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AN INVESTIGATION ON THE DISSOLUTION OF NITROFURANTOIN

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The problem of the existence of inter-lot and inter-tablet variation in the dissolution rates of nitrofurantion (NFT) marketed tablets, attracts, the attention for investigating the microcrystalline NFT powder used in formulating the marketed tablet products. The x-ray diffractometry and the differential scanning colorimetry of five microcrystalline NFT powders obtained from different manufacturers revealed that this drug is not exhibiting polymorphism. NFT hydrates of large particle size were observed to be formed when the drug was to be in contact with water with the pH values in the acidic range. The unexpected dissolution-pH profile of stored NFT suspensions prepared by precipitation at pH 5.4 from alkaline solution may be illustrated by the possibility of tautomeric transformations in the drug. This was more revealed by the observed reversible shift of the λ maxima on changing the pH of its solutions.

Nitrofurantoin, a urinary tract antibacterial agent, possesses relatively low aqueous solubility characteristics at pH values normally encountered in the various segments of the gastrointestinal tract[1]. As a result, it is not surprising that the drug displays a particle size dependence in its dissolution rate[2] and hence the rate and extent of its bioavailability in man[2-5].

Newton and Razzo[6] found that the solubility of nitrofurantoin is the major factor for contorlling the drug release from capsules. Frigerio and venier[7] found a good correlation between the bioavailability of commercial tablet products and both the tablet hardness and disintegration time. Mendes et al[8]

in an investigation for the bioequivalency of nitrofurantion, found that neither processing methods nor compression force would significantly affect the dissolution rate of the tablets. The results of another study done by the same authors[9] indicate the presence of a good rank order correlation between one hour cumulative dissolution of some formulations and their three hours cumulative excretion. They stated that, all formulations in which at least 25%of the drug is dissolved within one hour were bioequivalent.

The USP XIX[10] nitrofurantion monograph specifies that the time required for 60% of the labelled amount to dissolve is not less than one hour. In the light of the findings of Bates et al.[1], it was stated that, the rationale underlying the official dissolution rate specification for nitrofurantion tablets appear quite arbitrary and inconsistent with the dissolution profile and potential toxicity of the official suspension dosage form. Many authors[11-13] found that, although the tested commercial nitrofurantion tablet products met the USPXIII specifications, significant differences were observed in their availability.. In a recent, report, Groning[14] stated that the USP XIX dissolution test does not reflect the differences between dosage forms of nitrofurantion.

Mattok et al.[15] and Hossie and Mc Gilveray[16] reported the existence of inter-lot and inter-tablet variation in the dissolution rates of commercial nitrofurantion products and these variations could make the correlation with absorption parameters difficult.

However, numerous reports[11-13, 15-18] about nitrofurantion provide support for the contention that not all commercially available products meeting compendial requirements necessarily exhibit equivalent bioavailability.

Concerning the effect of the pH of the dissolution medium on the dissolution profile of nitrofurantion products,

Bates et al[19]. found that the pH 7.2 phosphate buffer medium suggested by the USP was unable to discern inherent particle size dependent differences in the rate of solution from tablets and capsules. They claim for the modification of the official USP dissolution specification for products of this drug. Moreover, Suttan et al.[20] stated that the dissolution rate of nitrofurantion tablets is highly brand-individualized and complex and the effect of pH of the dissolution medium on a particulate formulation is unpredictable. Also , they concluded that the value of any in-vitro procedure to predict bioavailability for nitrofurantion is questionable.

The aim of this study was directed to investigate the dissolution rate behaviour of NFT solid dosage forms available from the local market. A collection of five microcrystalline NFT powders used in formulating the drug was obtained from different manufacturers and subjected to thorough investigations.

EXPERIMENTAL

1- Materials:

1- Commercial formulation products:

- Four batches of nitrofurantion tablets supplied by manufacturer I.
- One batch of nitrofurantion tablets supplied by manufacturer II.
- One batch of nitrofurantion capsules supplied by manufacturer III.

2- Mitrofurantion powders :-

Five samples supplied by Marsing(Denmark), Smith Kline & French(England) and Kahira Pharm. & Chem. Ind. Co. (Egypt).

II- Reagents:-

Dimethyl formamide, Glacial acetic acid, Sod. acetate, Hydrochloric acid, Ammonium hydroxide, Acetone, Ethanol, Methanol; all reagents are of analytical grade.

III- Equipment:-

- Spectrophotometer, type Specktromom 204.
- X-Ray Diffractometer, type Philips PW 1050.
- Differential Scanning Colorimeter, type perkin-Elmer Model DSC-IB.
- Rotational apparatus for solubility study N . F XII[26].
- The apparatus system suggested by levy[21] for dissolution rate studies.

Determination of Nitrofurantion:

The samples were assayed spectrophotometrically at λ_{max} of 368 nm. according to the method adopted by the B.P.(1973) [22].

RESULTS and DISCUSSIONS

Table (1) shows that, although the commercial tablets are within the pharmacopoeial limits for both drug content and the disintigration, their dissolution efficiency[23] reveals a significant difference between the amount of nitrofurantion dissolved from the different batches of the same marketed tablet products. Figure 1 shows the inter-lot variation in the dissolution rate of nitrofurantion from the same product. An intro-tablet and capsule variation in the dissolution rates were also observed in the marketed tablet & capsule products (Fig. 2 & 3). These results are to be in agreement with many reported findings about the inter-lot and inter-tablet variation in the dissolution rates of nitrofurantion commercial solid dosage forms[6,8,11-13,15,16].

The nitrofurantion microcystalline powders used for the marketed tablet formulations were investigated to find out

the reasons for the variations in the dissolution rates of the manufactured drug products.

The X- ray diffaction patterns of the five microcrystalline nitrofurantion powders obtained from different manufacturers of the drug showed that there is no possible existence of different crystalline configurations in these powder samples.

