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PREPARATION AND EVALUATION OF HYDROXYZINE SUPPOSITORIES

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ABSTRACT

Hydroxyzine is a piperazine derivative recommended for treatment of anxiety. The drug was formulated in suppository forms using different types of fatty, emulsion and water soluble bases. Non ionic surfactants as well as aerosils were used as formulating additives. The drug release from the formulating bases as well as the tranquilizing potency in mice were evaluated. It was found that formulations which afford the higher release rates in the in-vitro study, give also the more pronounced tranquilizing effect in the animal testing.

INTRODUCTION

The importance of drug release studies from suppositories has been recognized by several workers[1-3]. The physicochemical properties of active ingrdients and the nature of suppository bases are the most important factors[4-8]. The effect of incorporating nonionic surfactants into the suppository bases has been extensively studied[9-18]. Colloided silica (Aerosil) is also incorporated to improve certain other properties of suppository bases. Its addition, generally, resulted in retarding or blocking the medicament release from the treated bases[19&20].

Various attempts have been made to correlate the *in-vitro* and *in-vivo* data regarding drug release from suppositories. Kuhne[21] concluded that the *in- vitro* results cannot serve as basis for the prediction of *in-vivo* absorption profile. The conclusion was based on the fact that the *in-vitro* conditions can not take into account the conditions prevailing in the rectum specially the fluid content, the viscosity and chemical

composition of the mucous and the pressure exerted by the rectum walls on the suppository.

Hydroxyzine HCl is a piperazine derivative, classified as an antihistaminic drug, CNS depressant, anticholinergic and skeletal muscle relaxant. It is widely used in the management of anxiety, tension and to control motion sickness, nausea and vomiting of various etiologies[22&23]. Anxiety is frequently associated with clinical or pathological conditions in which the oral route is inconvenient or even impossible. On the other hand, parenteral administration of many antianxiety drugs is not recommended due to their several complications.

In recent years, the rectal absorption of similar drugs has been studied. The potential success of this route attracts the attention to formulate Hydroxyzine HCl in suppositories. Different suppository bases were employed to formulate Hydroxyzine HCl. Non-ionic surfactants as well as aerosils were also investigated as formulating additives.

EXPERIMENTAL

Materials :

Hydroxyzine HCl; Hz.HCl (Roerig, U.S.A.). Cacao butter (B.P. grade). Witepsol H_{15} and Witepsol E_{75} (Dynamit Nob., Germany). Polyethylene glycols (PEG's) 400, 600, 1000, 1500, 4000 and 6000 (Fluka, A.G. Switzerland). Span 60; Polysorbates (Tweens) 20, 60, 61 and 65; Myrjs 52 and 53; Brijs 35, 52 and 68 (Atlas Chem. Ind. U.S.A.). Aerosils (Degussa, U.K.). Semipermeable cellophane membrane (30/32, Fischer Sci. Co., U.K.). All other chemicals were of analytical reagent grades and were used as received without further purification.

Apparatus :

Thermostatically controlled water bath fitted with shaker (Unitronic 320 OR, Selecta, Italy); Melting point apparatus (Gallenkamp, Germany), Erweka hardness tester SBT and disintigration time tester SSP (Erweka, Germany); Locally manufactured apparatus for the determination of liquifaction point; pH meter (Tacussel Solea, Lyon, France); Rota-rod treadmills for mice (UGO, Italy).

Preparation of Suppositories :

Twelve bases were employed to prepare Hz-HCl suppositories. The composition of these bases is presented in Table 1. Both the fatty and the polyethylene glycol bases were prepared according to the fusion technique. The emulsified bases were prepared by dissolving the selected surfactant (s) in either the hydrophilic or lipophilic phase. The two phases were then mixed thoroughly at 40°C and left to cool. Hz- Hcl (size fraction 63-90 um) was used in a concentration of 25 mg/each suppository. Certain other formulations were also prepared by the use of a blend of Witepsol H_{15} and either hydrophilic or hydrophobic aerosil (1,2 & 3%) or any of the tested nonionic surfactants (5%) as the base.

Evaluation of Hydroxyzine HCl Suppositories :

1-Drug Content :

The prepared suppositories were evaluated for their drug content and weight variation according to

B.P.C. 1973[24] and B.P. 1980[22] respectively. The procedure adopted to determine drug content varied according to type of the base as follows : a) for fatty bases : the drug was extracted from the melted suppositories using five successive portions (10 ml each) of warmed distilled water. b) for water soluble bases : the tested suppository was dissolved in an appropriate volume of warmed distilled water. c) for emulsified bases : the suppositories were firstly dissolved in ether then, the drug was extracted by the use of five successive portions of distilled water (20 ml each).

2-Physical Stability :

The prepared suppositories were examined visually, during a period of one year after preparation, for the following: fissures, wrinkles, blooming, colour change and crystalline materials on the surface.

3-In-Vitro Release Characteristics :

The release of Hz-HCl from the prepared suppositories was carried out using the dialysis technique[25]. The dialysis system was prepared as follows : A piece of standard cellophane membrane, 4 x 4 cm, was soaked in distilled water over night before use. The membrane was firmly stretched over the lower opening of a glass cylinder (internal diameter = 28 mm) to form the donor. The donor was placed into a beaker containing 200 ml of saline solution at 37°C (acceptor). The dialytic unit was placed in a thermostatically controlled water bath and machanically shaken at 25 shake/min. One suppository, along with 10 ml of saline solution, at 37°C, was introduced into the donor compartment. The donor was located in the system in a manner that the cellophane membrane just in contact with the upper surface of the sink solution. After time intervals, a 5 ml smaple was withdrawn from the acceptor and immediately replaced by an equal volume of saline solution at 37°C. The amount of drug released into the sink medium was determined by measuring the absorbance at 230 nm.

4-Assessment of Pharmacological Potency :

A-Formulation

Four bases were selected to prepare the rectal formulations. The composition of the formulating bases is given in Table 2.

