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FORMULATION AND EVALUATION OF DIFFERENT CHLORDIAZEPOXIDE HYDROCHLORIDE SUPPOSITORIES .

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ABSTRACT

Chlordiazepoxide hydrochloride (CDZ); is formulated in different suppository bases. Its in vitro release from these selected suppository bases was studied and found to be base dependent. The effect of drug concentration was also studied. The percentage of drug diffused, through cellophane membrane, increased with decreasing the drug concentration. Drug particle size was found to have an insignificant effect on the release rate.

Histological studies of the rabbit rectal mucosa after the the rectal insertion of the tested suppository bases either alone or in the presence of CDZ showed insignificant histological changes.

INTRODUCTION

Rectal administration of drugs is becoming more popular due to convenience of the suppository dosage form. Moreover, the absorption from the rectum can be enhanced in such a manner so as to be more rapid and regular than that from the stomach or intestine [1-4]. On the other hand, in certain cases, the rectal administration of either the base alone or in presence of the therapeutic agent was found to induce a severe histological damage [5-7]. The drug release pattern from suppositories is markedly influenced by the nature of the base used [8-11], particle size and the drug concentration [12-18].

CDZ is widely used as antianexiety agent. It can be effectively used as a hypnotic, anticonvulsant or in the treatment of alcohol withdrawal syndromes[19]. The absorption of CDZ after i.m. injection was found to be erratic and slower than after oral administration. Moreover, the i.m. injection of CDZ is painful.

The rectal administration of some benzodiazepines namely; diazepam and lorazepam was studied in humans and experimental animals. Diazepam rectal solution gave faster and regular absorption than the oral or the i.m. administration with no observed differences in the bioavailability[20-22]. The absorption pattern of diazepam suppositories was found to be similar to that of its rectal solution in geriatric epileptic patients[23]. It was reported that lorazepam suppositories formulated in water soluble bases gave the same extent of the absorption as that of an oral solution of the drug in mongrel dogs[24].

Literature on chlordiazepoxide hydrochloride revealed that there is no work done on this drug as a suppository dosage form. Hence, the aim of the present work is to formulate chlordiazepoxide hydrochloride in suppositories so as to study the effect of particle size, the drug concentration as well as the nature of the suppository bases on the in vitro release profile of the drug. The kinetics of drug release from the tested suppository bases were also investigated. Three types of suppository bases were tested for their ability to release the medicament. These bases were fatty, water soluble and emulsion.

Also this study concerned with the possible mucosal damage induced by the formulated suppositories.

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EXPERIMENTAL

Materials:

Cacao butter (B.P. grade), Witepsol H_{15} and Witepsol E_{75} (Nobel Dynamit, GFR), Carbowaxes 400, 600, 1500, 4000 and 6000 (Fluka AG, Switzerland), Sodium alginate (Judes Lab, England), Sodium Carboxymethylcellulose (Roth, GFR), Polysorbate 20 and Span 60 (Atlas Chem. Ind., USA), Chlordiazepoxide hydrochloride (Kindly supplied by Memphis CO. Egypt) and standard cellophane membrane (30/32 Fisher Sci. Co., England).

Procedures:

1- Preparation of CDZ Suppositories:

Fourteen different suppository bases were selected to cover the fatty, soluble and emulsion bases. The fatty bases are represented by cacao butter, witepsol H_{15} and witepsol E_{75}. The composition of water soluble as well as emulsion bases is surveyed in Table 1. The water soluble bases, 4-9, were formulated in the specified ratios so as to cover a wide range of melting point. Different trials were conducted to prepare different emulsion bases. The most suitable formulations were selected for the present study and represented by bases 10-14, Table 1.

Suppositories of infantile size, each containing 25 mg of CDZ were prepared adopting the fusion method. The prepared suppositories were placed in a refrigerator for three days, then removed and left at room temperature for one day before testing. In a similar manner suppositories containing 12.5, 25 and 50 mg of the medicament were prepared using the tested fatty bases. The effect of drug particle size on the drug release pattern was tested using witepsol H_{15} as a representative base. The drug was used in the fraction size ranges: <63, 63 - 90 and 90 - 200 um. It should be noted that for each, a blank suppository was similarly prepared.

Evaluation of Chlordiazepoxide Suppositories:

The prepared suppositories were evaluated for drug content uniformity, melting-point range, solidification point, disintigration time, liquification

time, and breaking test. The tested physical parameters are tabulated in Table 2. Weight variation and drug content were determined according to B.P. 1980[25] and B.P.C. 1974[26] respectively.

Release of Chlordiazepoxide Hydrochloride from Suppositories:

The prepared suppositories were subjected to the in vitro release test of the medicament through a cellophane membrane. The membrane was cut into 4 x 4 cm pieces and soaked in distilled water over night, withdrawn and rinsed with distilled water. The membrane was firmly stretched over the end of a glass tube (28 mm internal diameter) by means of a cotton thread. The prepared tube was suspended in a 500 ml beaker containing 200 ml of distilled water. A volume of 10 ml distilled water was poured into the glass tube. The system was placed into a constant temperature water bath at 37°C ± 0.5°C and one suppository was introduced into the tube. Water inside the external vessel was stirred by the aid of a magnetic stirrer. At specified time intervals, a volume of 5 ml sample was withdrawn from the acceptor and replaced with the same volume of water at the same temperature. The amount of CDZ released was spectrophotometrically determined at 260 nm against a blank similarly treated. The release data were mathematically analysed according to zero order, first order kinetics and the diffusion controlled release mechanism.

Histological Studies of Rectal Mucosa:

Adult male healthy rabbits weighing about 1.5 - 2 Kg were used. The rabbits were kept under control for one week before study. For each study, one suppository was inserted deeply in the rectum of the rabbit. The anus was closed immediately after insertion with a thick plaster for at least one hour to prevent any leakage. The insertion was repeated daily for ten days. At the end of this period the rabbit was sacrified. The rectum including the anus was removed as one segment (about 5 cm-length) and preparations of rectal segments for microscopic observations were made. The preparations were stained with haematoxylin and eosin and examined by the light microscope. Five formulations including plain as well as medicated bases were tested. Three rabbits were used for each formula as well as for the control (untreated rabbits).

Formulation and Evaluation of Different Chlordiazepoxide Hydrochloride Suppositories.