In the aim of preparing different crystalline structures of the drug, nitrofurantion was crystallized from ethanol, methanol and acetone at different conditions of crystallization. The X-ray diffractometry of these crystallizates showed that they possess different crystalline structures(Fig. 5). On the other hand, an amorphous form of the drug (Fig. 4) was obtained when the drug was dissolved in sodium hydroxide and then precipitated by gradual addition of dil.Hcl until the pH of the solution was dropped to 5.4. Generally, these results lead to the conclusion that nitrofurantion can hardly suffer from the polymorphic tranformations specially if we take in our consideration that this drug melts with decomposition (Fig. 5).

The dissolution rate study of the commercial drug powders revealed that these powders (of average particle size = 50 u) have significantly different dissolution rates(Fig.6)

On the other hand, two of the five samples under investigation showed different solubility patterns than the other samples (Fig. 7). In general, a decline in the solubility values of all the powders was observed during the first sixty minutes of the experiment.

It was found that during this period of time the crystals of the drug were enlarged five times(from 50u to reach 260u particle size) and changed from rod shaped crystals to needle shaped ones. This could be attributed to the formation of drug hydrates having lower solubility patterns(Fig. 7). Also, the solubility of one of the commercial powders was carried out at different pH values and it was found that the solubility behaviour of the drug still

showing a similar common pattern of the solubility of the drug in distilled water. Therefore, the tendency of nitrofurantion to form hydrate in aqueous medium is still present whatever the pH values of the medium (compare Fig.7 &8) From figure 8, it is clear that at thirty minutes of the experiments the drug possess of more solubility values at pH 3 than that observed at the other pH values. This coincides with the observations of Chen et al.[24] who explain this phenomenon by the electron dislocalization of the three nitrogen atoms of nitrofurantion molecule at lower pH values. This observation was revealed when the dissolution-pH profile was carried out for nitrofurantion suspenion prepared by precipitation of the drug from its alkaline solution(Fig. 9) and stored for one month. This complicated and unexpected solubility patterns leads to the conclusion that the drug is not simply behaving as a weak acid[25].

A trial to investigate the possibility of the presence of a tautomeric transformation of the drug was done by tracing any change can existe in the position of three characteristic λ maxima of the drug (at 237, 270 and 370 nm.) by changing the pH of the drug solution. Table 2 showed that the three λ max of the drug were changed by changing the pH of the solution which was found to be a reversible change.

CONCLUSIONS

The inter-lot & inter-tablet variations in the dissolution rates of NFT from its commercial products are mainly attributed to the dissolution rate behaviour of the drug powders used for the formulations of the marketed solid dosage forms. These variations cannot be attributed to polymorphic transformations in the crystalline powders of the drug.

The hydrate formation and the unusual solubility and dissolution rate behaviour of the drug in different pH media attract the attention to the possibility that NFT may exhibit tautomeric transformations. This assumption was supported by the results showing that a reversible change of the three characteristic λ max of the drug occurted by changing the pH of the drug solution.

Table 1- Weight Variation, Potenoy, Disintegration Time, Per Cent Dissolved After 30 Minutes, D.K. 30% of Commercial Nitrofurantion Tablets (product I & II) and Capsules.

Formulation	Weight		Potenoy(mg)		Di intogration Time (minutes)	Per Cent Dissolv after 30 minutes	$D.E.^{30}_{\%}$	Relative $D.E.^{30}_{\%}$ (related to B)
	Average (mg)	Deviation (%)	Claimod	Found*				
Tablets								
Product I:								
A	151	2.66	100	95	12	4.64	2.53	48.19
B	159	3.8	100	98	12	9.50	5.25	100
C	161	1.25	100	95	11	8.31	4.28	81.52
D	158	2.5	100	96	14	7.56	3.83	72.95
Product II	357	2	100	97	15	6.85	4.88	92.95
Capsules	339	1.5	50	51	14	3.26	1.87	

N.B:* Average of Five Determinations.

$D.E.^{30}_{\%}$ * Dissolution Efficiency after 30 minutes Expressed as per cent

Table 2- Effect of the solution pH on the shift of λ_{max} of NFT.

pH	*Wavelength of the λ_{max} of NFT*		
	237	*270*	*370*
2.2	226	266	370
2.4	237	267	369
3.4	236	268	370
4.4	235	266	370
5.4	234	266	370
6.4	234	270	375
7.4	233	280	383
8.0	226	280	388

