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FORMULATION AND STABILITY OF HEPTAMINOL SUPPOSITORIES

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ABSTRACT

The chemical stability of Heptaminol Base and of Heptaminol Hydrochloride was determined after shelf-life storage in an aqueous solution at room temperature. Under these conditions, the Base was found about 10.54 times more stable than the hydrochloride. Heptaminol Base, therefore, was formulated in four different suppository bases. The prepared suppositories were subjected to the usual quality-control tests, both when fresh and after shelf-storage for one year. The results of physical examination were so variable that a sharp conclusion to a preferred formula was not possible. However, studies of medicament dissoltuion revealed that quick and full-dose release of heptaminol was achieved from glycerogelatin-based suppositories. On the other hand, suppositories based with polyethylene glycols have shown a prolonged heptaminol dissolution rates. The chemical stability of the medicament in the four different suppository bases was also investigated in absence and presence of several stabilizers. The stability was found decreasing in the order of: Glycerogelatin, Cacao-Butter, Witepsol-E-75, and then Poly-ethylene Glycols. Butylated hydroxyanisole (BHA) was the best stabilizer in the two fatty-based formulae, while tocopherol succinate was the best stabilizer, while the mixture of sodium formaldehyde sulfoxylate (SFS) with sodium edetate was the worst.

INTRODUCTION

For systemic action, the use of suppository offers many advantages over all dosage forms. Among these are that:

a- The portal circulation is by-passed, thus preventing or retarding biotransformation by the liver[1,2].

b- The influence of gastric pH or enzymatic activity is circumvented.

c- The medicament can be administered to subjects who cannot swallow.

d- Absorption from the rectum can be more rapid and more regular than from the stomach or intestine[3,4].

e- Duration of action may be prolonged[5].

EXPERIMENTAL

Materials and Apparatus:

11- Pure samples of Heptaminol Base and of Heptaminol Hydrochloride*.

2- Pharmacopoeial or pure grade of chloroform, sodium hydroxide, glacial acetic acid, mercuric acetate, perchloric acid, cacao butter, glycerin, gelatin, polyethylene glycols 4000 and 6000**, Witepsol-E-75***, 0.1 N Hydrochloric acid, methyl red test-solution, propyl gallate, butylated hydroxyanisole, tocopherol succinate, sodium thiosulphate, sodium formaldehyde sulfoxylate, and sodium ethylene diamine tetracetic acid (EDTA-Sod.).

3- Potentiometer, PYE-UNICAM, Model 290 MK.

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* Adequate sample was kindly supplied by SWISSPHARMA S.A.A., Cairo, Egypt, free of charge.

** Farbwerke Höchst AG., Frankfurt/M.-Höchst, West Germany.

*** Chemische Werke Witten, Ruher, West Germany.

4- Erweka Breaking-Strength(Hardness) Tester for Suppositories, type S.P.T.

5- Erweka Disintegration Tester for Suppositories, type S.S.P.

6- Erweka Dissolution Tester for Tablets.

Methods:

1- Comparative Stability of Heptaminol Base and Heptaminol Hydrochloride:

Heptaminol Base,15 g., were dissolved in 100.0 ml. of distilled water and the solution filled in 2-ml. mpoules and sealed. A similar solution of Heptaminol Hydrochloride in water, 5 per cent w/v,was also prepared but filled in 5 ml.ampoules for ease of disintegration during this study. Sets of about 50 ampoules of each group were stored on the shelf at room temperature protected from direct sunlight. At suitable intervals, samples were removed for chemical assay by nonaqueous titration[6,7], and the results are compiled in Tables 1 and 2 .

2- Formulation and Characterization of Heptaminol Suppositories :

One general formula has been employed for the preparation of Hepatminol Suppositories, in which 15g of Heptaminol were incorporated into 85 g. of the chosen suppository base. Four different bases were tried in this work, which are: Cacao Butter (B.P. 1980), Glycerogelatin (B.P.C. 1973), Polyethylene Glycol 4000 and 6000 in distilled water (28.05 g. + 39.95 g. + 17.00 g.)[8], and Witepsol-E-75[9]. One-gram suppositories were produced, packaged in plastic containers, and stored at room temperature for one year. Fresh and stored samples were examined with regards:

1- Colour: visually.