RESULTS AND DISCUSSION

1- Physical Properties:

The physical properties of CDZ prepared suppositories are listed in Table 2. The determined hardness values (0.6 - 3.6 Kg) are in agreement with Erweka requirements. All the prepared suppositories were found to meet the acceptable limits of weight variation according to B.P. 1980 (± 5%).

Drug content per suppository (mg ± SD) was found to be 25.39 ± 0.75, 25.17 ± 0.71 and 24.88 ± 0.81 when witepsol H_{15}, witepsol E_{75} and cacao butter were used respectively. The drug content suppository was 24.79 ± 0.37 in carbowax base number 9 and 24.61 1.21 mg in emulsion base number 14. These results indicate the agreement of the drug content uniformity with the stated limits of B.P.C. 1973.

2- In Vitro Release Characteristics of Chlordiazepoxide Hydrochloride from its Prepared Suppositories.

The in vitro release of CDZ from the tested bases through the cellophane membrane was studied at 37°C. The release data were analysed according to zero, first order and diffusion controlled mechanism [27]. The results of the data analysis appear in Table 3 The high correlation coefficient values, obtained by the least square regression analysis, of the logarithm of the amount of d... retained versus time give an evidence that release pattern follows first order kinetics. Further confirmation applying the equation:

$$\log Q = \log K + \tfrac{1}{2} \log t$$

Which is commonly used in case of diffusion controlled mechanism[28] assures the previous finding, as the slope was not found to be equal to ½ as required by the linear correlation. The description

of the release process, as it obeys a single mechanism is an indication to the presence of the drug as one moiety. A result which may indicate the absence of the drug- base interaction.

The rate of drug release from fatty bases as illustrated by Figure 1 seemed to be dependent on both the melting point as well as the chemical composition of the tested bases. In this respect, both witepsol H_{15} and cacao butter which are characterized by having the same melting range (33-35°C) but vary mainly in that the former contains self emulsifier; monoglyceride,. Witepsol H_{15} releases the drug in a higher rate as compared with cacao butter base. At the same time, witepsol H_{15} and witepsol E_{75} which have the same chemical composition but vary in the melting range, were found to have different release rates of the medicament. Witepsol H_{15} exhibited a higher release rate than witepsol E_{75}. This finding may be attributed to the lower melting rang of witepsol H_{15} (33-35°C) than that of witepsol E_{75} (37-39°C).

Different concentration levels of CDZ, in witepsol H_{15}, namely 12.5, 25 and 50 mg/ suppository were tested for their effect on the release pattern. An increase in the medicament concentration in the tested formulae was found to decrease the percentage amount released (Figure. 1). An effect which may be attributed to the limiting capacity of the membrane towards drug diffusion. The effect of CDZ fraction size on the in vitro release from witepsol H_{15} is shown in Figure 2. Suppositories formulated with CDZ of fraction size less than 63 um exhibited the least release rate. However, when the drug was formulated in large fractions the release rate was slightly high. This can be explained on the basis that as the particle size increased, the ability of the particles to settle down in the melted base increased. The settled particles will rapidly come in contact with the aqueous medium. Statistical analysis of the release data concerning the effect of particls size (Table 4) showed an insignificant difference between the coarse fractions ; 63-90 and 90-200 um.

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Figure 3 shows the in vitro release profile of CDZ from the tested carbowax bases. The release is a biphasic pattern consisting of an intitial fast release phase, during the first hour, followed by a slow release one. The release phase may be attributed to dissolution of carbowaxes in the aqueous phase of the donor compartment creating an increase in the osmotic pressure. An effect which may lead to an influx of water molecules from the acceptor into the donor compartment. Consequently, a decrease in the concentration gradient was attained resulting in slowing of the release rate. Also, the increase in the viscosity due to the dissolution of carbowaxes, hence a decrease in the diffusion rate of the drug, may explain the slow release phase. The tested carbowax bases can be arranged according to their abilities to release the medicament as follows: base 9 > base 8 > base 7 > base 6 > base 5 > base 4. This can be clearly observed from Table 3 and Figure 3. This sequence of arrangement is in agreement with the determined melting behavior of the tested base (Table 2). The lower the melting range of the base the easiness is the softening and melting hence, the medicament will move fast towards the aqueous phase. This leads to a fast release of the drug through the cellophane membrane. The base No. 5 has to be excluded since it developed a yellow color within three days after preparation.

The in vitro release pattern of CDZ from the tested emulsion bases is shown in Figure 4 and Table 3. The tested bases could be arranged according to their release rate as : base 14> base 13> base 12> base 11> base 10. This arrangement of bases is the reverse as that according to both the melting range and disintegration time of the tested bases (Table 2). A result which indicates that the lower the melting range and the shorter the disintegration time of the base, the higher is the release thereof.

The base components were found to determine the melting range as well as the disintegration time of the base. In this respect, witepsol H_{15} when used as the oily phase it leads to the formation

of an emulsion base with lower melting range and shorter disintegration time compared to the use of witepsol E_{75}. Also the use of sodium alginate was found to give shorter disintegration time when compared with the use of sodium CMC. A result which may be attributed to the more gelling effect exhibited by sodium CMC rather than sodium alginate. Experimentally, the viscosity of 0.2% w/v aqueous solution of sodium alginate was found to be less than that of 0.1% w/v aqueous solution of sodium CMC.

Base 14; in which polyethylene glycols substitute the aqueous phase of the emulsion bases, was found to have a higher release rate compared to the tested emulsion bases. The high release rate of that base may be attributed to the concomitant rapid disintegration of the suppository and dissolution of the polyethylene glycol constituents.

Histogramic representation for the percentage of CDZ released from the tested suppository bases is shown in Figure 5.

3- Effect of Different Suppository Formulations on the Rabbit Rectal Mucosa.

Different suppository bases were tested for their effect on the rectal mucosa of the rabbit. Photomicrographs of the rectal mucosa before and after treatment are presented in Figure 6 (A-F). Photomicrograph A shows the normal rectal mucosa of the rabbit (control) displaying normal folds, healthy intact lining epithelium. The lamina propria consists of loose connective tissue fibres and cells mainly fibroblasts. Photomicrograph B shows the rectal mucosa after treatment with plain PEG base. The lining epithelium is still showing normal appearance with an insignificant loss of apical surface of the cells. The lamina propria showed few dilated blood capillaries and slight oedema of the lower part. An increase in the thickness of the lining epithelium with upward displacement of their nuclei was also observed compared to the control.