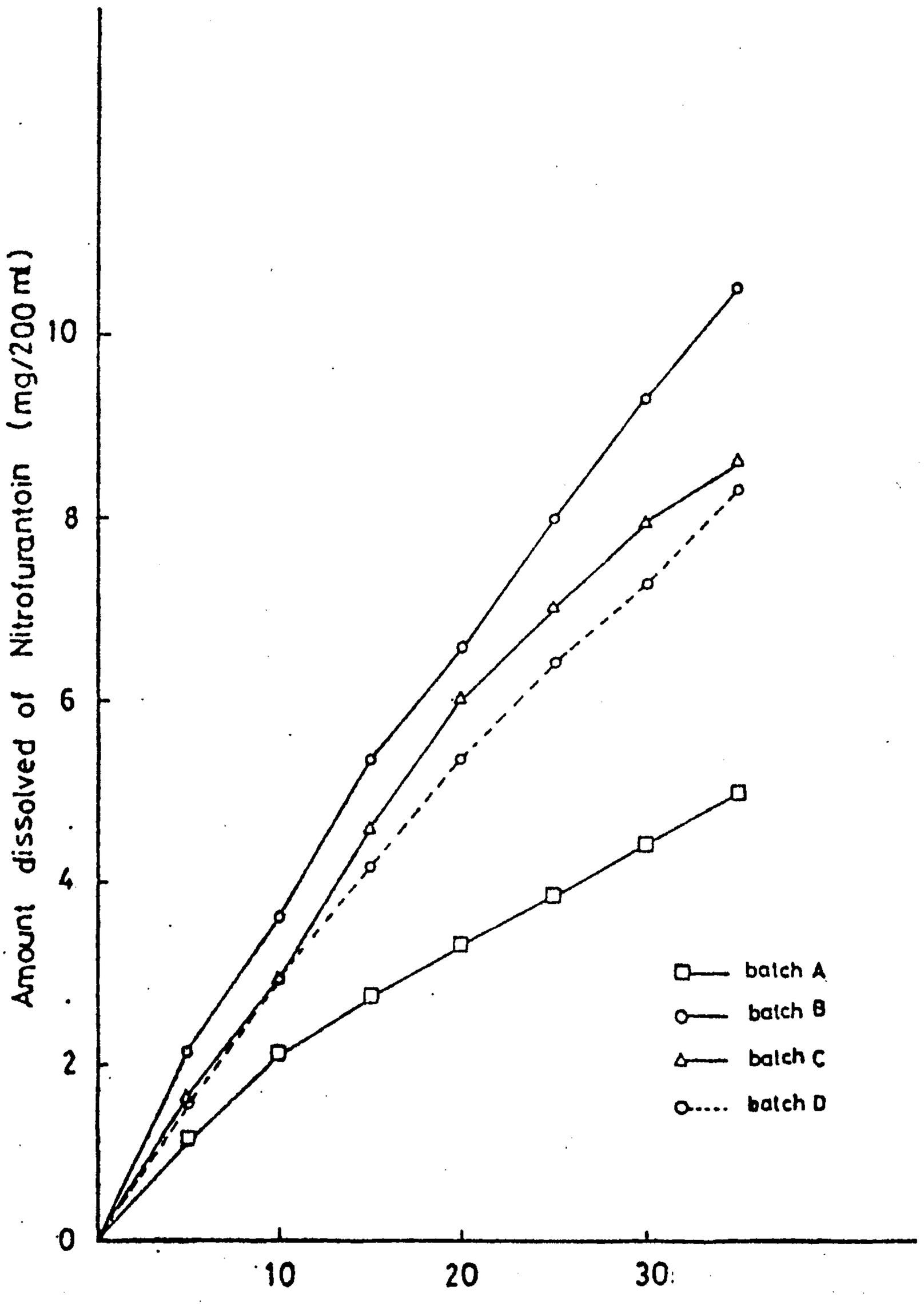


FIG.(1) DISSOLUTION RATES OF DIFFERENT BATCHES OF NITROFURANTOIN TABLETS PRODUCT I IN DISTILLED WATER AT 37°C

