Bull. Pharm. Sci., Assiut University
Vol. 7 Part 2, pp. 288 - 294

FORMULATION AND STABILITY OF HEPTAMINOL SUPPOSITORIES

PART III: Chemical stability of Heptaminol suppositories

Ali.A. Kassem, Mohamed F. El-Miligi, and Siham A. Ali
Department of Pharmaceutics, Faculty of Pharmacy, Cairo University.

ABSTRACT

The chemical stability of Heptaminol base in four different suppository bases was 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 Polyethylene-Glycols. Butylated hydroxyanisol (BHA) was the best stabilizer in the two fatty-based formulae, while tocopherol succinate was the worst. In the water-soluble bases, sodium thiosulphate was the best stabilizer, while the mixture of sodium formaldehyde sulfoxylate (SFS) with sodium edetate was the worst.

INTRODUCTION

In completion to a previous work[1], Heptaminol base was formulated in four different suppository bases with and without certain stabilizers. The prepared suppositories were shelf-stored and their chemical stability assessed.

EXPERIMENTAL

Material and Apparatus:

1- Heptaminol base

2- Pharmacopoeial or pure grade of cacao-butter, glycerin, gelatin, polyethylene-glycols 4000 and 6000**, Witepsol-E-75***

* Adequate sample was kindly supplied by SWISSPHARMA S.A.A. Cairo, Egypt, free of charge.
** Farbwerke Hochst AG., Frankfurt/M.-Hochst, West-Germany.
***Chemische werke Witten, Ruhr, West-Germany.

propyl gallate, butylated hydroxy-anisole, tocopherol succinate, sodium thiosulphate, sodium formaldehyde sulfoxylate , sodium ethylene diamine tetraacetic acid (EDTA-Sod.), chloroform, sodium hydroxide, glacial acetic acid, mercuric acetate, and perchloric acid.

3- Potentiometer PYE-UNICAM, Model 290 MK.

Methods:

Suppositories of Heptaminol base were prepared according to the four previously-outlined[1] 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.

Appropriate stabilizer have also been incorporated in each of the four suppository formulae. The concentration of each stabilizer was chosen to be 0.1 percent. 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 sodium thiosulphate. The stabilized suppositories were also stored as well as the unstabilized ones, and their chemical stability was similarly followed during 450 days, using in evaluation potentiometric non-aqueous titration[2,3]. The results of the present investigation were processed into a final Table 1 and visualized in Fig. 1.

DISCUSSION

For the determination of the order of the decomposition reaction of Heptaminol base in suppositories, the statistical technique reported by Miligi et al[4]. was applied to a hypothetical mean course of decomposition calculated from true decomposition results

obtained from the four plain suppository formulae. This treatment proved that the reaction followed a first-order pathway as indicated by a value of 0.97% C.V.% and as compared to 3.1 and 5.5 percent 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. Glycero-gelatin suppositories have conferred stability to Heptaminol base by 18.6 percent more than cacao butter, by 32.8 percent than in Witepsol-E-75, and by as high as 39.2 percent than in polyethylene glycols. Their half-life values varied within 354.9 and 494.1 days pertinent to polyethylene glycols and gly-cerogelatin, respectively. This range may be regarded indica-tive of low stability, since it cannot be accepted to market a suppository formula in which 50 percent loss of potency is expected in a year or so.

In this study stabilizing agents 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 percent propyl gallate and particularly tocopherol have decreased the stability of Heptaminol to the extent of 18.59 and 46.74 percent , respectively.

In a similar way, the stabilizers acted in Witepsol-E-75 suppositories, with the exception that polyethylene glycols this time caused slight stability increase. Relative to the control formula, the extent of improvment reached 19.5 percent for poly-ethylene glycols and as much as 55.41 percent for BHA. Tocopherol did not stabilize heptaminol in this formula.

As to the water-soluble suppository formulae, interesting results have been obtained. Thus, glycerogelatin control formula showed the best stability relative to the other three control formulae of the different bases tried. This stability was seen

to be enhanced by any of the stabilizers except the combinations SFS and EDTA-Sod. This latter combination recorded a 4.82 percent decrease in heptaminol stability. However, sodium thiosulphate with EDTA-Sod. enhanced the stability by 19.33 percent, while sodium thiosulphate with SFS recorded a 60.03 percent improvement. Sodium thiosulphate alone, however, increased heptaminol stability by 144.57 percent, i.e. to about 2.45 times the control formula. These results indecated that the presence of EDTA-Sod. was unsuitable 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 percent, and only by 18.66 percent when simultaneously present with EDTA-Sod. SFS has exhibited a detraction from stability by 4.89 percent only when combined with sodium thiosulphate, but by 9.03 percent 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 other primary amines[5], giving a compound 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.1, and the histogram indicates that the best heptaminol stability may be attained in a glycerogelatin suppository in presence of sodium thiosulphate, preferably alone.