Hz-HCl was incorporated into each base, at concentrations of 0, 0.60, 0.12, 0.24, 0.48, 0.96 and 1.92 mg/ul of the melted base. The same concentrations were also prepared but in 0.2 ml of water for injection, instead of the melted base, for use in the i.p. injection.

B-Principles :

The pharmacological basis used in the evaluation of these formulations depends on the drug effect on the motor coordination.

C-Apparatus :

The rotated apparatus as modified by Kalir et al[26]. was used, Fig. 1. The apparatus is basically consisted of five drums which are suitably machined to provide grip; six flanges divide the drums, enabling five mice to be on the treadmill simultaneously. The apparatus is provided with five second counters.

D-Procedure :

350 mice, each weighing 18-20 g, were used in this study, The mice were divided into groups, each of ten mice. One group was used for each of the aforementioned concentrations. The melted rectal formulations were inserted inside the rectum using a specially designed applicator. The anus was immediately closed using one drop of polyurethane solution in ether. Each mouse was tested for its motor coordination after 30 minutes of drug administration. This time was experimentally determined and gives an indication to the drug absorption rate for the tested formulations. The test was done by determining the mouse ability to remain on the rotating rod without falling for 15 minutes. The apparatus was set in motion before placing the mice in position. The mice were then placed one by one in their respective sections. At the same time the zero key of the corresponding counter was turned off and the time was recorded for each mouse.

RESULTS AND DISCUSSION

Hz-HCl suppositories were prepared using different suppository bases. The prepared suppositories were found to comply the pharmacopeial requirements for weight variation[22] as well as drug content[24]. It should be noted that all the prepared Hz-HCl suppositories were found to show neither color devlopment nor surface changes during one year of storage.

In-Vitro Release of Hz-HCl from Suppositories :

The *in-vitro* release of Hz-HCl from the tested suppository through cellophane membrane, was investigated at 37°C. The drug release data were analyzed according to zero-order and first order kinetics as well as the diffusion controlled model. A good correlation was obtained when the data were treated according to first order mechanism.

Figure 2 shows the release profile of Hz-HCl from the tested fatty bases. It could be observed that the formulating bases can be arranged according to the drug release rate thereof as Witepsol H_{15} > Cacao butter > Witepsol E_{75}. The results can be attributed to the release rate dependency on both the melting behaviour and chemical composition of the tested bases. In this repect Witepsol H_{15} which has the same composition as witepsol E_{75} but of lower melting range, it exhibited a higher release rate. On the other hand, Cacao butter which has the same melting range as Witepsol H_{15} but differs in chemical composition, it gave a slower rate of release. The presence of monoglyceride in case of witepsol H_{15}, as a self emulsifier, enhance the release thereof.

Figure 3 shows the release pattern of the drug from different PEG bases. These water soluble bases could be arranged in the following ranked order according to their ability to release the medicament as:

PEG 4> PEG 3> PEG 2> PEG 1.

This arrangement could be explained on the basis of the dissolution time (Table 1), which in turn, is a function of the molecular weight. Addition of water (PEG 2) was found to be accompanied with an increase in the drug release rate. This finding is in agreement with that obtained by Puffer and Crowell[27] and Kellaway and Marriott[28].

The release pattern of Hz-HCl from the emulsion bases is depicted in Figure 4. The tested bases could be ranked according to their tendency to release the medicament as follows : $E_4 > E_3 > E_2 > E_1$. These results could be explained according to the fact that as the disintegration time decreased (Table 1) the base will exhibit an enhanced tendency to release the medicament. In this respect, the use of Witepsol E_{75} as an oily phase, was found to be accompanied by a longer disintegration time. Accordingly the formulated suppository bases with E_{75} (E_1 and E_2) exhibited lower release rates. When Witepsol H_{15}, the reverse effect was attained (E_3 and E_4). At the same time the use of sodium alginate was found to shorten the disintegration time. An effect which enhances the release rate (E_2 and E_4) compared with those bases containing CMC (E_1 and E_3). The use of a blend of fatty and water soluble bases (B_1) was found to exhibit a marked increase in the release rate. A result which can be attributed to the rapid disintegration of such formulation.

The effect of incorporating different nonionic surfactants on the *in-vitro* release of Hz-HCl from Witepsol H_{15} was studied. The tested surfactants were selected to cover a wide range of HLB values as well as different chemical composition.

The incorporation of 5% w/w of either polysorbate 20 or 60 was observed to enhance significantly, the release rate of Hz-HCl, Table 3. On the other hand, when polysorbate 61 or 65, is incorporated into Witepsol H_{15}, there was insignificant effect on the amount of the drug released. In view of these results, the HLB and chemical composition as well as the effect on the physical properties of the tested base, appeared to be effective parameters.

Brijs 35, 52 and 58 were found to enhance the amount of drug release to approximately the same extent Table 3. From this result, it could be deduced that, the HLB values of the tested Brijs can not account for their effect on the observed drug release pattern.

The incorporation of 5% either Myrj 52 or Myrj 53 was found to have insignificant effect on the amount of drug released.

Figure 5 shows that the addition of both types of aerosils has a retarding effect on the release profile. Both hydrophilic and lipophiiic aerosils were found to elevate the m.p. and prolong the disintegration time of the base to a value dependent on the concentration of aerosil added. In addition to their effect on the physical properties of the base, aerosils were found to retard the sedimentation of the suspended drug particles through the melted base via increasing viscosity and in turn, will result in a decrease in the amount of the drug released. These results are in agreement with those previously reported by Liebl et al[30], who concluded that the addition of aerosils decreased the re-

lease of both suspended and dissolved drugs from triglyceride supportories.

