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RELEASE AND RHEOLOGICAL CHARACTERISTICS OF CHLORTETRACYCLINE HYDROCHLORIDE OPHTHALMIC OINTMENTS

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The release of chlortetracycline from absorption and emulsion ointment bases were studied. The drug release rates from the emulsion bases were found to be Hkigher than that from the absorption bases. The presence of sod. metabisulphite and EDTA in the ointment systems under test was found to increase the release rate of the drug. Inclusion of a buffer in the aqueous phase of the emulsion systems was found to retard the release of the drug. The rheological data reveals that there is a correlation between the breakdown of the system and the release of the drug from the system accompanying the addition of sod. metabisulphite-EDTA mixture and buffer solution to the ointment bases.

A variety of factors influence the ophthalmic use of drugs and/or semisolid bases. The primary site of drug action in the eye is the cornea. Although recent studies[1,2] indicated precorneal tear film to be lipid in nature, most drugs probably penetrate to the cornea from semisolid bases with little influene from this thin precorneal tear film.

The rheological evaluation of pharmaceutical semisolids is useful in that it provides both a method of quality control during and after manufacturing processes[3-5]. Viscosity[6], i. e, resistance to flow of a fluid under stress , has been directly related to both diffusion rate of a drug from a semisolid base and the therapeutic efficacy of the drug in the base.[6-9] Higuchi[10], pointed out that the diffusion coefficient of the drugs is inversely proportional

to the viscosity of the vehicle. Lund[11] reported that the reason for the differences in absorption must lie in the differences in viscosity of the basis at the least temperature. Strong correlation between rheological parameters of ointments and the rate of release and resorption of drugs incorporated in them was found by Khristov[12] and Khristov and Draganova[13]. However, one study[14] of some organogel-type bases made from carboxy vinyl polymers and involving ocular absorption of several drugs from the bases showed no correlation between viscosity of the base and drug release.

The purpose of this study is to investigate the release of chlortetracycline hydrochloride from absorption and emulsion ointment bases in the presence of some additives. Rheological studies on the drug ointment systems was carried out to find out any correlation between the rheological properties of the ointment systems and the drug release.

EXPERIMENTAL

Materials

Chlortetracycline hydrochloride (Merk Co. LTD,Germany), white soft paraffin, liquid paraffin, cetyl alcohol, lanoline, propylene glycol, benzalkonium chloride, sod. metabisulphite, EDTA, tween 40, span 40, disod. hydrogen phosphate, monosod. dihydrogen phosphate and sodium chloride.

Solutions

- Phosphate buffer solution at pH 6.8[15].
- Isotonic solution of sod. chloride.

Equipment

- Spectrophotometer, type Spektromom 204.
- Ferranti-Shirley cone-plate rheoviscometer,

Preparation of Chlortetracycline hydrochloride(CTC HCI) Ophthalmic Ointments:

While soft paraffin was heated in an oven at 160°C for one hour together with activated charcoal to remove the irritating materials present, after that the white soft paraffin was filtered while hot through a filter paper. All

the oleo-genous materials listed in table (1)were sterilized at 160°C for two hours before formulating the CTC HCI ointments.

The CTC HCI was formulated in the absorption ointment bases (BI and BII) according to the composition listed in table (1), by incorporating the drug in the melted base at low temperature. The ointment was continuously stirred until cold in order to achieve homogeneity of the drug in the base. The emulsion types of the drug ointment(BIII is the O/W type and BIV is the W/O type) in the composition listed in table (1) were prepared by dissolving the drug in the aqueous phase then warming and stirring in the melted oleo-genous phase of the ointment bases. The concentration of chlortetracycline HCI used in all the ointment types is 0.5% w/w.

Benzalkonium chloride was used as a preservative in all the formulations (F1). Both sod. metabisulphite and EDTA were used as antioxidant and chelating agent, respectively, in all the formulations symbolized by (F2).