This formula is preferable to the other three bases by 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: Mathematical 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 Coeffic-ient) x 10^{-4}	$t_{\frac{1}{2}}$ (days)
Cacao Butter	Control	- 7.220	1.900	1 16.629	416.742
	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	283.933
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	- 5.104	1.935	11.755	589.536
	SFS + " "	- 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	- 8.916	1.980	20.533	337.505
	" "+Na EDTA	- 7.146	2.009	16.458	421.072
	SFS + " "	- 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 anisol
SFS = Sodium formaldehyde sulfoxylate
T.S. = Tocopherol Succinate
Na EDTA = Sodium edetate

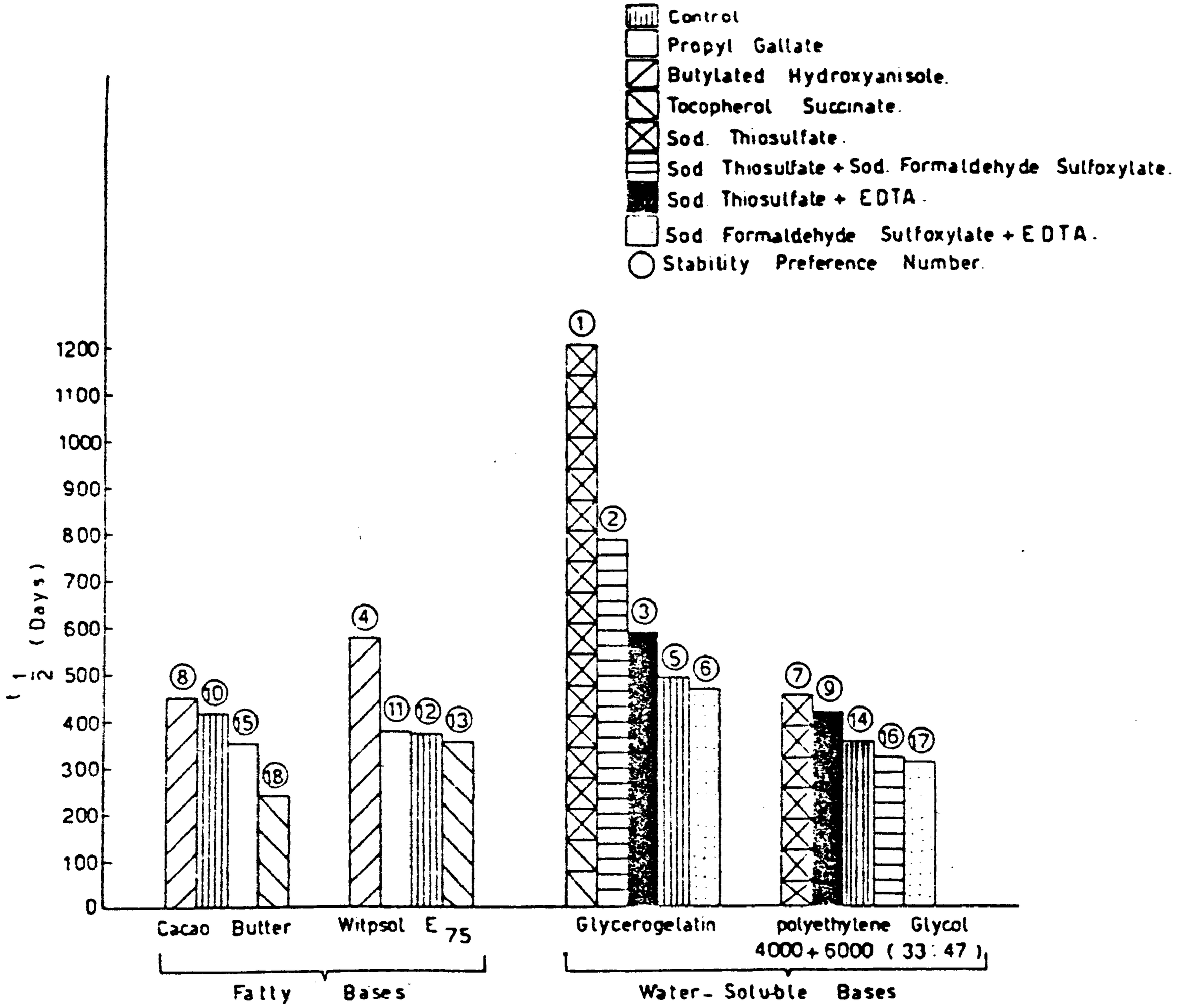

Fig. 1: Collective histogram of the stability of Heptaminol in different suppository bases

REFERENCES

1) A.A.Kassem, M.F. El-Miligi and S.A. Ali ; Formulation and Characterization of Heptaminol Suppositories, in press.

2) British Pharmacopoeia, Volume 11, A 89, London (1980)

3) A.A.Kassem, M.F. El-Miligi and S .A.Ali; Experimental Evaluation of Heptaminol, in press

4) M.F. El-Miligi, M.A.Kassem E. Nour El-Din; J. Drug Research Cairo, in press.

5) Bentley and Driver's Textbook of Pharmaceutical Chemistry, Oxford University Press, London, 7th Edition (1960), P.402

صياغة وثبات اقماع الهبتامينول

الجزء الثالث : الثبات الكيمائى لأقماع الهبتامينول

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

تمت دراسة الثبات الكيمائى لقاعدة الهبتامينول فى اربع قواعد مختلفة للأقماع فى وجود وفى عدم وجود مجموعة من المثبتات ،حيث اتضح ان الثبات الكيماوى للمادة الدوائية يقل فى القواعد المذكورة بالترتيب التالى : جليسروجيلاتين ثم زبدة الكاكاو ثم ويتيسول - هـ - ٧٥ ثم جلايكولات عديد الايثلين . وأفادت الدراسة ان مادة بيوتيل ايدروكسى انيول (ب هـ أ) هى افضل مادة مثبتة للاقماع المصاغة فى قواعد دهنية بينما وجدت مادة سكسينات التوكوفيرول اسواها .

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

received in 10/2/1983 & accepted in 11/10/1984