Bull. Pharm.Sci., Assiut University
Vol. 7, Part 2: pp. 251 - 260

FORMULATION AND STABILITY OF HEPTAMINOL DROPS

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

ABSTRACT

Several aqueous solvents were tried for the formulation of Heptaminol base in oral drops. Also, some stabilizing agents were evaluated for their action on the stability of Heptaminol base in the selected solvents. It was observed that distilled water conferred the best stability to Heptaminol base even when compared to market drops. Inclusion of 0.1 percent sodium thiosulphate in the latter solvent seems to be ineffective for further stabilization. In other solvents, the antioxidants tried largely detracted from the stability of Heptaminol base. In addition, 50 percent sorbitol in water was clearly found the worst solvent with regards to Heptaminol stability.

INTRODUCTION

The oral use of liquid pharmaceuticals has generally been justified on the basis of ease of administration to those individuals who have difficulty in swallowing solid dosage forms[1]. However, if the drug is inherently unstable, this property is magnified when the drug is formulated in solution. with these considerations in mind, it was intended to formulate heptaminol in the form of drops, that were subjected to both physical and chemical stability studies and to compare the results with commercial Heptaminol drops*

* Cotesor Drops, Batch No.060, SWISSPHRMA S.A.A., Cairo, Egypt .

EXPERIMENTAL

Material and Apparatus:

Pure pharmaceutical grades of Heptaminol base*, citric acid, sodium metabisulphite, sodium thiosulphate, methyl paraben, propyl paraben, sorbitol, glycerin, propylene glycol, and polyethylene glycol 200.

Methods:

Heptaminol base was suggested for the dosage form of oral drops[2]. The first solvent tried was distilled water . The following general formula was employed:

R/

Heptaminol base.....	15.00 g.
Methyl paraben	0.18 g.
Propyl paraben	0.02 g.
Antioxidant,if any, ...	0.10 g.
Citric acid	0.S.to pH 3.1-3.6[2]
Distilled water.....	100.00 ml.

Sodium thiosulphate and sodium metabisulphite were the stabilizers, and a blank formula was also included in the study, without a stabilizer. Two-ml ampoules were filled from each batch and accelerated stability was detected at the two elevated temperatures of 40° and 60°. Samples were assayed for their Heptaminol base content periodically at 15-days intervals, employing the potentiometric method of non-aqueous titration[3,4]. Mathematical and kinetic data pertinent to this study are given in Table No. 1.

Defferent vehicles, in 50 percent concentration in water, have also been tried compared to distilled water as to their

---

* Adequate sample of pure Heptaminol base was kindly supplied by SWISSPHARMA S.A.A. Cairo, Egypt, free of Charge.

action on the stability of Heptaminol base. Market drops were also examined along with this series. Shelf-life stability was followed this time for 476 days, and the overall picture is showm in Fig 1.

Sodium thiosulphate and sodium formaldehyde sulfoxylate were studied as stabilizers in the different vehicles just investigated. Physical stability was estimated after 15 months and chemical stability was followed at intervals of 20,27,37,56 and 476 days of room-temperature storage away from direct sunlight. The results of this study are given in Tables No. 2 and 3.

DISCUSSION

Three groups of Heptaminol oral drops were formulated and examined in the present work. The first group consisted of Heptaminol base in water with and without sodium thiosulphate or sodium metabisulphite as a stabilizer. The stability in this group was followed by the accelerated technique, and the results obtained have shown the order of decomposition to be of first-order nature as determined by the method reported by Miligi et al[5]. The calculated values of C.V.% were 1.479, 0.605, and 2.733 for zero-, first-, and second-orders, respectively. From Table No. 1, it is obvious that the accelerated stability technique would be only inaccurately applicable, since the energy of activation, E_a, of the decomposition reaction for Heptaminol base under the present conditions was found out of the range 10-30 Kilo calories[6]. Arbitrarily speaking, however, the half-life values of the three examined formulae may be taken as 518.8, 624.0, and 201.5 days, respectively. This indicates an inactivity of sodium thiosulphate to stabilize Heptaminol base and a deleterious effect of

the metabisulphite on the drug, for which reason the latter stabilizer was omitted from further investigation.