2- Surface Inspection: visually.

3- Hardness: by Erweka Breaking-Strength Tester, type S.P.T.

4- Softening Point: by the capillary-tube method.

5- Disintegration Time: by Erweka Disintegration Tester, type S.S.P.

6- pH-Measurement: One suppository was digested with 10 ml. of water, filtered, and the pH of the filtrate measured by pH-meter.

The results of this physical examination are compiled in(Table 3) .

Fresh suppository samples were, in addition, subjected to a dissolution-pattern testing[10]. For this purpose, one suppository was put in the cylindrical basket of an Erweka Tablet Dissolution Apparatus, and the basket was then placed over a piece of about 15 x 15 cm. of cellophane, previously soaked in water for an overnight. The ends of the cellophane were then firmly held together around the basket axis by a rubber band to tightly enclose the basket after introducing 2.0 ml. distilled water into the cellophane. The basket, as such, was suspended in a 100-ml beaker containing 75 ml. of distilled water as the dissoltuion medium. Care was taken to keep the suppository below the surface of water inside and the level of water outside the basket. The temperature of the dissolution medium was kept at $37^{\circ} \pm 0.5^{\circ}$. The whole contents of the beaker were removed for chemical assay and replaced by fresh 75 ml of water at suitable time intervals. Chemical assay for Hepatminol Base was effected by acid-base titration[6,7]. The results are given in Tables 4 and 5), and visualized in Fig. 1).

3- Chemical Stability of Heptaminol Suppositories:

Suppositories of Heptaminol Base were prepared according to the four previously-outlined formulae. These were subjected to shelf storage and chemical-stability examination. The suppositories were packed in conventional plastic containers, well covered, and stored at room temperature.

Different stabilizers have also been incorporated in each of the four suppository formula . The concentration of each stabilizer was chosen to be 0.1 per cent. Fat-soluble stabilizers were restricted to fatty-based suppositories, while water-soluble ones were admixed with water-soluble suppository bases. The stabilizers employed were: propyl gallate (PG), butylated hydroxyanisole (BHA), tocopherol succinate (TS), sodium thiosulphate with and without sodium edetate, sodium formaldehyde sulfoxylate (SFS) with sodium edetate or with sodium thiosulphate. The stabilized suppositories were also stored as the unstabilized ones, and their chemical stability was similarly followed during 450 days, using potentiometric non-aqueous titration[6,7]. The results of the present investigation were processed into a final Table 6 and visualized in Fig 2 .

DISCUSSION

1- Comparative Stability of Heptaminol Base and Heptaminol Hydrochloride:

From the present work, it is quite obvious that Heptaminol Base is by far more stable than its hydrochloride. This observation is based on examination of their aqueous solutions stored at room temperature for periods of 476 and 580 days for the base and the hydrochloride, respectively, It may be

expected that in solid forms the results can be altered. However, under the present conditions, the half-life periods for the base and its salt were calculated to be 2432.7 and 230.7 days, respectively. This means that the base is about 10.54 times more stable than the hydrochloride. By this finding, it is a self-explanatory suggestion to employ the base form of Heptaminol for new formulations, unless some other properties of the hydrochloride are seen to overweigh the stability of the medicament.

2- Formulation and Characterization of Heptaminol Suppositories:

Starting with visual standardization of the different Heptaminol suppositories, the glycerogelatin formula exhibited when fresh a yellowish transparent colour, while the Polyethylene Glycol (PEG) formula has shown a white translucent appearance. Both formula did not change in colour after storage for 12 months. Suppositories of cacao butter and of Witepsol-E-75 have acquired appreciable darkening after storage . Nevertheless, they did not change in surface appearance, contrary to PEG-suppositories that exhibited an obvious loss of gloss. Glcerogelatin suppositories neither changed in colour, nor in surface appearance, provided that the packaging container was tightly closed. A container loosely sealed has permitted moisture to leak through and the glycerogelatin to fully deliquesce.

