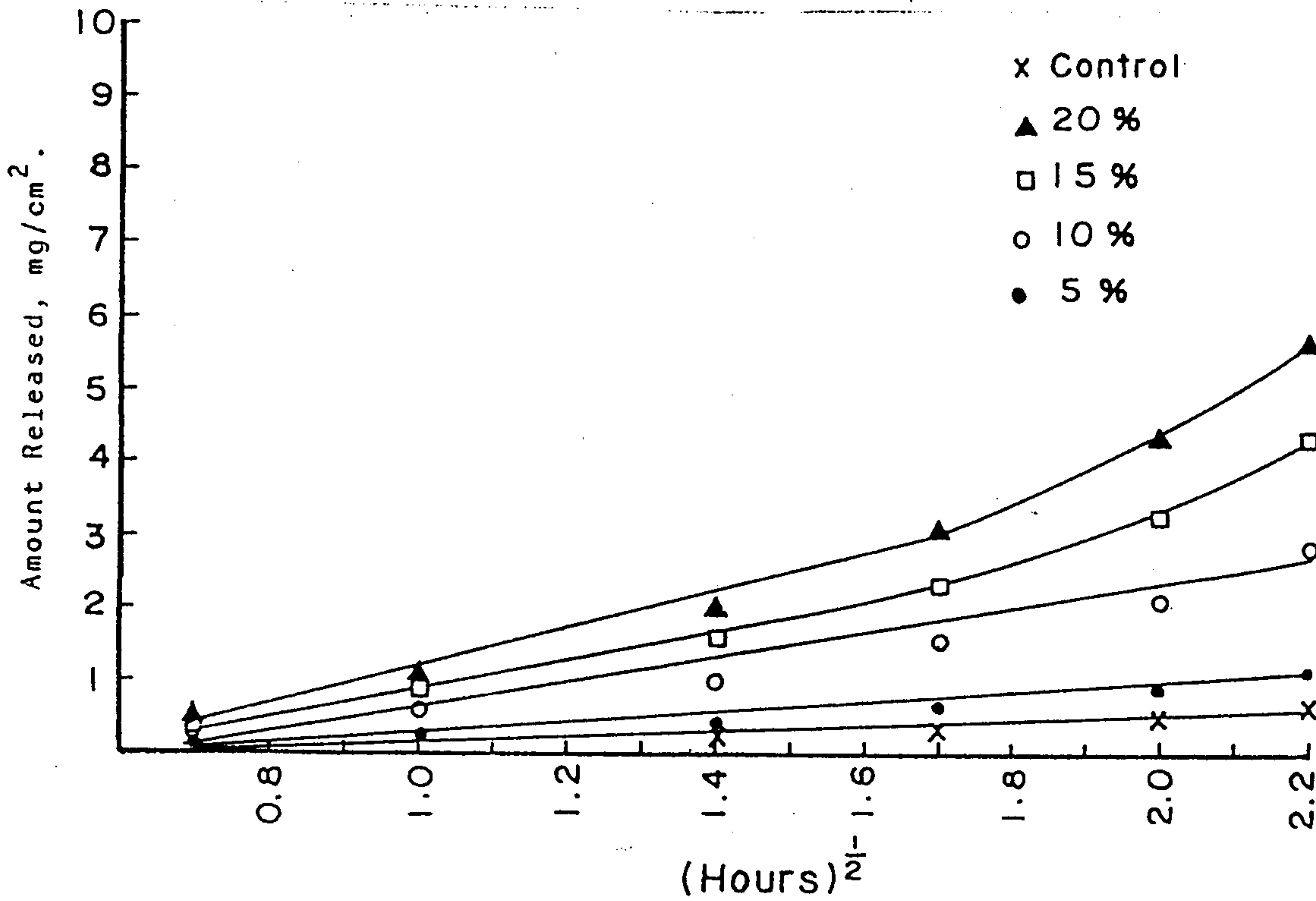


Figure 9- Effect of Dimethylphthalate Concentration on the Diffusion-Controlled Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Medicated Films.

