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MANUFACTURE AND DISSOLUTION CHARACTERISTICS OF NEOMYCIN SULPHATE TABLETS

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ABSTRACT

Some direct compression vehicles, viz., Avicel PH 101, Celutab, Sta-Rx 1500 Starch, Emcomress, and Solka-floc were employed in different concentrations for the preparation of neomycin sulphate tablets. The physical properties of the produced tablets were determined. The effect of incorporation of the different excipients on the dissolution characteristics of neomycin sulphate have been investigated. Neomycin sulphate tablets were successfully prepared by mixing with the suggested vehicles and drying before compression. Of the used vehicles, Celutab and Emcompress proved to be the best in improving the mechanical properties of the produced tablets. This improvement increased on increasing the proportion of the excipient. On the other hand, Avicel in spite of producing tablets having high hardness and low friability values, extended the disintegration time of the tablets. The drug dissoluted from these tablets very rapidly, but the rate decreased on increasing Avicel proportion.

INTRODUCTION

Neomycin sulphate is thermostable[1] and hygroscopic[2], so on compressing into tablets, it sticks to punches and dies of the machine. Certain precautions are to be considered during

compression particularly with regard to a dehumidified atmosphere (less than 45% relative humidity).

Neomycin sulphate tablets were prepared by moist granulation technique using starch and sodium carboxymethyl cellulose and bound with ethyl cellulose[3]

Direct compression technique is simple and economic[4-7] and no data are given in the literature concerning the manufacture of neomycin sulphate tablets by this technique.

So, the objective of this investigation is to try the manufacture of neomycin sulphate tablets using direct compression technique. A comparative study of five types of direct compression vehicles was done and the tablets prepared were evaluated for their mechanical properties, disintegration time and dissolution rat.

EXPERIMENTAL

Materials:

Neomycin sulphate (kindly supplied by Memphis Chemical Co., Cairo, Egypt), Avicel PH 101 (F.M.C. Corporation, Pannsylvania, USA), Sta-Rx 1500 Starch (Staley Mfg. Co., 111, USA). Celutab, Emcompress (E.Mendel Co., Inc. Carmel N.Y. USA), Solka-floc (Kindly supplied by El-Kahira Co. for Pharmaceuticals, Cairo, Egypt.) and analytical grades of stearic acid, amaranth and potassium hydrogen phthalate.

Apparatus:

Erweka Tablet Compression Machine, Erweka Tablet Hardness Tester, Erweka Friabilator and Automatic Erweka Dissolution Tester (Erweka - Apparatabeau, Frankfurt, Germany), Manesty Tablet Disintegration Test Unit (Manesty Machines,

Ltd. Liverpool England), Baty Micrometer Model 120-1206 (Baty & Co. Ltd., Sussex, England) and Unicam Spectrophotometer, model Sp 600.

Procedures:

1- Formulation:

Neomycin sulphate was compressed into tablets using each time one of the selected direct compression vehicles. The formulae prepared were as follows: Neomycin sulphate: Excipient (87:10), (77:20), (67:30), (57:40) and (47:50), and 3% w/w stearic acid was used as lubricant. A control formula was also devised containing 97% w/w neomycin sulphate and 3% w/w stearic acid.

The excipients were mixed with neomycin sulphate and the lubricant in a drum mixer, which was left to rotate for a period of 15 minutes, then dried in a hot air oven at 50° for one hour before compression.

2- Compression:

The mixed powder was compressed into flat tablets, each weighing about 150 mg. using constant medium pressure A minimum of 1000 tablets were produced for each batch.

3- Evaluation of Tablets:

All the manufactured tablets were evaluated for uniformity of weight, uniformity of thickness, hardness, friability, disintegration time according to the procedure previously published by Sakr et al[8] and dissolution rate using 500 ml distilled water equilibrated at $37^{\circ} \pm 0.5^{\circ}$. Five tablets were placed in the basket which was allowed to rotate at a rate of 100 r.p.m. Samples of solution were withdrawn, meanwhile, an equivalent volume of distilled water was added. Samples were analyzed by the pro-

cedure of McGinity & Hill[9]. Data obtained were treated kinetically as shown in Table 2 and Figures 6-10.

RESULTES AND DISCUSSION

Tablets of the control formula containing only neomycin sulphate and st aric acid were very difficult to prepare; only very few tablets could be obtained. On the other hand, tablets containing the direct compression excipients, even at low concentration, did not exhibit any problem on compression.

Uniformity of Weight & Thickness:

All the manufactured tablets fulfilled the requirements of the B.P. 1980 for weight uniformity regardless the type and concentration of the excipient. The capability of an excipient to produce more uniform tablets than the other was interesting. The excipients investigated can be arranged in descending order, regarding their capability of yielding uniform tablets at aconcentration of 50% w/w as follows:

Solka-floc>Emcompress> Celutab>STA-Rx1500 Starch>Avicel.

It is also clear that on increasing the proportion of direct compression excipient, the uniformity of weight of the produced tablets is improved (Table 1). This is due to the improvement in the flow and compressiblity of the mixture.

The uniformity of thickness, in spite of being non official, its importance has been reported by Sorensen[10]. The variation of the thickness values was parallel to that of weight (Table 1). These results were expected, as the weight and thickness of the tablets are a function of the easiness of powder flow.

Mechanical Properties:

The mechanical properties of the produced tablets were tested. The results are shown in Figures 1&2. It was found that the control neomycin sulphate tablets showed very bad mechanical properties manifested by low hardness (Fig. 1) and high friability (Fig. 2) . In general, all the tested excipients improved the mechanical properties of the produced tablets to varying degrees depending upon the excipient type. Increasing the excipient concentration, generally improved the hardness and reduced the friability (Fig. 1&2). It is clear from Fig. 1 that Avicel and Celutab produced the highest hardness values of the produced tablets as their concentrations were increased. The friability results (Fig. 2) confirmed those of hardness; also Avicel and Celutab produced the lowest friability results. If the studied excipients are compared at a concentration of 50% w/w according to their beneficial effect on the mechanical properties they may be arranged in the following decreasing order:

a) Hardness:

Avicel >Emcompress> Celutab >Sta-Rx 1500 Starch> Solka-floc.

b) Friability:

Celutab> Emcompress> Sta-Rx 1500 Starch> Avicel> Solka-floc

Comparisons on the basis of the hardness-friability ratio and hardness friability index according to Mendes and Brannon[11] reveal that increasing the excipient concentration caused an increase in the mechanical strength of the tablets as whown by increase in the hardness/friability index (Fig. 4). From Fig. 3&4, it is clear that Celutab is

superior to all other excipients used in improving the mechanical properties of neomycin sulphate tablets followed by Avicel and Emcompress.