These results can be attributed to the dehydrating effect of the base resulting in withdrawal of water towards the lumen. Photomicrograph C shows the rectal mucosa after treatment with plain witepsol H_{15} base. Insignificant loss of luminal surface of the lining epithelial cells accompanied by insignificant changes in other mucosal or submucosal tissues was observed. This means that the rectal membrane was hardly affected by the tested plain base. Photomicrograph D shows the picture after treatment with medicated witepsol H_{15}. Insignificant histological changes were observed in the rectal mucosa. The mucous membrane of the rectum appears to be thinner with few folds, however, the lining epithelium was almost normal with the same picture as that in case of treatment with plain witepsol H_{15}. Also, the lamina propria showed numerous glands, more congested vessels with few perivascular eosinophilic cells and plasma cells. These effects are usually associated with the absorption process.

The medicated emulsion base (photomicrograph E) showed an increase in number of goblet cells, mucosal glands, capillary dilatation and perivascular cell infiltration. These changes are, also concomitant with absorption process. With medicated cacao butter base, (photomicrograph F) it was found that the formula did not injure the mucosa. The same features were as those observed with the medicated emulsion base.

Finally, it could be concluded that the tested plain as well as the medicated bases did not injure the rectal mucosa in rabbits. The observed changes are considered as a reaction process normally accompaning the absorption process. The tested bases are safe for the formulation of the rectal preparations. These bases are favorable for clinical use without undesirable side effects.

Table (1): Composition of Suppository Bases Used.

Base No.		Composition	% W/W
		A- FATTY BASES	
1		Witepsol H_{15}	100
2		Witepsol E_{75}	100
3		Cacao butter	100
		B- WATER SOLUBLE BASES	
4	PEG_1	PEG 400 PEG 6000	40 60
5	PEG_2	PEG 400 PEG 6000 Distilled water	20 60 20
6	PEG_3	PEG 1500 PEG 6000	70 30
7	PEG_4	PEG 400 PEG 1500 PEG 4000	30 30 40
8	PEG_5	PEG 1000 PEG 4000	70 30
9	PEG_6	PEG 1000 PEG 4000	97 3
		C- EMULSION BASES	
10	E_1	Witepsol E_{75} Sod. CMC Tween 20 Distilled water	50 1 4 45
11	E_2	Witepsol E_{75} Sod. alginate Tween 20 Distilled water	50 2 4 44
12	E_3	Witepsol H_{15} Sod. CMC Tween 20 Distilled water	50 1 4 45
13	E_4	Witepsol H_{15} Sod. alginate Tween 20 Distilled water	55 2 4 39
14	E_5	Witepsol H_{15} Tween 20 Span 60 PEG 1500 PEG 600	34 5 1 40 20

Table (2): Physical Parameters of Chlordiazepoxide hydrochloride Suppositories Prepared in Different Suppository Bases.

Suppository base	Hardness Kg	Melting Range °C	Softening Point °C	Liquification Point °C	Flow Point °C	Disintigration or (Dissolution) time (min.)	Average weight (g. ± SD)
				Fatty bases			
1	2.1	33-35	32.0	34.5	35.0	11	1.048 ± 0.009
2	2.6	37-39	35.0	38.0	38.5	18	1.112 ± 0.008
3	0.6	33-35	27.0	34.0	33.0	8	0.976 ± 0.008
				Polyethylene Glycol bases			
4	3.6	58-59	5 .0	60.0	60.0	40	1.307 ± 0.009
5	2.6	46-47	44.5	48.0	48.5	28	1.260 ± 0.012
6	3.0	50-51	48.0	52.0	52.0	30	1.315 ± 0.007
7	2.8	47-48	45.0	48.0	48.0	24	1.299 ± 0.007
8	2.5	44-45	42.0	45.0	45.0	19	1.251 ± 0.004
9	0.8	36-37	29.5	37.5	37.5	13	1.195 ± 0.006
				Emulsion bases			
10	0.6	-	29.0	37.5	-	33	1.118 ± 0.019
11	0.6	-	27.0	37.0	-	26	1.113 ± 0.014
12	0.6	-	25.0	35.0	-	27	1.099 ± 0.015
13	0.6	-	26.0	35.0	-	19	1.034 ± 0.010
14	0.8	-	32.0	34.5	35.0	8	1.024 ± 0.007

Table (3): Release Characteristics of Chlordiazepoxide hydrochloride from Different Suppository Bases

Suppository base	Zero order		First order		Higuchi diffusion model I Q/A vss $t^{\frac{1}{2}}$		Higuchi diffusion model II log Q vss log t	
	r	$Kx10^2$	r	$Kx10^3$	r	$Dx10^4$	r	Slope
				Fatty bases				
1	0.987	7.18	0.999	5.18	0.998	11.16	0.977	0.833
2	0.981	0.97	0.991	0.417	0.958	0.19	0.986	0.947
3	0.996	2.03	0.999	0.731	0.957	0.58	0.999	1.055
				Polyethylene glycol bases				
4	0.954	18.60	0.977	2.86	0.989	4.83	0.989	0.648
5	0.950	20.60	0.978	3.31	0.986	6.01	0.983	0.655
6	0.953	19.50	0.978	3.06	0.989	5.31	0.980	0.655
7	0.966	21.00	0.989	3.51	0.994	6.09	0.982	0.640
8	0.956	22.70	0.986	4.03	0.994	7.17	0.978	0.649
9	0.963	24.00	0.97	4.30	0.993	7.99	0.985	0.619
				Emulsion bases				
10	0.996	2.10	0.995	0.093	0.969	0.0055	0.995	1.054
11	0.997	5.16	0.996	0.551	0.976	0.0335	0.998	1.002
12	0.998	10.40	0.999	1.230	0.991	1.378	0.992	0.750
13	0.981	11.00	0.988	2.34	0.998	1.575	0.990	0.695
14	0.974	24.70	0.997	5.21	0.997	8.255	0.990	0.547

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Table (4): Effect of Chordiazepoxide hydrochloride Fraction Size on its in Vitro Release Profile from Witepsol H_{15} Suppository Base.

