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MEDICAMENT RELEASE FROM OINTMENT BASES: II. TESTOSTERONE: IN VITRO RELEASE AND EFFECTS OF ADDITIVES ON ITS RELEASE.

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ABSTRACT

The in vitro release of testosterone from three different ointment bases including, the water washable, the modified Beller and the modified hydrophyllic ointment base, U.S.P. were studied. Among the bases evaluated, the water washable ointment base provided the better release of the drug. In addition, the effects of various additives (3,5 and 10% urea, 5% ethyl alcohol, 5% DMSO, 3,5 and 10% PEG-400, and a combination of 5% ethyl alcohol and 5% DMSO) on the release of testosterone from the water washable base were investigated. The additive ingredients at 3 and 5% level had little or no effect on the release of drug when compared to the control water washable base. However, the release was significantly

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higher from the same ointment base containing 10% by weight of PEG-400 and 10% by weight of urea respectively. In addition, the values for the release rate constant, the diffusion coefficient, the permeability coefficient and the partition coefficient were calculated to develop the meaningful kinetic parameters to assess the release of this hydrophobic drug from a topical dosage form.

INTRODUCTION

In vitro procedures have been widely used to evaluate drug release from various types of pharmaceutical formulations especially ointment by utilizing diffusion processes {1, 2, 3}.

Testosterone and its derivatives are the most commonly used androgenic steroids. In addition to their androgenic properties, they exert anabolic effects {4}. Testosterone when injected as a solution in oil is so quickly absorbed, metabolized, and excreted that the androgenic effect is minimal. Testosterone given by mouth is readily absorbed, but it is even less effective since most of the hormone is metabolized by the liver before reaching the systemic circulation {5}.

During the process of drug absorption from ointments it is likely that diffusion plays an important role, and the drug must be released from the ointment vehicle before absorption takes place. In addition, the release

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of the drug from the vehicle depends on physicochemical parameters such as the diffusion coefficient, the permeability coefficient and the partition coefficient. These parameters may serve as a model for predicting drug release patterns and screening formulations with maximum therapeutic activity. The aim of this investigation was to formulate a testosterone ointment dosage form which will overcome some of the above mentioned shortcomings associated with testosterone therapy. Also, to study the in-vitro release of testosterone from different ointment bases, the influence of the additives on its release rate, and calculate the diffusion coefficient, the permeability coefficient and the partition coefficient values.

EXPERIMENTAL

Materials

The following chemicals were used as received from the manufacturers: Testosterone[1], multisterol extract of lanolin[2], isopropyl lanolate[3], glyceromonostearate self-emulsifying[4], polyoxyethylene stearate[5], stearyl alcohol[6], and cellophane membrane (molecular weight cut-off point 1000)[7]. All other chemicals were of reagent grades and used as received.

Ointment Formulations

Testosterone was formulated in ointment dosage forms by utilizing water washable base, revised

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Table I. Testosterone Ointments

Ingredients	% w/w
Water Washable Base	
Multisterol extract of lanolin	5.000
Isopropyl ester of lanolin fatty acids	2.000
Petrolatum USP	20.000
GMS-SE	5.000
Myrj-52	4.000
Stearyl Alcohol	3.000
Propyl Paraben	0.067
Methyl Paraben	0.150
Glycerin	5.000
Testosterone	1.000
Additives	3, 5 or 10
Distilled Water q.s.to	100.000
Revised Hydrophilic Ointments USP (o/w)	
White Petrolatum	25.000
Stearyl Alcohol	15.000
Sodium Lauryl Sulfate	1.000
Propylene Glycol	12.000

hydrophilic ointment USP and revised Beller's base as shown in Table I. All ointments were prepared by the fusion method.

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Table I. Testosterone Ointments (continued)

Ingredients	% w/w
Propyl Paraben	0.015
Methyl Paraben	0.025
Testosterone	1.000
Distilled Water q.s. to	100.000
Revised Beller's Base (o/w)	
Cetyl Alcohol	15.000
White Wax	1.000
Stearyl Alcohol	2.000
Propylene Glycol	10.000
Sodium Lauryl Sulfate	2.000
Propyl Paraben	0.015
Methyl Paraben	0.025
Testosterone	1.000
Distilled Water q.s. to	100.000

Release Studies

A preweighed one ounce ointment jar having surface area of 6.83 cm^2 was filled with each ointment formulation. The excess of the ointment was removed from the edge of the jar with a spatula to produce an even surface, and the weight of the ointment in the jar was determined. The open end was covered by a semipermeable

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cellophane membrane, previously soaked in phosphate buffer (pH = 6) for 6 hours. It was carefully pressed to ensure a complete contact of the membrane with the ointment and sealed by a silk thread.