Maximum hardness when fresh was offered by the Witepsol formula, (2575 g.), and intermediate value for cacao-butter suppositories, (1950 g.), and a minimum resistance for PEG, (950 g.). These values dropped by 2.91, 2.56, and 15.75 per cent respectively. Due to the known elasticity of glycerogelatin suppositories, they were omitted from this test.

Again, with the exception of PEG suppositories, softening point studies revealed all suppositories to soften at or below 37.0° when fresh. After storage for one year, only Witepsol suppositories softened instead at 32.5°. PEG-suppositories required heating to about 50.3° to soften when fresh which decreased slightly to 49.5° after storage. The recorded decrease in softening points for Witepsol-and PEG-formulae may, or may not, be due to interaction of heptaminol with the surfactants of Witepsol or with PEG, respectively. Probably too, this interaction could be the reason for the recorded decrease in hardness of these formulae.

Disintegration-time testing proved the values for fresh suppositories to differ only slightly after storage. pH-Values for PEG suppositories were constant, both when fresh, and when stored. For cacao butter, glycerogelatin , and Witepsol the pH decreased with storage to the extents of 10.52, 6.54, and 14.16 per cent respectively.

Medicament dissolution was followed on fresh samples of each of the four suppository formulae. Cumulative rather than individual dissoltion will be considered as it is the one which gives meaningful results. A hypothetical mean course of cumulative dissolution has been calculated and the statistical technique reported by Miligi et al[11]. was followed to establish the order of dissolution . The calculated C.V.% values were 24.90, 18.16, and 20.16 per cent for zero-, first-, and second orders, respectively. This certifies the dissolution to be of first order nature, but, due to magnitude of the least C.V.%, it could not have followed a single-staged pattern. Rather, multiple-staged dissolution is probable . The first-order C.V.% values for 2-stages and for 3-stages

were found to be 7.60 and 2.44 per cent, respectively. This indicates a triple-staged dissolution with the inflection points at 15 and 30 minutes, as evidenced by visual inspection of the true points in Fig 1 .

The general course of dissolution from all found formulae is characterized by a high-rate initial stage, a slower second stage, then finally a terminal stage with a further decreased dissolution rate. The three stages are those of: initial-dissolution, bulk-dissolution, and deflection stage.

Exceptionally, the initial-dissolution stage for Witepsol suppositories was proved to end 5 minutes earlier than in all other formulae, as verified by a C.V.% of 2.48 instead of 6. 78 per cent if it were to end at the fifteenth minutes. This may be attributed to the surfactants in Witepsol that made the drug lend itself easier and earlier to bulk dissolution. Within the initial stage, heptaminol was released at a rate decreasing in magnitude from Witepsol-E-75, through cacao butter, PEG, and finally glycerogelatin bases. The relevant $t_{1/2}$ values are 2.30, 2.72, 2.95, and 3.00 minutes, respectively. This may indicate that fatty-natured bases more readily offer their water-soluble heptaminol content than do the water-soluble bases. These, initially hesitate to do so, but rather tend to keep their medicament content dissolved inside their own matrix. Probably, partition-coefficient phenomena, thus prevail.

Within the bulk-dissolution stage, highest rate is observed from glycerogelatin base, then from Witepsol, polyethylene glycol, and finally from cacao butter. The $t_{1/2}$

values are 7.95, 12.61, 14.69, and 24.89 minutes, respectively. Glycerogelatin suppositories accomplish total medicament release within this stage. This is understandable since both the medicament and the base are fully and relatively rapidly water-soluble (cf. disintegration time 10 minutes).

The deflection stage is a terminal stage, in which the suppositories are depleted from their residual heptaminol content, if any. Glycerogelatin base possesses no such stage. Witepsol suppositories terminated peceptible heptaminol amounts within 60 minutes, cacao butter within 90 minutes, and polyethylene glycol within 105 minutes.

Summing up, it may be stated that glycerogelatin-based suppositories released their heptaminol content within 30 minutes, of which 28.2 per cent were available within 15 minutes. Witepsol-E-75 suppositories offered the whole medicament content within 60 minutes, of which 26.9 per cent were in action within 15 minutes. From cacao-butter suppositories heptaminol was fully released in 90 minutes and 44.7 per cent of the heptaminol were free within 15 minutes . Lastly, polyethylene glycol suppositories have shown full release at 105 minutes, but only 24-per cent release within 15 minutes.