The in-vitro release study of CTC HCI from various ointment bases:

1 gm. of the CTC HCI ointment was accurately weighed and placed on a semipermeable fischer cellulose membrane (30/32) to occupy a circle of 2 cm in diameter. The loaded membrane with the ointment was stretched over the open end of a glass tube (2 cm in diameter) which was made water tight by rubber band. The inverted tube was suspended so that the membrane was just below the surface of a predetermined quantity of 30 ml. isotonic solution of sodium chloride at 35° ($\pm$2), contained in a 250 ml beaker[16]. 5 ml. samples were withdrawn from the beaker after $\frac{1}{4}$, $\frac{1}{2}$,2 , 3 , 4 , 5 and 6 hours. The volume of the diffusion medium in the beaker was compensated by addition of a 5 ml volume of isotonic sod. chloride solution directly after withdrawal of the sample for the assay .

The amount chlortetracycline hydrochloride released was determined spectrophotometrically at 368 nm. The amount of the drug determined was corrected by considering the drug content of the 5 ml samples taken for the assay.

The rheologicalstudies of the CHC HCI ointments:

After adjustment at the required temperature (35°C), the cone and plate rheoviscometer was adjusted so as to obtain a top rate of shear of 100 sec^{1}. and a sweeping time of 60 sec. (120 sec. for the upward and downward curves). The sample was then placed on the plate which was slowly raised so as to expose it to minimum shearing. The flow curve was drawn after 10 minutes of standing.

Figure 4 represents the rheograms of the different ointment bases BI, BII, BIII & BIV(table 1). From the flow curves the yield value of the ointment systems after shear (y) and also the ultimate yield value (x) of the systems in dynes/cm^2 were calculated[17]. The per cent change in the value x - y (Table 2) was taken as a measure of the changes in the system breakdown (happened upon adding certain additives to the ointment systems)which was found to be a rather good measure than the thixotropic coefficients B & M[6]. The plastic viscosity of the systems were calculated from the contangent of the down curves of the system rheogram[6,18].

RESULTS AND DISCUSSTIONS

Absorption Bases:

Figure 1 represents the release rate pattern of chlortetracycline hydrochloride from absorption bases BI & BII at 35°C. The figure shows that the CTC HCI was released from the base containing lanoline at a rate higher than that from the base containing cetyl alcohol, BI and BII respectively. Addition of sod. metabisulphite and EDTA to both the absorption bases (BI F2 and BII F2) was found to improve the release of the drug from the oitment bases. This may be attributed to the role of EDTA on chelating the heavy metal ions, detected in the ointment bases, with subsequent prot-

ection of the CTC HCI molecules to be complexed with the heavy metal ions[19] which in turn affects the amount of free drug molecules that diffuse from the ointment base.

Concerning the rgeological properties of CTC HCI ointments, table 2 shows that systems containing lanoline (BI) have higher yield values after shear (y) and also higher plastic viscosity (U) than the systems containing cetyl alcohol (BII). The addition of the antioxidant-chelating agent mixture(F2) was found to increase the yield value(y) and decrease the per cent breakdown (per cent x-y) of both systems BI and BII. As regards the plastic viscosity, it was observed to be either not changed in the ointment containing cetylalcohol or lowered in the ointment containing lanoline upon adding such additives (compare F1 and F2 in both bases BI and BII).

So, the increase in the release rate of CTC HCI from the absorption base ointment that was observed upon adding sod. metabisulphite-EDTA mixture can be correlated with the decreade in the breakdown of the system.

Emulsion Bases:

The release of CTC HCI from the ointments was found to be significantly increased upon formulating the drug in the emulsion types of ointments(compare figures 2 and 3 for the emulsion bases with figure 1 for the absorption bases). These results are in agreement with the findings of Peteanu et al.[20] as they found that the addition of nonionic surfactants (span and tween) improves the release of CTC HCI from ointment bases containing vaseline.

