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SODYUM KARBOKSİMETİLSELÜLOZ SÜSPANSİYONLARI İÇİNDEKİ KLORAMFENİKOLÜN REOLOJİK YÖNDEN İNCELENMESİ

RHEOLOGICAL STUDIES OF CHLORAMPHENICOL IN SODIUM CARBOXYMETHYL CELLULOSE SUSPENSIONS

M. Alam* – C.M. Ashraf** – S. Asghar – M.A. Khan

SUMMARY

Rheological studies of various pourable suspensions (1.50, 1.75, 2.00, 2.25 and 2.50 % w/v) and citrate phosphate buffers at pH 3.5, 5.0 and 8.0 have revealed that its 2.25 % (w/v) dispersion is suitable for a pharmaceutical formulation. It has been inferred from a variety of rheological characteristics that quite a stable suspension of chloramphenicol palmitate may be formulated using 2.25 % (w/v) dispersion of this suspending agent at pH 5.0. These results have also been compared with the sample of chloromycetin suspension (Parke Davis) as standard.

ÖZET

Sodyum karboksimetilselülozun distile su içinde % 1.50, 1.75, 2.00, 2.25, 2.50 konsantrasyonlarda ve pH = 3.5, 5.0 ve 8.0'de sitrat ve fosfat tmponlarında çeşitli dökülebilir süspansiyonları reolojik yönden incelendi. Formasötik formülasyona en uygun dispersiyonun % 2.25 olduğu gözlendi. Reolojik çalışmalar süspanse edici ajan olan sodyum karboksimetilselüloz % 2.25 oranında dağıtıldığında ve pH = 5'te kloramfenikol palmitatın oldukça stabil bir süspansiyon oluşturduğunu göstermiştir. Bu sonuçlar, standart chloromycetin süspansiyonu (Parke Davis) ile çalışılarak karşılaştırılmıştır.

* Department of Pharmacy, University of the Punjab, Allama Iqbal Campus, Lahore–54000, Pakistan.

** PCSIR Laboratories Complex, Lahore–54600.

INTRODUCTION

Many substances are insoluble in aqueous as well as in some non-aqueous media. These are dispersed in a solution of high consistency, which could support the insoluble substance, so that they remain dispersed in the vehicle(1). Advantage of this property has been taken in pharmaceutical preparations, which consists of finely divided drug particles distributed uniformly through the vehicle in which the drug exhibits elegant stability(2).

The drug selected for the current study was chloramphenicol palmitate, since it gives better therapeutic results than all its other derivatives, so it is widely used as antibacterial agent(3). The stabilising and thickening agent chosen for this study was sodium carboxymethyl cellulose (CMC – grade 1190), as it is cheap, easily available in the market and finds extensive use in pharmaceutical formulations(4,5). This necessitated the determination of the rheological characteristics suitable for the formulation of chloramphenicol suspension. In this connection studies were undertaken for different formulations of chloramphenicol palmitate with sodium carboxymethyl cellulose and the results compared with the market sample (Chloromycetin – Parke Davis).

MATERIALS AND METHODS

Material

Sodium carboxymethyl cellulose (CMC – grade 1190).

Apparatus

"Contex Mixer", Brookfield Viscometer – Model LVT.

Method

Different concentration of sodium carboxymethyl cellulose in distilled water and citrate phosphate buffer having pH 3.5, 5.0 and 8.0 were prepared using procedure described by Smith(6).

Viscosity measurements

Various dispersions (600 ml) of sodium carboxymethyl cellulose (1.5, 1.75, 2.00, 2.25 and 2.50 %, w/v) in distilled water and citrate

phosphate buffer at pH 3.5, 5.0 and 8.0 were respectively stirred with "Contex Mixer" at 300 RPM and allowed to stand for 24 hours. Their viscosity measurements were carried out at 28 °C using Brookfield Viscometer (Model-LVT) by employing appropriate spindle at 20 RPM. The scale readings were, then, converted to centipoise units by multiplying with appropriate Brookfield factor for the spindle used. The viscosity measurements of each dispersion was studied for two weeks and results are given in Table – I and plots of log of viscosity versus time are shown in Figs. 1–3(7).