Disintegration Time:

It was found that the control tablets disintegrate rather rapidly. This may be attributed to the high solubility of neomycin sulphate or to the low hardness and high friability values of these tablets. Avicel, was found to increase the disintegration time of neomycin sulphate tablets although it is usually used as disintegrant. This is in agreement with the results of Lerk et al[12] who found that combination of soluble substances with non-dissolving disintegrants, like Avicel, resulted in a remarkable increase in disintegration time of the tablets. This phenomenon can be attributed to antagonistic effects, as the dissolution of neomycin sulphate in the tablets is retarded by a barrier of microcrystalline cellulose, where as the disintegration of the microcrystalline cellulose is inhibited by a high concentration of dissolved neomycin sulphate.

Celutab improved the disintegration properties of neomycin sulphate tablets. This improvement is directly proportional to the excipient concentration. On the other hand, Sta-Rx 1500 starch at 10% concentration, increased the disintegration time from 17 minutes for the control to 20.6 minutes. On further increasing the concentration of Sta-Rx 1500 Starch, the disintegration time decreased again, reaching 10 minutes at 50% concentration. Such a result may be explained on the basis that Sta-Rx 1500 Starch acts both as disintegrant and binding material, the former property being obvious at high proportions[13].

Solka-floc and Emcompress have also a disintegrating effect in neomycin sulphate tablets. Such an effect was, more or less, related to their concentration. Thus, at 50% w/w the prepared tablets disintegrated within 12.8 and 9.3 minutes respectively.

Dissolution Behaviour:

Data acquired were treated kinetically and dissolution was found to follow the first order equation (Table 2 and Figure 6-10). Dissolution results revealed that the dissoltuion rate is greatly affected by the type and concentration of the incorporated excipient. Thus, the initial dissolution rate increased significantly by increasing the direct compression excipient. This may be due to the decrease in the disintegration time of the produced tablets, perhaps due to absorption of excessive quantities of the dissolution fluid by the tablets, leading to a faster breakdown of the tablet structure[14].

On incorporating Celutab, the rate of dissoltuion decreased relative to other excipients and the total amount released after 120 minutes was even smallar. On the other hand, tablets prepared using Solka-floc showed the highest dissolution rate among the obtained tablets with the smallest $T_{50\%}$. This may be due to increased capillarity which promotes the penetration of the dissolution medium into the tablets.

Tablets prepared using Emcompress exhibited low rates of dissolution except at 50% concentration. The dissoluted amounts of neomycin sulphate after 2 hours were 40.1 % and 62% with 10% and 20% of Emcompress respectively.

From the data given in Table 2 and Figure 6, Avicel is shown to offer rapid dissolution of neomycin sulphate from its tablets up to 30% Avicel, but it decreases on further

increase of Avicel. Tablets containing 50% w/w Avicel release neomycin sulphate slower than those containing 10% w/w Avicel. This may be due to the binding effect between Avicel particles which in turn results in increased hardness. The two effects retard dissolution of neomycin sulphate. Similar results were reported by Kitazawa *et al*[15]. The tested excipients can be arranged with respect to their effect on dissolution rate after 15 minutes at 50% concentration in the following sequence:

Sta-Rx 1500 Starch > Sollka-floc > Celutab > Emcompress > Avicel. An identical result was obtained if we compare the T_{50} of the various tablets prepared by 50% of the tested excipients.

Table 1: Effect of different direct compression excipients on the Uniformity of weight and thickness of neomycin sulphate tablets.

Excipient		*Weight (g)*			*Thickness S (mm)*		
Concentration % w/w		*Mean[a]*	*S.D.*	*C.V.%*	*Mean[a]*	*S.D.*	*C.V.%*
Control		0.1567	0.0114	7.28	3.57	0.2120	5.94
Avicel PH 101	10	0.1585	0.0149	9.41	3.60	0.3105	8.62
	20	0.1548	0.0112	7.24	3.50	0.2417	6.90
	30	0.1462	0.0071	4.83	3.35	0.1445	4.31
	40	0.1357	0.0056	4.17	3.09	0.1162	3.76
	50	0.1330	0.0042	3.17	2.99	0.0671	2.24
Celutab	10	0.1542	0.0105	6.80	3.55	0.1762	4.97
	20	0.1598	0.0084	5.23	3.64	0.1538	4.23
	30	0.1621	0.0066	4.05	3.67	0.1301	3.57
	40	0.1712	0.0055	3.20	3.88	0.1166	3.00
	50	0.1748	0.0045	2.56	3.98	0.2298	1.40
Sta-Rx 1500 Starch	10	0.1770	0.0114	6.43	3.95	0.2388	7.16
	20	0.1769	0.0083	4.69	3.89	0.2355	6.06
	30	0.1713	0.0058	3.41	3.87	0.2318	5.98
	40	0.1694	0.0055	3.26	3.86	0.1710	4.43
	50	0.1522	0.0048	3.14	3.79	0.0599	1.58
Emcompress	10	0.1602	0.0091	5.67	3.47	0.1620	4.67
	20	0.1729	0.0090	5.29	3.53	0.1523	4.32
	30	0.1783	0.0089	5.00	3.73	0.1502	4.23
	40	0.1820	0.0064	3.52	3.81	0.1511	3.96
	50	0.1860	0.0045	2.41	3.89	0.0889	2.29
Solka-floc	10	0.1461	0.0110	7.50	3.26	0.1447	4.44
	20	0.1333	0.0068	5.12	2.93	0.1228	4.20
	30	0.1219	0.0070	5.74	2.76	0.1000	3.63
	40	0.1112	0.0048	4.33	2.63	0.0468	1.78
	50	0.1111	0.0026	2.33	2.69	0.0421	1.57

a = mean of 20 tablets

Table 2 : Dissolution rate constant and T_{50} of neomycin sulphat tablets prepared by direct compression excipients.

Excipient *Concentration % w/w*		*K min.$^{-1}$*	*T_{50} (min)*
Control		0.00502	138.11
Avicel PH 101	10	0.02982	23.24
	20	0.02802	24.73
	30	0.02107	32.90
	40	0.01687	41.08
	50	0.00610	113.53
Celutab	10	0.01234	56.14
	20	0.01265	54.75
	30	0.02184	31.72
	40	0.03149	22.00
	50	0.03840	18.04
Sta-Rx 1500 Starch	10	0.01805	38.39
	20	0.00711	97.37
	30	0.02252	30.77
	40	0.03252	21.31
	50	0.05969	11.62
Emcompress	10	0.00596	116.21
	20	0.00818	84.64
	30	0.02341	29.61
	40	0.01235	56.01
	50	0.03318	20.89
Solka-floc	10	0.01550	44.70
	20	0.01722	40.24
	30	0.02894	24.28
	40	0.03444	20.12
	50	0.04415	15.70

