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FORMULATION AND STABILITY OF HEPTAMINOL INJECTABLE SOLUTION

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ABSTRACT

The present work consists of a study of formulated aqueous injectable solutions of Heptaminol hydrochloride with respect to their physical and chemical stability as such, under different sterilization conditions, in presence, and in absence of antioxidants and bactericides. It was concluded that chlorocresol was incompatible with Heptaminol hydrochloride giving a pink colour. Also , inclusion of an antioxidant improved the shelf-life of Heptaminol injection. Sodium thiosulphate was regarded the first choice among the stabilizers tested. In addition, it was proved that different heat-sterilization techniques adopted variably influenced the medicament stability depending upon the particular antioxidant in the formula. Market injections were also tested and their stability was found to occupy the first place.

INTRODUCTION

Heptaminol hydrochloride injectable solution may be administered intramuscularly or intravenously[1]. It is mainly used to re-inforce the systolic contraction of the myocardium, to supplement the action of cardiac glycosides, to augment the volume of coronary circulation, and to relieve arterial hypotension. Injectable solutions containing 5 percent of Heptaminol hydrochloride in water are generally recommended . This concentration produces a molecular concentration isotonic with blood serum; a fact that excludes the necessity to isotonicity-adjusting substances. However, different antioxidants may be employed to increase the stability of the solution and various adjuvants may be added for pH-adjustment or for sterilization purposes. The present work, thus, embraces the study of formulated

aqueous injectable solutions of Heptaminol hydrochloride with respect to their physical and chemical stability as such, under different autoclaving and sterilizing conditions, in presence and in absence of antioxidants[2], and bactericides.

EXPERIMENTAL

Materials and Apparatus:

- Pure grades of Heptaminol hydrochloride*.
- Phenyl Mercuric Nitrate[3], Chlorocresol[3], Sodium Thiosulphate, Sodium Formaldehyde Sulfoxylate, Sodium Sulphate, and Sodium Metabisulphite.

Methods:

Heptaminol hydrochloride, 5 g. percent 100 ml. of water for injection, was used throughout the present study. Five groups of 5 ml. ampoules of Heptaminol injection were prepared filled and sealed. The first group of ampoules was a plain formulae of the medicament in water. The subsequent four groups of ampoules contained in addition 0.1 percent of one of the four antioxidants,:sodium thiosulphate, sodium formaldehyde sulfoxylate, sodium sulphite, or sodium metabisulphite. Samples of each of these five groups were subjected to autoclaving at 115.5° for 30 minutes and some samples at 121° for 20 minutes, or including in the formula 0.002 percent phenyl mercuric nitrate or 0.2 percent chlorocresol and heating at 100° for 30 minutes. Shelf-storage at room temperature protected from direct sunlight was followed for 18 to 19 months. Market ampoules** were also included in the present study. Non-aqueous titration for Heptaminol hydrochloride was employed[4,5]. The results are compiled

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

** " Cotesor injection", SWISSPHARMA S.A.A., Batch No. 016.

in Tables No. 1 through 3 and visualized in Fig. 1 and 2.

DISCUSSION

Immediately upon preparation of the formula containing chlorocresol and even before heating at 100°, it was observed that the injectable solution of Heptaminol hydrochloride acquired a distinct pink colour; for which reason the ampoules containing chlorocresol were abandoned from any further investigation.

All samples examined after 18 months of shelf-storage were found to deviate in no way from the fresh injection with respect to both colour and clarity; all solutions remained colourless and clear. (cf. Table 1. In water for injection, Heptaminol hydrochloride gives a pH between 6 and 7. There was no deviation from this limit in the first group of ampoules both fresh and after 18-months storage. In the second group, stabilized with 0.1 percent sodium thiosulphate, the only deviation was in the control sample to pH of 5.7 both fresh and after storage. In the third group, the stabilizer sodium formaldehyde sulfoxylate seems to have caused an acidic reaction in the injectable solution to a pH value of about 4.4 to 4.5. This initial acidic value in fresh solutions was reverted back to the normal range after the nominated storage period. In the fourth group sodium sulphite has shown almost no appreciable alteration in this factor both fresh and after storage. Remarkable, however, sodium metabisulphite with its acidic reaction shifted the pH of fresh samples to the acid range of 2 to 2.5, a value which was sustained during the indicated storage period.