Assessment of the Pharmacological Potency of Hz-HCl Rectal Formulations:

The tranquilizing potency of Hz-HCl rectal formulations were evaluated adopting the "Rota-rod" technique[26]. In this study, drug induced-ataxia in mice, was evaluated after rectal administration of graded doses of the drug formulated in four selected suppository bases. The same doses of the drug were injected intraperitoneally, and their effects were also investigated. The mean indurance time, in seconds, was determined for each dose of the tested formulations and the i.p. injection, Table 4. The percentage response was calculated in each case, Table 5, using the following equation :

$$\% \text{ response} = \frac{100\ (C-X)}{C}$$

where; C is the mean indurance time control and X is the mean indurance time after 0.5 hr of drug administration. The medium effective doses (ED_{50}) and its 95% confidence limits for interference with coordination was calculated adopting the method of Litchfield and Wilcoxon[31]. The relative potency of each rectal formulation to i.p. injection was also calculated. The results are tabulated in Table 6 and graphically in Figures 6 & 7. From these results, it is clear to observe that, the drug is adequately absorbed from the rectal formulations in mice. Comparing the potency of the tested Hz-HCl rectal formulations revealed that formulation III is equipotent as formulation IV which, in turn, is more potent than formulation II. However, formulation I was found to have the least tranquilizing effect. It was noticed that, the bases afforded the higher in-vitro release rate of the drug; III & IV, gave also the more pronounced tranquilizing effect in the animal testing. The same conclusion on comparing formulation II with formulation I can be withdrawn.

It is worthy to note that the tranquilizing effect of the i.p. injection of Hz-HCl is more pronounced than any of the tested rectal formulation. This result does not mean a lower bioavailability of the drug from the ractal formulations, but may be attributed to the fact that the test is being done 0.5 hr after administration. This means that the drug level at its site of action, following rectal administration is still in the absorption phase and does not reach the peak concentration. However, the absorption of the drug after i.p. injection was so rapid that it attains the peak level at a relatively shorter time.

CONCLUSION

On the basis of the previous findings the following could be deduced :

1-Hydroxyzine was found to be rectally absorbed.

2-The rectal absorption profile of the drug is formulation dependent.

3-There is a correlation between the *in-vitro* release rate of the drug and its pharmacological effect.

Table 1 : Characteristics of the Tested Suppository Bases

Base No.	Composition	%w/w	L.P. °C	D.T. (min.)	H. Kg.
	A- Fatty Bases				
1	Witepsol H_{15}	100	34.5	11	2.1
2	Witepsol E_{75}	100	38.0	18	2.6
3	Cacao butter	100	34.0	8	0.6
	B- Water Soluble Bases				
4 (PEG_1)	PEG 400	40	60.0	40	3.6
	PEG 6000	60			
5 (PEG_2)	PEG 400	20	48.0	28	2.6
	PEG 6000	60			
	Distilled water	20			
6 (PEG_3)	PEG 1000	70	45.0	19	2.5
	PEG 4000	30			
7 (PEG_4)	PEG 1000	97	37.5	13	0.8
	PEG 4000	3			
	C- Emulsion Bases				
8 (E_1)	Witepsol E_{75}	50	37.5	33	0.6
	Sod. CMC	1			
	Tween 20	4			
	Distilled water	45			
9 (E_2)	Witepsol E_{75}	50	37.0	26	0.6
	Sod. alginate	2			
	Tween 20	4			
	Distilled water	44			
10(E_3)	Witepsol H_{15}	50	35.0	27	0.6
	Sod. CMC	1			
	Tween 20	4			
	Distilled water	45			
11(E_4)	Witepsol H_{15}	50	35.0	19	0.6
	Sod. alginate	2			
	Tween 20	4			
	Distilled water	44			
	D- Blend of water soluble and fatty bases				
12 (B_1)	Witepsol H_{15}	34	34.5	8	0.8
	Tween 20	5			
	Span 60	1			
	PEG 1500	40			
	PEG 600	20			

L.P. Liquifaction point, D.T. Disintegration or dissolution time, H. Hardness at 25°C

Table 2 : Composition of the Formulating Bases.

Formulation	Ingredient %						
	Witepsol H_{15}	Tween 20	Span 60	PEG 600	PEG 1000	PEG 1500	PEG 4000
I	100	-	-	-	-	-	-
II	97	5	-	-	-	-	-
III	-	-	-	-	97	-	3
IV	34	5	1	20	-	40	-

Table 3 : Analysis of Variance of the Mean Percentage Released of Hydroxyzine Hydrochloride from Witepsol H_{15} Containing 5% of Different Non-ionic Surfactants.

Surfactant used	Treatment mean % released	Difference between means								
	X_i	X_i-X_k	X_i-X_j	X_i-X_H	$X_{Ui}-X_G$	X_i-X_f	X_i-X_E	X_i-X_D	X_i-X	X_i-X_B
Tween 20	X_A = 13.30	6.25^{XX}	5.56^{XX}	5.49^{XX}	5.33^{XX}	4.91^{XX}	3.75^{XX}	3.14^{XX}	2.5^{XX}	2.13^{X}
Brij 35	X_B = 11.17	4.02^{XX}	3.25^{XX}	3.36^{XX}	3.20^{XX}	2.78^{XX}	1.62	1.01	0.37	
Tween 60	X_C = 10.80	3.65^{XX}	3.15^{XX}	2.99^{XX}	2.83^{XX}	2.41^{XX}	1.35	0.64		
Brij 52	X_D = 10.16	3.01^{XX}	3.51^{XX}	2.35^{XX}	2.19^{X}	1.77^{X}	0.61			
Brij 58	X_E = .9.55	2.40^{XX}	1.90^{X}	1.74^{X}	1.58	1.16				
Tween 61	X_F = .9.39	1.24	0.74	0.58	0.42					
Myrj 35	X_G = .7.97	0.82	0.32	0.16						
Tween 65	X_H = 7.81	0.66	0.16							
Myrj 52	X_J = 7.65	0.50								
Control	X_K = 7.15									

LSD = 2.30 (P = 0.01) & 1.73 (P = 0.05).

Table 4 : Mean Indurance Time (Seconds ± S.E. in Rota-Rod after, 0.5 Hour of Administration of Graded Doses of Hydroxyzine Hydrochloride in Various Formulations.