Fraction Size (u)	Amount of medicament released (%) after the following specified time intervals, in minutes					
	15	30	45	60	90	120
< 63	5.50	11.40	17.62	21.60	29.89	36.77
63-90	5.62	11.82	19.67	25.02	35.53	43.68
90-200	5.91	14.28	20.38	25.59	36.75	40.84

Analysis of Varience

Source of Variation	S.S	DF.	SS/D.F	F Calculated	F Tabulated P=0.01	F Tabulated P=0.05
Treatment	55.913	2	27.957	10.33^{xx}	7.56	4.10
Time intervals	2697.739	5	539.550	199.37^{xx}		
Error	27.063	10	2.706			
Total	2780.715	17				

L.S.D. at P = 0.01 = 3.009

L.S.D. at P = 0.05 = 2.116

Fraction size (u)	Mean % released X_i	Difference between means $X_i - X_e$	$X_i - X_b$
90 - 200	$X_A = 24.616$	4.154^{xx}	1.059
63 - 90	$X_B = 23.557$	3.095^{xx}	
<63	$X_C = 20.462$		

^{xx}Highly Significant

S.S: Sum of squares deviation

D.F: Degree of Freedom

SS/DF: Variance estimate = S^2

L.S.D: The least significant difference = $t\sqrt{\frac{2 \times S^2}{n}}$

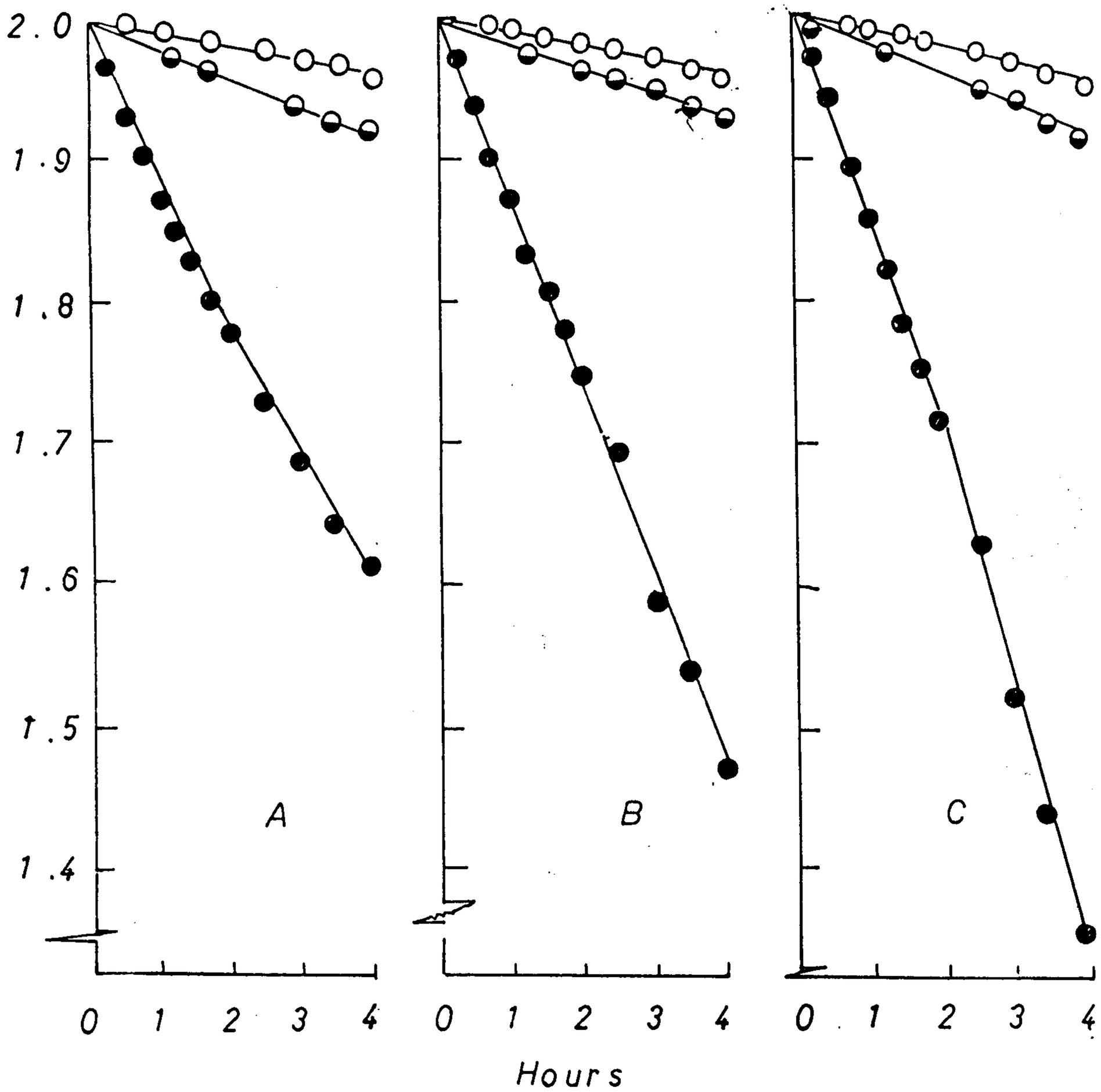

Figure 1 : First-order Release Profile of Chlordiazepoxide hydrochloride from its Fatty Bases Formulated with Different Concentrations of the Drug. (A) 50 mg/supp., (B) 25 mg/supp., and (C) 12.5 mg/supp. key: (○) Witepsol E_{75}, (◒) Cacao butter, and (○) Witepsol H_{15} .

