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FORMULATION AND STABILITY OF HEPTAMINOL SUPPOSITORIES

PART II: Formulation and characterization of Heptaminol suppositories:

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ABSTRACT

Heptaminol base 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 dissolution 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.

INTRODUCTION

For systemic action, the use of suppository offers many advantages over all dosage forms of these, the possibility of administration to unconcious subjects, as those suffering from hypotension, was the real motive to attempt the formulation of the hypotensive drug "Heptaminol" into suppositories.

EXPERIMENTAL

Materials and Apparatus:

1- Heptaminol base*

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

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

3- Analytical grade of 0.1 N hydrochloric acid and methyl red test-solution.

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.

7- pH-Meter PYE-Unicam, Model 290 MK.

Methods:

One general formula has been employed for the preparation of Heptaminol suppositories, in which 15 g. of Heptaminol were incorporated into 85 g. of the chosen suppository base. Four different bases were tried in this work, namely: Cacao butter (B.P. 1980), Glycerogelatin (B.P.C. 1973), Polyethylene Glycol 4000 and 6000 in distilled water (28.05 g. + 39.95 g. + 17.00g.[6]), and Witepsol-E-75[7]. 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.

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

6- 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 1.

Fresh suppository samples were, in addition , subjected to a dissolution-pattern testing[8]. 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 dissolution 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 $37^{o} \pm 0.5^{o}$. 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 Heptaminol base was effected by acid-base titration[9,10]. The results are given in Tables 2 and 3, and visualized in Fig. 1.

DISCUSSION

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 formulae did not change in colour after storage for 12 months. Suppositories of cacao butter 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. Glycerogelatin 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 was expected to full deliquescence.

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, (950g.). These values dropped by 2.91, 2.56, and 15.75 percent, respectively. Due to the known elasticity of glycerogelatin suppositories, they were not submitted to this test.

Again, with the exception of PEG suppositories, softening point studies revealed that all suppositories softened at or below 37.0° when fresh. After storage for one year, only Witepsol suppositories softened at 32.5°. PEG-suppositories required heating to about 50.3° to soften when fresh which decreased slightly 49.5° on storage. The recorded decrease in softening points for Witepsol-and PEG-formulae may be due to the interaction of heptaminol with the surfactants of Witepsol or with PEG, respectively.This interaction might be the reason for the recorded decrease in hardness of these formulae.

Disintegration-time testing proved that the value for fresh suppositories differ only slightly after storage. PH-values for PEG suppositories were constant either when fresh or when stored. For cacao butter, glycerogelatin, and Witepsol the pH decreased on storage to the extents of 10.52, 6.54, and 14.16 percent, respectively.

Medicament dissolution test was followed on fresh samples of suppositories of each of the four suppository formulae. Cumulative rather than individual dissolution 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 behaviours. The calculated C.V.% values were 24.90, 18.16, and 20.16 percent for zero-, first-, and second-order, rspectively. This certifies the dissolution to be of first-order nature, but 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 percent, 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 four 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 : inital-dissolution, bulk-dissolution, and deflection stage.

Exceptionally, the initial-dissolution stage for Witepsol suppositories was proved to end 5 minutes earlier than other formulae, as verified by a C.V.% of 2.48 instead of 6.78 percent if it were to end at the fifteenth minute. 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 $t_{\frac{1}{2}}$ 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 tend to keep their medicament content dissolved inside

their own matrix, due to the prevailing partition-coefficient phenomena.

Within the bulk-dissolution stage, highest rate is observed from glycerogelatin base, then from Witepsol, polyethylene glycol, and finally from cacao butter. The $t_{\frac{1}{2}}$ values are 7.95, 12.61, 14.69, and 24.89 minutes, respectively. Glycerogelatin suppositories accomplish total medicament release within this stage. This is logic, 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. Glycerogelatin base possesses no such stage. Witepsol suppositories terminated perceptible heptaminol amounts whithin 60 minutes, cacao butter within 90 minutes , and polyethylene glycol within 105 minutes.

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

Table 1: Physical characteristics of Heptaminol suppositories on storage

Formula No.	Base	Colour		Surface Inspectation		Hardness (g)		Softening Point °C		Disintegration 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	Glycero-gelatin	Y.T.	Y.T.	S.G.	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 2: 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 %
1	3.21	3.21	2.14	2.14	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	55.58	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 3: 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	1.445	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}