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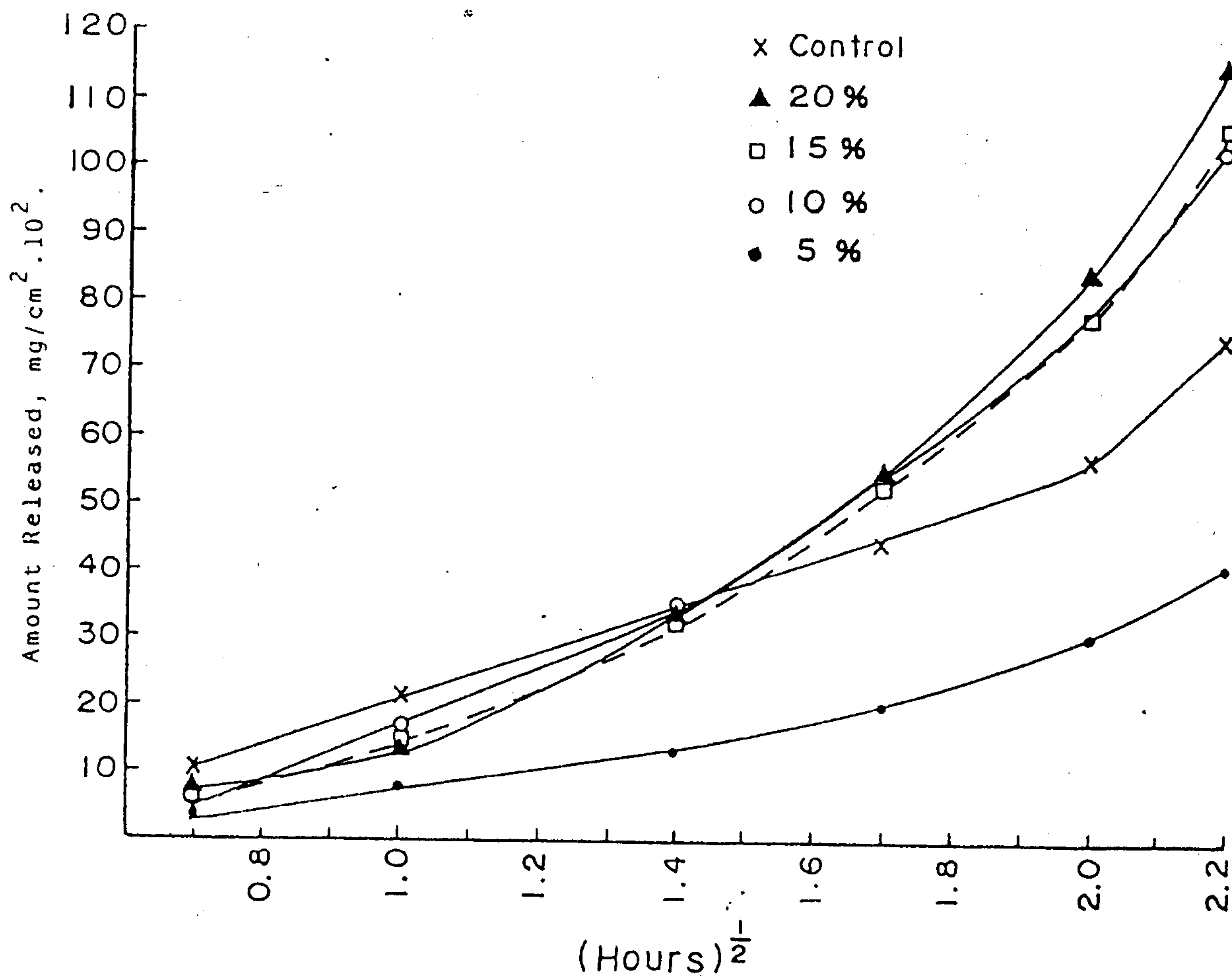


Figure 9- Effect of Diethylphthalate Concentration on the Diffusion-Controlled Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Medicated Films.