In subsequent stability determinations, shelf-life storage was resorted to. In the second group of Heptaminol drops formulated in several aqueous vehicles as well as market drops, the results (cf. Fig. 1) have shown plain water to be the best vehicle tested. The extent of such superiority, based on calculated K-values, is 2.99 times that in 50% propylene glycol, 3.34 times that in 50% glycerin, 4.02 times that in 50% polyethylene glycol 200, and 9.21 times that in 50% sorbitol. Compared to market drops, the stability of the control is 2.6 times as much. The expiry dates, based on $t_{90\%}$-values, for the investigated drops was 12.33 months in plain distilled water, 4.13 months in 50% propylene glycol, 3.69 months in 50% glycerin, and 3.07 months in 50% sorbitol. In the tested market drops, the expiry date was 4.75 months, i.e. only 0.39 times the expiry period in water. Fig. 1 and particularly the histogram therein, demonstrates the previous discussion.

For completion of the present work, the influence of sodium thiosulphate or sodium formaldehyde sulfoxylate as an antioxidant on the stability of Heptaminol base in the previous vehicles was studied. After 15 months of shelf-storage the general physical characteristics of the different formulae exhibited almost no change, (cf. Table No. 2). On the other hand, chemical-stability data (cf. Table No. 3) have shown some interesting facts. A striking observation was the fact that Heptaminol base in distilled water seems to be utterly the most stable of all tested formulae. Another observation is that the inclusion of either of the stabilizers, particularly sodium formaldehyde sulfoxylate in water, detracts from the stability of the medicament rather than improving it. A third remarkable result is that sodium thiosulphate improved the stability of the drug in 50% polyethylene glycol 200 to the extent of 3.35 times the relevant blank. Fig.2

is a histogram that helps grading all tested-formulae as indicated by a stability preference number (S.P.No.). Therefrom, the examined market drops are seen to occupy the fourth position on the list with an almost identical stability as the formula in 50% propylene glycol containing 0.1 percent of sodium thiosulphate.

An inevitable conclusion to this work, is that distilled water seems to be the vehicle of choice to formulate Heptaminol base in the form of oral drops.

Table 1: Mathematical and kinetic data pertinent to the accelerated chemical stability study of different formulae for Heptaminol drops.

Stabilizer 0.1 %	K_{60} *(day^{-1})*	K_{40} *(day^{-1})*	*Energy of Activation Cal./mole)*	K_{25} *(day^{-1})*	$t_{\frac{1}{2}}$ *(day)*
Control (1)	0.004	0.002	6634.264	0.001	518.790
Sodium thiosulphate (2)	0.007	0.003	8589.205	0.002	425.971
Sodium Metabisulphate (3)	0.006	0.004	2711.741	0.003	201.477

Table 2: Physical characteristics of Heptaminol drops in different vehicles with and without stabilizer.

Vehicle 50%	Stabilizer 0.1%	Colour		Clarity		pH	
		Fresh	After 15 months	Fresh	After 15 months	Fresh	After 15 months
Water	Control	Colour-less	Colour-less	Clear	Clear	3.70	3.75
	Sod. Thio.	"	"	"	"	3.80	3.80
	S.F.S.	"	"	"	"	3.60	3.80
	Sod. Meta.	"	"	"	"	3.60	3.80
Glycerin	Control	"	"	"	"	3.70	4.00
	Sod. Thio.	"	"	"	"	3.00	4.10
	S.F.S.	"	"	"	"	3.75	3.80
Propylene Glycol	Control	"	"	"	"	3.47	3.90
	Sod. Thio.	"	"	"	"	3.75	3.80
	S.F.S.	"	"	"	"	3.45	3.80
PEG 200	Control	"	Pale Yellow	"	"	3.55	3.60
	Sod. Thio.	"	Colour-less	"	"	3.50	3.70
	S.F.S.	"	Yellow	"	"	3.50	3.60
Sorbitol	Control	Colour-less	Colour-less	Clear	Clear	3.60	4.00
	Sod. Thio.	"	Pale Yellow	"	"	3.85	4.00
	S.F.S.	"	Colour-less	"	"	3.75	3.90
Market drops		Colour-less	Colour-less	Clear	Clear	3.50	3.60

Sod. Thio. = Sodium thiosulphate.