The jars were invertedly immersed in a 250 ml. beaker containing preheated 100 ml. of phosphate buffer (pH = 6.00) and maintained at 37 ± 1°C in a constant temperature water-bath. At 5, 15, 30, 45, 60, 90 and 120 minutes the aliquots of the diffusion medium were drawn off and replaced with equal volume of the phosphate buffer. During the experiment the diffusion medium was constantly stirred to maintain sink conditions. The samples were assayed spectrophotometrically at 240 nm and the concentrations of testosterone released were determined from a standard curve constructed from known concentrations of drug in the same diffusion medium.

RESULTS AND DISCUSSION

The in vitro data of testosterone from the three bases and the effects of the additives on its release from water washable base are shown in Fig. 1 and 2 respectively. These logarithmic presentations were constructed by plotting log (100-R), where R is the mean percent release vs time. These lines indicate a linear relationship for all cases except for the water washable base with 10% PEG-400 as shown in Fig.2. Since PEG-400

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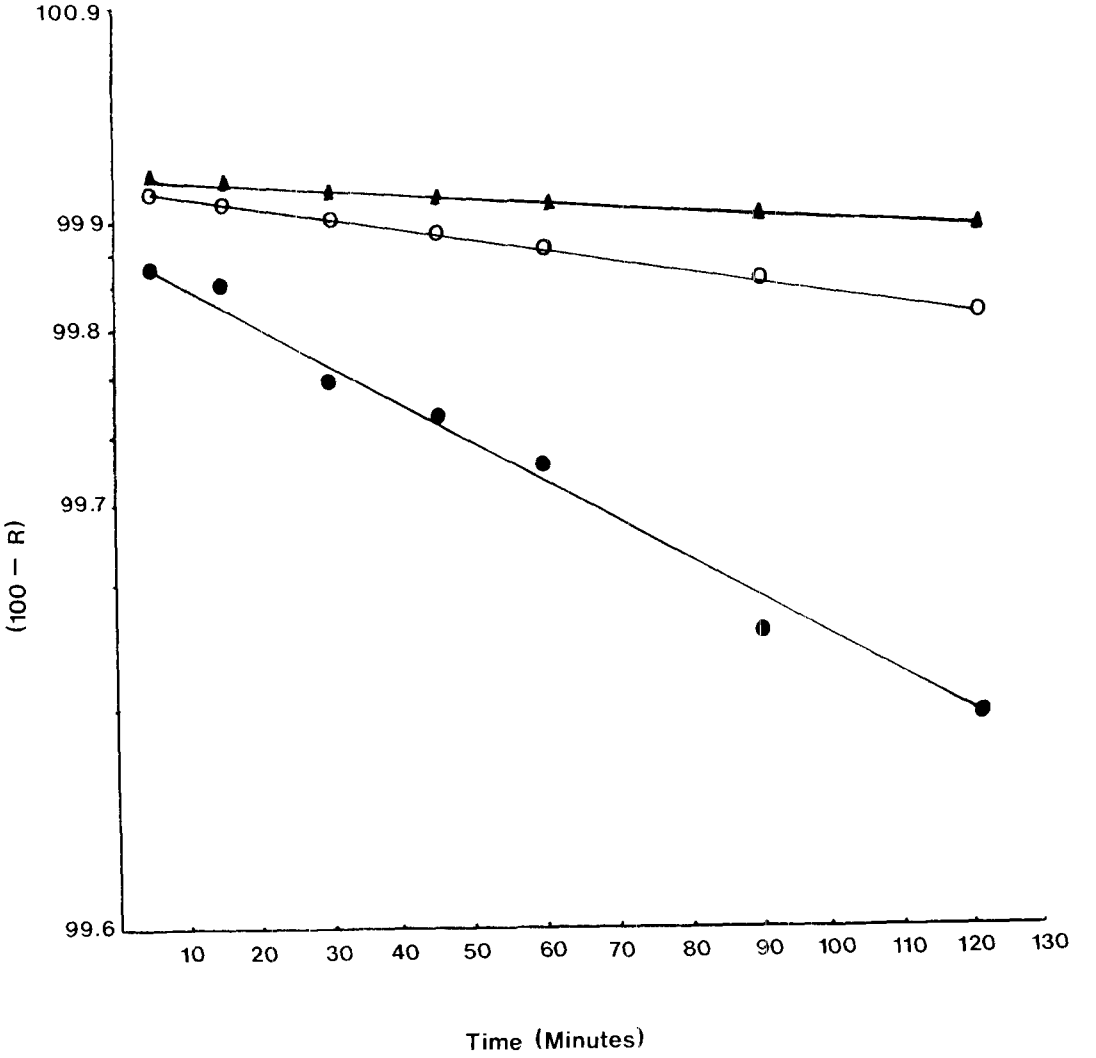