3- Chemical Stability of Heptaminol Suppositories:

For the determination of the order of the decomposition reaction of Heptaminol Base in Suppositories, the statistical technique reported by Miligi et al[11] was applied to a hypothetical mean course of decomposition

calculated from true decomposition results obtained from the four plain suppository formulae. This treatment proved the reaction to have followed a first-order pathway as indicated by a value of C.V.% of 0.97 per cent and as compared to 3.1 and 5.5 per cent for zero- and second-order rates, respectively.

According to first-order decomposition rate constants, the four suppository formulae may be classified in decreasing order of preference as follows: glycerogelatin, cacao-butter, Witepsol-E-75, and then polyethylene-glycols formula. Glycerogelatin suppositories have conferred stability to Heptaminol Base by 18.6 per cent more than in cacao butter, by 32.8 per cent than in Witepsol-E-75 , and by as high as 39.2 per cent than in polyethylene glycols. Their half-life values varied within 354.9 and 494.1 days pertinent to polyethylene glycols and glycerogelatin, repectively. This range may be regarded indicative of low stability, since it cannot be accepted to market a suppository formula in which 50 per cent loss of potency is expected in a year or so.

Stabilizing agents were, therefore, included in the study. These were found to influence the stability of Heptaminol Base quite variably.

In cacao-butter suppositories, BHA only has improved the stability of the medicament by about 7.8 per cent over the control formula. Propyl gallate and particularly tocopherol have, amazingly enough, decreased the stability of Heptaminol to the extent of 18.99 and 46.74 per cent, respectively.

In a similar way, the stabilizers acted in Witepsol-E-75 suppositories, with the exception that polyethylene glycol this time caused a slight stability increase. Relative to the control formula, the extent of improvement amounts to

1.95 per cent for polyethylene glycols and as much as 55.41 per cent for BHA. Tocopherol did not stabilize heptaminol in this formula.

As for the water-soluble suppository formula , interesting results have been obtained. Thus, glycerogelatin control formula showed the best stability relative to the rest three control formulae of the different bases tried. This stability was seen to be enhanced by any of the stabilizers except the combination SFS and EDTA-Sod. This latter combination recorded a 4.82 per cent decrease in heptaminol stability. However, sodium thiosulphate with EDTA-Sod. enhanced the stability by 19.33 per cent, while sodium thiosulphate with SFS recorded a 60.03 per cent improvement. Sodium thiosulphate alone, however, increased heptaminol stability by 144.57 per cent, i.e., to about 2.45 times the control formula. These results suggest that the presence of EDTA-Sod. is objectionable, contrary to what was expected.

In polyethylene-glycol-based suppositories, the results obtained exhibited almost the same trend. Thus, the control formula occupied a middle position of stability between an increased stability on one side, due to the presence of sodium thiosulphate with or without EDTA-Sod., and a decreased stability, on the other side, when SFS was included with either of sodium thiosulphate or EDTA-Sod. Sodium thiosulphate alone improved the stability by about 28.63 per cent, and only by 18.66 per cent when simultaneously present with EDTA-Sod. SFS has exhibited a detraction from stability by 4.89 per cent only when in combination with sodium thiosulphate , but by 9.03 per cent when combined with EDTA-Sod. This confirms the deleterious effect of EDTA-Sod. on the stability of Heptaminol Base.

EDTA-Sod., being an acid salt, may have reacted with the NH_2 group of Heptaminol Base as all primary amines do[12], giving a compound somehow more sensitive to degradation. This assumption is supported by the observation that tocopherol succinate exhibited a marked deleterious effect on the stability of Heptaminol Base too, probably through its free-COOH group from the succinate moiety.

An overall picture may be obtained from the attached Fig. 2 . The first sight at the histogram inevitably indicates that the best heptaminol stability may be secured in a glycerogelatin suppository in presence of sodium thiosulphate , preferably alone. The extent of preference of this formula to the best of the three other bases may be considered 2.7 times the BHA formula of cacao-butter base, 2.1 times the BHA formula of Witepsol-E-75 base, and 2.6 times the sodium thiosulphate formula of the polyethylene-glycols suppository base.