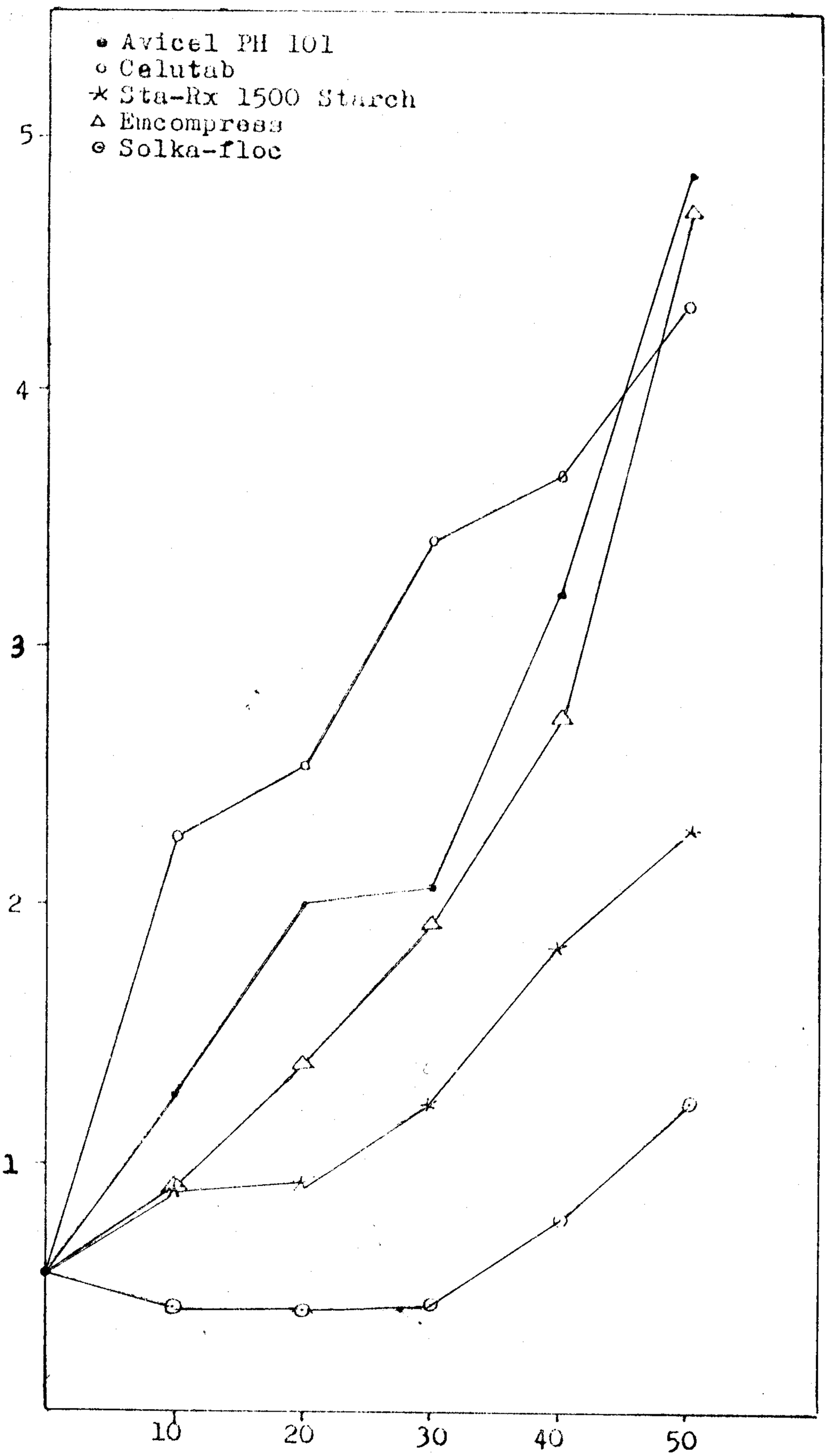

Fig. 1: Effect of different excipients on the hardness of neomycin sulphate tablets