S.F.S. = Sodium formaldehyde sulfoxylate.

Sod. Meta. = Sodium metabisulphate.

Table 3: Mathematical and Kinetic data pertinent to the stability study of the Heptaminol in Heptaminol drops, using different vehicles, with and without stabilizer.

Vehicle	*Stabilizer 0.1%*	*b (slope) x 10^{-4}*	*a(Y-Inter-cept)*	*K Decompo-sition Coeffic-ient x 10^{-4}*	$t_{1/2}$ *(days)*	$t_{90\%}$ *(days)*
Water	Control	-1.237	1.983	2.849	2432.77	369.93
	Sod. Thio.	-1.310	1.985	3.017	2296.91	349.27
	S.F.S.	-4.667	1.981	10.748	644.77	98.04
	Sod. Meta.	-2.245	1.990	5.169	1340.58	203.85
Glycerin	Control	4.128	1.929	9.507	1728.90	110.84
	Sod. Thio.	17.587	1.939	40.504	171.09	26.00
	S. F.S.	-1.990	2.041	45.838	151.18	21.58
Propylene Glycol	Control	-3.692	1.977	8.503	814.97	123.92
	Sod. Thio.	-3.261	1.994	7.511	922.60	140.29
	S.F.S.	-5.705	1.938	13.138	527.48	80.21
PEG 200	Control	-4.977	1.897	1.459	604.76	91.96
	Sod. Thio.	-3.417	1.951	7.867	2028.15	308.40
	S.F.S.	4.519	1.940	10.407	665.90	101.26
Sorbitol	Control	-15.758	2.013	26.244	264.05	40.15
	Sod. Thio.	-5.387	1.996	12.407	558.56	84.93
	S.F.S.	-4.241	1.973	9.767	709.56	107.90
Market drop*		-3.211	1.970	7.396	937.03	142.49

Sod. Thio. = Sodium thiosulphate.

S.F.S. = Sodium formaldehyde sulfoxylate.

Sod. Meta. = Sodium metabisulphate.