Sedimentation studies in buffer solutions

Various dispersions of sodium carboxymethyl cellulose (1.50, 1.75, 2.00, 2.25 and 2,50 % w/v) in citrate phosphate buffers at pH 3.5, 5.0 and 8.0 were prepared and placed in graduated cylinders (100 ml). These were allowed to stand for one month. The sedimentation rates were determined and then F-ratio was calculated using the following relationship:

F-ratio $= V_u/V_o$

Where, V_o = Original volume (100 ml)

V_u = Ultimate volume of sedimentation at time "t"

F-ratio of different percentages of sodium carboxymethyl cellulose at different pH are given in Table – II.

Effect of aging on viscosity mearsurements

Effect of aging on viscosity measurements along with their F-ratio of chloromycetin (Parke Davis) and chloramphenicol palmitate in 2.25 % (w/v) sodium carboxymethyl cellulose at pH 5.0 are shown in Table – III.

In this connection a standard doze of drug was prepared by dissolving 125 mg of chlorampenicol palmitate in water (5 ml) which contained 2.25 % (w/v) sodium carboxymethyl cellulose. The sample (600 ml) was stirred with "Contex-Mixer" at 300 RPM. The sample was allowed to stand for 24 hours, after that the viscosity of the formulation was studied for eight weeks. Similary, the viscosity of chloromycetin palmitate suspension marketed by Parke Davis was also studied for

Table – I : Viscosity measurement in centipoise (Brook Field) versus time in sodium carboxymethyl cellulose with spindle 2, 3 and 4 at 20 RPM

Time in days / Dispersions w/v%	0	1	3	4	6	8	10	12	14
	Viscosity (log viscosity)								
Distilled Water									
1.50	1310 (3.1173)	1370 (3.1367)	1325 (3.1222)	1280 (3.1072)	1240 (3.0934)	1220 (3.0864)	1165 (3.0663)	1130 (3.0531)	1090 (3.0374)
1.75	1940 (3.2878)	2250 (3.3522)	2062 (3.3143)	1840 (3.2648)	1780 (3.2504)	1700 (3.2304)	1600 (3.2041)	1100 (3.0414)	1000 (3.0000)
2.00	3675 (3.5653)	4500 (3.6532)	4500 (3.6532)	4500 (3.6532)	4250 (3.6284)	4000 (3.6021)	3500 (3.5441)	3300 (3.5185)	2500 (3.3979)
2.25	4700 (3.6721)	6700 (3.8261)	6700 (3.8261)	6700 (3.8261)	6700 (3.8261)	6700 (3.8261)	6700 (3.8261)	6700 (3.8261)	4750 (3.6767)
2.50	5130 (3.7101)	5433 (3.7350)	5252 (3.7203)	5065 (3.7046)	4895 (3.6898)	4704 (3.6725)	4612 (3.6639)	4570 (3.6599)	4530 (3.6561)
pH 8.0									
1.50	3565 (3.5521)	3612 (3.5575)	2500 (3.5441)	3464 (3.5396)	3315 (3.5205)	3280 (3.5159)	3200 (3.5052)	3152 (3.4986)	3109 (3.4926)
1.75	4122 (3.6151)	4345 (3.6380)	4235 (3.6269)	4170 (3.6201)	4100 (3.6128)	4000 (3.6021)	3975 (3.5993)	3972 (3.5990)	3912 (3.5924)
2.00	4538 (3.6663)	4615 (3.6642)	4575 (3.6604)	4490 (3.6522)	4420 (3.6454)	4380 (3.6415)	4335 (3.6370)	4300 (3.6335)	4300 (3.6335)
2.25	4985 (3.6977)	5180 (3.7143)	5100 (3.7076)	5064 (3.7045)	5008 (3.6997)	4972 (3.6965)	4900 (3.6902)	4863 (3.6869)	4785 (3.6798)
2.50	5600 (3.7482)	5782 (3.7621)	5752 (3.7598)	5680 (3.7543)	5593 (3.7476)	5410 (3.7332)	5450 (3.7364)	5402 (3.7326)	5345 (3.7279)
pH 5.0									
1.50	88 (1.9445)	83 (1.9191)	82 (1.9138)	80 (1.9031)	78 (1.8921)	71 (1.8513)	75 (1.8751)	64 (1.8062)	53 (1.7243)
1.75	110 (2.0414)	120 (2.0792)	110 (2.0414)	110 (2.0414)	115 (2.0607)	120 (2.0792)	130 (2.1139)	135 (2.1303)	120 (2.0792)
2.00	450 (2.6532)	460 (2.6628)	460 (2.6628)	440 (2.6434)	430 (2.6334)	420 (2.6232)	410 (2.6128)	400 (2.6021)	380 (2.5798)
2.25	960 (2.9823)	970 (2.9868)	960 (2.9823)	960 (2.9823)	960 (2.9823)	960 (2.9823)	960 (2.9823)	940 (2.9731)	920 (2.9638)
2.50	1825 (3.2613)	1925 (3.2844)	1950 (3.2900)	1975 (3.2956)	1900 (3.2788)	1875 (3.2730)	1875 (3.2730)	1800 (3.2553)	1775 (3.2492)
pH 3.5									
1.50	25 (1.3979)	32 (1.5052)	28 (1.4472)	35 (1.5441)	30 (1.4771)	35 (1.5441)	40 (1.6021)	45 (1.6532)	38 (1.5798)
1.75	30 (1.7710)	40 (1.6021)	45 (1.6532)	48 (1.6812)	40 (1.6021)	50 (1.6990)	46 (1.6628)	45 (1.6532)	35 (1.5441)
2.00	54 (1.7324)	65 (1.8129)	69 (1.8388)	78 (1.8921)	82 (1.9138)	75 (1.8751)	70 (1.8451)	80 (1.9031)	82 (1.9138)
2.25	92 (1.9638)	102 (2.0086)	125 (2.0970)	110 (2.0414)	135 (2.1303)	116 (2.0645)	131 (2.1173)	150 (2.1761)	132 (2.1206)
2.50	120	158	150	161	170	198	215	231	250