Figure 3 shows that the addition of sod. metabisulphite and EDTA to the O/W emulsion ointment (BIII) increases the release rate or CTC HCI from the ointment. On replacing the watery phase of the emulsion system(BIII F2) by solution of phosphate buffer at pH 6.8, to resemble the pH of the tears, the release rate of CTC HCI from formula BIII F3 was found to be significantly lowered even when compared with the control formula BIII F1 (see Figure 2). The

effect of buffer on decresing the release rate of CTC HCI from the O/W emulsion ointment base can be referred to the effect of pH of the buffer solution on increasing the concentration of the more lipid soluble zwitterionic form of the drug[21]. So, a significant amount of the drug was retained in the lipid phase of the emulsion system and subsequently the amount of CTC HCI released from the whole systme was decreased.

The rheolgical data presented in Table 2, revealed that the yield value (y) of the O/W emulsion system was increased upon adding the sod. metabisulphite-EDTA mixture while it was not changed upon inclusion of the buffer components in the emulsion system. The data of the formule BIII BIII F2 was cancelled as the system show a separation during the rheologic measurement. However, paralellism was found between the decreased release of the drug when the system contains the buffer components and the decreased values of both the plastic viscosity and the breakdown of the system (Figure 2 and Table 2),

The release rates of CTC HCI from the different formulations of the drug in the W/O emulsion ointment system (BIV) showed that the addition of sod. metabisulphite-EDTA mixture and the buffer components to the W/O emulsion system still elicit the same increasing and decreasing effect, previously observed in the O/W emulsion, respectively(Figure3) The increase in the release rate of the drug from the W/O emulsion ointment base in formula BIV F2 and the decrease in the rate of drug release in formula BIV F3 can also be attributed to the effect of chelating agent and pH of the buffer respectively.

Table 2 shows that the yield value (y) of the W/O emulsion system was found to be decreased by the addition of sod. metabisulphite-EDTA mixture (BIV F2) and buffer components (BIV F3) to the ointment system. Both the plastic viscosity and the breakdown of the system were observed to be increased in the presence of antioxidant-chelating agent

mixture. The rheologic data of the ointment system DIV F3 excluded because of the system seperation during measurement.

Regarding the increase in release rate of the drug from W/O emulsion ointment that was observed in the presence of the antioxidant-chelating agent mixture, it can be correlated with the observed increase in both the plastic viscosity and the breakdown of the ointment system.

CONCLUSIONS

1- The release rate of CTC HCI from absorption ointment bases was increased when the base contained lanoline.

2- The emulsion ointment system released the drug at a higher rate than the absorption bases did, and the O/W emulsion base released it were rapid than the W/O emulsion base did.

3- EDTA, as a chelating, was observed to exert an increasing effect on the drug release rate from the ointment bases tested. The effect was attributed to its protection of the CTC HCI against complexation by the heavy metal ions present in the ointment bases with the subsequent increase of the amount of free drug released.

4- Inclusion of buffer components in the aqueous phase of the emulsion systems to bring its pH value to 6.8 showed a detrimental effect on the release rate of the drug from the O/W and W/O emulsion ointments. This was referred to the effect of pH on increasing the concentration of the more lipid soluble zwitterionic form of the drug which is retained in the lipid phase of the emulsion system with a subsequent decrease in the amount of drug ready to be released from the system.

5- A correlation was found to be present between the effect of some additives on the release rate of CTC HCI from different ointment bases and certain rheological properties of the systems.

In the absorption ointment bases, the drug release was found to be increased as the system breakdown was decreased.

on the other nand, the drug release from the emulsion ointment bases was increased as both the plastic viscosity and the breadkown of the systems were increased and decreased by their decrease.