In a previous work[6], the chemical decomposition reaction of Heptaminol was found to be of first-order nature, a fact which is also true under the present conditions. On this basis, the stability data of this work were interpreted taking in consideration the multiple-purpose objective of this study.

First of all, it was intended to estimate the effect of the nominated antioxidants on the stability of the heptaminol injection as compared: on one side to a blank and on another to a market injection. The second objective was to evaluate, in each case separately, the effect of the three sterilization techniques on the chemical stability of the injections. The final goal was to obtain a full comparative picture of all the previous results together.

As to the first aim, Fig 1 demonstrates that any of the tested stabilizers may improve the stability of the drug. On kinetic basis, the increase in stability amounts to about 14.5 percent with sodium sulphite, 15.4 percent with sodium metabisulphite, 31.9 percent with sodium formaldehyde sulfoxylate, and 41.7 percent with sodium thiosulphate. On the other hand, the market injection exhibited undoubted superiority to any of these samples, which amounts to 2.3 times that of the plain solution and 1.6 times that of the formula containing the best stabilizer.

For the evaluation of the three sterilization techniques compared here, the series of data in the attached tables are helpful. In absence of any stabilizer, sterilization by heating with phenyl mercuric nitrate reduced the heptaminol stability by about 27.6 percent below the control. Contrarily, autoclaving by either method has shown potency preservation higher even than the control. This finding can be attributed either to experimental error or possibly to certain bacterial interference in the unsterilized blank. In the group of ampoules

stabilized with sodium thiosulphate, the control sample exhibited maximum stability over those sterilized, regardless of how. Bactericidal sterilization caused a drop in potency by 8.3 percent, autoclaving at 121° for 20 minutes a loss of 36.2 percent, and sterilization at 115.5° for 30 minutes a decrease of 66.9 percent relative to the control. In the third group with sodium formaldehyde sulfoxylate, the control has also exhibited highest stability that decreased by only 14.3 percent with autoclaving at 115.5° for 30 minutes, by 23.4 percent with heating at 121° for 20 minutes, and by 24.3 percent when heated with the bactericide at 100° for 30 minutes. In presence of sodium sulphite, the chemical stability of the fourth group of ampoules was almost affected by the three methods of sterilization. The loss of potency than the control was 8.7 percent due to sterilization at 115.5° for 30 minutes, 6.8 percent after sterilization at 121° for 20 minutes, and 6.1 percent after sterilization by boiling with the bactericide. In the fifth group, sodium metabisulphite seems to give good protection to heptaminol against autoclaving. At 121° for 20 minutes, identical stability with the control was recorded, while at 115.5° for 30 minutes a decrease in potency of only 5.4 percent was detected. Hot bactericidal sterilization diminished the drug potency by 12.7 percent .

In order to have an overall picture of the most prominent results in this investigation the histogram in Fig. 2 was developed which assigned each a Stability Preference Number (S.P.No.). By this system, the market ampoules tested have clearly demonstrated the best stability over the 20 samples formulated and examined. Among the formulated Heptaminol injections, however, the first choice is the fourmula containing sodium thiosulphate and heat-sterilized. For this, sterilization by filtration may be the practical alternative.

Summing up the rest results, it may be stated that sodium

thiosulphate was found the first choice to improve shelf-life stability of heptaminol injection, followed by sodium formaldehyde sulfoxylate, sodium metabisulphite, and lastly by sodium sulphite. The different sterilization techniques examined seemed to influence the drug stability variably , depending upon which of the antioxidants is included in the formula.

Table 1: Physical characteristics of Heptaminol hydrochloride injectable solutions on storage.