FIGURE 1

Logarithmic Presentation of Release of Testosterone from Ointment Bases: Key: ▲, Revised Beller's Base; O, Revised Hydrophilic Ointment Base; ◐, Water Washable Base.

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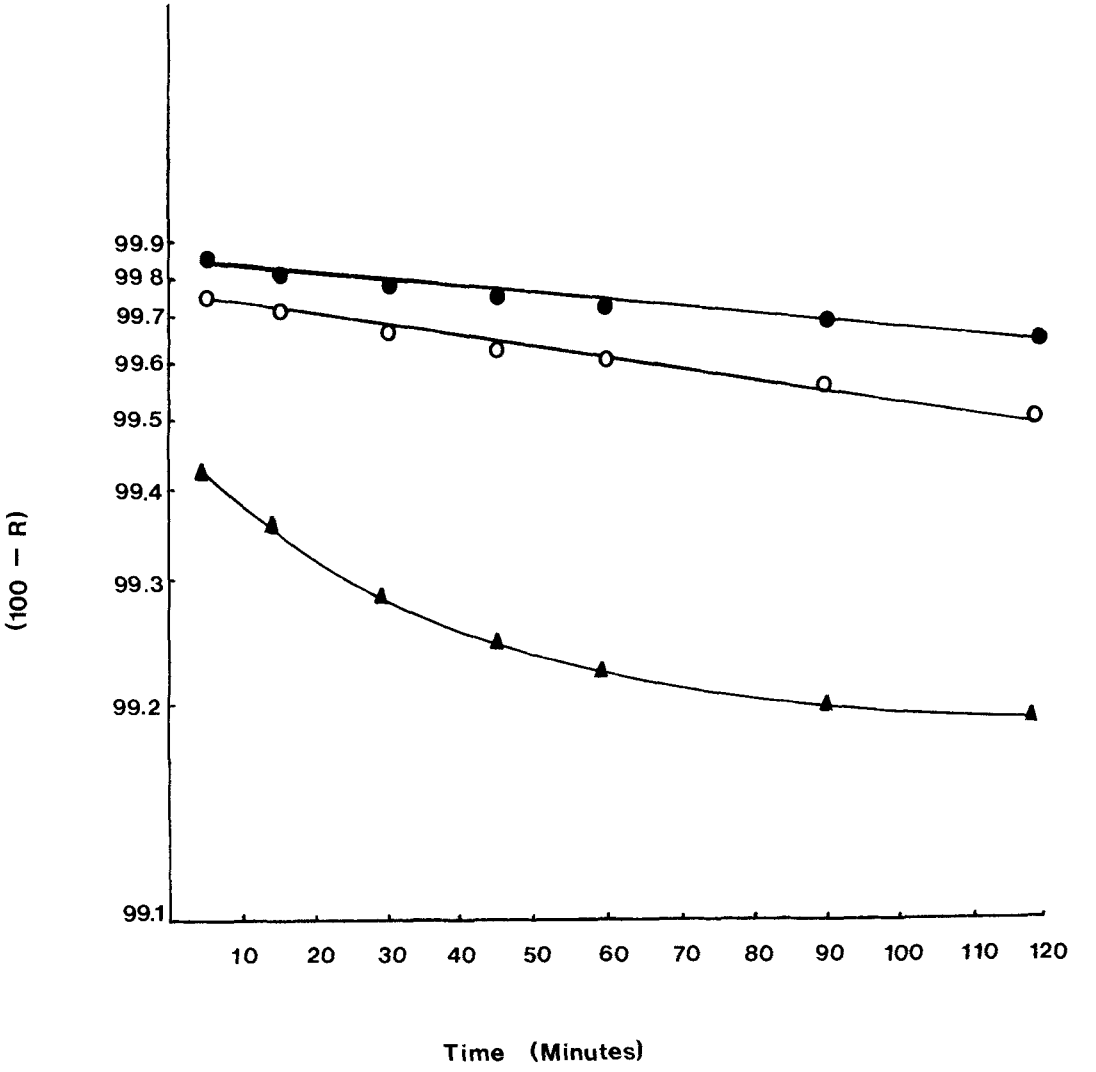

FIGURE 2

Logarithmic Presentation of Release of Testosterone from Water Washable Base: Key: ●, Water Washable Base; O, 10% Urea; ▲, 10% PEG-400.