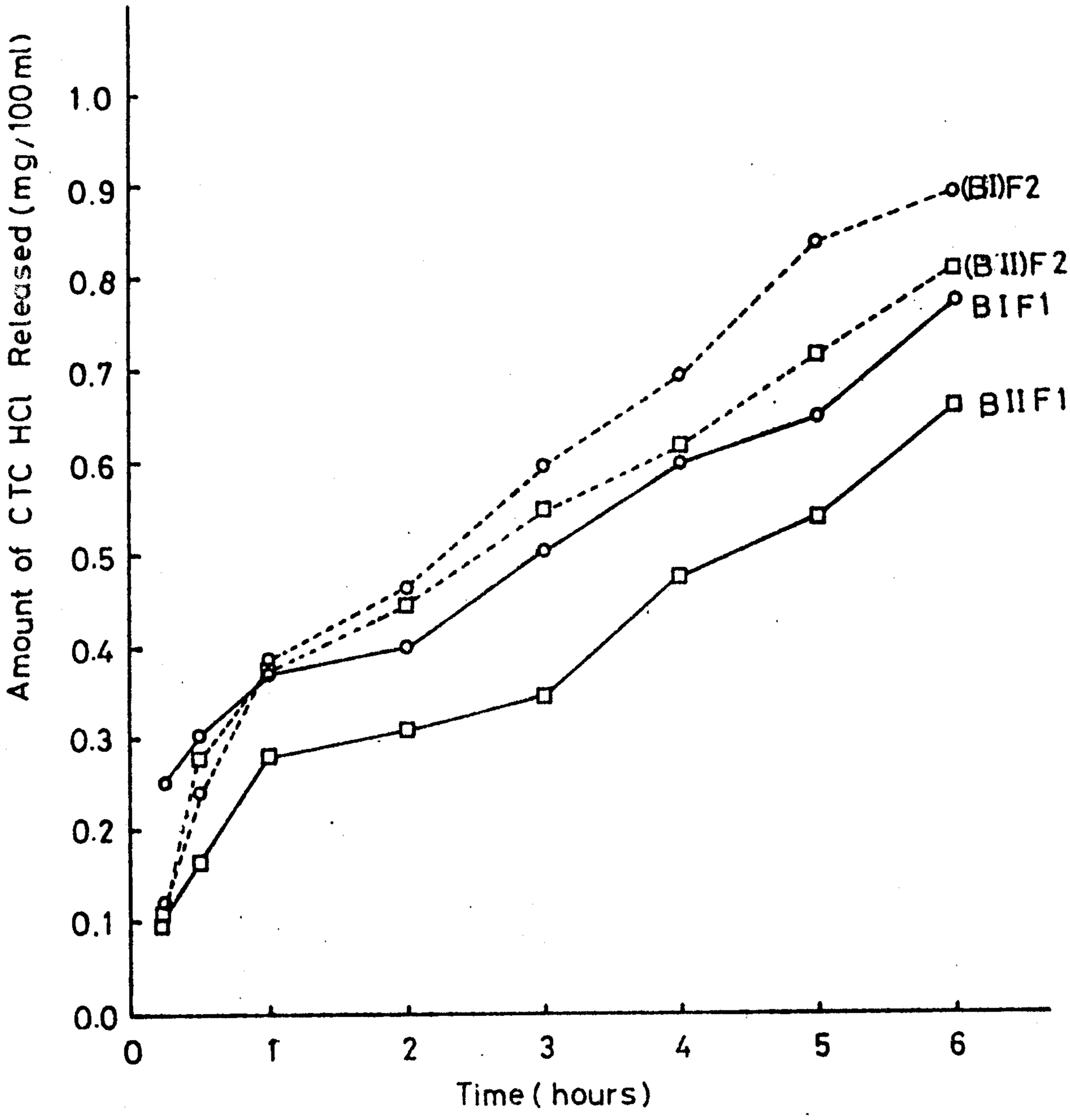
Table 1 Composition of Ophthalmic Ointments Containing 0.5 % Chlortetracycline Hydrochloride

Formula	Constituents %											
	White soft Paraffin	Liquid paraffin	Cetyl alcohol	Lanoline	Propylene glycol	Benzalkonium chloride	Sodium metabisulfite	EDTA	Tween 40	span 40	Phos. buffer	Dist. water
Absorption Bases												
BI F1	70	15	--	15	--	0.01	---	---	--	-	--	--
BI F2	70	15	--	15	--	0.01	0.5	0.3	--	-	--	--
BII F1	70	20	10	--	--	0.01	---	---	--	-	--	--
BII F2	70	20	10	--	--	0.01	0.5	0.3	--	-	--	--
Emulsion Bases												
O/W BIII F1	25	12	25	--	--	0.01	---	---	5	-	--	33
BIII F2	25	12	25	--	--	0.01	0.5	0.3	5	-	--	33
BIII F3	25	12	25	--	--	0.01	0.5	0.3	5	-	33	--
W/O BIV F1	30	--	15	--	20	0.01	---	---	-	5	--	30
BIV F2	30	--	15	--	20	0.01	0.5	0.3	-	5	--	30
BIV F3	30	--	15	--	20	0.01	0.5	0.3	-	5	30	--