Formula	Colour		Clarity		pH	
	Fresh	After 18 months	Fresh	After 18 months	Fresh	After 18 months
Control	colourless	colourless	Clear	Clear	6.63	6.50
C + Auto.115.5°	"	"	"	"	6.50	6.60
C + Auto at 121°	"	"	"	"	6.20	6.60
Ph. Hg. NO_3	"	"	"	"	7.05	6.80
Chlorocresol	Pink	-	Clear Pink	-	--	--
Control	Colourless	Colourless	Clear	Clear	5.70	5.70
S.Th.+Auto.at 115.5°	"	"	"	"	6.10	7.10
S.Th.+Auto.at 121°	"	"	"	"	6.60	7.00
S.Th.+Ph Hg NO_3	"	"	"	"	6.00	7.00
S.F.S.	Colourless	Colourless	Clear	Clear	4.50	6.50
S.F.S.+Auto.115.5°	"	"	"	"	4.40	6.20
S.F.S.+Auto.at 121°	"	"	"	"	4.40	6.30
S.F.S.+Ph Hg NO_3	"	"	"	"	6.50	6.00
S.S.	Colourless	Colourless	Clear	Clear	6.90	7.10
S.S.+Auto.at 115.5°	"	"	"	"	6.30	6.30
S.S.+Auto.at 121°	"	"	"	"	6.20	6.30
S.S.+Ph.Hg. NO_3	"	"	"	"	6.35	7.05
S.Meta.	Colourless	Colourless	Clear	Clear	2.00	2.20
S.Meta+Auto.at 115.5°	"	"	"	"	2.00	2.10
S.Meta+Auto.at 121°	"	"	"	"	2.40	2.40
S.Meta+Ph.Hg NO_3	"	"	"	"	2.50	2.50
Market Amp.	"	"	"	"	6.80	6.80

C = Control; S.Th. = Sodium Thiosulphate; S.F.S. = Sodium Formaldehyde Sulfoxylate
S.S. = Sodium Sulphite; Auto. = Autoclaved;
Ph.Hg NC_3 = Phenyl Mercuric Nitrate; S.Meta = Sodium Metabisulphite.

Table 2: Chemical stability of Heptaminol hydrochloride injectable solutions on storage

Formula	*Percentage Concentration of Heptaminol HCl Remained After the Following Time Intervals (Days)*						
	Fresh	*30*	*60*	*96*	*135*	*163*	*580*
Control	99.98	98.00	92.50	78.95	66.51	57.62	18.17
- +Autoclav.115.5°	99.98	99.69	95.09	92.67	89.23	72.00	24.72
- +Autoclav. 121°	99.98	99.42	98.00	97.87	88.91	71.42	20.22
- +Ph.Hg.NO_3	95.06	88.30	65.62	60.60	57.37	44.28	8.35
Sod. Thiosulphate	99.42	97.98	93.81	90.30	90.20	90.00	31.84
- +Autoclav. 115.5°	100.64	99.99	98.80	92.91	87.63	71.32	14.27
- +Autoclav. 121°	99.99	99.40	98.25	90.20	83.50	65.14	20.22
- +Ph.Hg.NO_3	98.75	97.32	94.23	92.65	90.88	88.56	27.43
Sod.Formald.Sulfoxyl.	99.98	99.06	92.50	90.02	89.92	88.72	12.36
- +Autoclav. 11.5°	99.80	99.53	98.64	95.32	93.02	90.63	23.59
- +Autoclav. 121°	99.98	99.48	92.36	89.23	88.92	85.36	20.67
- +Ph.Hg.NO_3	98.75	97.71	90.64	88.83	87.00	79.55	20.23
Sod. Sulphite	98.36	96.01	92.63	89.33	82.41	79.02	22.47
- +Autoclav. 115.5°	98.25	97.75	96.96	86.20	84.38	71.42	20.21
- +Autoclav. 121°	97.56	96.80	95.33	90.55	88.63	84.66	20.69
- +Ph.Hg.NO_3	98.63	97.44	94.80	92.20	89.52	87.94	21.00
Sod.Metabisulphite	97.50	93.28	90.20	89.87	87.22	85.47	22.47
- +Autoclav. 115.5°	98.53	94.37	91.42	88.27	86.05	85.89	20.95
- +Autoclav.121°	98.86	97.81	94.57	97.32	90.00	87.23	23.60
- +Ph.Hg.NO_3	97.97	94.79	89.63	86.72	78.96	62.35	18.83
Market Ampoules	104.00	100.22	-	-	-	-	48.65