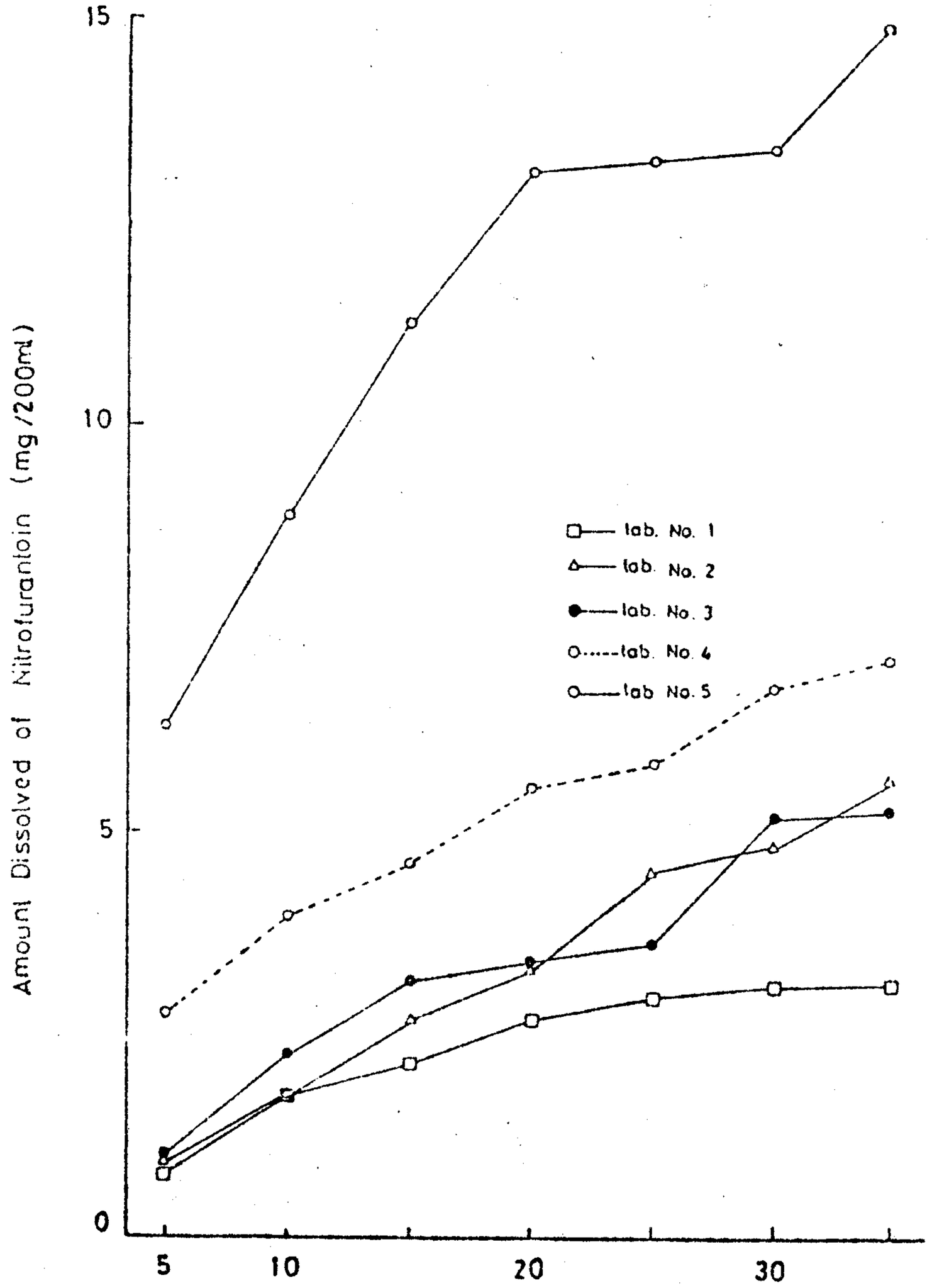
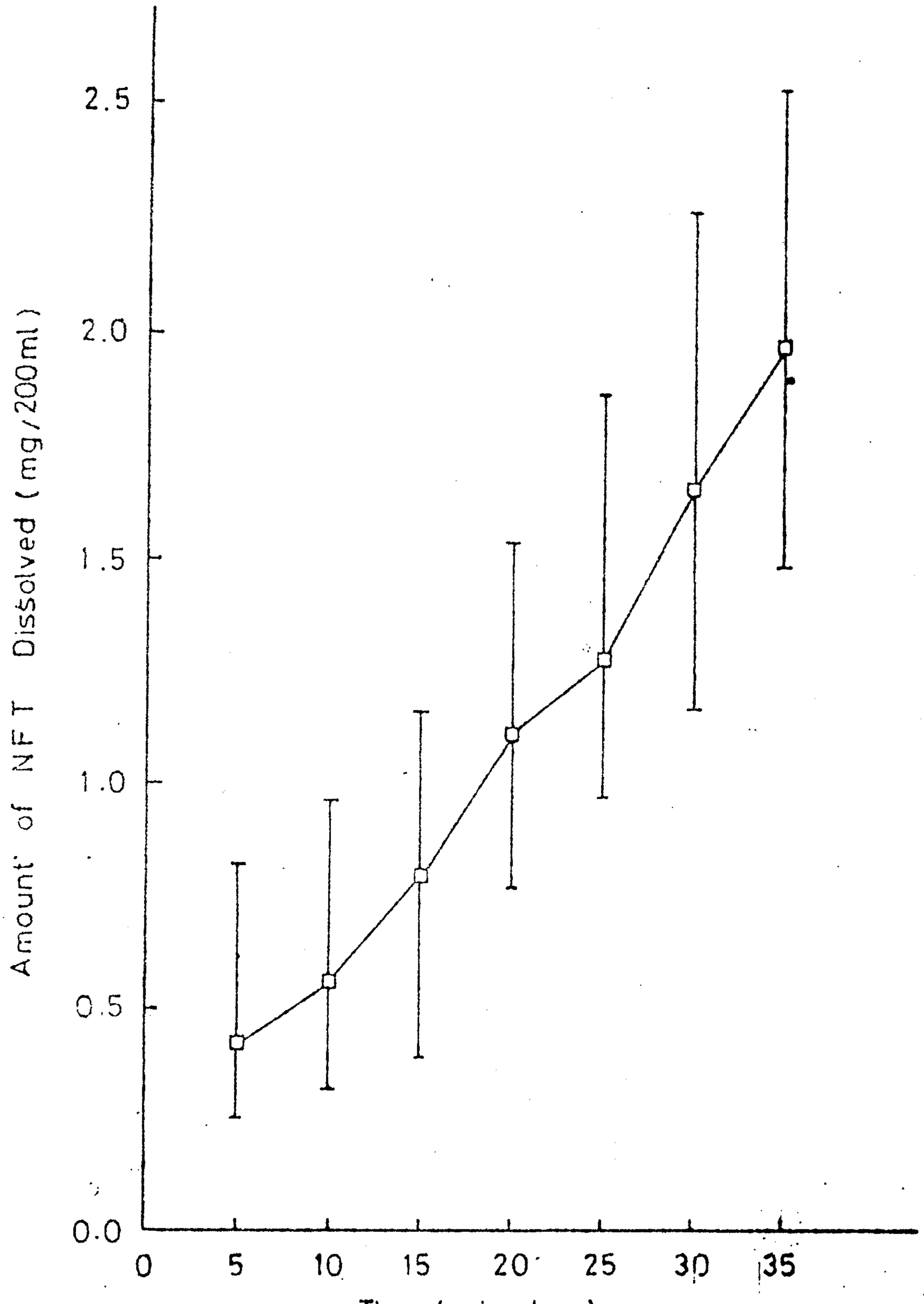
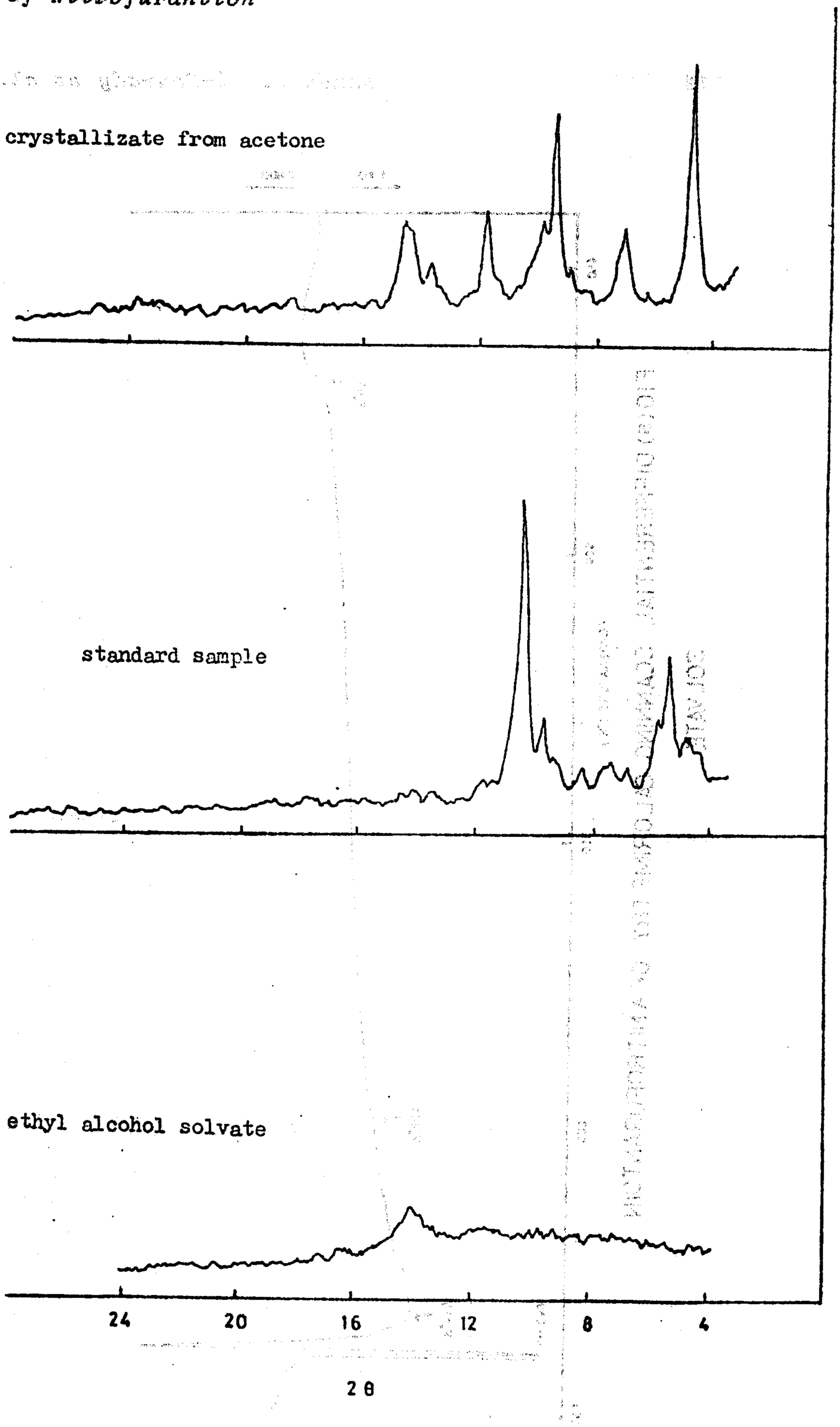