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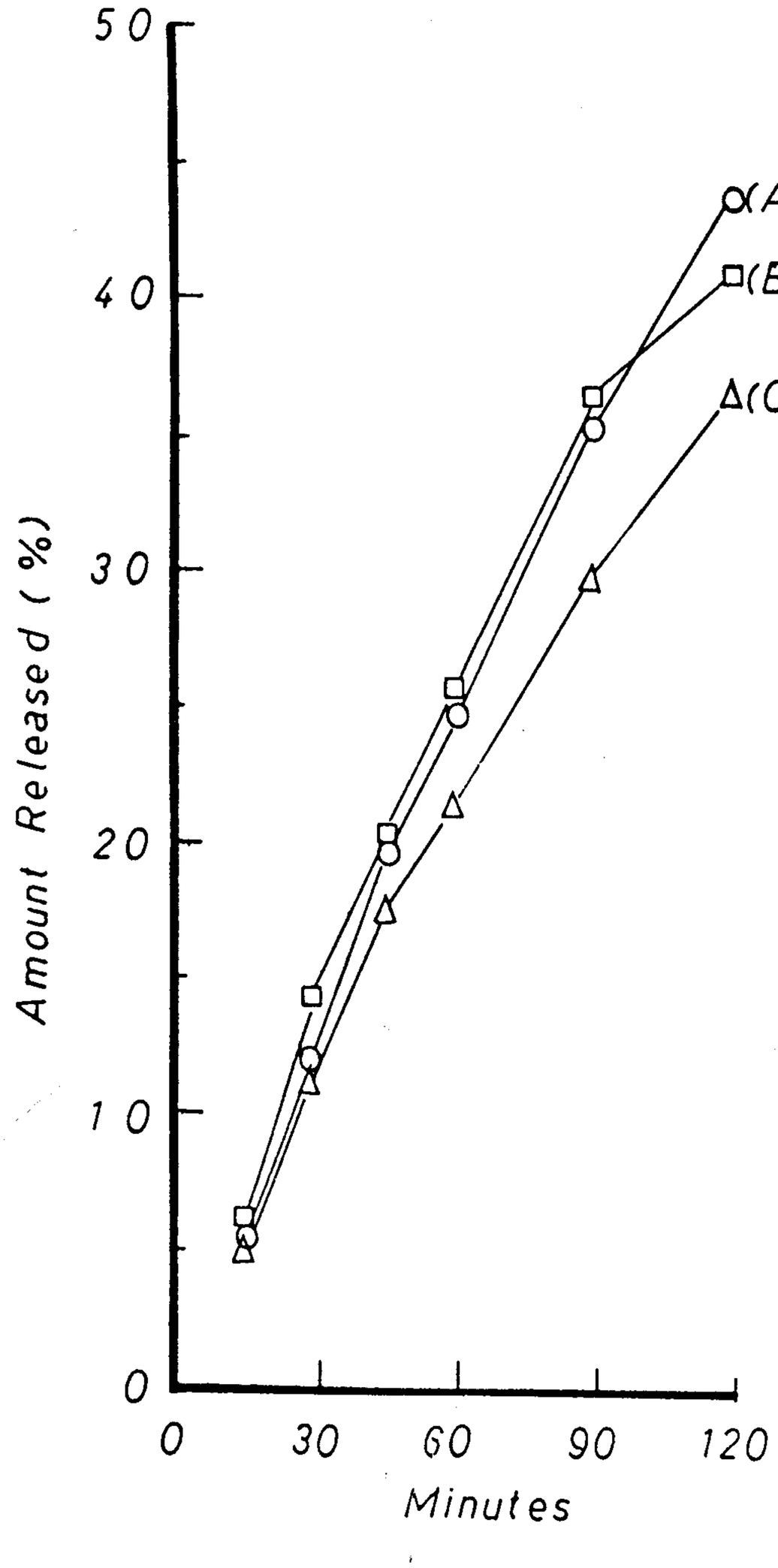

Figure 2: Effect of Chlordiazepoxide Hydrochloride Fraction Size on Its in Vitro Release from Witepsol H_{15} Suppository Base.