comparison. The rheogram of chloromycetin and chloramphenicol suspensions are given in Table – IV and a plot of their log of viscosity versus RPM have been shown in Fig.4.

Table – II : Sedimentation rate (F-ratio) of different percentages of sodium carboxymethyl cellulose at different pH (after one month)

Dispersion % , w/v	F-ratio at pH		
	3.5	5.0	8.0
1.50	0.61	0.64	0.59
1.75	0.65	0.76	0.71
2.00	0.82	0.88	0.79
2.25	0.83	0.95	0.88
2.50	0.94	1.00	0.95

Table – III : Viscosity measurements in centipoise (Brook Field) and F-ratio versus time of chloromycetin (Parke Davis) and chloramphenicol in 2.25 % (w/v) of sodium carboxymethyl cellulose at pH 5.0

Time in weeks.	Viscosity		F-ratio	
	Chloromycetin (Parke Davis)	Chloramphenicol (Prepared)	Chloromycetin (Parke Davis)	Chloramphenicol (Prepared)
Initial	275	1550	1.00	1.00
Ist	275	1850	0.97	0.93
2nd	275	1500	0.96	0.91
3rd	250	1450	0.94	0.89
4th	250	1450	0.92	0.86
5th	250	1450	0.91	0.85
6th	250	1450	0.90	0.84
7th	250	1450	0.89	0.83
8th	250	1450	0.88	0.82

Table – IV : Rheograms of chloromycetin (Parke Davis) and chloramphenicol suspension in 2.25 %, (w/v) of sodium carboxymethyl cellulose at pH 5.0

RPM of Viscometer	Viscosity	
	Chloromycetin	Chloramphenicol
2.5	1600	4400
5.0	945	3000
10.0	500	2100
20.0	275	1500
50.0	135	970
100.0	95	710
50.0	160	1025
20.0	300	1550
10.0	600	2160
5.0	975	3300
2.5	1700	4500

