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RETARDATION OF NITROFURANTOIN RELEASE BY COACERVATION

M.S. Mesiha : H.A. El-Sourady
Departments of Industrial Pharmacy and Pharmaceutics, Faculty of Pharmacy, University of Assiut. Assiut , Egypt.

ABSTRACT

Gelatin-acacia coacervation was employed to microencapsulate paraffin oil and soft paraffin droplets containing suspended nitrofurantoin, and for direct encapsulation of the drug. Dissolution characteristics of the encapsulated paraffins suspensions of nitrofurantoin , the directly encapsulated drug and nitrofurantoin powder were compared in buffer solutions of pH 1.12 and 7.2. The most rapid dissolution was shown by the nitrofurantoin powder followed by the directly encapsulated drug, the emulsified paraffin oil suspension of nitrofurantoin.

The drug was released from oil-containing microcapsules in successive stages representing initial release from capsular layer followed by sustained release from the oily core material.

Formalization of the gelatin-acacia coacervates should be allowed for enough time in order to obtain enteric protection.

No correlation was found between the equilibrium solubility of the drug in the buffer and the corresponding release profile in the same buffer.

The rate of release was slower as the viscosity of the core oil increased.

INTRODUCTION

Nitrofurantoin is a bactericidal to most urinary tract pathogens[1]. Its clinical use was accompanied by gastrointestinal side effects, specially nausea and vomiting[2]. The crystal size of nitrofurantoin affects its dissolution rate, bioavailability and the incidence of side effects[3-5]. The large crystal sizes provoked less emesis in dogs than the fine powder. However, larger crystals were less well absorbed and excreted in the urine in man and a suitable compromise was found in macrocrystals of 75 to 180 um size fraction which produced enough urinary concentration with satisfactory total urinary excretion[4].

The biological half-life of nitrofurantoin in man appeared to be 30 minutes or less[6,7].

To overcome the difficulties in obtaining the drug in a specified crystal size[8], nitrofurantoin was suggested to be coated to retard its release using sodium carboxymethyl cellulose[9].

Microencapsulation of water-insoluble drugs using gelatin-acacia ceacervation is an attractive tool for the prolongation of drug release[10]. Various studies were reported [11,12] on the effect of different factors on coacervation behaviour. However, few attempts have been made to study the release of a drug suspended in an emulsifiable inert carrier enclosed in microcapsules. By changing the carrier properties, such as its viscosity, or changing the globule size of the dispersed oil, it may be possible to control the drug release.

The work presented here represents an attempt to study the release of nitrofurantoin as a model drug of limited water-solubility (1: 5000)[1] from an encapsulated oil carrier system, in comparison with the raw drug and the drug directly encapsulated.

EXPERIMENTAL

Materials:

Nitrofurantoin: courtesy of Kahira laboratories, Cairo, Micronized to mean crystal size 40 μ at maximum length of the crystal, the size ranged between 12-60 μ as determined microscopically.

Gelatin: 250 B acid processed pigskin (Hodgson Ltd.).

Acacia: Acid insoluble ash, not more than 0.25%. Ash not more than 4% (May & Baker).

Paraffin oil and white soft paraffin: were pharmaceutical grades available in the local market.

Formaldehyde solution: 37% HCHO, (El-Nasr).

Other chemical used (Buffers components) were analytical grade reagents.

Microencapsulation of Nitrofurantoin: The microcapsules were prepared by complex gelatin-acacia coacervates, using a technique similar to those reported previously[12,13]. In the procedure employed for this study, the drug (0.5g) was suspended in acacia dispersion, 3% w/v, or suspended first in paraffin oil (2.0g), or in liquefied soft paraffin at 50°, then the oily suspension was emulsified in the acacia dispersion at 50° and pH 6.0 using mechanical homogenizer which produced homodispersed emulsions of fairly regular particle size and particle size distribution. Two minutes

of homogenization was sufficient to result in the desired particle size reduction. The gelatin dispersion (3% w/v)at 50° and pH 6.0 was added to the previously prepared drug suspensions in gum acacia with continuously stirring at 600 rpm of the two colloids. The pH of the system was lowered to a value of 3.8 using dilute hydrochloric acid solution to cause maximum complex formation between acacia and gelatin to encapsulate the nitrofurantoin or its oily suspension by the resulting coacervate.