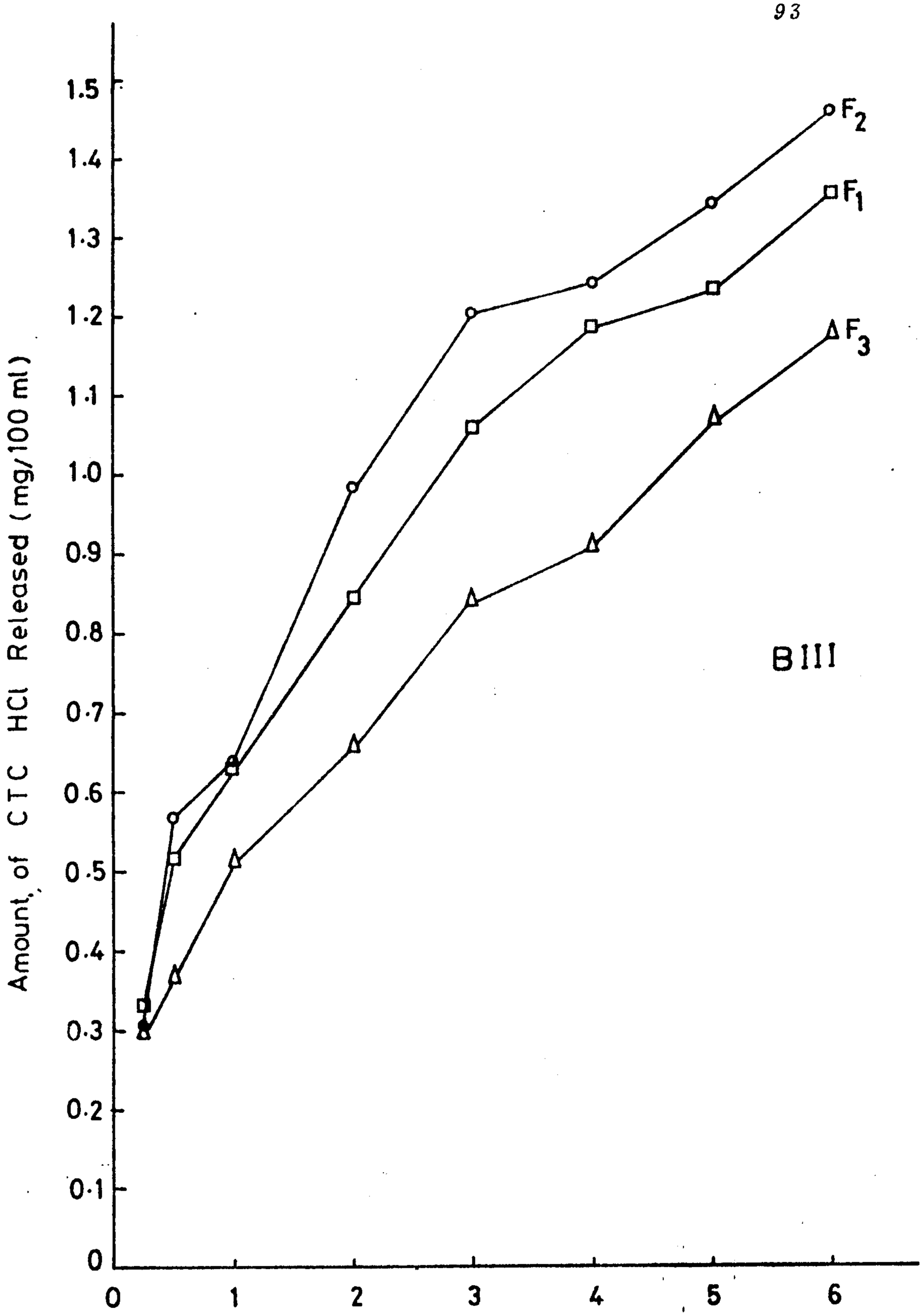
Table 2: Rheological Characteristics of Chlortetracycline Hydrochloride Ointment Systems at 35°C.