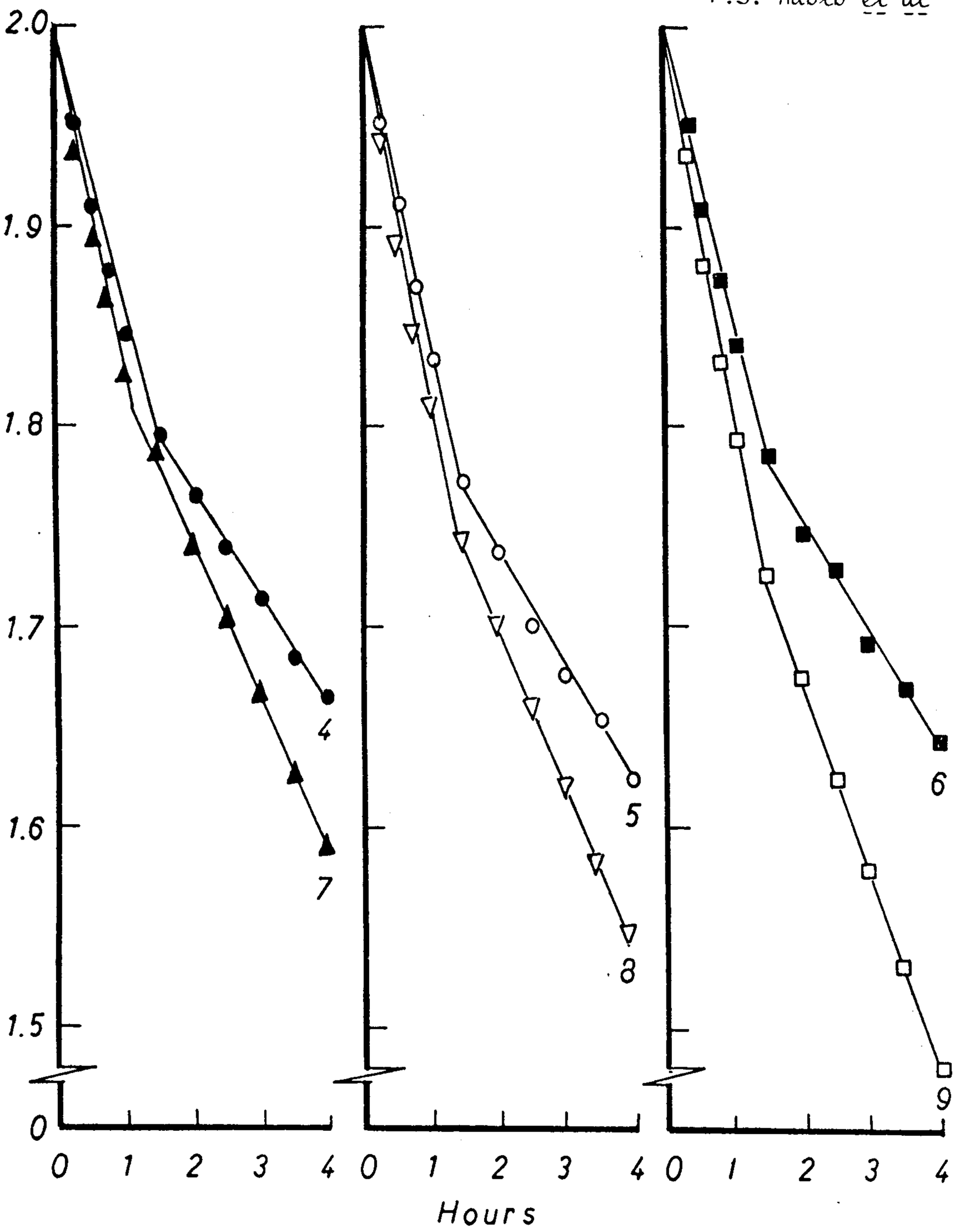

Figure 3: First-order Release Profile of Chlordiazepoxide Hydrochloride from Its Polyethylene Glycol Bases (PEG 4-9)

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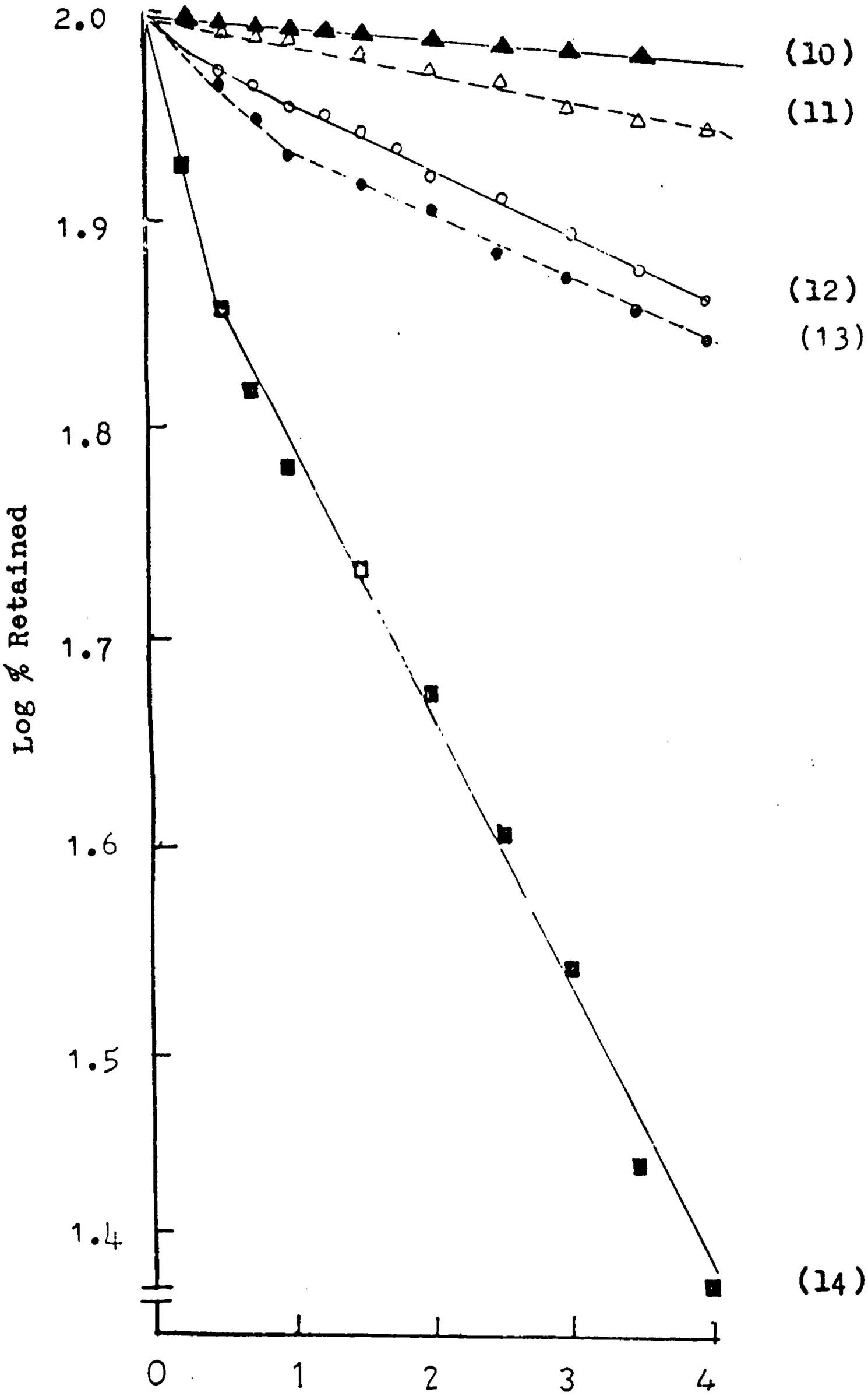

Figure 4 : First-order Release Profile of Chlordiazepoxide hydrochloride from Its Emulsion Suppository Bases

key: (▲) 10, (Δ) 11, (o) 12, (●) 13, and (■) 14 .