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has excellent solubility in water, during the experiments it was observed that the water washable ointment with the 10% PEG-400 absorbed water to the extent that the surface of the membrane became visibly concave. From these figures the release rate constants were calculated and the data are exhibited in Table II. From this, it is apparent that testosterone was released to a greater extent and at a faster rate from the water washable base than the other formulations. Furthermore, the presence of additives in the water washable base had no effect on the release, with the exception of 10% urea which increased the release by 50% and 10% PEG-400 which is almost doubled the release of testosterone as from the control and is shown in Fig. 2.

The release of a drug from an ointment in which the drug is initially uniformly dissolved, generally follow the well-known Higuchi Equation (2,6).

$$Q = 2\, C_O \left(\frac{D\, t}{\pi}\right)^{\frac{1}{2}} \qquad \text{(Eq. 1)}$$

where, Q = amount of drug release per unit area (mg/cm^2)
C_O = initial concentration of drug in ointment (mg/cm^3)
D = diffusion coefficient of drug in ointment (cm^2/sec)
t = time after application (sec).

Equation (1) theoretically, states that the amount of drug release per unit area is directly proportional to the square root of time; C_O, D and A being constant

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TABLE II

Diffusion Coefficient, Permeability Coefficient, Partition Coefficient and Release Rate Constants of Testosterone from Various Ointments

Ointment	Diffusion Coefficient from graphs (cm^2/sec) D	Diffusion Coefficient from experimental points* (cm^2/sec) D	Permeability Coefficient (cm/sec) P	Release Rate Constant (min^{-1}) k	Partition Coefficient K_p
Water washable	1.12×10^{-6}	1.22×10^{-6}	3.05×10^{-6}	4.90×10^{-4}	0.2
Hydrophilic revised	3.60×10^{-7}	3.35×10^{-7}	1.55×10^{-6}	3.65×10^{-3}	0.371
Beller's revised	1.20×10^{-7}	1.30×10^{-7}	9.94×10^{-7}	3.84×10^{-3}	0.6137
Water washable with 10% urea	1.10×10^{-6}	3.60×10^{-6}	5.30×10^{-6}	4.22×10^{-3}	0.1185
Water washable with 10% PEG-400	2.12×10^{-6}	1.40×10^{-5}	1.10×10^{-5}	-----	0.061

* each is the average of values determined at the end of 30, 60, 90 and 120 minutes.

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for a particular system. To ensure that the experiments were carried out under "sink" condition throughout the two hours, an equilibrium study was undertaken and the results are shown in Fig. 3 and 4. It is apparent that by the end of eight hours the diffusion medium was able to accomodate the released testosterone. And, when the amount of drug released per unit area was plotted against the square root of the time, a straight line was obtained indicating a linear relationship as shown in Fig. 5 and 6.

By utilizing the data from figures 5 and 6 the diffusion coefficient were calculated and are reported in Table II. Simultaneously the diffusion coefficient values calculated from the actual experimental data are reported in Table II. As it is seen from the data in Table II, a good agreement is found between the values of diffusion coefficients calculated from the slope of the lines and the calculated values obtained from experimental data.