In all experiments, the volume of acacia dispersion was equal to the volume of gelatin dispersion and calculated to give a theoretical core: wall ratio of 1:4 by weight. The wall was considered to be composed of equal weights of the two colloids.

Formaldehyde solution in a volume of 5 ml per each 100 ml of the working system, was added while stirring for 10 or 60 min to harden the coacervates. The system was rapidly cooled to 5° using an immersion cooler (Julabo, Ft 200). The hardened coacervates were filtered and washed with cooled distilled water. The wet mass was dispersed in 70% isopropanol solution[13] , previously cooled to 5°. The obtained microcapsules were filtered and air dried for 24 hrs to yield free flowing discrete particles.

The same procedure was run to produce batches of microcapsules, but with no formaldehyde treatment and similar batches devoid of the drug were also prepared as a blank for analytical purposes.

Determination of Nitrofurantoin: To determine the total content of nitrofurantoin in the microcapsules, they were extracted with dimethylformamide by shaking an accurately weighed sample containing about 50 mg of nitrofurantoin

with 25 ml dimethylformamide in a 100 ml stoppered flask by mechanical shaker for 1 hour. The contents were centrifuged at 5000 rpm for 5 minutes.

An accurately measured volume of the extracted nitrofurantoin solution was diluted quantitatively with water, and the amount of nitrofurantoin was determined spectrophotometrically at 367 nm (Pye Unicam SP6-400, 1 cm cell) using the corresponding placebo batch similarly treated as the blank.

Equilibrium Solubility Determination: The equilibrium solubility of nitrofurantoin at 37°, was determined in pH 1.12 hydrochloric acid buffer and pH 7.20 phosphate buffer media (USP XX) and in the same media containing 1% w/v gelatin-acacia or formaldehyde separately added to each buffer. Excess quantities of nitrofurantoin powder were placed into 30-ml stoppered tubes together with 20 ml portions of the solvent system. The tubes were shaken mechanically in a covered water bath protected from light and maintained at $37^{\circ} + 0.2^{\circ}$ until equilibrium was attained. The tubes were contrifuged, reequilibrated and a sample was diluted with buffer solution and assayed spectrophotometrically at 367 nm, using the solvent system as the blank.

Dissolution Rate Determination: The dissolution apparatus (Erweka DT-6) consisted of set of 1-liter, three-necked round bottom flasks, containing 900 ml of pH 1.12 hydrochloric acid buffer solution (USP XX) or pH 7.20 phosphate buffer solution (USP XX). The dissolution medium was maintained at $37^{\circ} + 0.2^{\circ}$ and agitated at 100 rpm by means of PTFE-coated stirring blade.

An accurately weighed sample equivalent to 50 mg of nitrofurantoin was introduced to the medium. All the bat-

ches studied were freely suspended in the dissolution medium under the conditions of the test. After 5, 10, 15, 30, 45, 60 min., then at 30 min intervals, 2-ml samples were withdrawn from the flask using a filtering pipette, diluted with the diusoltuion medium and assayed spectrohotometrically at 367 nm using a blank obtained by similar treatment of the appropriate placebo microcapsules. Immediately, the samples were replaced with fresh medium kept at 37°, and appropriate corrections were made for such dilution effect.

All the studies reported here were done using the microcapsules that passed through 630 µm sieve but were retained on a 400 µm sieve.

RESULTS AND DISCUSSIONS

The encapsulated system showed the characteristics presented in Table 1. Dissolution studies of nitrofurantoin are shown in Fig. 1,2. All samples at different pH values showed the familiar pattern of a rapid initial release followed by a slower sustained release with the encapsulated systems. The plain powder obviously gave the most rapid dissolution, followed by the directly encapsulated nitrofurantoin. The encapsulated mineral oil or soft paraffin systems, containing nitrofurantoin, showed two successive release rates, the initial rapid rate is attributed to the drug contained in the capsular layer of the coacervates. The second rate period followed a lag peroid, then the drug was slowly released. This slow rate may represent the drug release from the oily core. This explains the slower release of the drug from system of nitrofurantoin in soft paraffin

than from nitrofurantoin in liquid paraffin, while no significant difference was observed in the initial release rate period. The effect of the viscosity of the oil on the diffusion of the drug is expected, as nitrofurantoin slowly migrated to the attrition wall of the oil droplets due to the high viscosity . The reduction in the permeation rate of nitrofurantoin from drug suspensions prepared with viscous methyl cellulose solutions was previously reported[14,15].