Dose mg/kg	Mean indurance time				
	Rectal formulation				Intrapretonial injection
	I	II	III	IV	
Control	900	900	900	900	900
3	900	900	900	900	623(17.06)
6	900	862(14.48)	839(13.31)	844(12.68)	373(11.91)
12	867(15.39)	801(16.15)	657(18.36)	635(14.22)	179(10.30)
24	681(27.17)	588(15.53)	519(15.24)	413(10.96)	36(2.14)
48	425(22.56)	298(19.50)	245(15.93)	210(13.31)	16(1.91)
96	352(20.04)	200(19.74)	129(13.85)	123(9.08)	Convulsion

* This figure repesents the cut - off time

S.E : Standard error.

Table 5 : Mean Percent Inhibition of Motor Coordination in Mice, 0.5 an hour after Administration of Various Hydroxyzine hydrochloride Fromulations.

Dose mg/kg	Mean Precent Inhibition of Motor Coordination				
	Rectal formulation				Intraperitonial injection
	I	II	III	IV	
3	0	0	0	0	30.78
6	0	4.22	6.78	6.22	58.56
12	3.67	11.00	27.00	29.44	80.11
24	24.33	34.67	42.33	54.11	96.00
48	52.78	66.89	72.78	76.00	98.22
96	60.89	75.56	85.67	86.33	Convulsion

Table 6 : Specified Effective Doses and Relative Potency of Various Hydroxyzine hydrochloride Formulations on "Rota-rod" Motor Coordination in Mice.

Parameter evaluated	Calculated Values for the Corresponding Parameter				
	Rectal administration				Intraperitonial injection
	I	II	III	IV	
ED_{16} (mg/kg)	19.00	14.0	10.0	10.0	2.05
ED_{50} (mg/kg)	45.00 (30.0-67.5)	36.0 (24.0-54.0)	24.0 (15.5-37.2)	27.0 (16.5-44.55)	5.00 (3.29-7.60)
ED_{84} (mg/kg)	105.00	78.0	60.0	68.0	12.00
Potency ratio[2]	9.0 (5.00-16.20)	7.2 (4.00-12.69)	4.8 (2.60-8.88)	5.4 (2.84-10.26)	-
Relative potency to I.P. injection	0.11 (0.062-0.20)	0.14 (0.077-6.250)	0.21 (0.113-0.385)	0.19 (0.097-0.352)	1.00

(1) Figures between brackets represent the 95% fiducial limits.

(2) Figures represent the ratio between the potency of Hz-HCl after I.P. injection and that of the corresponding rectal administration.

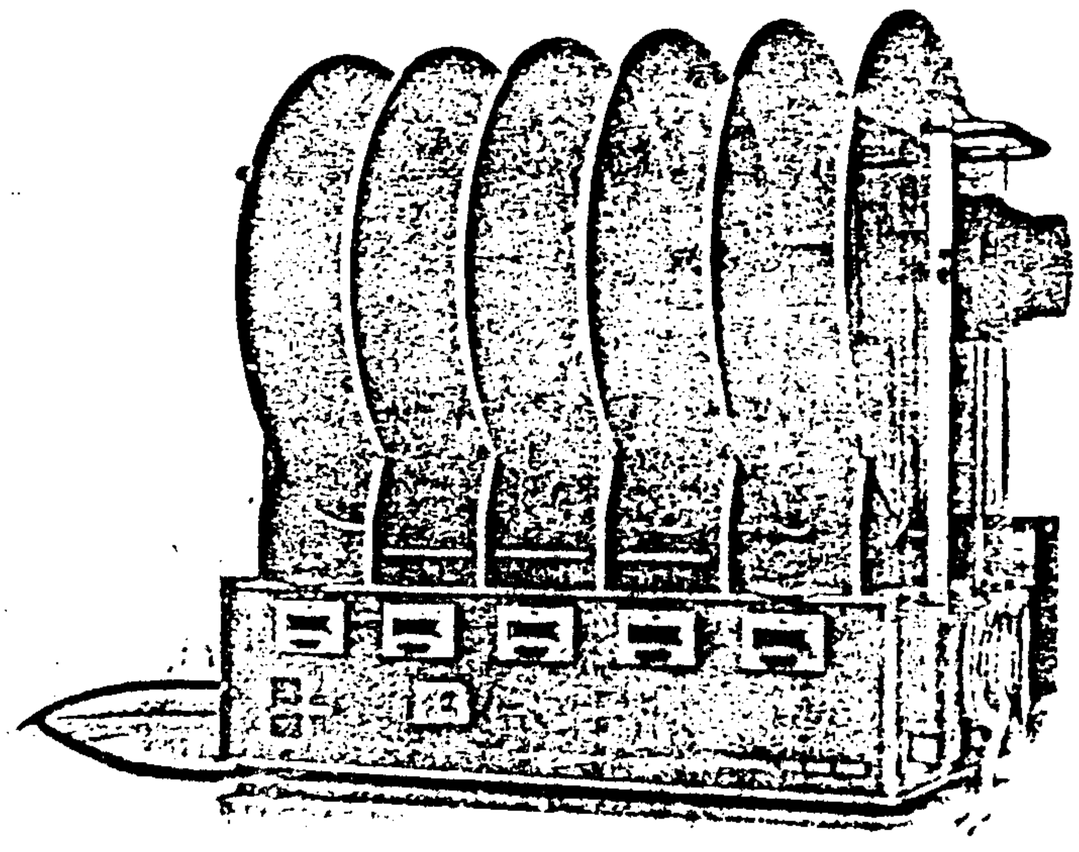

Figure (1): Rotarod Apparatus Used for Evaluation of Drug Induced-Ataxia in Mice.