Formula	Yield value after shear (Y) dynes/cm^2	Ultimate Yield Value (X) dynes/cm^2	(X-Y)	% (X-Y)	Plastic Viscosity (U) poise
Absorption bases					
BI E1 base	200	850	650	100	10.163
BI F1	200	2150	1950	300	10.163
BI F2 base	550	4400	3900	100	4.936
BI F2	220	1350	1130	28.97	6.678
BII F1 base	100	520	420	100	7.259
BII F1	100	480	480	90.47	7.259
BII F2 base	150	3850	3700	100	7.259
BII F2	150	2450	2300	62.162	7.259
Emulsion bases					
O/W					
BIII F1 base	1400	12400	11000	100	37.274
BIII F1	800	11400	10600	96.36	42.598
BIII F2 base	2700	10600	7900	100	31.948
BIII F2	2700	10400	7700	97.468	0.376 @
BIII F3 base	1200	5400	4200	100	42.598
BIII F3	800	4500	3700	38.09	39.936
W/O					
BIV F1 base	1800	6400	4600	100	42.598
BIV F1	1400	1400	2700	58.695	31.948
BIV F2 base	300	1800	1500	100	21.299
BIV F2	600	5300	4700	313.33	47.92
BIV F3 base	400	3600	3200	100	26.624
BIV F3	100	6700	6600	206.25	10.649 @