With all systems studies the fastest release occurred at pH 1.12, except with batches hardened by formalin solution for one hour. It appears that the shorter period of treatment with formalin, as well as the untreated coacervates do not produce enteric coating effect. It is interesting to note that the release rate of the drug did not depend upon the equilibrium solubility of nitrofurantoin in the buffer (Table 2). This may be due to the swelling and other physical properties of the coat in the buffers.

The hardening time using formalin solution should be increased enough in order to obtain the desired enteric coating. This finding agreed with those of Madan[16] who found a linear relationship between hardening time and the time for 50% release for clofibrate microcapsules made from simple coacervates.

In conclusion, the microencapsulation of the drug suspended in oil may be of value in the design of sustained release dosage forms. Formalization of the gelatin acacia coacervates should be allowed for enough time in order to obtain enteric protection. Solubility of the drug in the buffer system of the dissolution media is not the determining effect in its release. The more the viscous the oil, such as soft paraffin, the lower the dissolution rate.

The results obtained seem to be of great value to formulate nitrofurantoin powders in the form of microcapsules to overcome the gastrointestinal side effects encountered with the oral administration of nitrofurantoin dosage forms. This sustained release form of nitrofurantoin is of great help to increase the biologic half-life of the drug, and so the dosage regimen of nitrofurantion can, thus, be changed.

Table 1: Characteristics of the nitrofurantoin encapsulated systems

Encapsulated system	*Diameter of oil nucleus*[1] *(micrometers)*	*Wall thickness*[2] *(micrometers)*
Nitrofurantoin, directly encapsulated	-	16.3 ± 0.44
Nitrofurantoin in paraffin oil microcapsules, unformalized	85.7 + 1.21	7.6 ± 0.81
Nitrofurantoin in paraffin oil formalized microcapsules	84.1 ± 1.43	8.1 ± 0.39
Nitrofurantoin in soft paraffin, in unformalized microcapsules	87.8 ± 1.12	7.9 ± 0.43
Nitrofurantoin in soft paraffin, in formalized microcapsules	86.4 ± 1.73	7.7 ± 0.56

1. Each value is the average of at least 100 droplets, determined microscopically ($\bar{x} \pm$ S.D)
2. Each value is the average of at least 25 determinations ($\bar{x} \pm$ S.D)

Table 2: Equilibrium solubility of nitrofurantoin in buffer systems containing various additives, at 37°.

Buffer USP XX)	*Additive (1%)*	*Equilibrium Solubility mg/liter*
HCl, pH 1.12	none	109.2
	acacia	121.2
	gelatin	151.4
	formaldehyde	107.8
Phosphate, pH 7.2	none	363.5
	acacia	389.6
	gelatin	388.3
	formaldehyde	684.6