Table 3: Mathematical and kinetic data pertinent to the stability of Heptaminol hydrochloride injectable solutions

Formula	Slope(b) x 10^{-3}	Y-Intercept(a)	Decomposition Coefficient (K) x 10^{-3}	$t_{\frac{1}{2}}$ (Days)
Control	-1.31	2.01	3.02	229.159
- + Autoclav. 115.5°	-1.10	2.04	2.54	273.330
- + Autoclav. 121°	-1.27	2.06	2.93	236.616
- + Ph.Hg. NO_3	-11.81	1.97	4.18	165.940
Sodium Thiosulphate	-0.93	2.04	2.13	324.651
- + Autoclav. 115.5°	-1.55	2.08	3.56	194.463
- + Autoclav. 121°	-1.20	2.05	2.91	238.316
- + Ph.Hg.NO_3	-1.00	2.05	2.31	299.857
Sod.Formald.Sulfoxylate	-0.99	1.99	2.29	302.343
- + Autoclav. 115.5°	-1.14	2.07	2.62	264.423
- + Autoclav. 121°	-1.23	2.06	2.83	244.556
- + Ph.Hg.NO_3	-1.24	2.05	2.85	243.235
Sodium Sulphite	-1.15	2.04	2.64	262.440
- + Autoclav. 115.5°	-1.25	2.04	2.87	241.346
- + Autoclav. 121°	-1.22	2.06	2.82	245.762
- + Ph.Hg.NO_3	-1.21	2.06	2.80	247.315
Sodium Metabisulphite	-1.14	2.04	2.62	264.393
- + Autoclav. 115.5°	-1.20	2.50	2.76	250.905
- + Autoclav. 121°	-1.12	2.05	2.59	267.598
- + Ph.Hg.NO_3	-1.28	2.03	2.95	234.692
Market Ampoules	-0.57	2.02	1.31	527.180