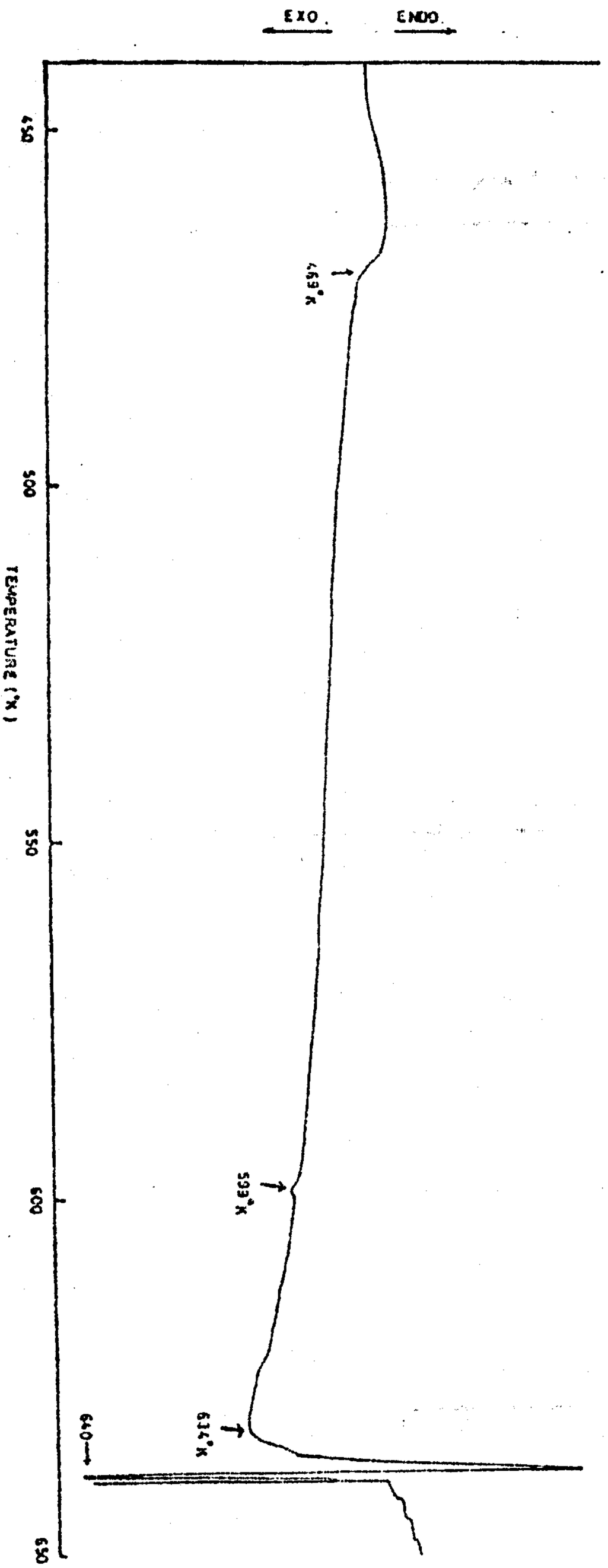
FIG.(2) DISSOLUTION RATES OF FIVE TABLETS FROM THE SAME BATCH OF NITROFURANTOIN TABLET PRODUCT II IN DIST. WATER AT 37°C



(Fig. 3) Dissolution Rate of Nitrofurantoin Capsules.



FIG(4) DIFFRACTOGRAMS OF NITROFURANTOIN SAMPLES



FIG(5) DIFFERENTIAL SCANNING CALORIMETRY OF A NITROFURANTOIN SOLVATE.