The permeability coefficients (P) for each base were determined by using equation 2 and are reported in Table II.

$$P = \frac{Q}{A\,C_o t} \qquad \text{(Eq. 2)}$$

where, Q = the amount of drug released (mgs) at time t, A = area (cm^2) and C_o = initial concentration of drug

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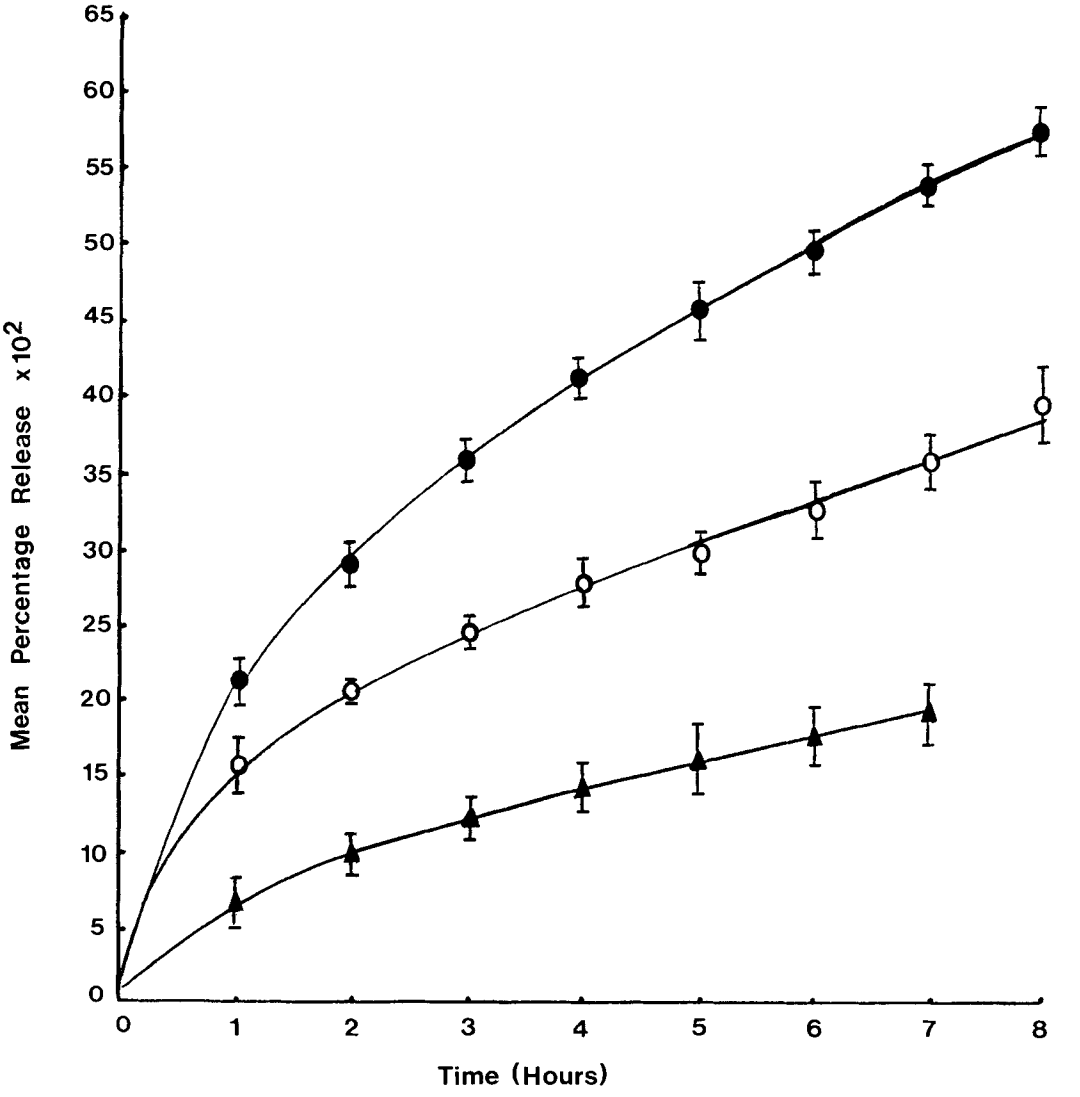

FIGURE 3

Release of Testosterone from Different Ointment Bases: Key: ▲, Revised Beller's Base; O, Revised Hydrophilic Ointment Base; ● Water Washable Base.