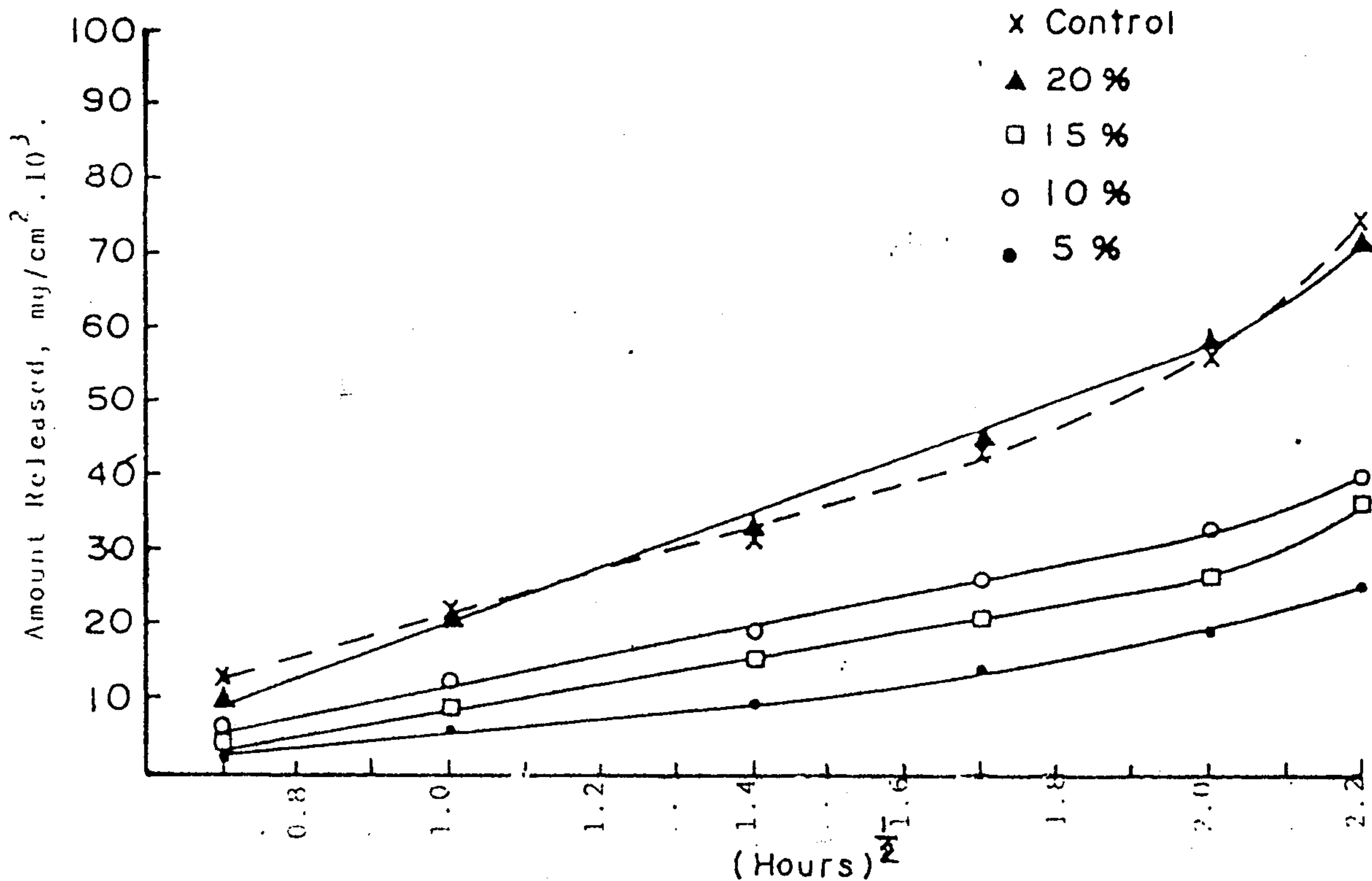


Figure 10- Effect of Propylene Glycol Concentration on the Diffusion-Controlled Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Medicated Films.