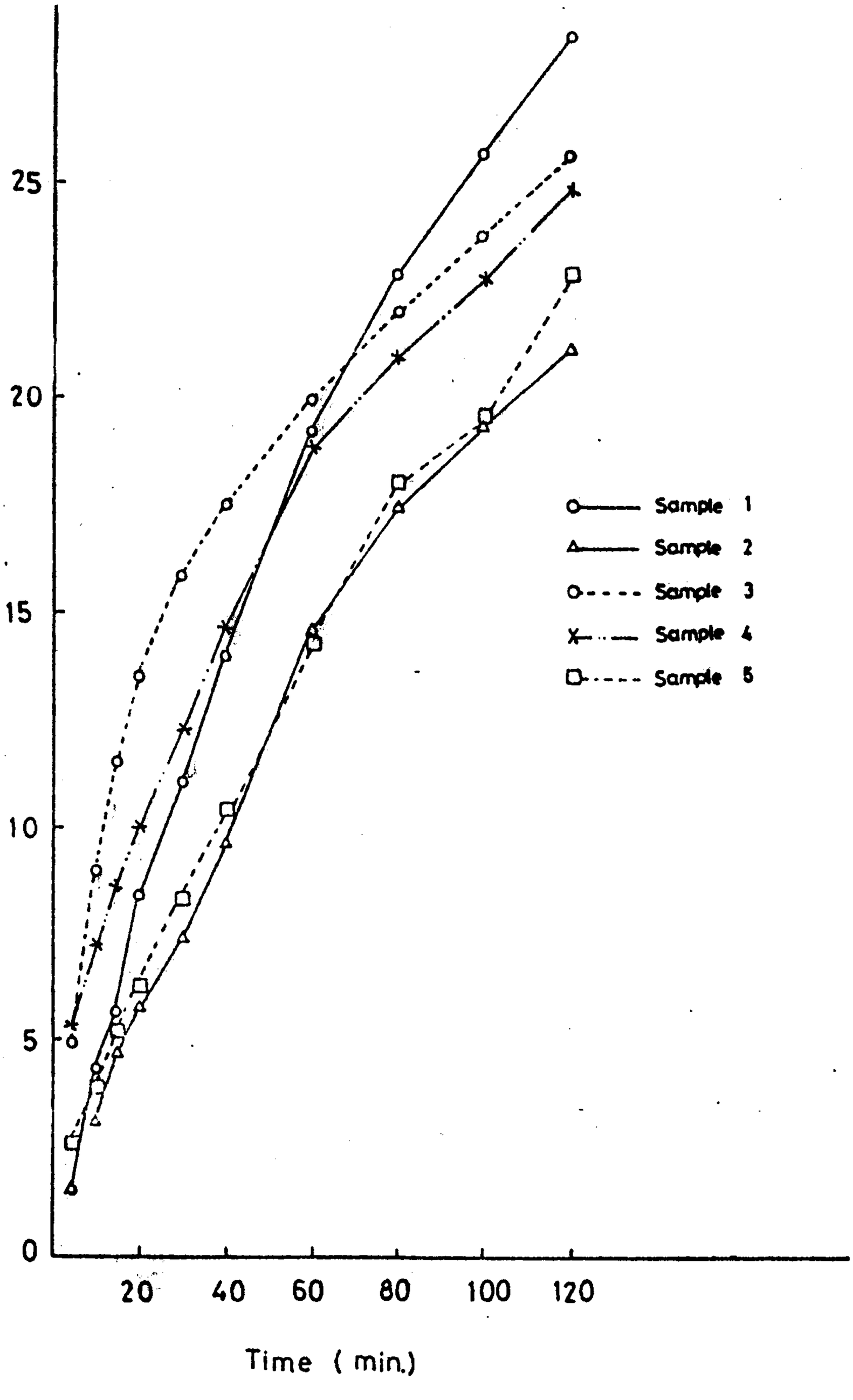


FIG.(6)Dissolution Of Different Commercial Samples Of Nitrofurantion In Distilled Water At $37^{o}C$.