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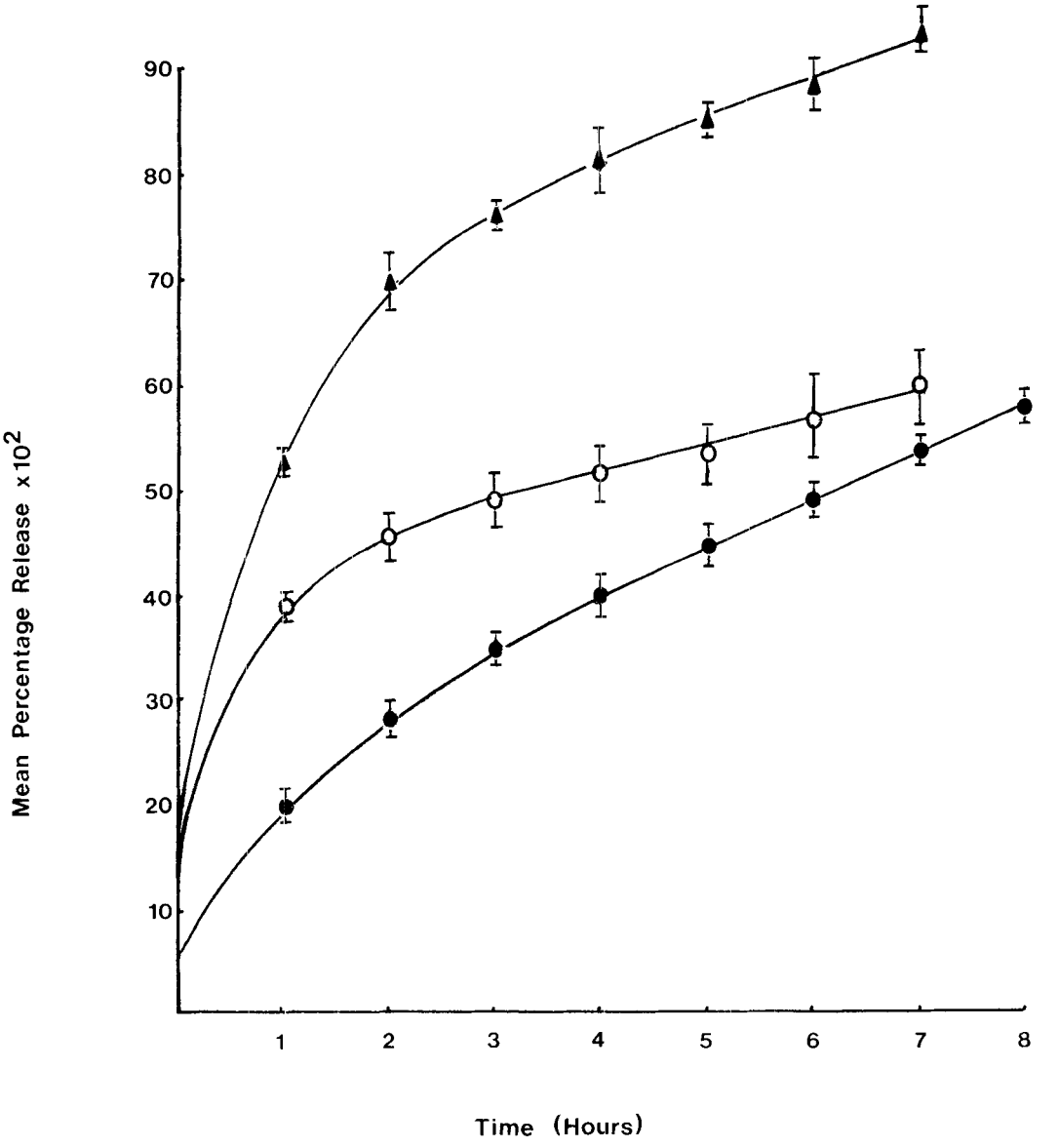

FIGURE 4

Effect of Additives on the Release of Testosterone from Water Washable Base: Key: ● , Water Washable Base; O , 10% Urea; ▲ , 10% PEG-400.