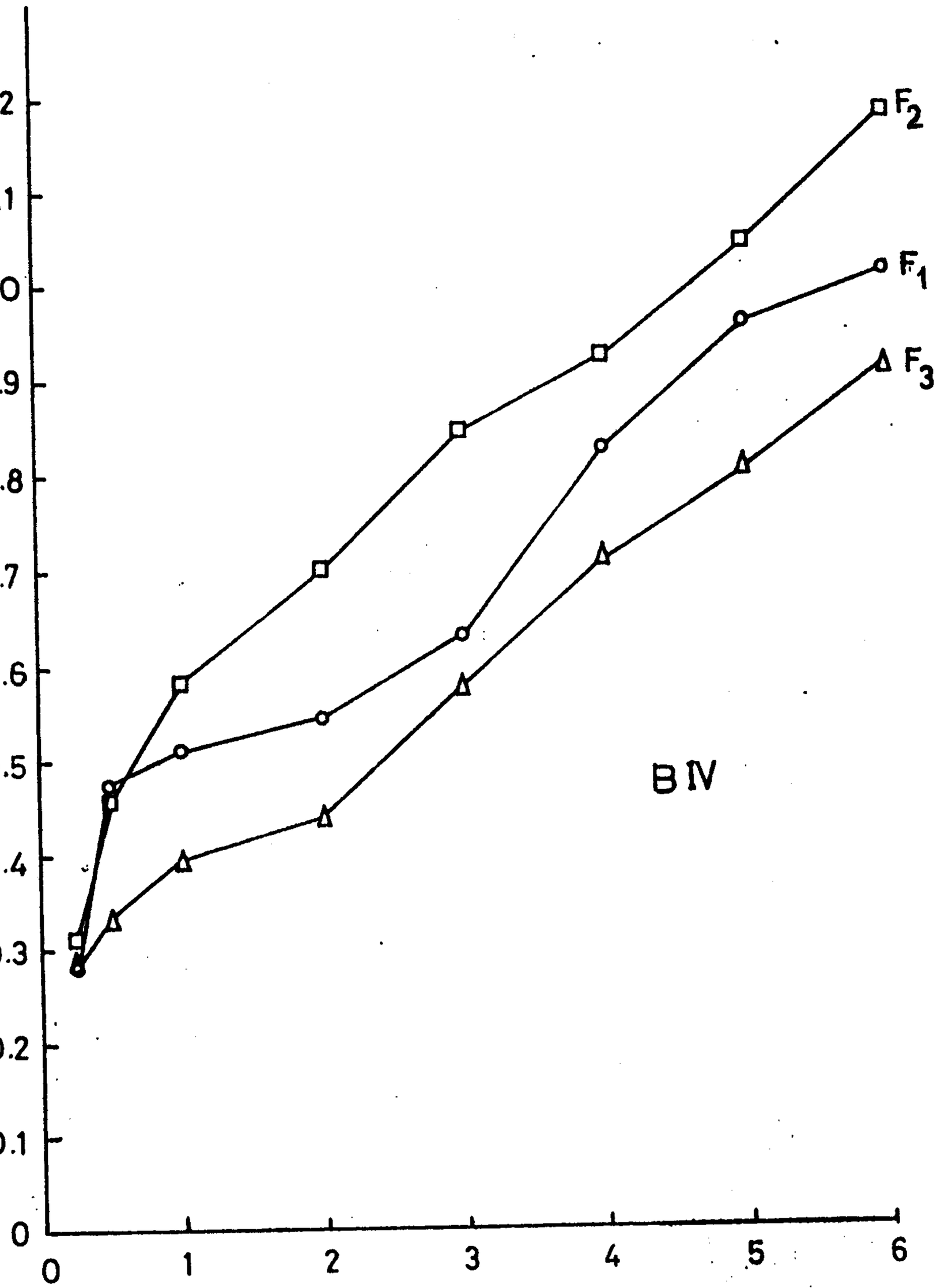
@ Separation of the system



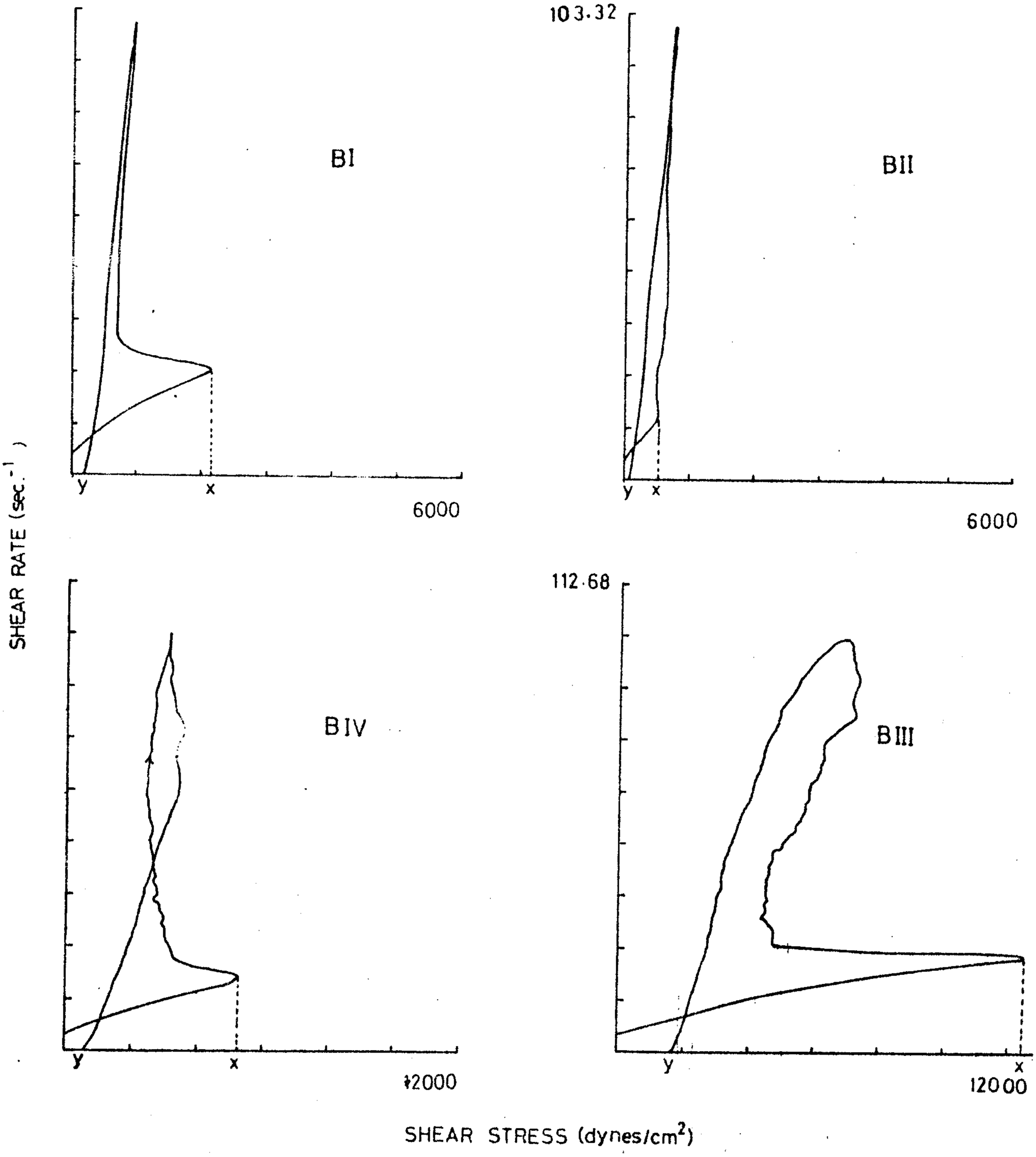
(Fig 1) Release of Chlortetracycline Hydrochloride from Absorption Ointment Bases (BI& BII) at 35° C.