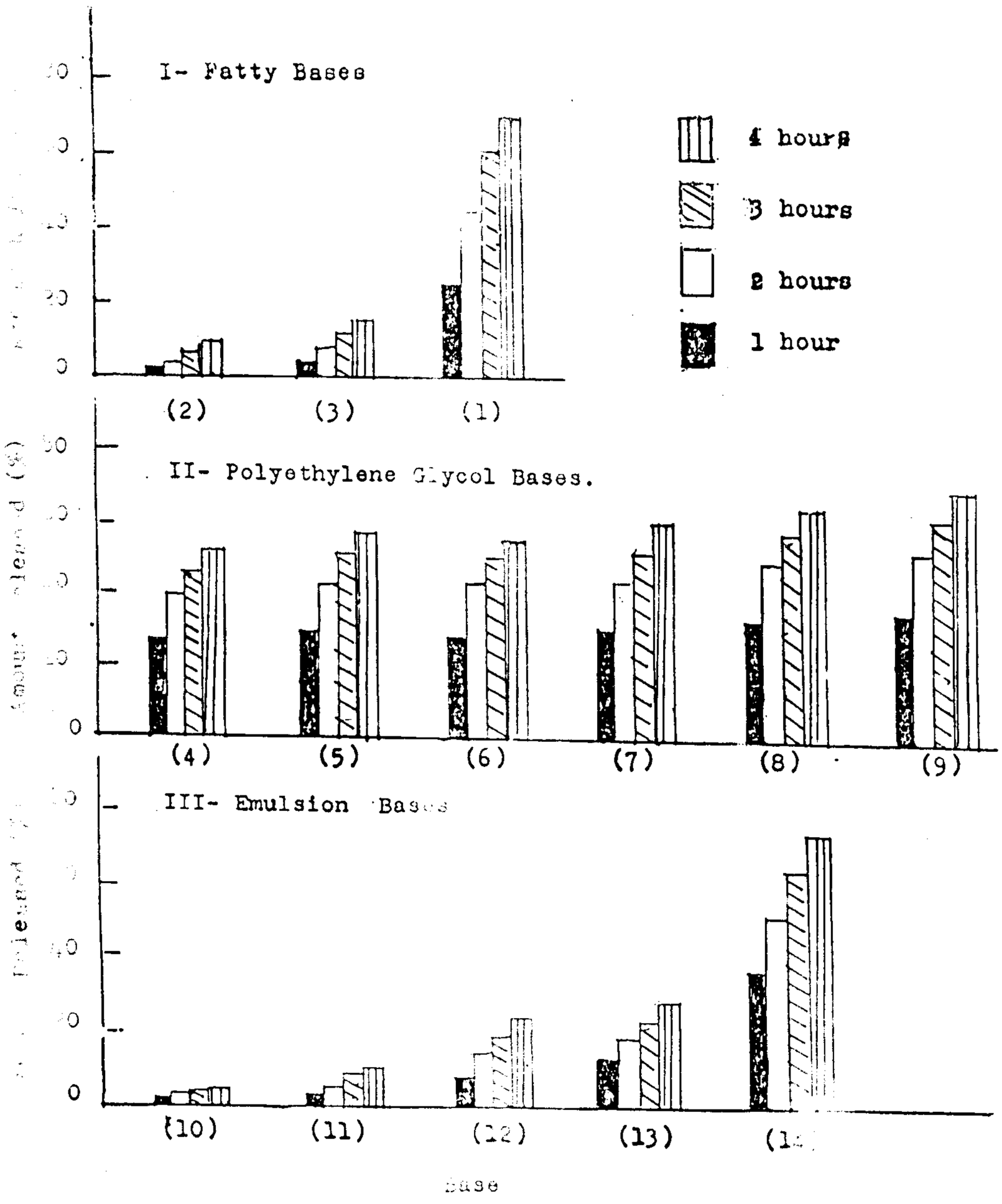

Figure 5: Histogramic Representation for the Percentage of CDZ Released from Different Suppository Bases.

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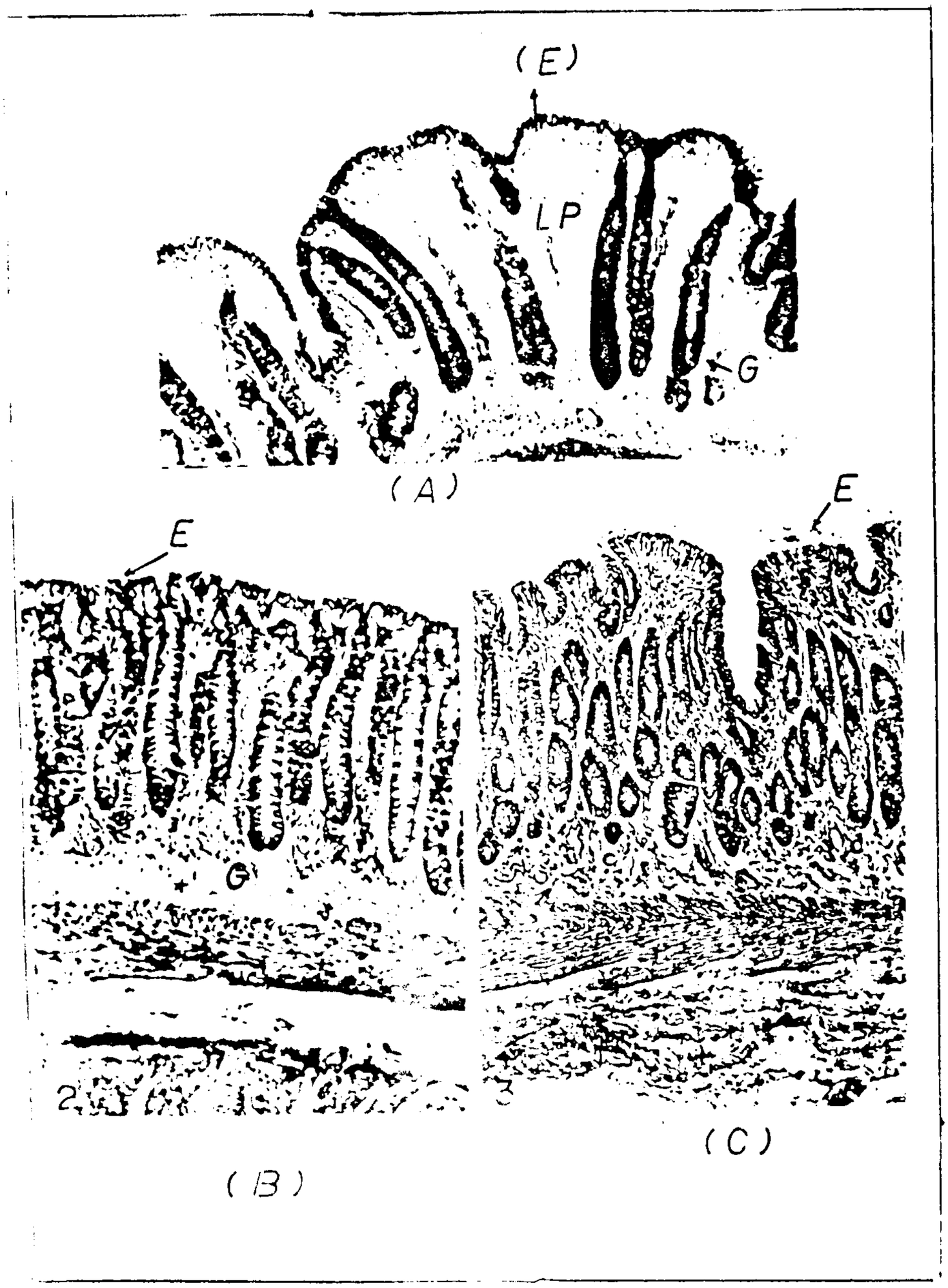