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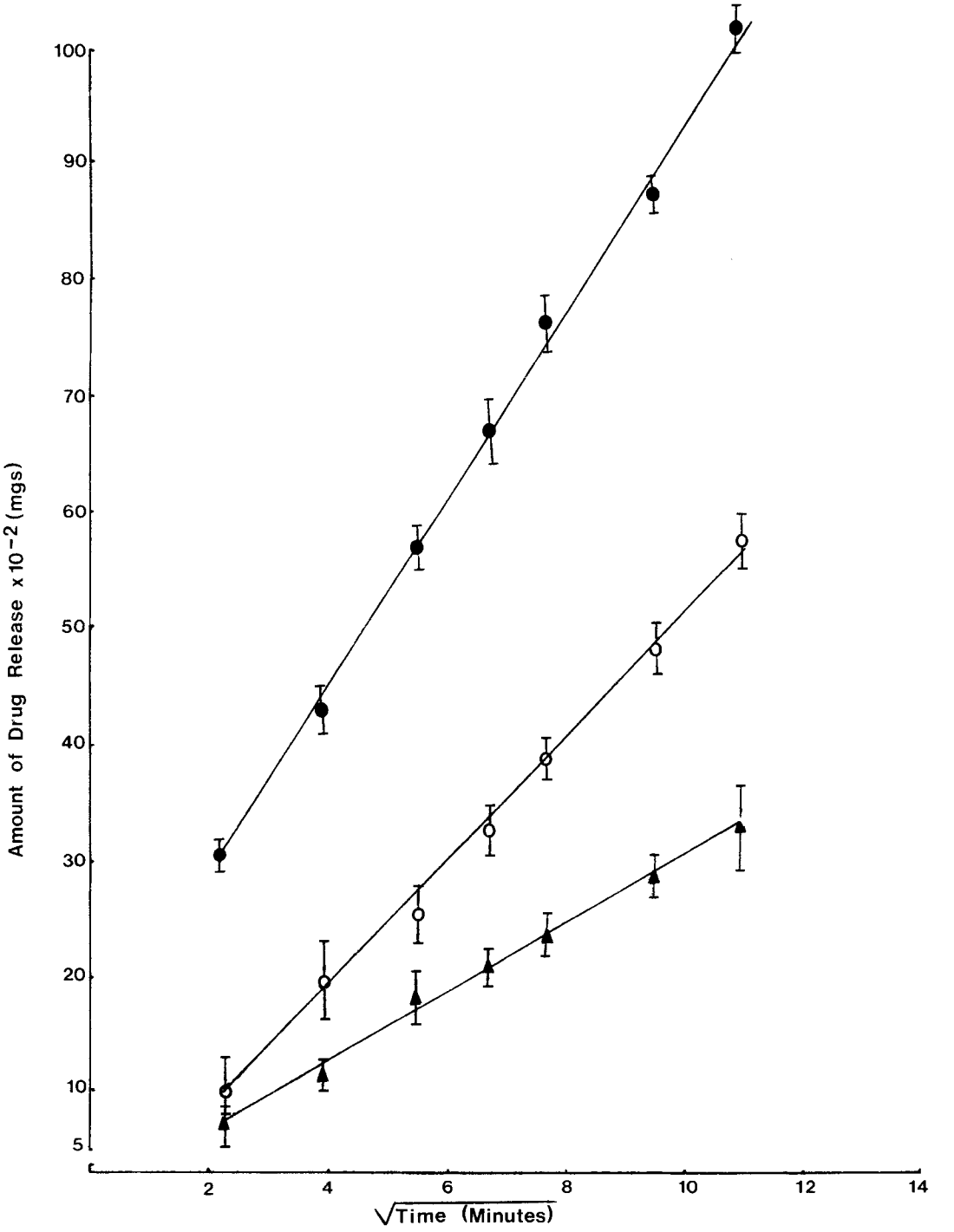

FIGURE 5

Amount of Testosterone Release as Function of $(time)^{1/2}$: Key: ▲, Revised Beller's Base; O, Revised Hydrophilic Ointment Base; ●, Water Washable Base.