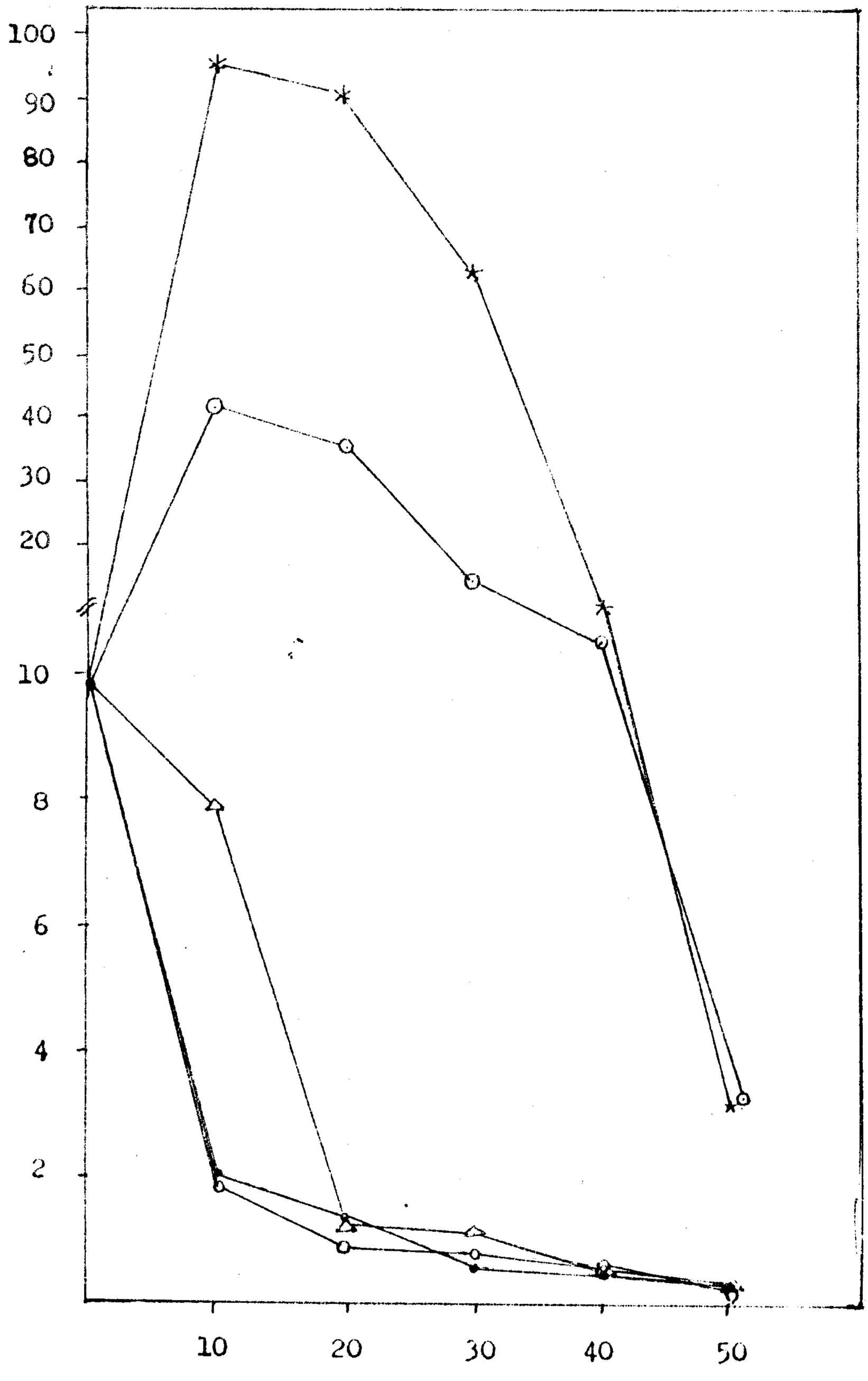

Fig. 2: Effect of different excipients on the friability of neomycin sulphate tableta
Key : The same as Fig. 1.

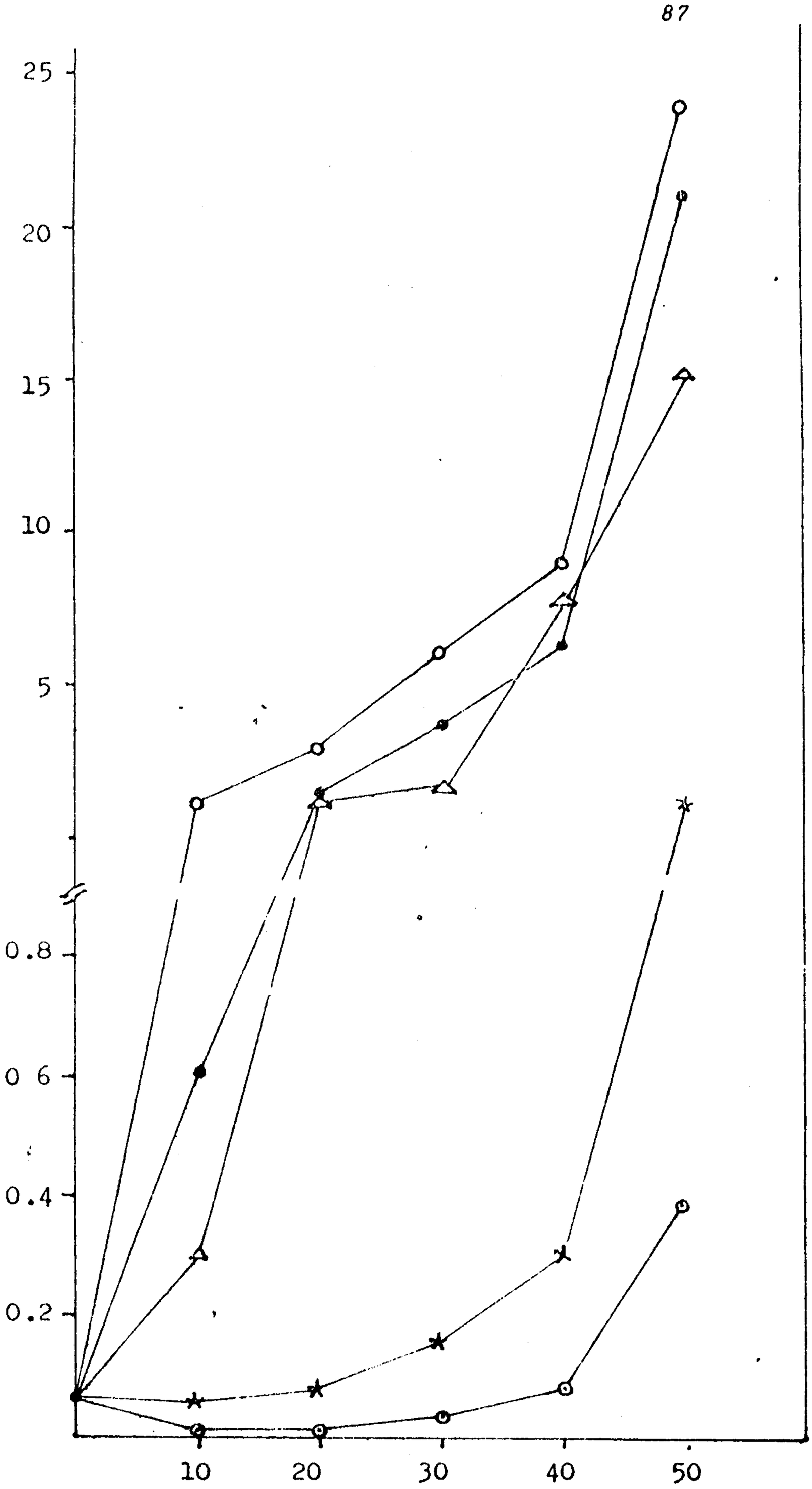

Fig. 3: Effect of different excipients on the hardness friability ratio of neomycin sulphate tablets

Key : The same as Fig. 1.