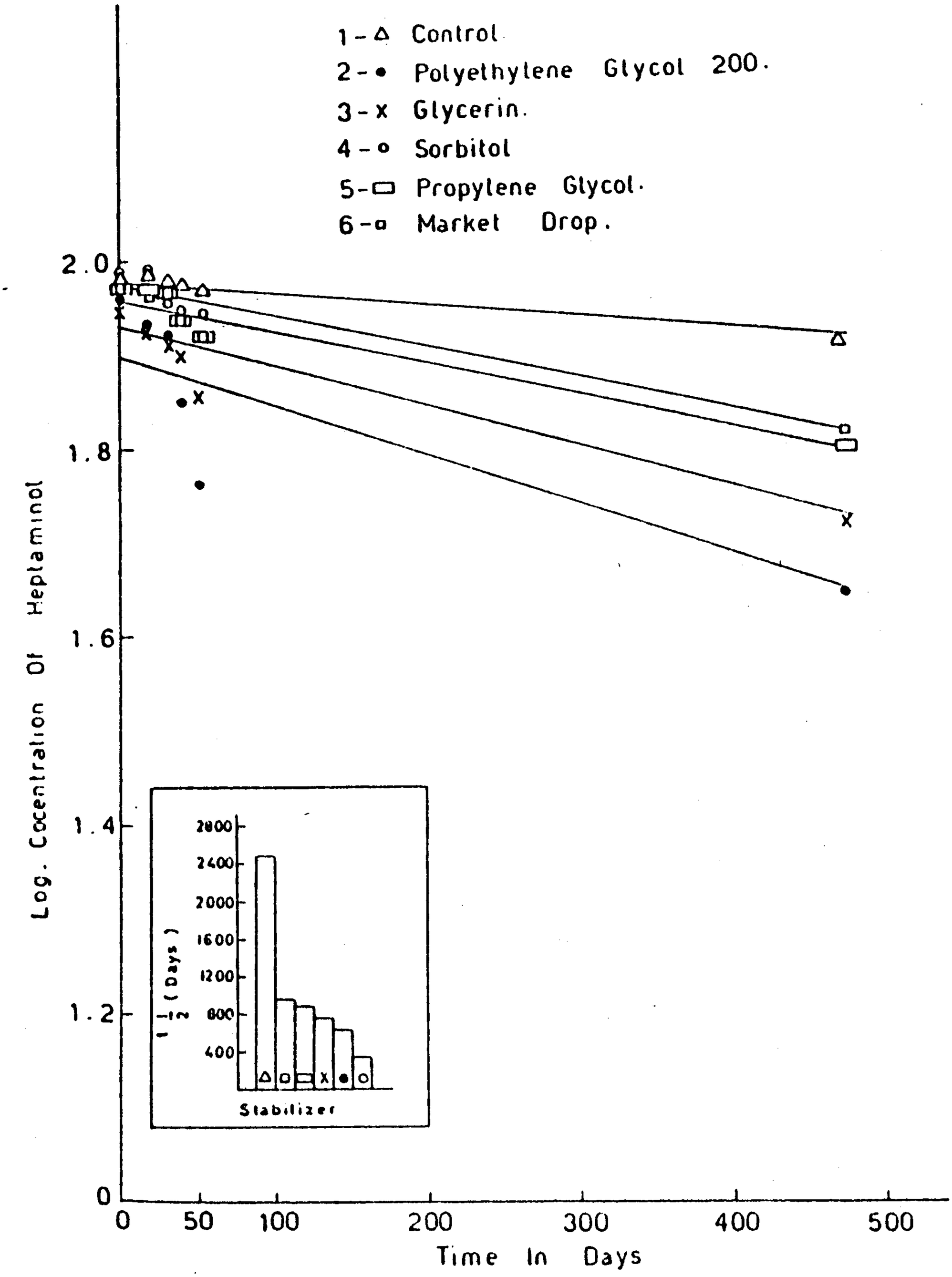

Fig: 1: Comparative shelf-life stability of Heptaminol drops in different vehicles.