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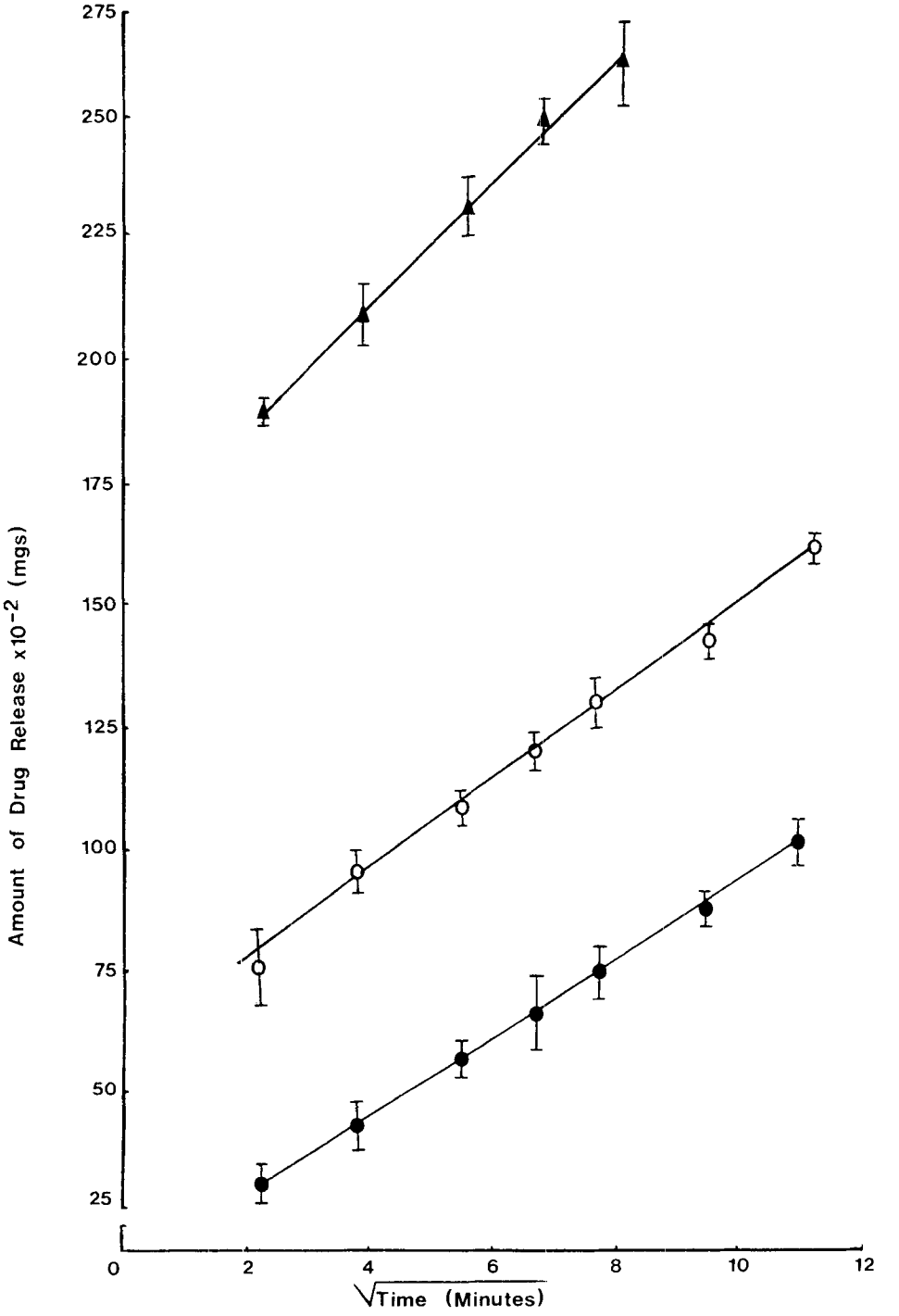

FIGURE 6

Amount of Testosterone Release as Function of $(time)^{1/2}$: Key: ●, Water Washable Base; O, 10% Urea; ▲, 10% PEG-400.

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(mg/cm^3). The data used for the calculation of the permeability coefficients were obtained from the Fig. 5 and 6.

The partition coefficients were calculated by utilizing the following equation and are also given in Table II.

$$K_p = \frac{P\ h}{D} \qquad \text{(Eq. 3)}$$

where, K_p is partition coefficient, P is permeability coefficient (cm/sec), h is thickness of the barrier (0.08 cm) and D is diffusion coefficient (cm^2/sec). It is evident from the data in Table II that the amount of drug released tends to decrease as the affinity of drug to the vehicle is increased.

The reasons for the enhanced release of testosterone from the ointment bases containing PEG-400 and urea are likely to be due to the co-solvency effect of PEG-400 and an increase in osmotic pressure of the base which could influence the penetration of the drug.

The in-vivo absorption properties of the drug are as important as the in-vitro release of the drug. Therefore, it is not necessarily possible to correlate the in-vitro and in-vivo data. However,the in-vitro release data serves as a model and makes it possible to screen formulations with optimum drug delivery for in-vivo evaluation. Based on these findings the in-vivo work is presently underway and the results will be reported accordingly.

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FOOT NOTES

[1] Roussel Corp., New York, NY

[2] Amerchol Cab, Amerchol Corp., NJ

[3] Amerlate P, Amerchol Corp., NJ

[4] Ruger Chemical Inc., NJ

[5] Myrj-52, I.C.I. United States Inc., NJ

[6] Amend Drug & Chemical Corp., NJ

[7] Spectrum Medical Industries, CA

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