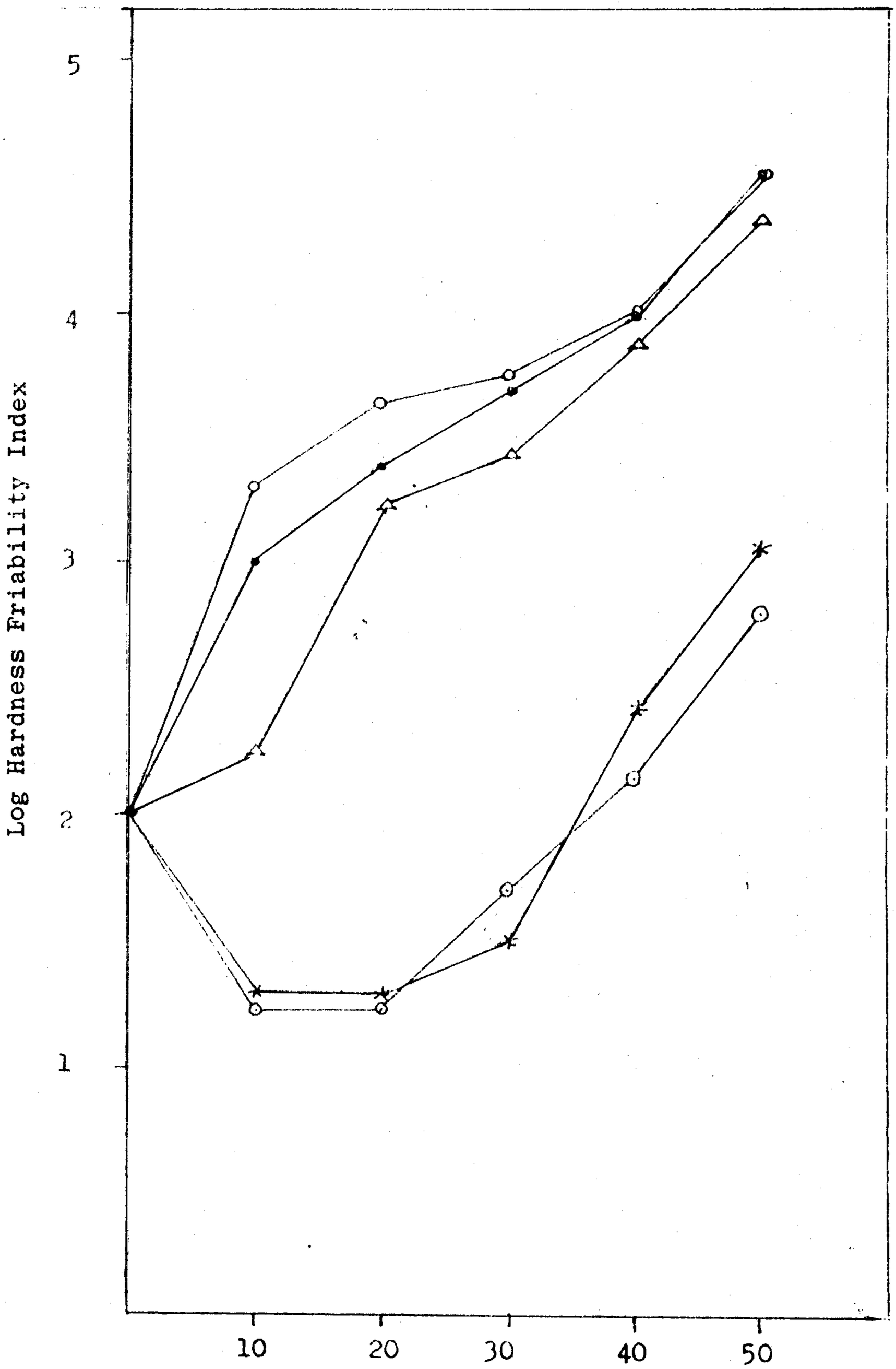

Fig. 4: Effect of different excipients on the hardness friability index of neomycin sulphate tablets

Key : The same as Fig. 1.

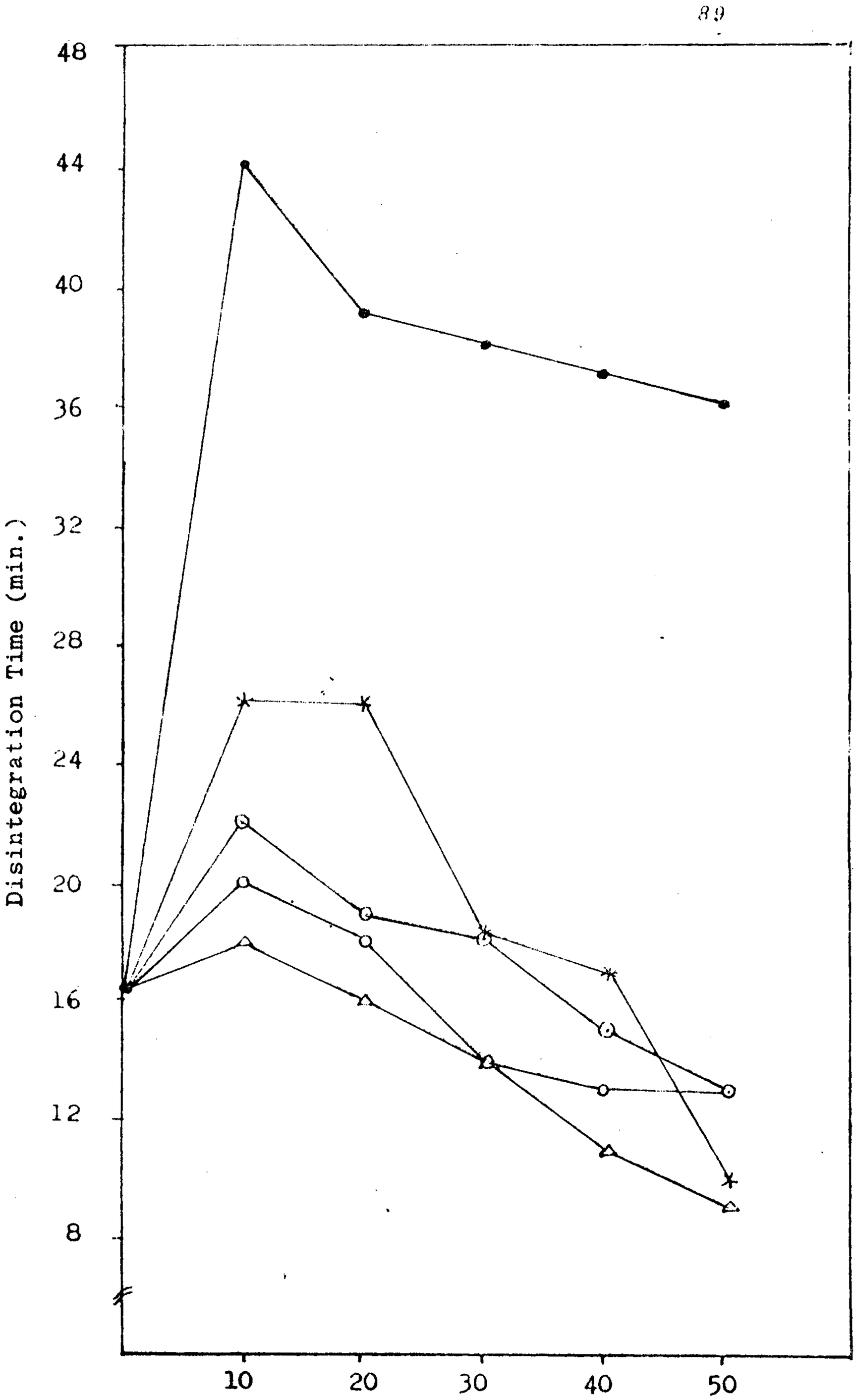

Fig. 5: Effect of different excipients on disintegration time (min.) of neomycin sulphate tablets

Key : The Same as Fig. 1.