Table – V : Relative stabilities of chloromycetin (Parke Davis) and formulated chloramphenicol suspension in terms of pH, centrifugation ratio and decomposition

Suspension	pH after 24 hours	Centrifugation Ratio (after one month)	Decomposition (after three months)
Chloromycetin (Parke Davis)	3.6	30	Nil
Chloramphenicol (Prepared).	4.0	20	0.4%

Stability of formulated chloramphenicol palmitate suspension

Formulated chloramphenicol palmitate suspension (10 ml) was diluted into absoluted ethanol (90 ml) and its λ_{max} was found to be 271 nm. Then, a standard graph was plotted between various concentrations of the formulated chloramphenicol palmitate and their absorbance at λ_{max}. The concentration of various sets were determined after one month from this standard plot and percentage of decomposition was calculated. The average value of decomposition is shown in Table – V.

RESULTS AND DISCUSSION

Rheological studies

Suspensions for oral use are becoming important due to their better absorption. It was observed that aqueous dispersion of sodium CMC below 1.50 % (w/v) had low viscosities and were, therefore, not considered suitable for use. Moreover, its dispersions above 2.50 % (w/v) produced very thick and unpourable gels, and hence their viscosity measurements were not undertaken. Consequently, viscosity measurements of pourable dispersions of 1.50, 1.75, 2.00, 2.25 and 2.50 % (w/v) of sodium-CMC in distilled water and citrate phosphate buffers at pH 3.5, 5.0 and 8.0 were recorded over a period of two weeks. These measurements were made on Brookfield viscometer with spindles 2, 3 and 4 at 20 RPM and the results are given in Table – I and plots of their log of viscosity versus time are shown in Figs.1– 3.

It is evident from Fig.1 that 2.25 % (w/v) dispersions of sodium-CMC in distilled water is considerable stable, since it does not change with time as compared with other concentrations. However, in a slightly alkaline medium at pH 8.0 (Fig.1), even the dispersion of 2.25 % (w/v) exuded and was not worth use. In addition, the dispersion at pH 3.5 indicated irregular behaviour (Fig.2), developed fungus and was, therefore, discarded. Thus, only the dispersion of 2.25 % (w/v) at pH 5.0 manifested reasonable stability over a trial period of two weeks (Fig.-3).