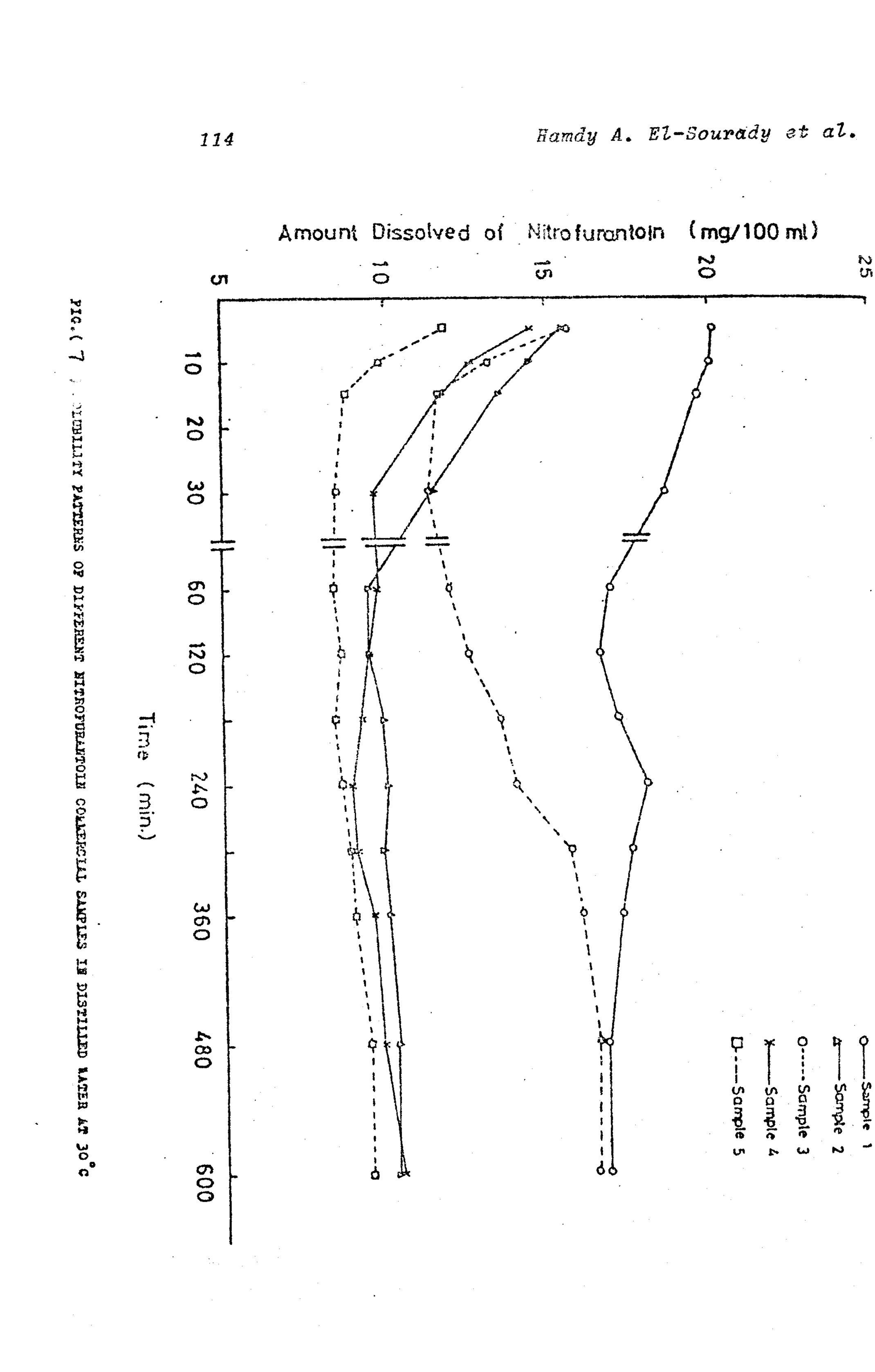
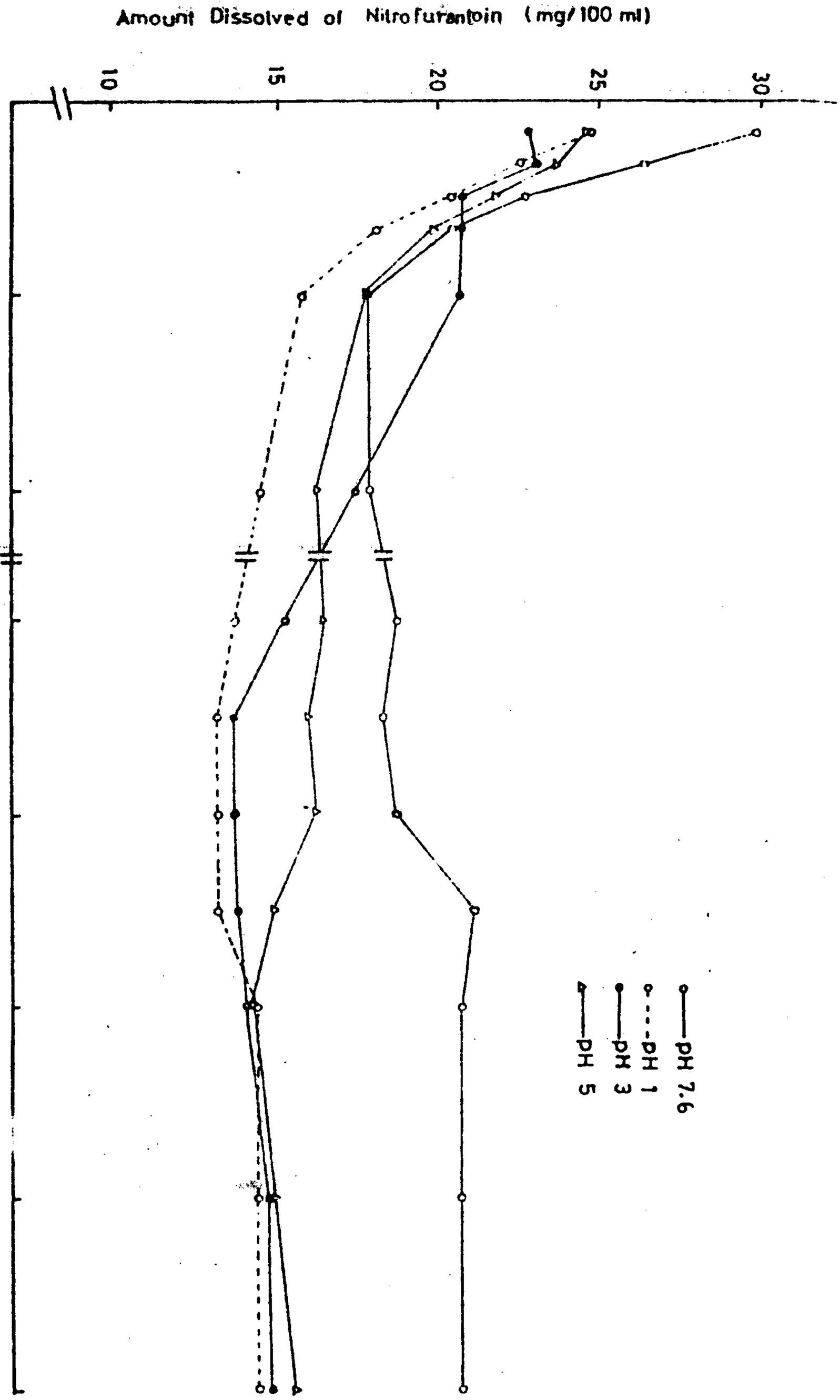


FIG. (7) DISSOLUTION PATTERNS OF DIFFERENT NITROFURANTOIN COMMERCIAL SAMPLES IN DISTILLED WATER AT 30°C



FIG(8) Solubility Patterns Of Nitrofurantion Sample 2. At Different Ph. Values At 37°C.