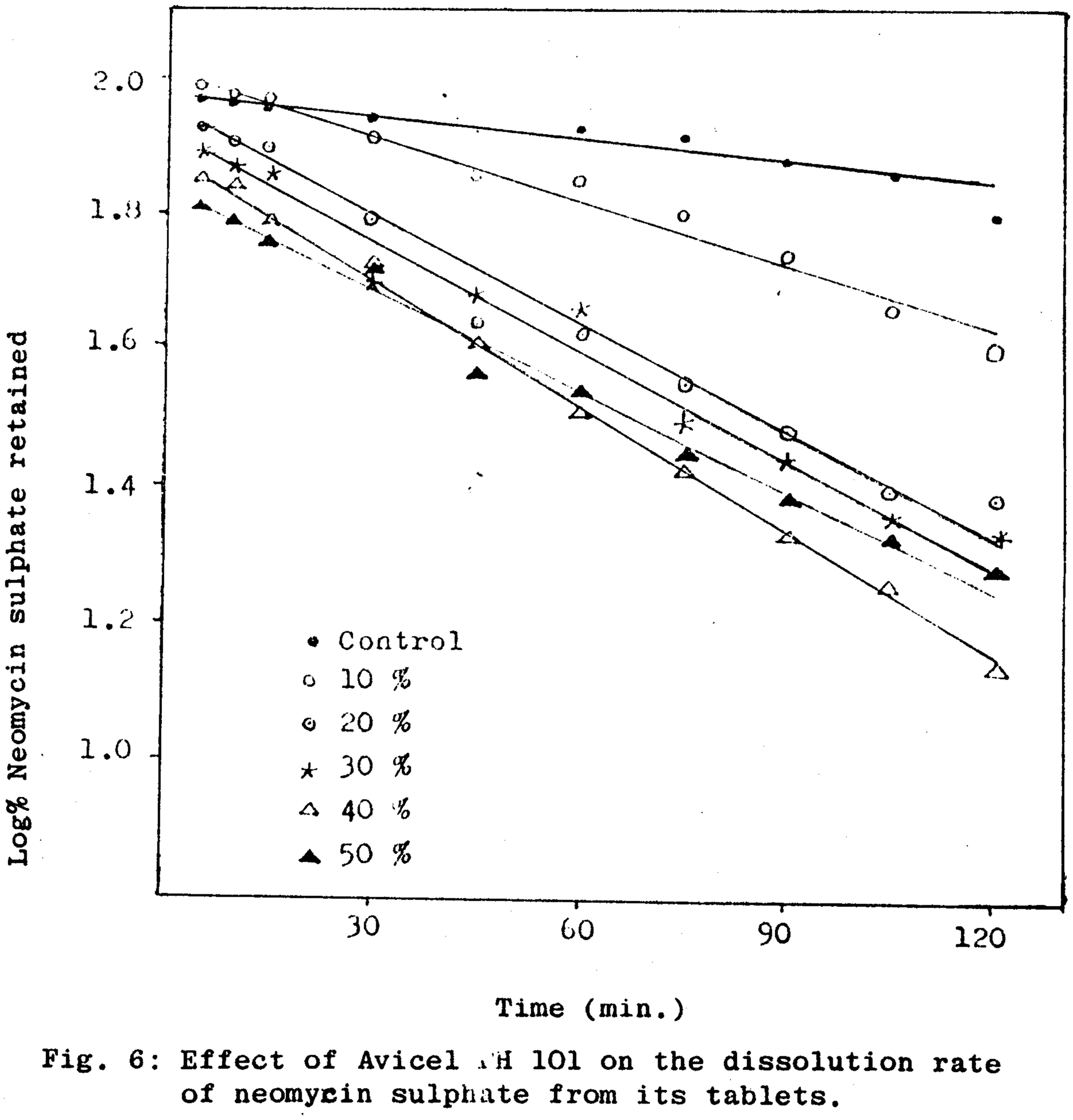

Fig. 6: Effect of Avicel PH 101 on the dissolution rate of neomycin sulphate from its tablets.

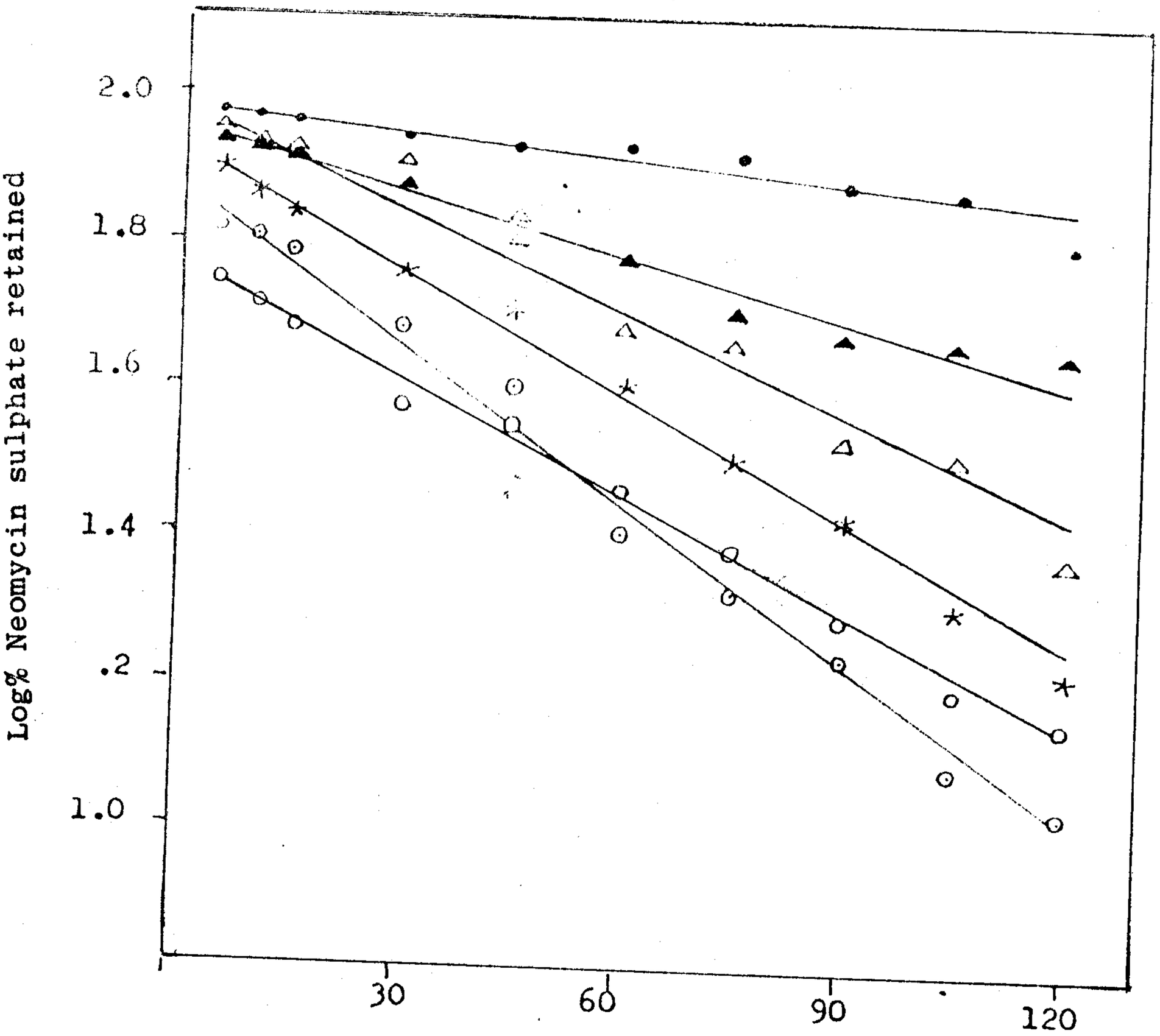

Fig. 7: Effect of Celutab on the dissolution rate of neomycin sulphate from its tablets

Key : The same as Fig. 6.