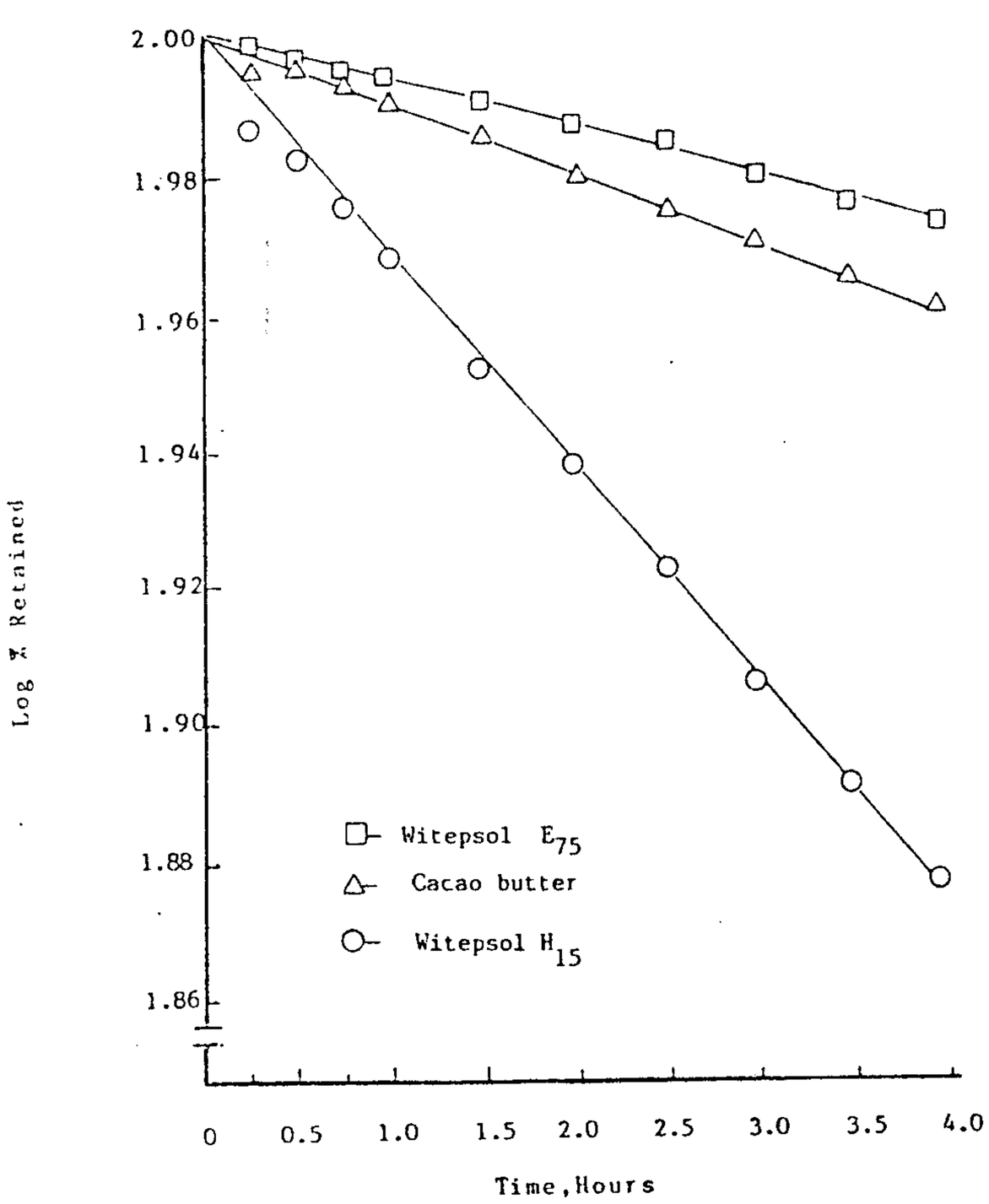

Figure (2): First-Order Release Profile of Hydroxyzine hydrochloride from Different Fatty Bases.