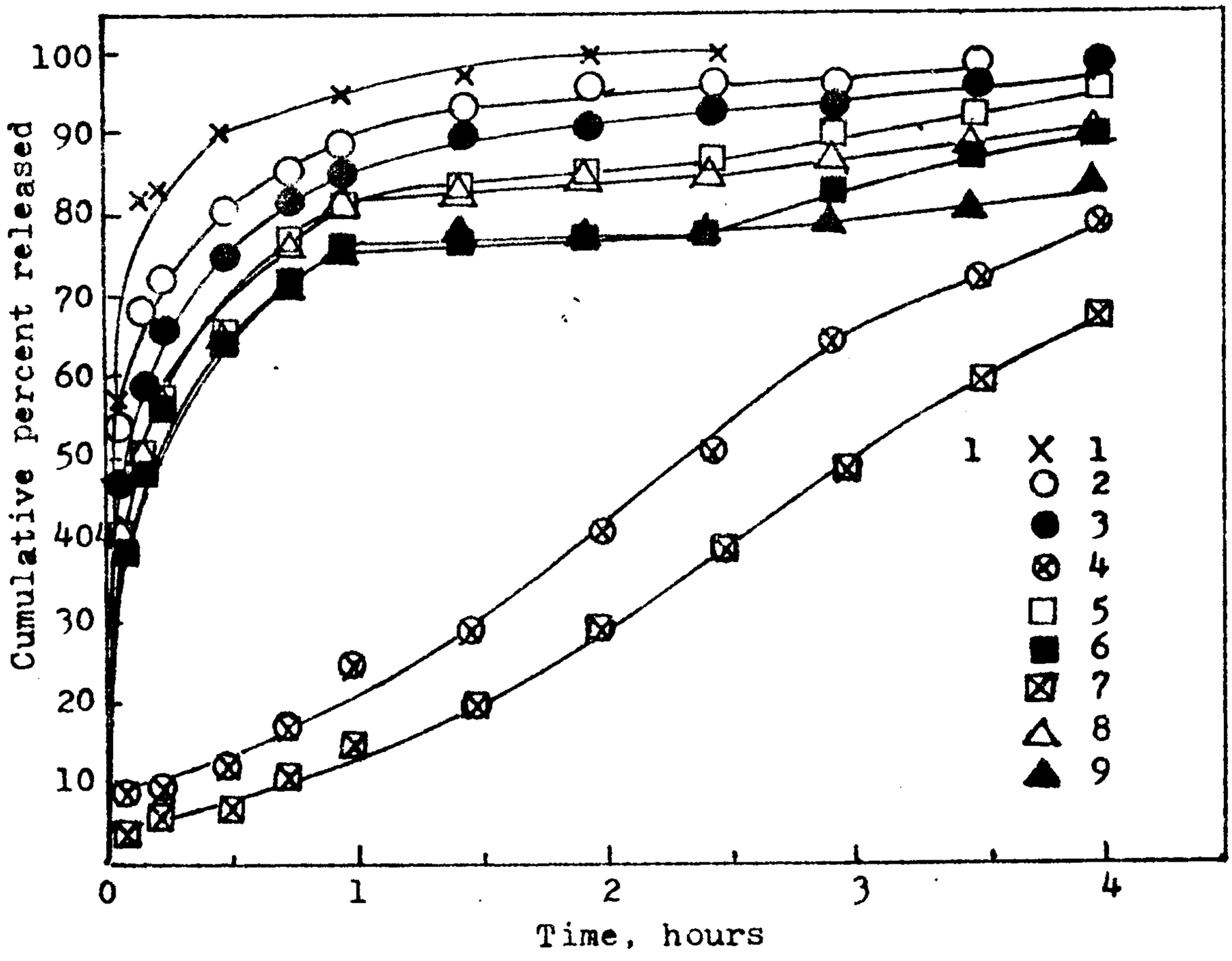

Fig. 1. Dissolution rate of nitrofurantoin at 37° in hydrochloric acid buffer at pH 1.12 from: plain powder(1); directly encapsulated crystals: unformalized(2), formalized for 10 min(3), and formalized for 60 min(4); encapsulated paraffin oil suspension: unformalized(5), formalized for 10 min(6), for 60 min(7); encapsulated soft paraffin suspension: unformalized(8) and formalized for 10 min(9).