Figure 6: The rectal mucosa of rabbits; untreated (A), treated with plain PEG base (B), and with plain witepsol H_{15} base (C).

c: Capillary vessels; E: Epithelium, G: Goblet cells; LP: Lamina Propria.

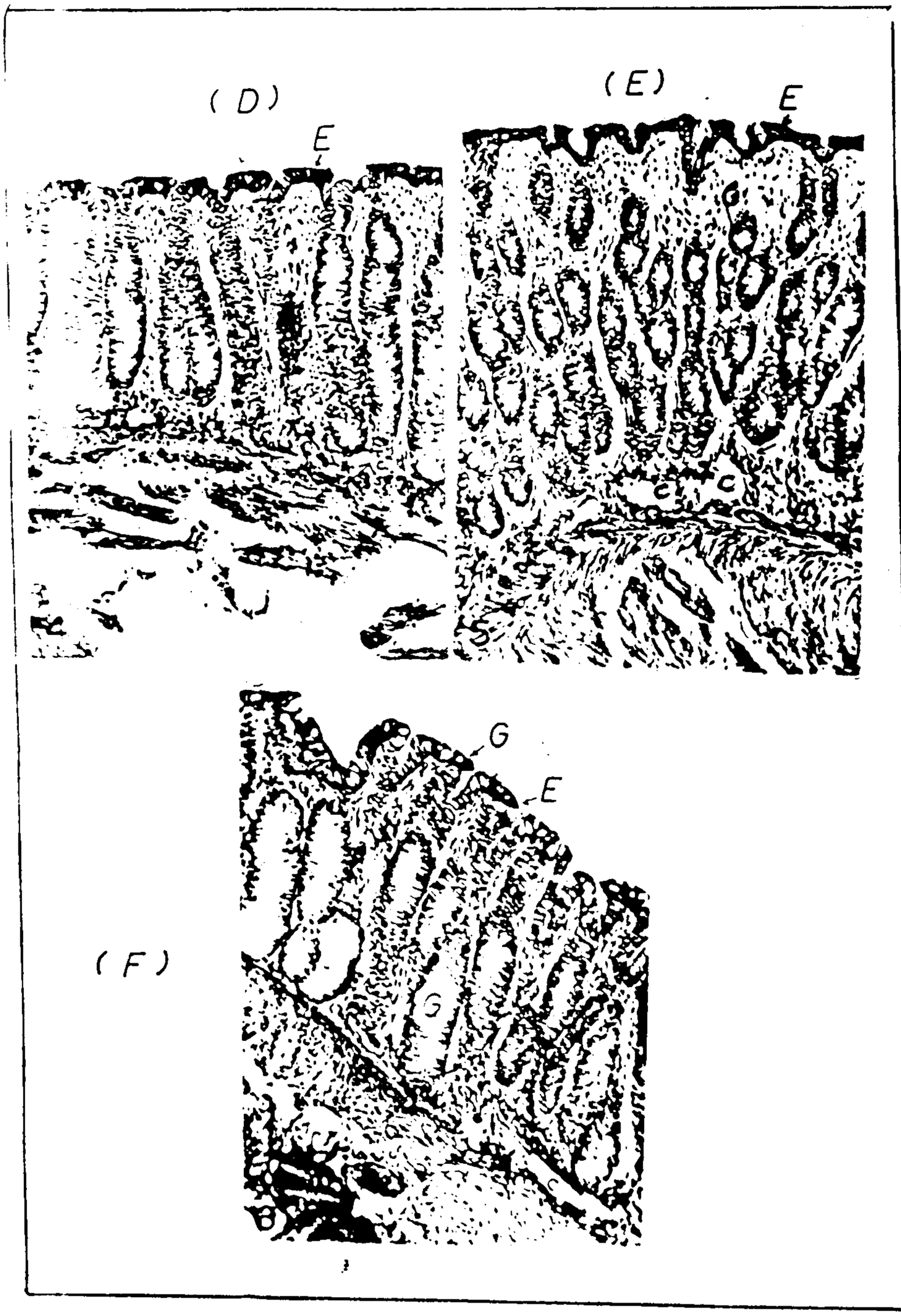

Figure 7 : The rectal mucosa of rabbits trated with medicated Witepsol H_{15} base (D), with medicated emulsion base (E) , and with medicated Cacao butter base (F).

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تحضير وتقويم صياغات مختلفة لأقماع هيدروكلوريد الكلورديازيبوكسيد

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تضمن هذا البحث عمل صياغات متعددة من الأقماع الشرجية لعقار هيدروكلوريد الكلورديازيبوكسيد ، وقد تم دراسة تأثير نوع القاعدة المستخدمة ومكوناتها على معدلات انطلاق العقار . كذلك تم دراسة تأثير تركيز العقار وحجم جزيئاته على انطلاقه من القواعد المختلفة . وقد أعطت كل من ويتبسول هـ ١٥ والقاعدة المكونه من خليط عديد اثيلين الجليكول ١٠٠٠ ، ٤٠٠٠ (٣:٩٧)وكذلك القاعدة المستحلبة المكونة من ويتبسول هـ ١٥ كوسط زيتى وعديد أثيلين الجليكول كوسط مائى أعلى معدلات لأنطلاق العقار . كذلك تم دراسة التغيرات التشريحية على أنسجة المستقيم للأرانب نتيجة لتعاطيها الأقماع الشرجية المحضره من القواعد المختلفة لمدة عشرة أيام متتالية فى وجود أو غياب العقار ولم يلاحظ أى تغييرات ملموسه على هذه الأنسجة .

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