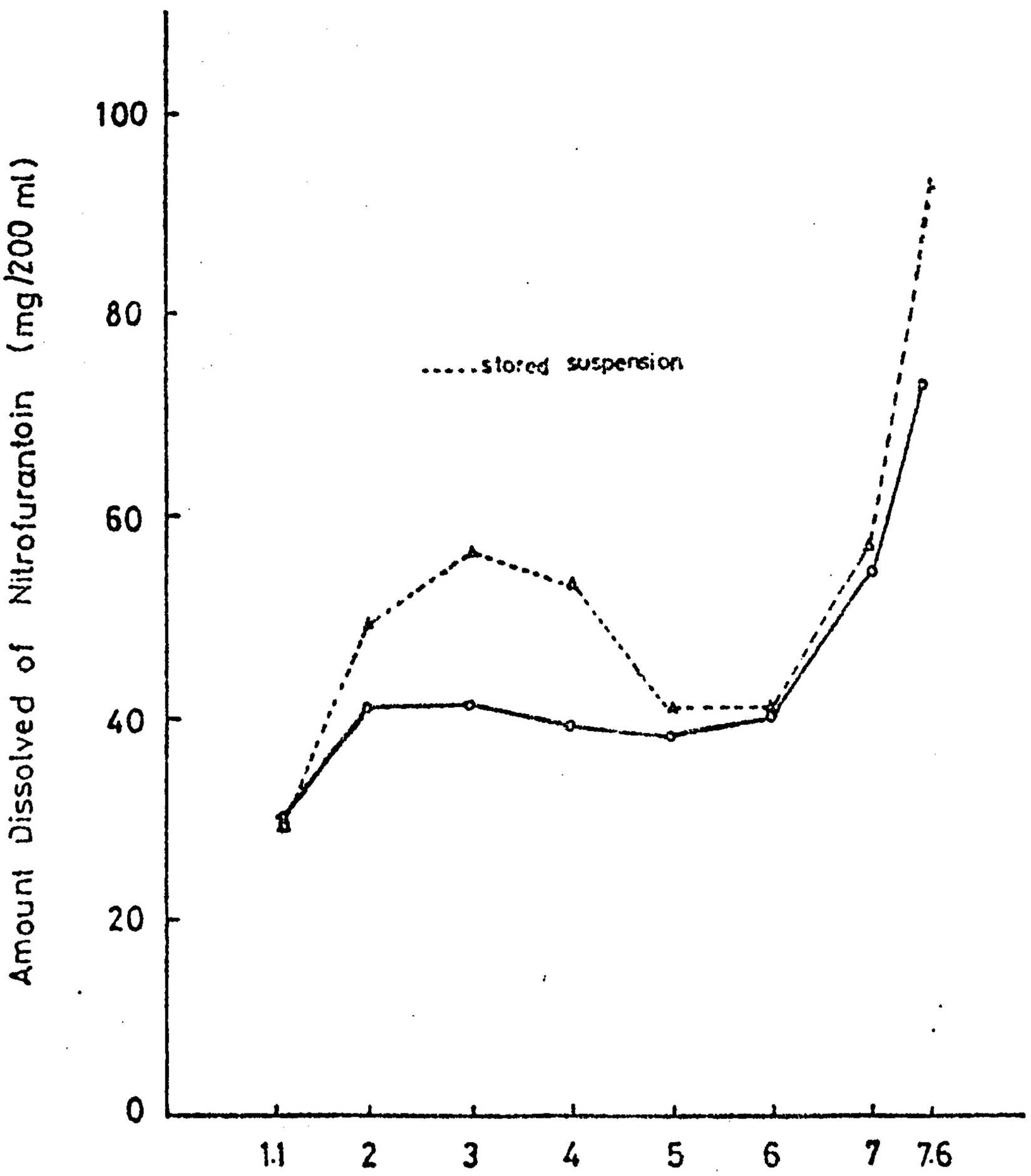


FIG.(9) 15-MINUTES DISSOLUTION-pH PROFILE OF NITROFURANTOIN SUSPENSIONS I AND II AT 37°C.

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دراسة على أذابة النيتروفيورانتوين

حمدى الصردى ـ على سينا ـ سيد على ابراهيم ـ خالد على خالد
قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة اسيوط

ع ٠ م ٠ ع

يناقش هذا البحث مشكلة وجود الاختلافات الواضحة فى معدلات اذابة عقار النيتروفيورانتوين من الاقراص سواء فى نفس التشغيلة او بين التشغيلات المختلفة لنفس نوع الاقراص المحتوية على العقار

وقد اثبتت نتائج حيود الاشعة السينية والتحليل الحرارى التفاضلى لخمسة مساحيق ذات لبلورات دقيقة للعقار وتستخدم فى تصنيع اقراص العقار ان الاختلافات الواضحة فى معدلات الاذابة فيما بينها لاترجع الى وجود ظاهرة التآصل البلورى فى العقار ـ كما لوحظ ان بلورات العقار يتضاعف حجمها خمس مرات وذلك عند وجود العقار كمعلق فى وسط مائى سواء كان حمضيا او متعادلا وقد اعطت هذه البلورات عند فصلها معدلات اذابة منخفضة بصورة ملحوظة وهو مافسر على ان هذه البلورات هى بلورات مائية للعقار ٠

كما اوضحت دراسة معدل اذابة معلق العقار فى الماء (المحضر من محلولة القاعدى بترسيبه عند الاس الايدروجينى ٤ر٥) فى اوساط مائية ذات اس ايدروجينى مختلف ـ احتمال وجود تحولات توتوميرية فى جزئ العقار الذى تأيد بحدوث تغيير عكسى فى طول الموجه ذات اقصى امتصاص للاشعة لمحلول العقار عند تغيير الاس الايدروجينى للمحلول ٠