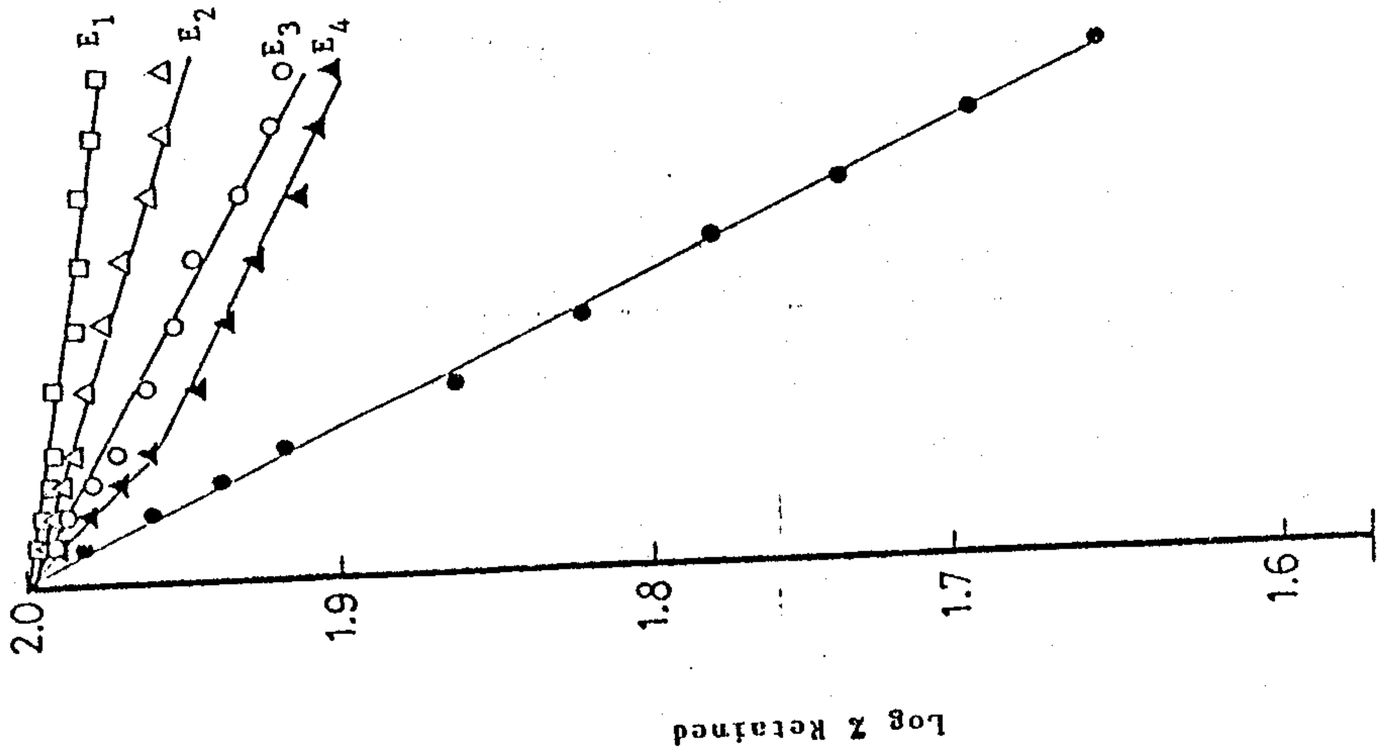

Figure (4): First-Order Release Profile of Hydroxyzine hydrochloride from Different Emulsion Bases.

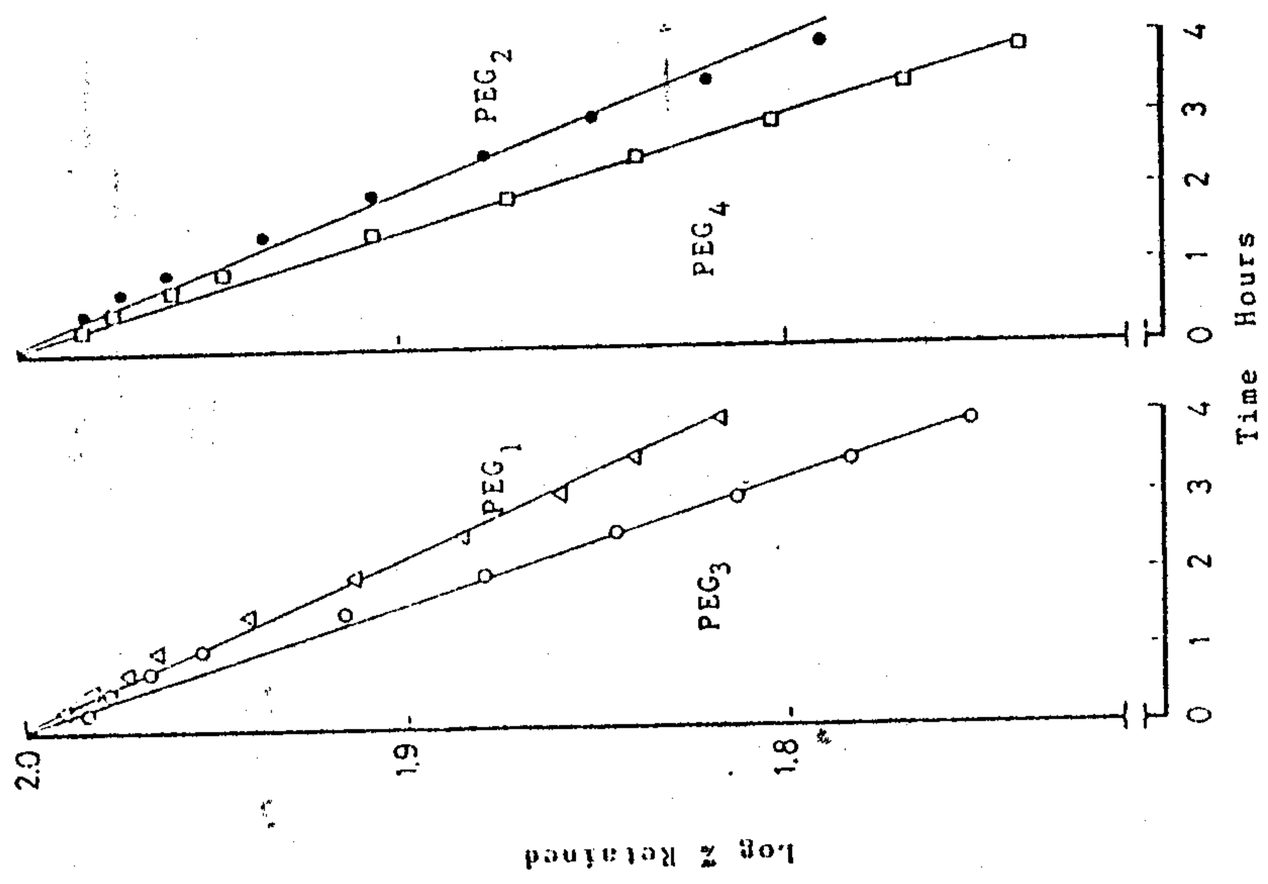

Figure (3): First-Order Release Profile of Hydroxyzine hydrochloride from Different Polyethylene Glycol Bases.