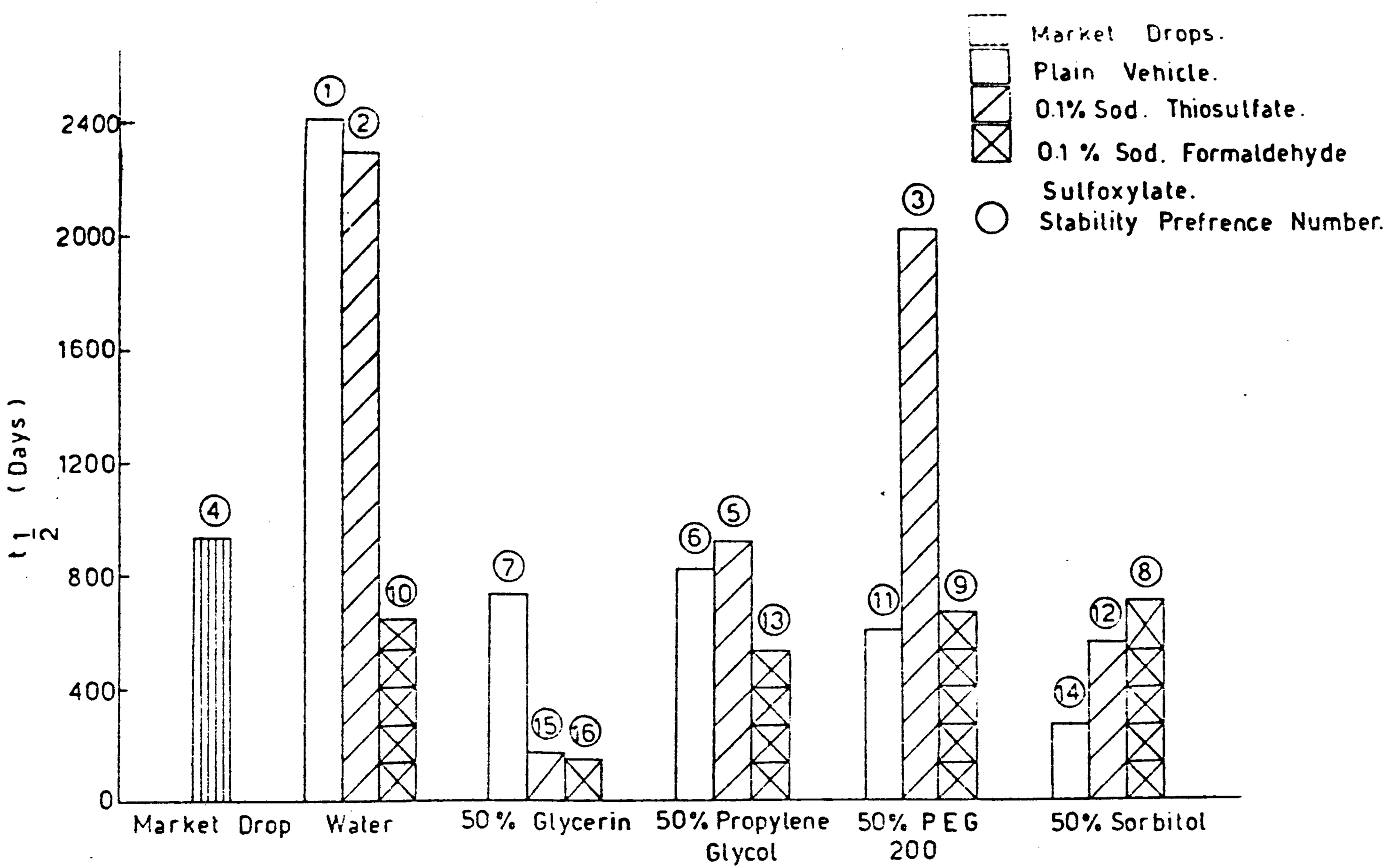

Fig. 2: Collective histogram of the stability of Heptaminol drops in different aqueous solvents with and without stabilizer

REFERENCES

1) L. Lachman, H.A. Liebermann and J.L. Kaning; " The Theory and Practice of Industrial Pharmacy", Lea and Febiger, Philadelphia, P. 671 (1970).

2) SWISSPHARMA S.A.A., Cairo, Egypt; personal communications.

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

4) The British Pharmacopoeia, Volume 11,; 89, London (1980).

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

صياغة وثبات نقط الهبتامينول

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

تمت تجربة مجموعة من المذيبات المائية لصياغة قاعدة الهبتامينول فى صورة نقط تتعاطى بالفم . كما تم تقييم بعض المواد الرافعة لدرجة الثبات من حيث كفأتها فى زيادة ثبات قاعدة الهبتامينول فى المذيبات المختارة . وقد لوحظ ان الماء المقطر الخالص قد اسبغ درجات الثبات على مادة الهبتامينول مقارنا بأى من المذيبات المدروسة وبما فى ذلك النقط المتداولة بالسوق المحلى . كما لوحظ انة لا جدوى من اضافة او. بالمائة من مادة ثيوكبريتات الصوديوم لرفع درجة الثبات فى المذيب المذكور . اما فى المذيبات الاخرى فقد اتضح ان هذة المادة المضادة للاكسدة قد اودت بكثير من ثبات قاعدة الهبتامينول . كما اثبتت الدراسة ان اسوأ المذيبات المدروسة على الاطلاق هو السوربيتول فى الماء بنسبة ٥٠ بالمائة وذلك من ناحية ثبات قاعدة الهبتامينول بة .

received in 10/2/1983 & accepted in 27/10/1984