Table 1: Percentage remained of Heptaminol Base and Heptaminol Hydrochloride in aqueous solutions kept at room temperature (20°-35°).

Time intervals (Days):	*Medicament* *Heptaminol*	*Heptaminol Hydrochloride*
0	99.98	99.98
20	98.00	-
27	96.53	-
30	-	98.00
34	94.72	-
56	92.96	-
60	-	92.50
96	-	78.95
125	-	66.51
163	-	57.62
476	79.27	-
580	-	18.17

Table 2: Mathematical and kinetic data pertinent to the stability study of Heptaminol Base and Heptaminol Hydrochloride in aqueous solutions at room temperature (20° - 35°).

Medicament	*b(Slope) x 10^{-4}*	*a(Y-interoept)*	*K (Decomposition coefficient) x 10^{-4}*	*$t_{\frac{1}{2}}$ (days)*	*t_{90} (days)*
Heptaminol	1.237	1.983	2.849	2432.774	369.930
Heptaminol HCl	13.046	2.010	30.045	230.654	35.070

Table 3: Physical Ccharacteristics of Heptaminol suppositories on storage.

Formula No.	Base	Colour		Surface Inspectation		Hardness)(g)		Softening point °C		Disintegrat. Time (min)		pH	
		Fresh	After 12 months	Fresh	After 12 months	Fresh	After 12 months	Fresh	After 12 months	Fresh	After 12 months	Fresh	After 12 months
1	Cacao butter	Y.	Y.B.	Smooth	smooth	1950	1900	35.0	35.0	7.0	8.0	11.4	10.2
2	Glycerogelatin	Y.T.	Y.T.	S.C.	S.G.	-	-	35.0	35.0	10.0	10.0	10.7	10.0
3	Polyethylene Glycol 4000+6000(33:47)	T.W.	T.W.	Glossy	not Glossy	950	800	50.3	49.5	27.5	28.0	10.3	10.3
4	Witepsol E_{75}	White	Y.W.	Smooth	Smooth	2575	2500	37.0	32.5	20.0	17.0	11.3	9.7

Y.W. = Yellowish white
T.W. = Translucent White
Y.B. = Yellowish brown
S.G. = Smooth glossy
Y.T. = Yellowish transparent
Y. = Yellow

Table 4: Release of Heptaminol from suppositories of different bases.

Time in min.	Cacao Butter		Glycero gelatin		PEG 4000 + 6000 (33 : 47)		Witepsol E_{75}	
	Ind. %	Cum. %	Ind. %	Cum. %	Ind. %	Cum. %	Ind. %	Cum. %
5	3.21	3.21	2.14	4.14	6.41	6.41	3.87	3.87
10	13.91	17.12	9.62	11.76	3.21	9.62	16.45	20.32
15	25.68	42.80	14.97	26.73	7.48	17.10	6.77	27.09
20	10.69	53.49	18.17	44.90	6.41	23.51	15.48	42.57
30	12.59	66.08	55.56	100.48	11.77	35.28	17.41	59.98
45	3.21	69.29	zero	-	14.52	49.80	24.92	84.90
60	6.41	75.70			22.78	72.58	1.93	86.83
90	3.21	78.91			7.74	86.75	zero	
105	zero	-			5.35	92.08		

Ind. = Individual
Cum. = Cumulative

Table 5: Mathematical and kinetic data pertinent to the dissolution of Heptaminol from different suppository Bases.

Factor	Y-Intercept (a)			Slope (b)			K (min^{-1})			$t_{½}$ (min)		
Stage / Formula No.	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
1	-0.008	1 1.465	1.785	0.111	0.012	0.001	0.255	0.028	0.003	2.717	24.889	228.667
2	-0.046	0.873	-	0.100	0.038	-	0.231	0.087	-	2.996	7.949	-
3	-0.007	0.940	1.450	0.102	0.020	0.005	0.234	0.047	0.012	2.959	14.685	56.521
4	-0.022	1.089	1.641	0.131	0.024	0.005	0.301	0.055	0.012	2.301	12.605	56.188

Formula No. : 1= Cacao butter base
2= Glycerogelatin base
3= Polyethylene glycol base 4000 + 6000 (33:47)
4= Witepsol E_{75}

Table 6: Mathematic and kinetic data pertinent to the stability study of the heptaminol base in different suppository bases with and without stabilizer.