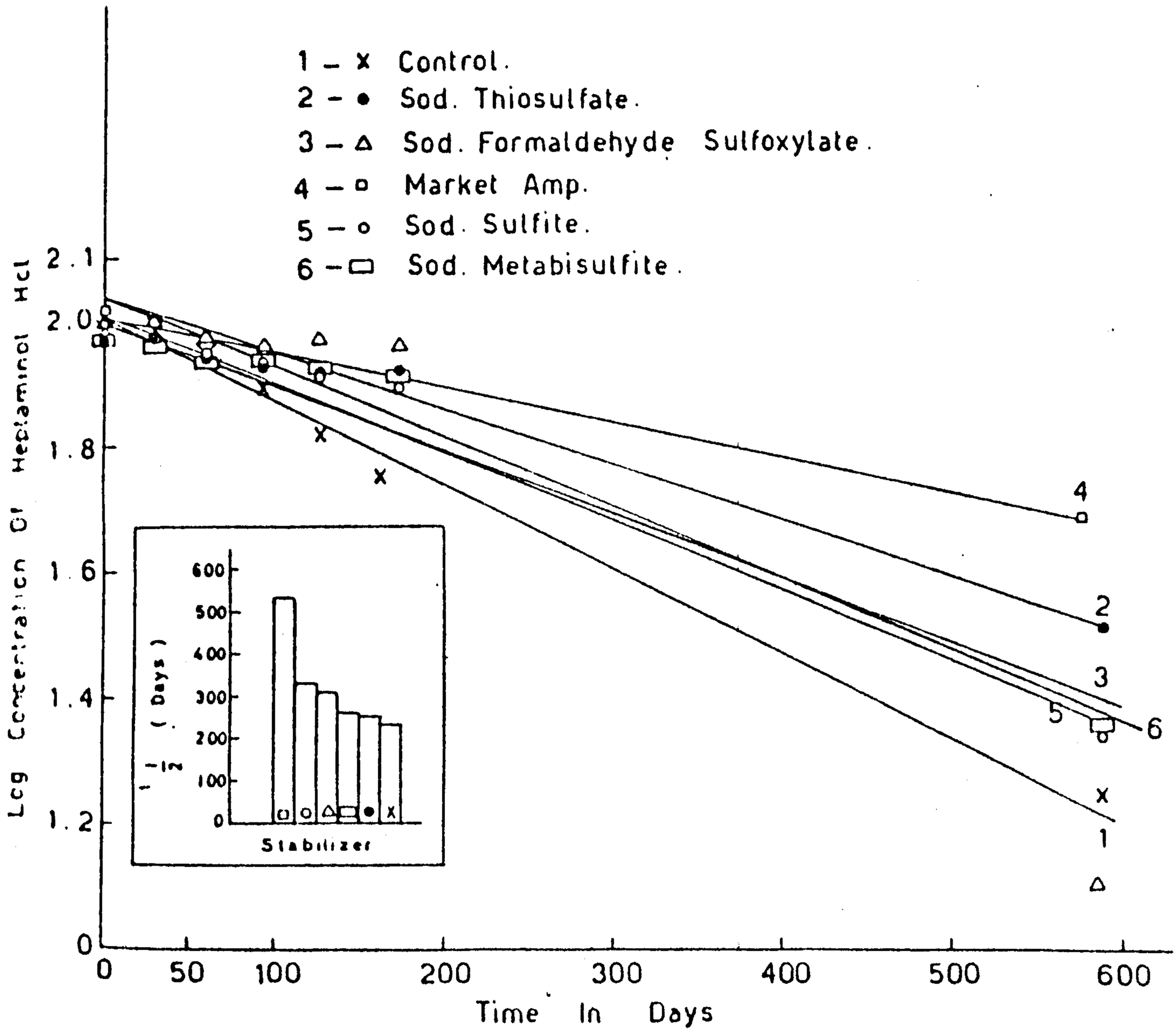

Fig. 1: Comparative shelf-life stability of Heptaminol HCl injectable solutions with and without stabilizer