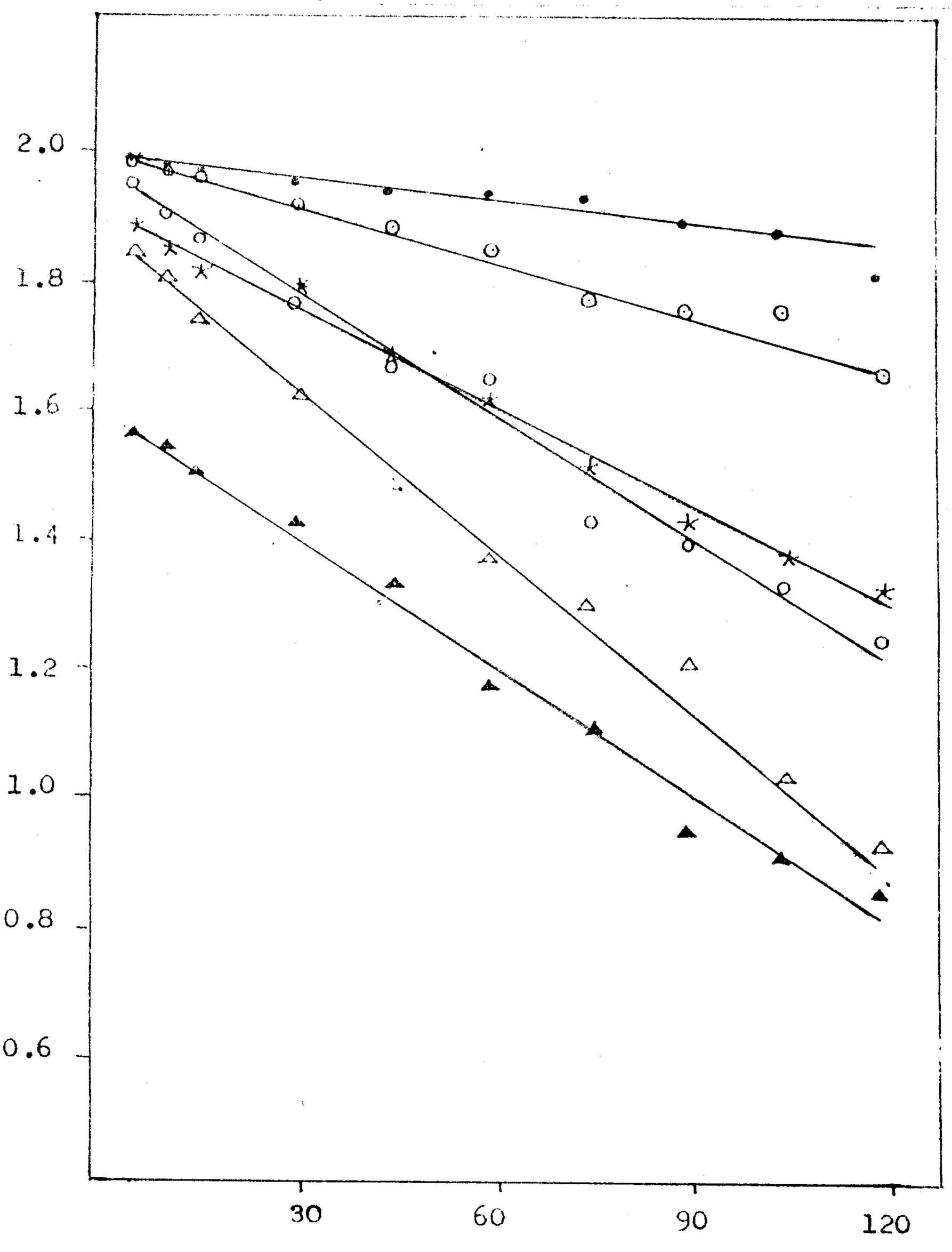

Fig. 8: Effect of Sta-Rx 1500 starch on the dissolution rate of neomycin sulphate from its tablets

Key : The same as Fig. 6.