Base	Stabilizer 0.1%	b(slope) x 10^{-4}	a(Y-intercept	K (Decomposition Coefficient) x 10^{-4}	$t_{\frac{1}{2}}$ (Days)
Cacao butter	Control	- 7.220	1.900	16.625	416.752
	P.G	-11.779	1.977	19.720	351.411
	BHA	- 6.699	1.979	15.426	449.212
	T.S.	-10.595	1.913	24.402	283.993
Glycero-Gelatin	Control	- 6.090	1.967	14.025	494.118
	Sodium thio.	- 2.490	2.007	5.735	1208.454
	Sod.thio.+SFS	- 3.805	1.995	8.764	790.717
	,, ,, Na EDTA	- 7.104	1.935	11.755	589.536
	SFS +Na EDTA	- 6.398	1.975	14.735	470.308
Polyethylene Glycol 4000 +6000 (33:47)	Control	- 8.480	1.941	19.529	354.857
	Sod.Thio.	- 6.592	1.993	15.182	456.462
	,, ,,+SFS	- 8.016	1.980	20.533	337.505
	,, ,,+Na EDTA-EDTA	- 7.146	2.009	16.458	421.072
	SFS +Na EDTA	- 7.333	1.996	21.468	322.806
Witepsol E_{75}	Control	- 8.088	1.972	18.627	372.041
	P.G.	- 7.934	1.974	18.271	379.290
	BHA	- 5.204	1.987	11.986	578.175
	T.S.	- 8.401	1.951	19.348	358.176

P.G. = Propylgallate
BHA = Butylated hydroxy anisole
SFS = Sodium formaldehyde sulfoxylate.
T.S.= Tocopheral succinate
Na EDTA==Sodium edetate