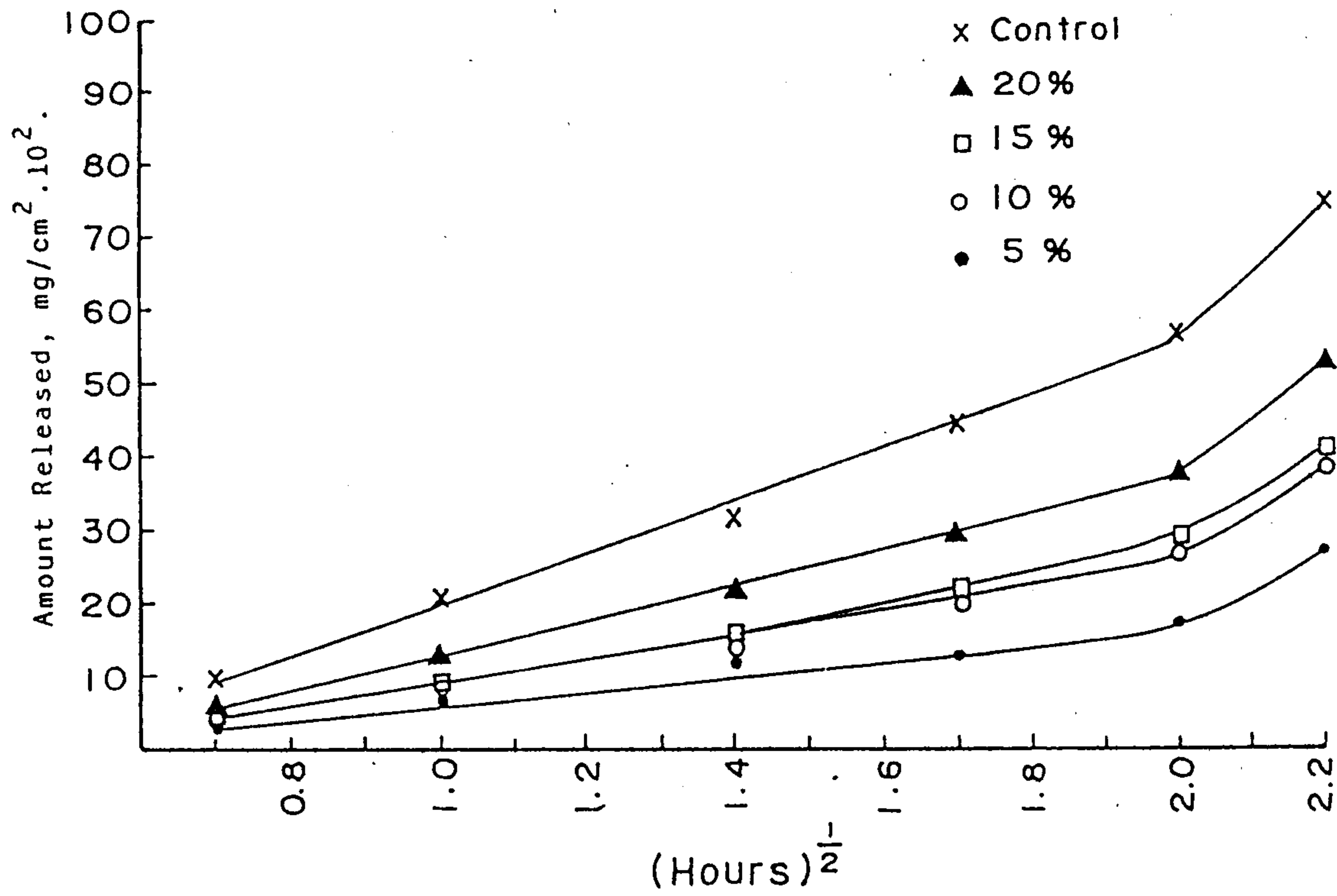


Figure 11- Effect of Castor oil Concentration on the Diffusion-Controlled Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Medicated Films.