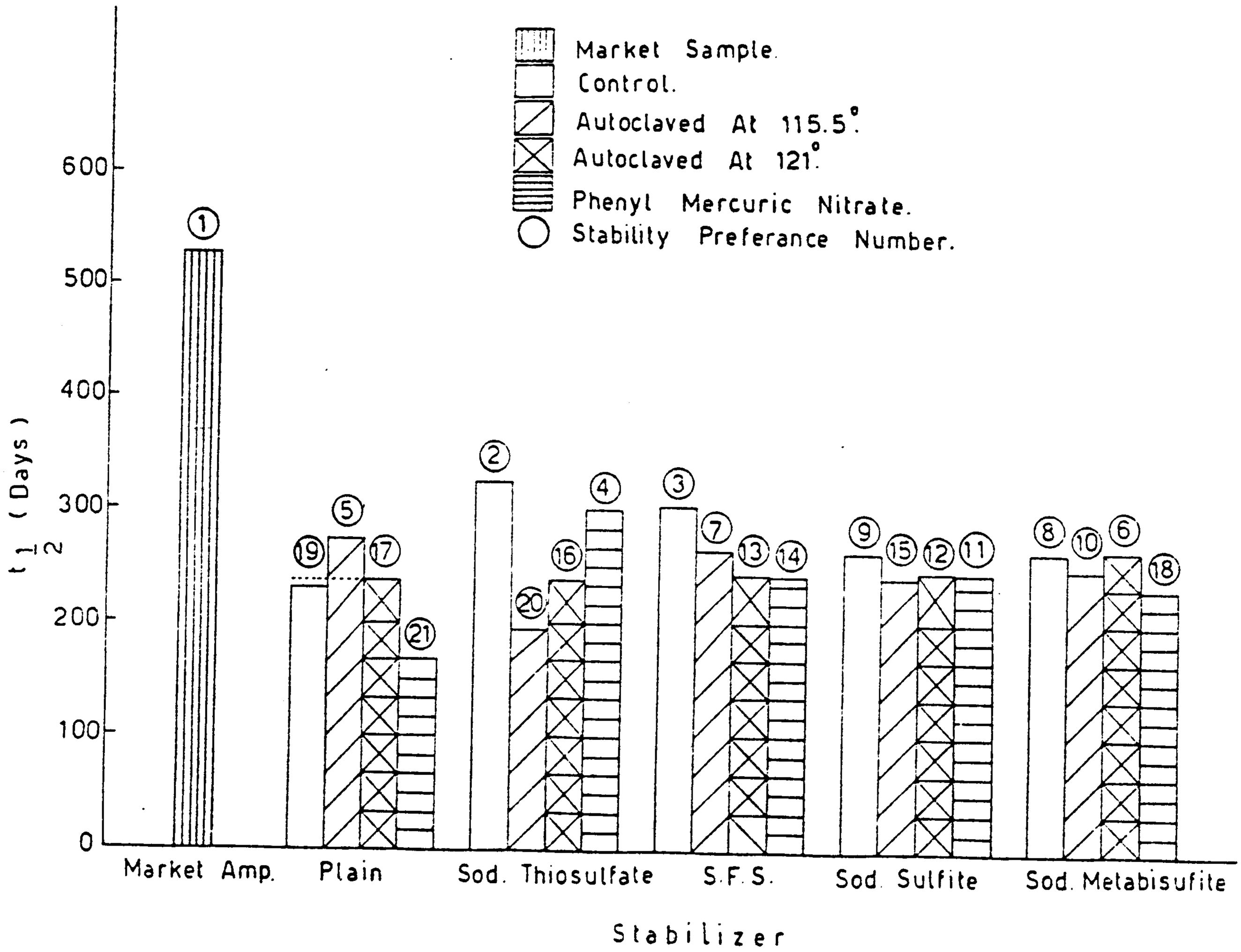

Fig. 2: Collective histogram of the stability of Heptaminol injectable solutions (S.F.S. 1 Sod. foramldhyde sulfoxylate

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صياغة وثبات محلول الهبتامينول المعد للحقن

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

فى هذا البحث تمت صياغة محاليل معدة للحقن من مادة ايدروكلوريد الهبتامنول ودراستها من ناحيتى الثبات الفيزيائى والثبات الكيماوى سواء على حالتها او بعد مختلف طرق التعقيم الحرارى وسواء فى وجود مضادات للاكسدة او مضادات للبكتريا او فى عدم وجودها . وقد تم التوصل الى اعتبار مادة الكلوروكريزول عديمة التوافق مع ايدروكلوريد الهبتامينول حيث انها تعطى لونا قرموزيا باهتا مع محاليل المادة الدوائية.

كما اثبتت الدراسة جدوى اضافة مادة مضادة للأكسدة حيث انها ترفع من ثبات حقن الهبتامينول خلال فترة التخزين وخصوصا مادة ثيوكبريتات الصوديوم التى تفوقت على مثيلاتها فى هذا العدد . كما اوضحت الدراسة ان لمختلف طرق التعقيم الحرارية المعتادة تأثيرات مختلفة على ثبات المادة الدوائية وحسب المادة المضادة للاكسدة المستخدمة . كما تبين خلال الدراسة ان حقن المادة المتداولة بالسوق ذات ثبات يحتل المرتبة الاولى بين المحاليل المختلفة التى تمت دراستها .

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