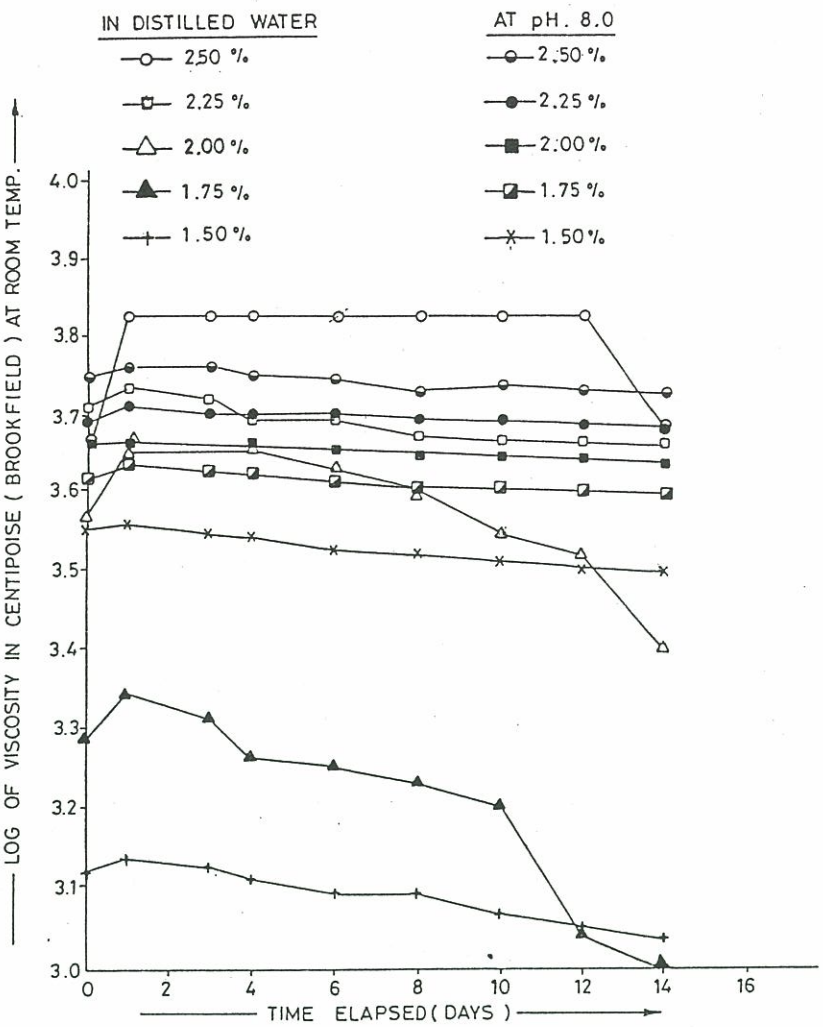

Fig.1. Viscosity measurements in centipoise (Brookfield) versus time in sodium carboxymethyl cellulose dispersions with spindles 2, 3, 4, at 20 RPM,

In order to substantiate this contention, sedimentation rates of all the dispersions (1.50, 1.75, 2.00, 2.25 and 2.50 % (w/v) were also determined after one month in buffer solutions at pH 3.5, 5.0 and 8.0 and are depicted in Table – II in terms of F-ratio. These results also support the view that dispersion of 2.25 % (w/v) at pH 5.0 should be suitable for formulation.

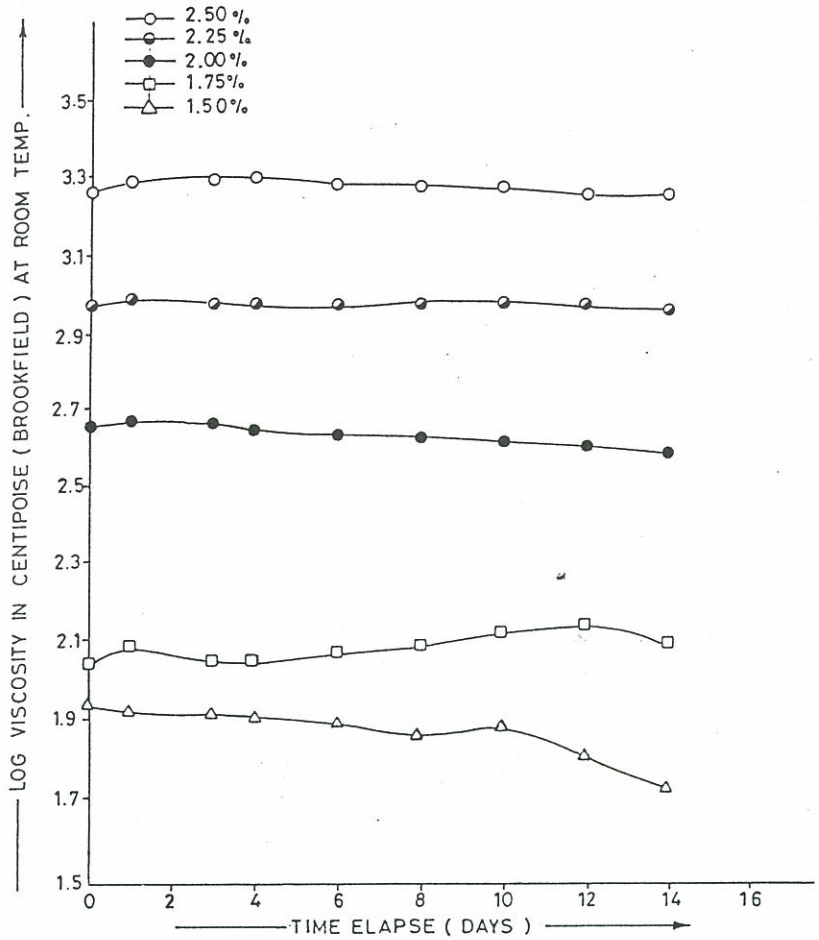

Fig.2. Viscosity measurements in centipoise (Brookfield) versus time in sodium carboxymethyl cellulose at pH 5.0 with spindles 2, 3, 4 at 20 RPM.