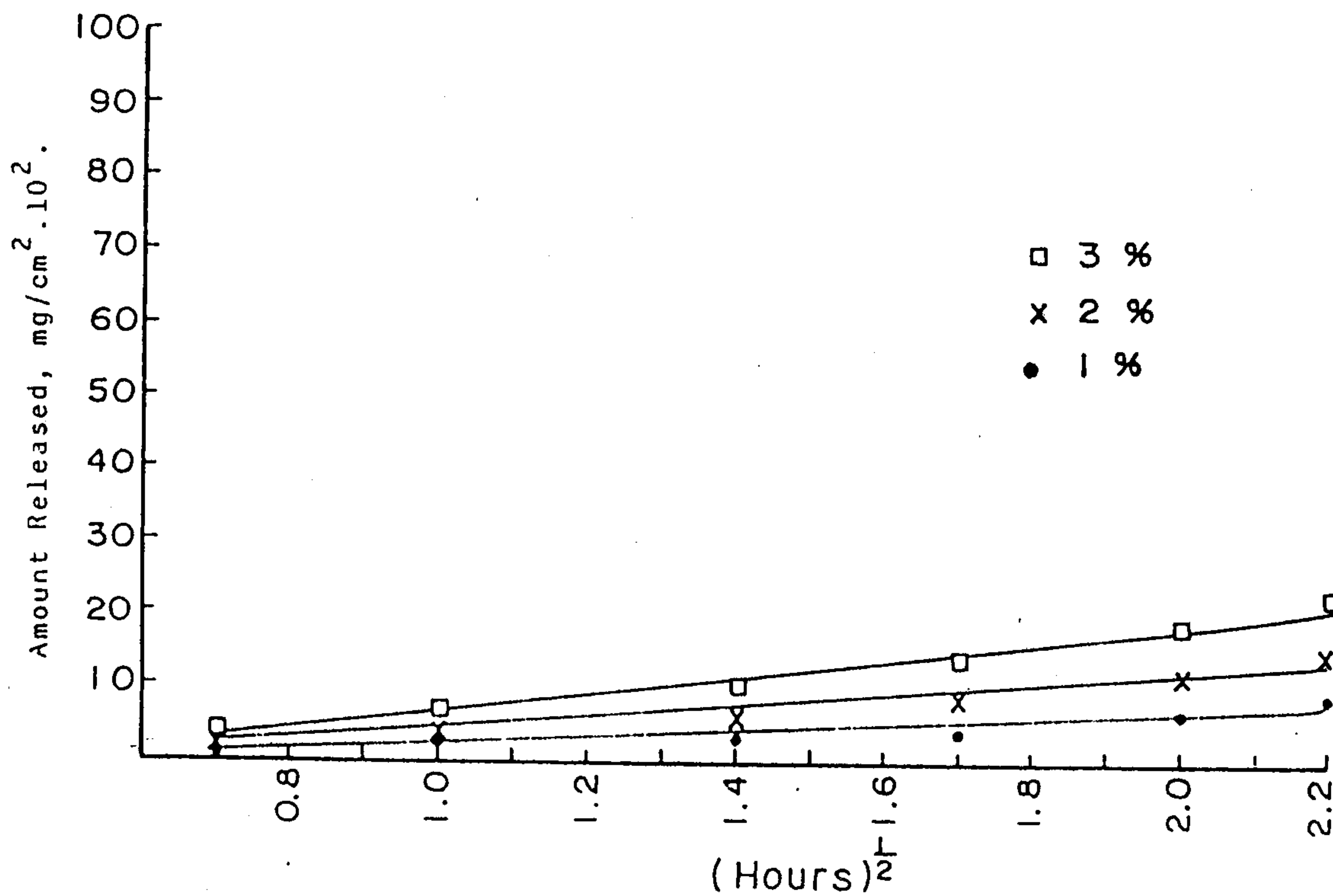


Figure 12- Effect of Drug Concentration on the Diffusion-Controlled Release Characteristics of Lignocaine Hydrochloride from Cellulose Acetate Butyrate Medicated Films.

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أغشية البوليمرات كأنظمة إيصال سطحية
للمضادات الحيوية والمخدرات الموضوعية

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يهدف هذا البحث الى دراسة امكانية استخدام أغشية البوليمرات كأنظمة إيصال سطحية لبعض الادوية . وقد تم اختبار كل من المضاد الحيوى كلورامفينكول والمخدر الموضعى هيدروكلوريد اللجنوكيين للقيام بمثل هذه الدراسة . وتركز البحث فى دراسة كل من نفاذيه بخار الماء خلال الاغشية المحضرة ومعدلات وميكانيكية انطلاق العقارين سابقى الذكر من هذه الاغشية كما تم ايضا دراسة خاصية تحمل الشد لهذه الاغشية .

وتم تحديد الاغشية من خلال بيوتيرات السيليلوز المذابة فى الكلورفورم وعين سمكها ووجد أنه ٥٠ ميكرون فى المتوسط . كما تم اختبار أربع من مكسبات المرونه لتأثيرهم على خصائص الاغشية المحضرة وقد أثبتت الدراسة أن احتواء الاغشية على عشرين بالمائه من أى من مكسبتى المرونه فثالات ثنائى المثيل اوفثالات ثنائى الاثيل يحسن كثيرا من خصائص تلك الاغشية . وقد أعطت الاغشية المحضرة اعلى معدلات انطلاق للعقار كما أبدت معدلات مناسبة لنفاذية بخار الماء وأظهرت خصائص جيدة فى تحملها للشد .