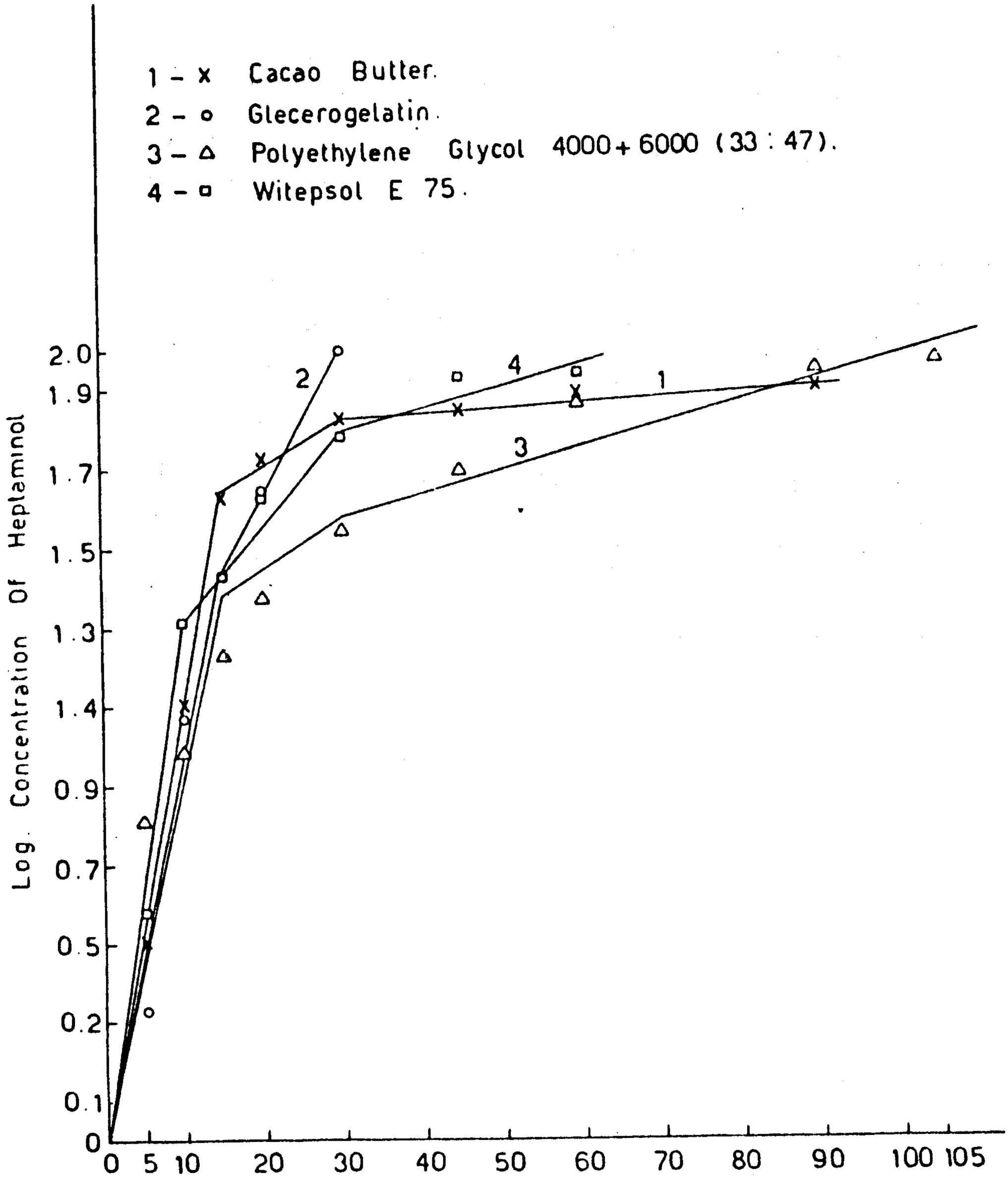

Fig. 1: Release of Heptaminol from suppositories of different bases.

REFERENCES

1) R. Bucher, Helv. Physical Pharmacol. Acta 6, 821(1948)

2) H. Gray, " Anatomy of the Human Body", Philadelphia, 24th Edition (1942).

3) J. Lensio, O. Branisteamu; Med., Raumania; 4,1 (1939).

4) W. Blume, and F.S. Nohors; Arch. Exp. Pathol. Pharmakol., 173, 413 (1933).

5) J. Delay, and J.E. Thuillier; Science 117, 57 (1953).

6) Cooper and Gunn's " Dispensing for Pharmaceutical Students" Pitman Medical and Scientific Publishing Co. Ltd. London, Twelvth Edition (1968).

7) O. Wies Fogi; Arch. Pharm. Chem. 61, 736 (1961).

8) J. Stenikar and B. Fontelli; J. Pharm. Sci., 51, 566 (1962).

9) SWISSPHARMA S.A.A., Cairo, Egypt, personal communications.

10) A.A.Kassem, Mohamed F. El-miligi and Siham. A. Ali ; Experimental Evaluation of Heptaminol, in Press.

11) Mohamed F. El-miligi, Mohamed A. Kassem and E. Nour El-Din; J. Drug Research, CAiro, in press.

صياغة وثبات اقماع الهبتامينول

الجزء الثانى : صياغة ودراسة خواص اقماع الهبتامينول

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

تمت صياغة قاعدة الهبتامينول فى اربع قواعد مختلفة للاقماع ،حيث تم اجراء اختبارات الجودة المعتادة عليها فور التحضير وبعد فترة تخزين على الرف لمدة عام كامل . وقد اوضحت النتائج انة لايمكن القطع بأفضلية 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 الجليسوجيلاتين بينما ينطلق الواء من الاقماع المصاغة فى قاعدة من جلايكولات عديد الاثيلين انطلاقا معتدا فى معدّلة .

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