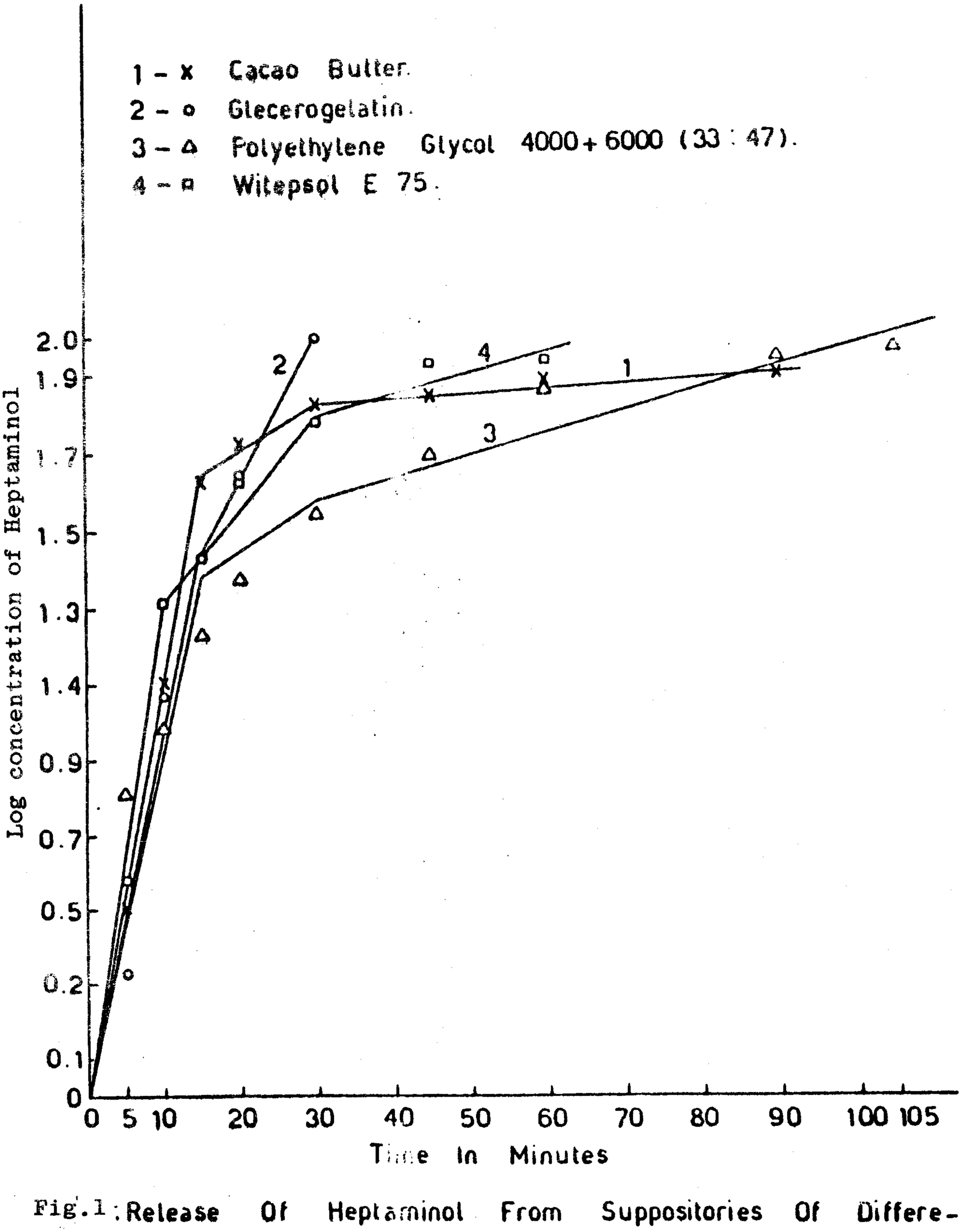

Fig. 1: Release Of Heptaminol From Suppositories Of Different Bases.