Formulation of stable chloramphenicol palmitate suspension

To assess the effect of aging on viscosity and F-ratio of chloramphenicol palmitate formulation, its suspensions in 2.25 % (w/v) sodium-CMC, prepared in accordance with the procedure described in the experimental section, required determinations were made, and the results are shown in Table – III, alongwith these of marketed sample of chloromycetin (Parke Davis). It is obvious from these results that there is a very little change in their respective viscosities and F-ratio even after eight weeks, thus supporting the validity of the above mentioned results.

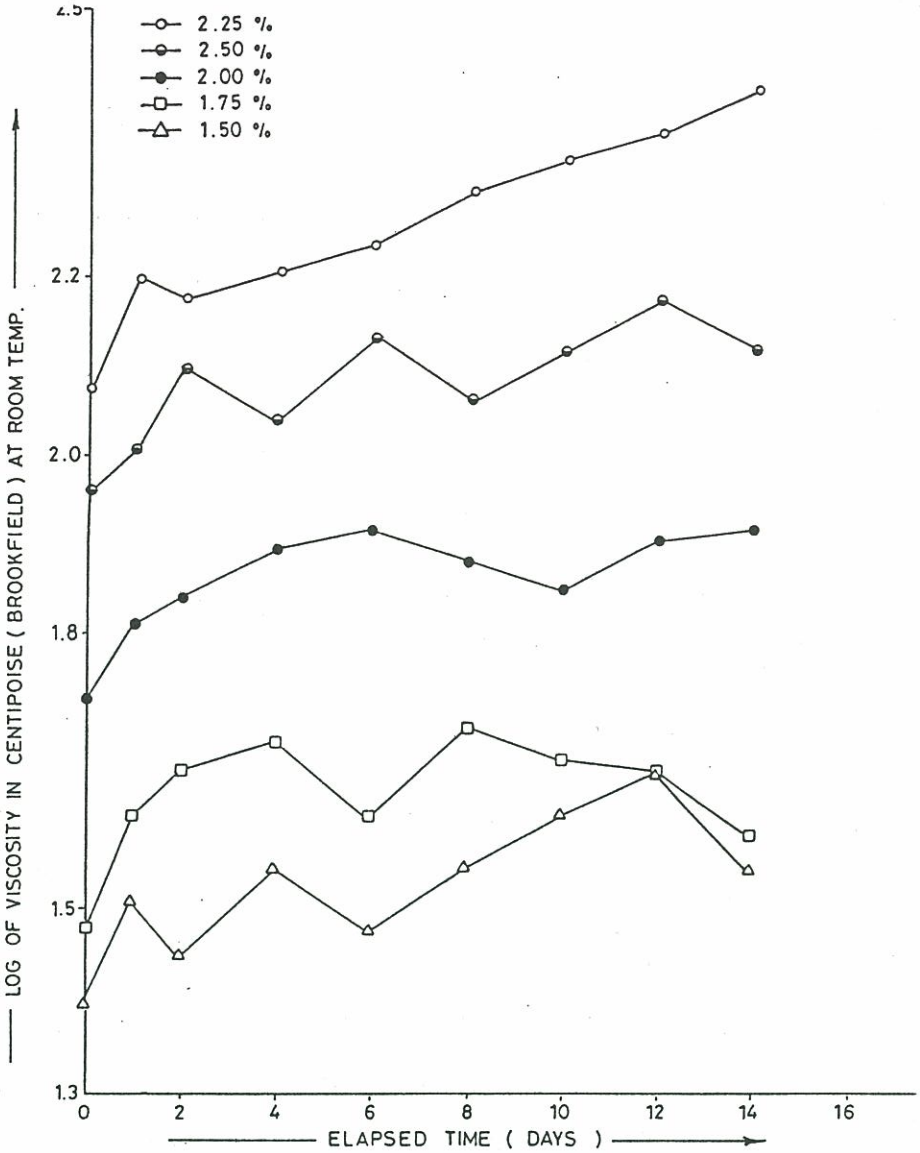

Fig.3. Viscosity measurements in centipoise (Brookfield) versus time in sodium carboxymethyl cellulose dispersions at pH 3.5 with spindles 2, 3, 4, at 20 RPM.