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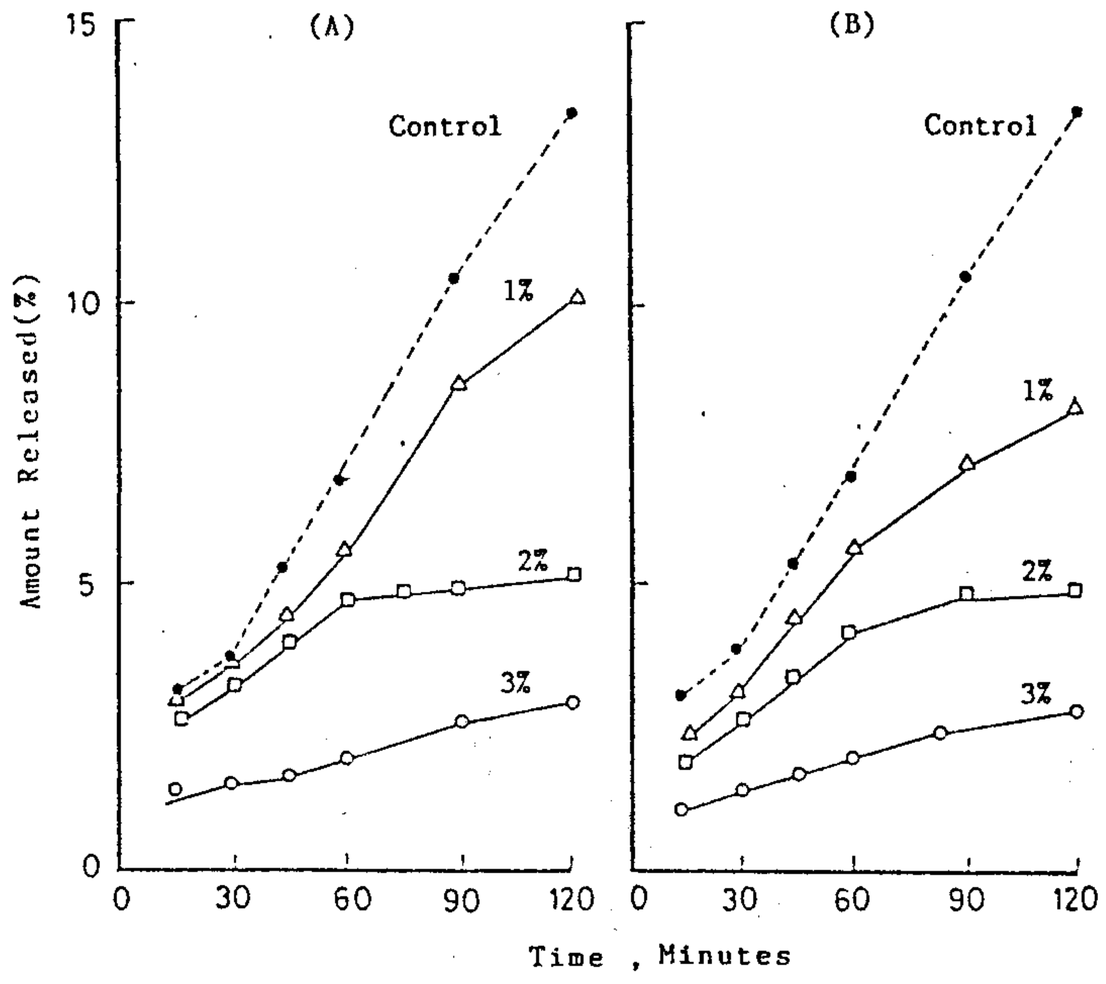

Figure (5) : In-vitro Release of Hydroxyzine hydrochloride from a Mixture of Witepsol H_{15} and Different Concentrations of Hydrophilic (A) and Hydrophobic (B) Aerosils.

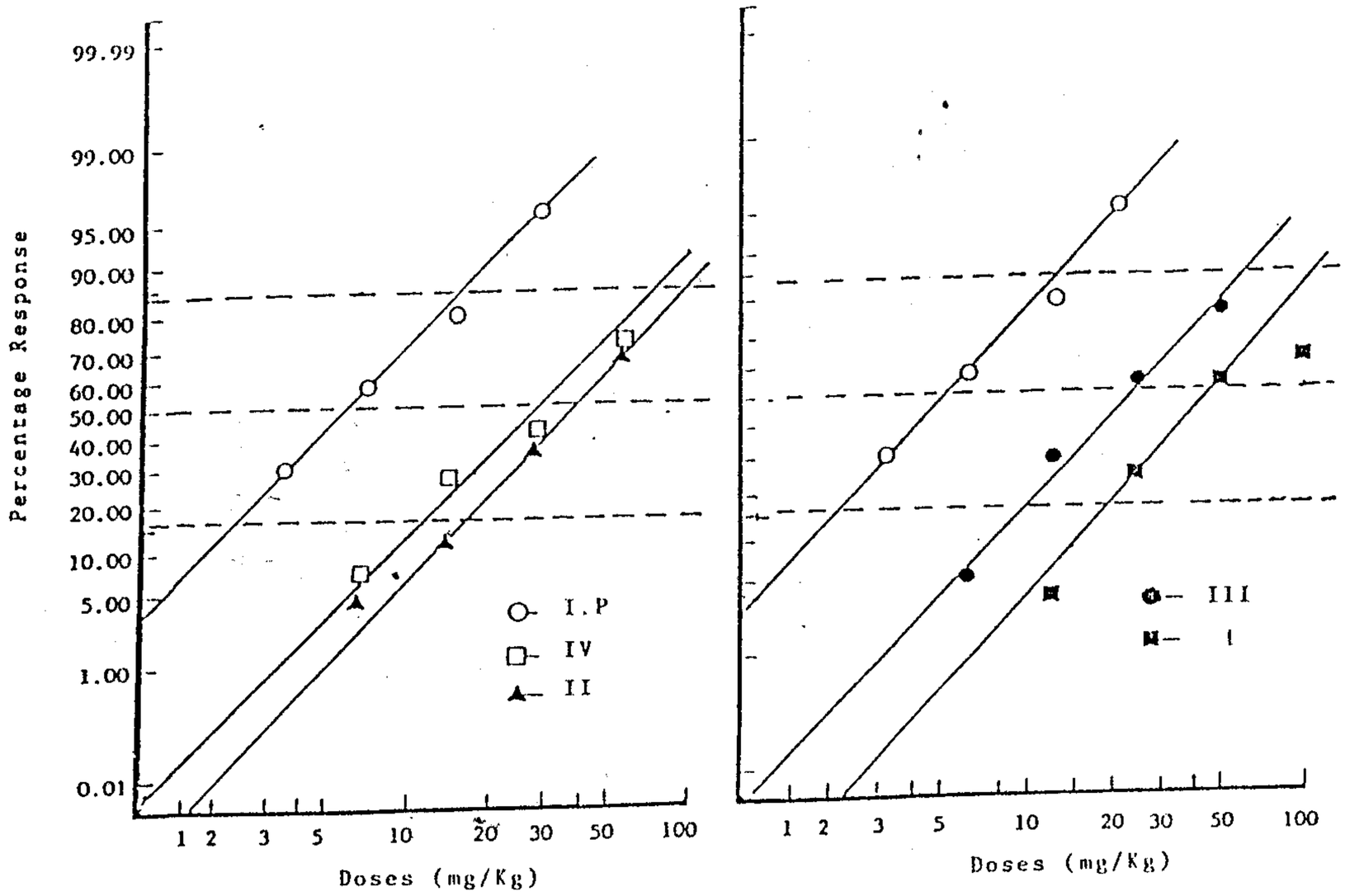

Figure (6):Best Fitting Dose-Response Line for Hydroxyzine hydrochloride on Rotarod Motor Coordination in Mice Following Rectal Administration of Various Suppository Formulations (I-IV) and The Intrapretonial Injection (I.P.)