(Fig. 2) Release of Chlortetracycline Hydrochloride from O/W Emulsion Ointment Base(B III) at 35°C.



(Fig.3) Release of Chlortetracycline Hydrochloride from W/O Emulsion Ointment Base at 35°C.



(Fig. 4) Rheograms of Four Ointment Bases: B I, B II, B III & B IV at 35°C.

y = Yield v. of the system after shear.

x = Ultimate yield value.

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الخواص المميزة لانطلاق ولزوجة مراهم العين
للكلور تتراسيكلين ايد روكلوريد

حمـــــــدى الصـــردى ــ محمـــد على عطيـــة ــ سهير الشنوانى
(قسم الصيدلانيات ــ كلية الصيدلة ــ جامعة اسيوط)

ج ٠ م ٠ ع

يتناول هـــذا البحث بالدراســة انطلاق عقار الكلور تتراسيكلين ايد روكلوريد من قواعد المراهم المتصـــة والمستحلبة ٠ حيث وجـــد ان معدل انطـــلاق العقـــار من القواعـــــد المستحلبة يكون اعلى من معـــدل انطـــلاقه من القواعد المتصـــة ٠ كما لوحـــظ ان وجـــــود الاديتا كمادة مخلبيـــة فى مختلف قواعد المراهـــم قد رفع الى حـــد كبير مـــــمعدلات انطلاق الدواء منها وقـــد اعـــزى ذلك الى حمايتهـــاللـــــــعقار ضد تكوين متراكبات غير منتشـــرة مـــع ايونـــات المعـــادن الموجـــــودة فى قواعد هذه المراهـــم ٠

وباضـــافة املاح منظمـــة للاس الايدروجينى للوسط المائى عند رقم ٦٫٨ فى كلا نوعـــى المراهـــــم المستحلبة فقـــد انخفض معدل انطلاق العقـــار من تلك المراهـــم بصـــــــورة كبيرة وقـــد فســـر ذلك على ضوء تاثير الاس الايدروجينى للمحلول فى زيادة تركيز الايونـــات المتعـــادلة للعقـــار ذات القابلية العاليـــة للذوبان فى الدهـــــون ٠

كما اظهـــرت نتائج دراسة لزوجـــة المراهـــم على ان هناك ارتباطا واضحا بين انهيار النظام التركيبى للمرهـــم ومعدلات انطلاق العقار منـــــه كمـــا وجـــد ان هذه العلاقـــــة تكـــون عكسيـــة فى المراهم المتصـــة وطـــردية فى المراهم المستحلبـــة ٠