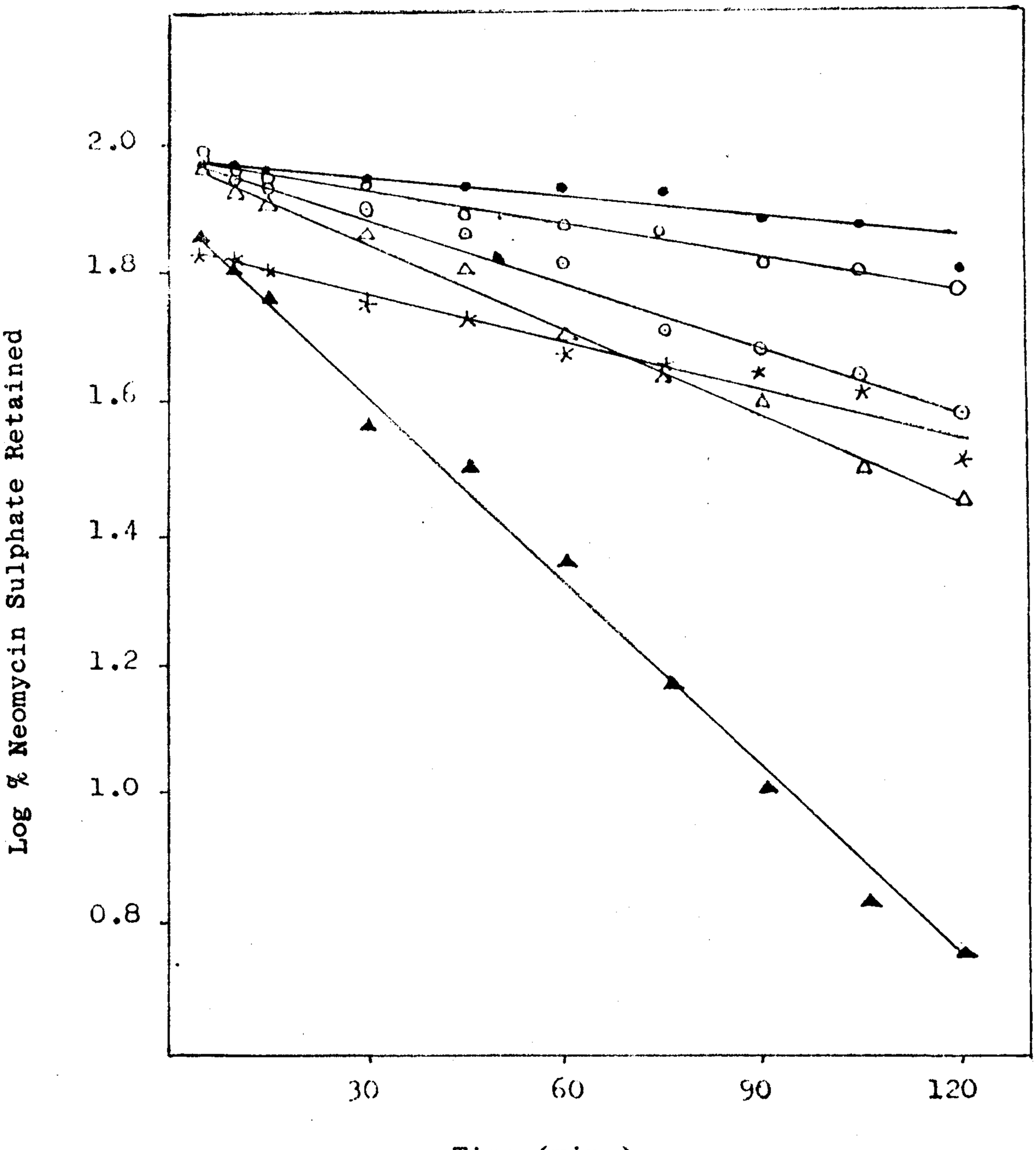

Fig. 9: Effect of Emcompress on the dissolution rate of neomycin sulphate from its tablets

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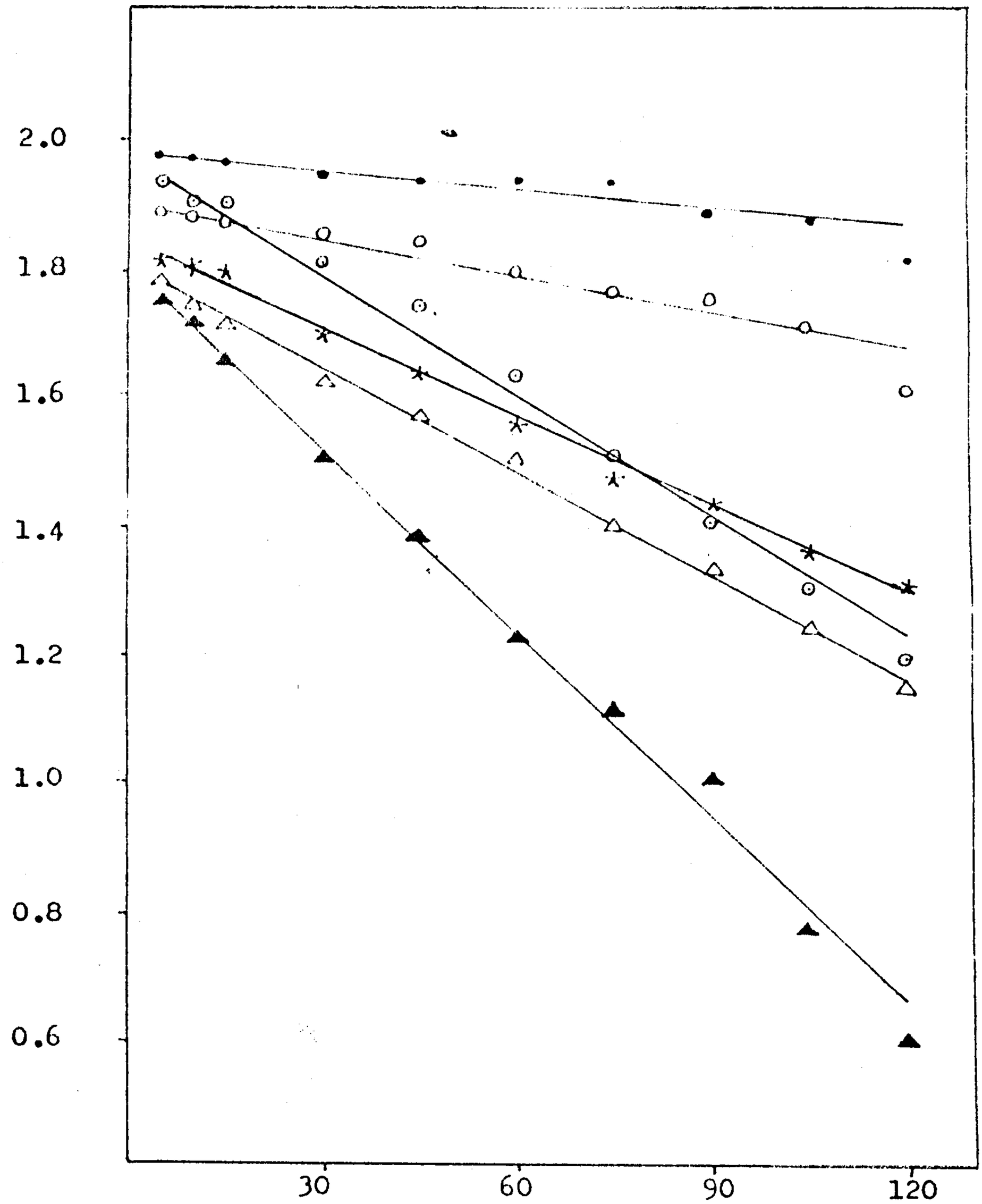

Fig. 10: Effect of Solka-floc on the dissolution rate of neomycin sulphate from its tablets

Key : The same as Fig. 6.

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تصنيع واتاحة اقراص النيومايسين

محمد على على قاسم - منى الخطيب

تم فى هذا البحث تحضير اقراص النيومايسين باستخدام صواغات الكبس المباشر وذلك لتفادى صعوبة الكبس بسبب تميؤها والتصاقها بماكينة الاقراص . وقد تم تقييم الاقراص المحضرة من حيث الصفات الميكانيكية وزمن التفتت وكذلك الاتاحة المعملية وقد اتضح من النتائج امكانية استخدام السلوتاب والايمكومبرس حيث تحسنت الصفات الفيزيائية للاقراص كما زادت اتاحة المادة الدوائية . اما الافسيل فقد اعطى للاقراص صفات ميكانيكية جيدة واتاح المادة الدوائية بسرعة فى التركيزات المنخفضة حتى ٣٠ فى المائة .

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