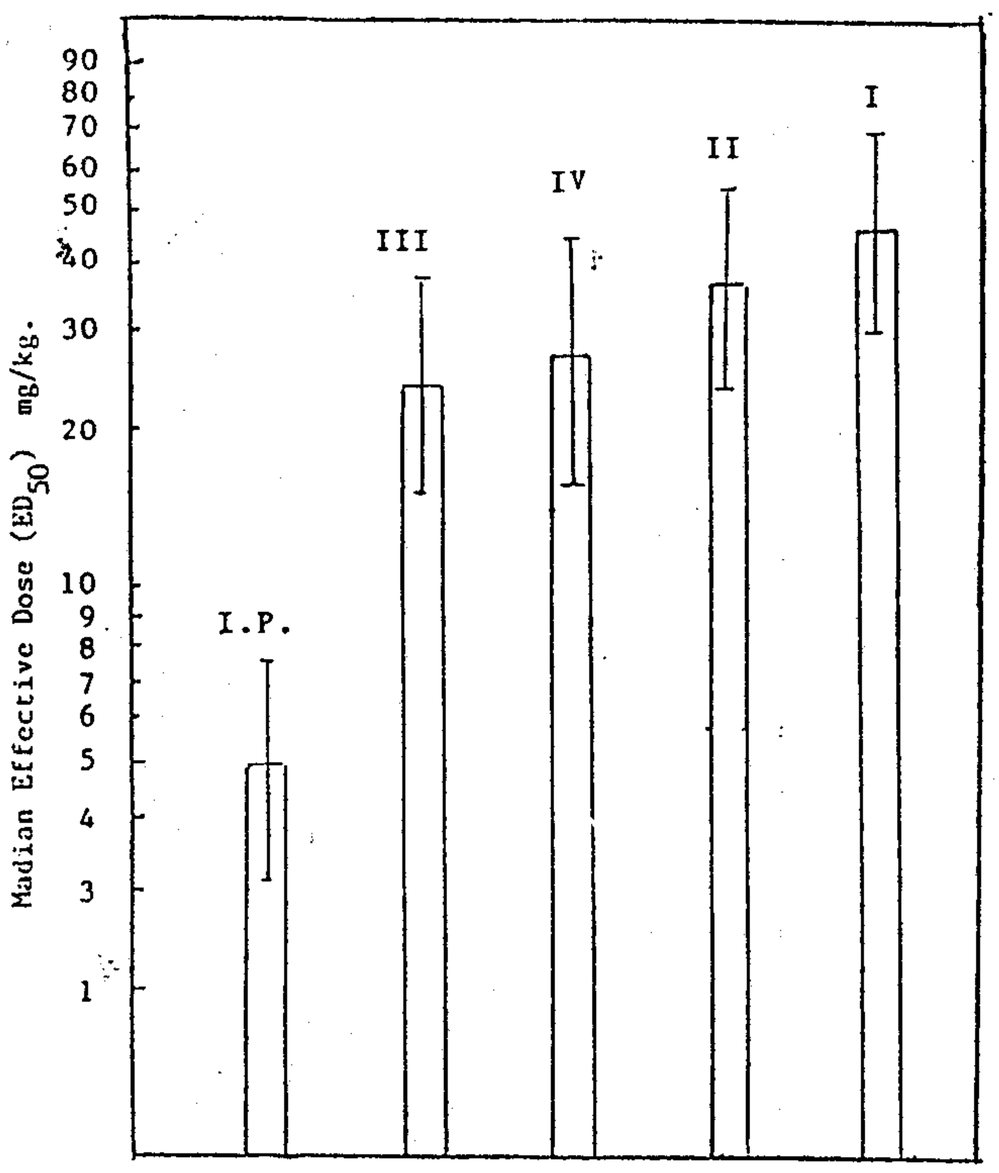

Figure (7): Calculated Values for Median Effective Doses (ED_{50}) of Hydroxyzine hydrochloride Following Rectal Administration of Different Suppository Formulations (I-V) and The Intrapretonial Injection (I.P.) in Mice.

1- *Vertical lines at the top of bars represent 95% fiducial limits*

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تحضير وتقييم اقمـاع الـهيدروكسازين

فوزيـة حبيب ـ حسين عبد المنعم ـ سـيد اسـماعيل ـ
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تضمنت الدراسة صياغة عقـار الهيدروكسازين الذى يعتبر من الادويـة الهامة فى علاج القلق وتوتر الاعصاب فى صورة اقماع شرجية وقد استخدمت فى هذه الصياغة العديد من القواعد الدهنية والمستحلبة والذائبة فـى الماء ، كذلك استخدمت خلطات من قاعدة الويتبسول الدهنية والعديد مـن المواد ذات النشاط السطحى والايروسيل بنوعيه .

وتم تقييم الاقماع المحضرة بدراسة كل من معدل الانطلاق معمليا ودراسة الفاعلية فى الفئران الصغيرة . واثبتت الدراسة ان القواعد التى تعطـى معدلات عالية لانطلاق العقار معمليا تعطى ايضا قدرا كبيرا من الفعالية فى فـئران التجارب .

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