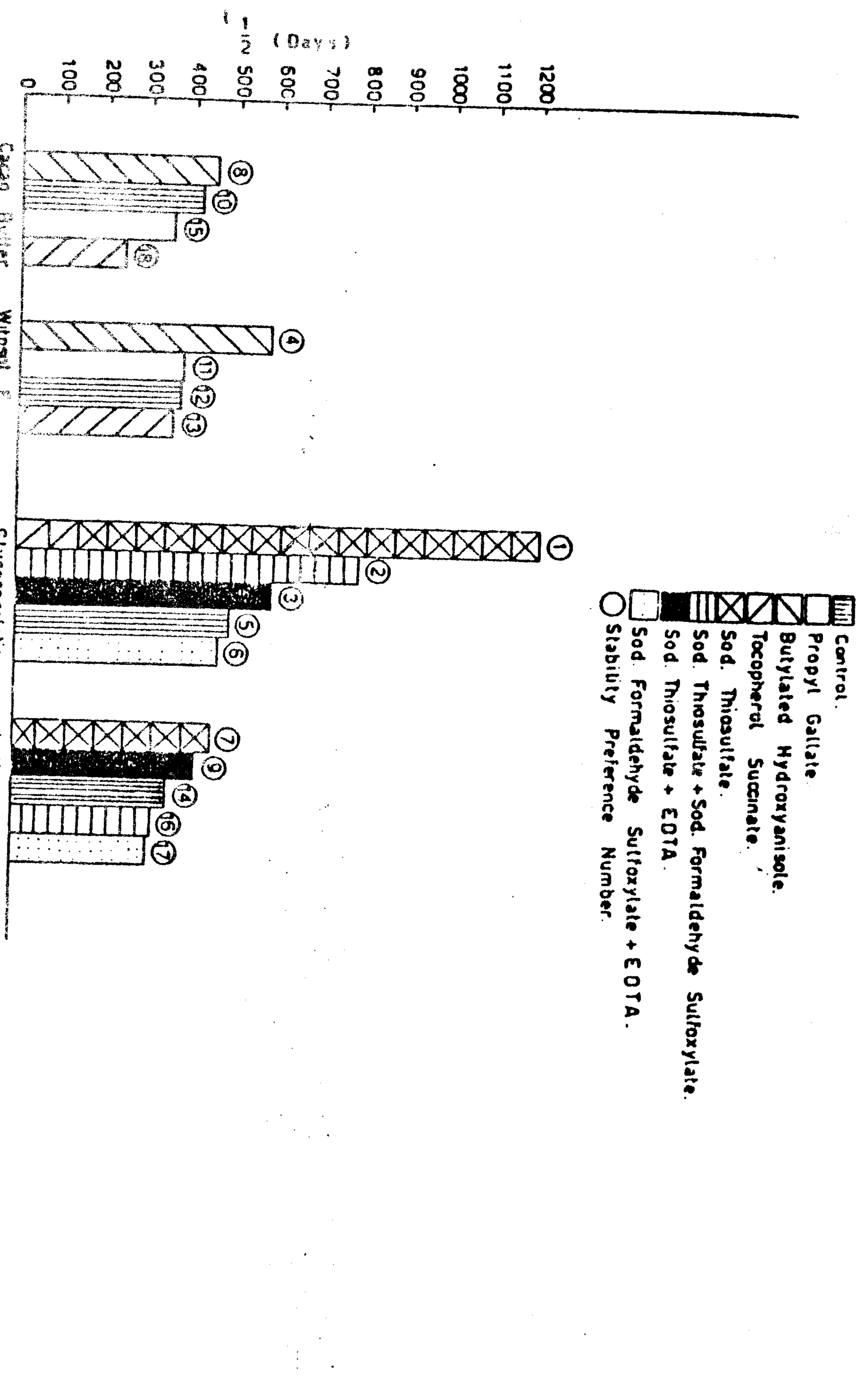

Fig. 2: Collective histogram of the stability of Heptaminol in different suppositories

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صياغة وثبات اقماع الهبتامينول

على على قاسم - محمد فريد المليجى - سهام عبد الحسينى على

كلية الصيدلة - جامعة القاهرة

تم فى هذا البحث تعيين درجة الثبات الكيماوى لمادتى قاعدة الهبتامينول وايدروكلوريد الهبتامينول خلال فترة تخزين على الرف لفترة تتراوح بين خمسة عشر وتسعة عشر شهرا فى محاليل مائية عند درجة حرارة الغرفة .

وقد ثبت تحت هذه الظروف ان ثبات قاعدة الهبتامينول يفوق ثبات ايدروكلوريد البتامينول باكثر من عشرة اضعاف ونصف .

كما تمت صياغة الهبتامينول فى اربع قواعد مختلفة للاقماع حيث تم اجراء اختبار الجودة المعتادة عليها فور التحضير وبعد فترة تخزين على الرف لمدة عام كامل . وقد اوضحت النتائج انة لايمكن القطع بافضلية صيغة على اخرى بمجرد الفحص الفيزيائى المذكور.

الا انة بدراسة اسلوب انطلاق المادة الدوائية من الاقماع المذكورة اتضح ان الهبتامينول ينطلق انطلاقا سريعا وكاملا من الاقماع المصاغة فى قاعدة من الجليسروجيسيلاتين بينما ينطلق الدواء من الاقماع المصاغة فى قاعدة من جلايكولات عديد الايثلين انطلاقا ممتدا فى معدلة .

تمت دراسة الثبات الكيمائى لقاعدة الهبتامينول فى اربع قواعد مختلفة للاقماع فى وجود مجموعة من المثبتات ،حيث اتضح ان الثبات الكيماوى للمادة الدوائية يقل فى القواعد المذكورة بالترتيب التالى :-

جليسروجيلاتين ثم زبدة الكاكاو ثم ويتيبسول - هـ ٧٥ ثم جلايكولات عديد الايثلين .

وافادت الدراسة ان مادة بيوتيل ايدروكس انيسول (ب هـ ا) هى افضل مادة مثبتة للاقماع المصاغة فى قواعد دهنية بينما وجدت مادة سكسينات التوكوفيرول اسوأها .

اما فى الاقماع المصاغة فى قواعد قابلة للذوبان فى الماء فان مادة شيوكبريتات الصوديوم تعد افضل المثبتات بينما ان مخلوط مادتى سلفوكسيلات فورمالدهيد الصوديوم (س ف ص) مع اديتات الصوديوم اسوأها فى هذا العدد .

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