A similar behaviour of these samples has been observed in their respective rheograms (Fig.-4). Their pH (after 24 hours), centrifugation ratio (after one month) and decomposition (after three months) were also determined (Table – V). It is obvious from this table that the formulated chloramphenicol has slightly higher pH, which indicates negligible decomposition (0.4 %) during the shelf-life of three months, while their

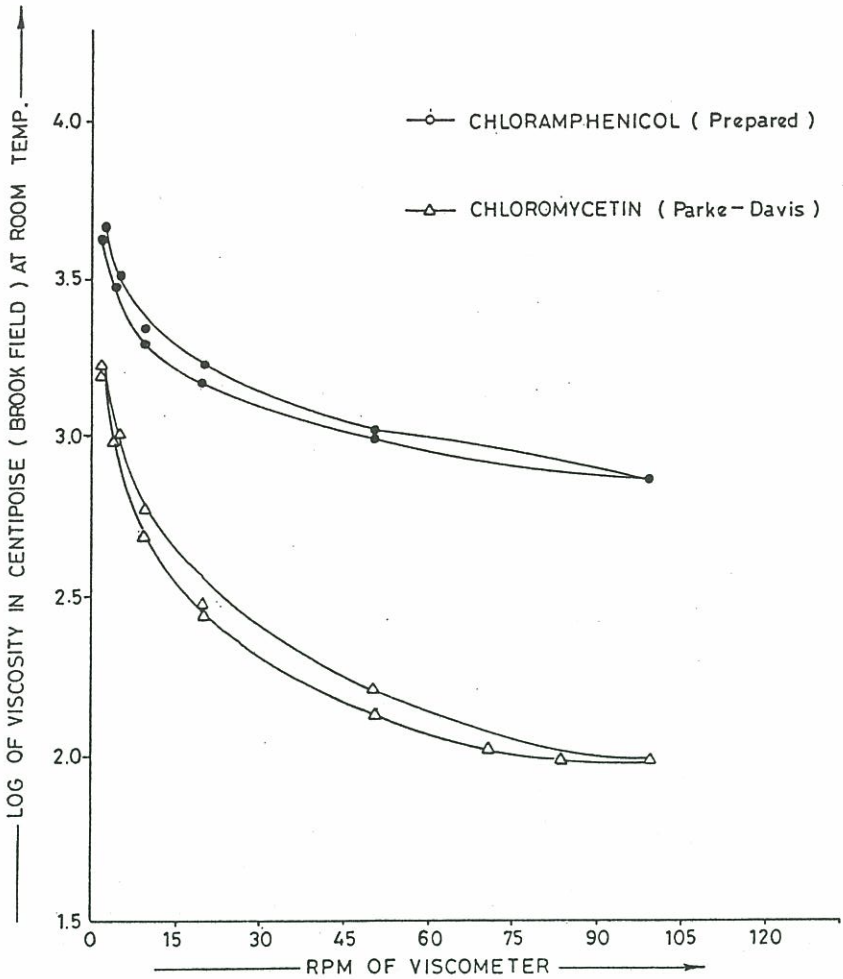

Fig.4. Rheograms of chloromycetin (Parke-Davis) & chloramphenicol suspension in 2.25 % (w/v) of sodium carboxymethyl celluose at pH 5.0.

centrifugation ratio, although different, were observed to be constant for the trial period of one month. It is concluded that the formulated chloramphenicol suspension in sodium-CMC (2.25 % w/v) in citrate phosphate buffer at pH 5.0 is reasonably stable and acceptable for use.

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