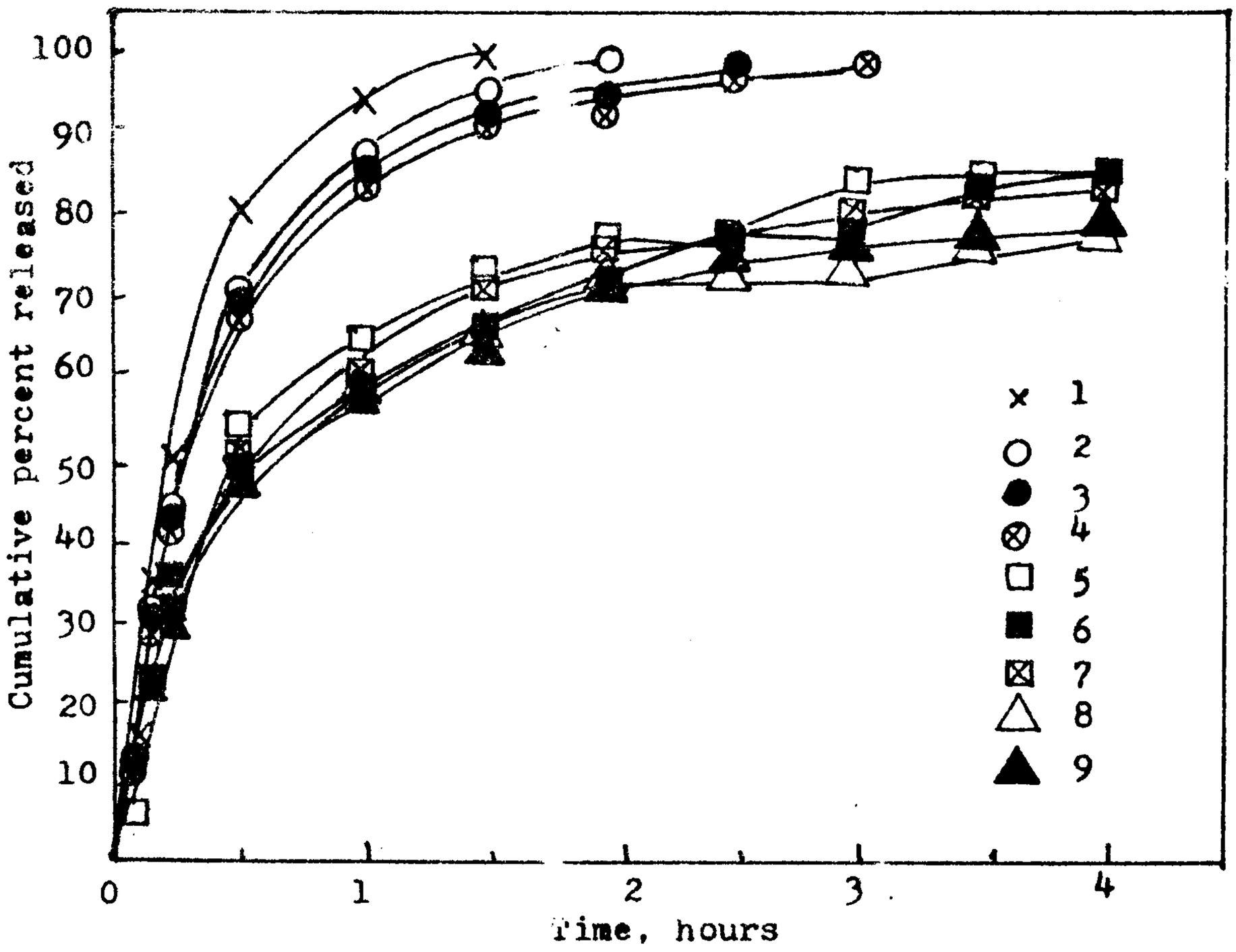

Fig. 2. Dissolution rate of nitrofurantoin at 37° in phosphate buffe pH 7.2 from different micro-encapsulated systems (key is the same as Fig.1).

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اطالة انطلاق النيتروفيورانتوين بالحوصلة

منير صبحى مسيحة - حمدى عبد الستار الصردى
قسمى الصيدلة الصناعية والصيدلانيات بكلية الصيدلة
جامعة اسيوط

تم تشتيت مادة النيتروفيورانتوين فى البرافين السائل ،وفى البرافين الرخو ثم حوصلتة باستخدام الجيلاتين والصمغ العربى. وقد اجرى اختبار قياس معدل الاذابة للمادة الدوائية من مسحوقها ومن حويصلاتها فى وسط منظم حمضى ذو رقم ايدروجينى قدرة ١٢و١ ،وفى وسط منظم ذو رقم ايدروجينى قدرة ٢و٧ - وتبين من النتائج ان الحوصلة قد اخرت انطلاق المادة الدوائية وكان معدل اذابة النيتروفيورانتوين اسرع لمسحوقة يليها حويصلاتة المباشرة ثم حويصلاتة مع زيت البرافين واخيرا حويصلاتة فى البرفين الرخو . كما اتضح ان المعالجة بالفومالين يجب ان تتاح لها الوقت الكافى حتى يمكن للحويصلات مقاومة الذوبان فى الوسط الحمضى .

ولم يلاحظ وجود علاقة بين ذوبان المادة الدوائية ومعدل اذابتها وانطلاقها من الحويصلات وعلى ذلك فقد اثبت البحث امكان اتباع هذة الطريقة للحوصلة باستخدام المادة الزيتية كحامل للمادة الدوائية قبل حوصلتها للعمل على امتداد معدل اذابة المادة الدوائية ومن ثم امتداد مفعولها .

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