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MICROENCAPSULATION OF NITROFURANTOIN BY COACERVATION USING CERTAIN POLYMERIC MATERIALS

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ABSTRACT

Microencapsulation of nitrofurantoin was carried out in order to prepare sustained release formulations with less side effects. Three coacervation techniques, using three different coating materials, were adopted for this purpose as follows : non - solvent addition using Eudragit RS 100 (ERS), temperature change using ethylcellulose (EC) and salt addition using sodium alginate (SA). The physical properties as well as the dissolution characteristics were investigated.

Microencapsulation of nitrofurantoin (NF) gave rise to sustaining its release at pH 1.12. NF-SA and NF-EC microcapsules showed more retarded release than NF-ERS microcapsules. Increasing the proportion of ERS in its microcapsules resulted in a marked sustaining of NF release whereas, no significant effect was obtained upon increasing the proportion of EC in NF-EC microcapsules. NF microcapsules showed fast release at pH 7.8 specially in case of SA. Regarding the release kinetics, first order model proved to be the most operative mechanism explaining the release of NF from NF-ERS microcapsules. On the other hand, Baker and Lonsdale equation was found to be the most suitable model for explaining the release of NF from EC or SA microcapsules.

INTRODUCTION

Microencapsulation may be thought of as a method of wrapping small entities in individual protective coatings. These coatings are designed mainly to control or prolong the action of the encapsulated drug and sometimes to protect or aid in storage and handling. Microencapsulation by coacervation phase-separation is the most commonly used method for this purpose. Coacervation may be induced by many different techniques such as non-solvent addition (solvent alteration), temperature change, addition of incompatible polymer or salt addition[1].

Nitrofurantoin is a drug which is widely used for the treatment of urinary tract infections with a broad spectrum activity. It has a short biological half-life (0.5 to 1 hour) and its oral administration causes nausea and vomiting occasionally[2].

The aim of this work was to prepare NF microcapsules by coacervation phase separation method using three different techniques : (a) non-solvent addition using Eudragit RS 100 (ERS) as the coating material. (b) temperature change using ethyl cellulose (EC). and (c) salt addition using sodium alginate (SA).

EXPERIMENTAL

Materials :

-Nitrofurantoin, Berk Pharmaceuticals Ltd., Shalford, England.

-Eudragit RS 100, Rohm Pharma GmbH, Germany.

-Ethyl cellulose, type N (ethoxy content; 47.5-49.9 %), Hercules, Wilmington, U.S.A.

-Sodium alginate, Judex Laboratory Reagent, Middlesex, England.

-Diethylether, chloroform, acetone, ethyl alcohol, dimethyl formamide and calcium chloride, El-Nasr Chem. Co., Cairo, Egypt.

Methods

Preparation of NF-ERS microcapsules :

NF-ERS microcapsules were prepared by non-solvent addition as previously described[3]. Chloroform was used as the polymer solvent and cyclohexane was used as the non-solvent vehicle or the coacervating agent. 1 : 1, 1 : 2 and 1 : 3, drug : polymer, ratios were prepared.

Preparation of NF-EC microcapsules:

The method used was similar to those of Miller et al.[4] and Jalsenjak et al.[5]. At a continuous stirring rate of 400 rpm and at 50°, ethyl cellulose in an amount depending on the core : wall ratio was added to 300 ml of cyclohexane and the temperature was raised to 80 °C over one hour. The system was allowed to cool to 35° and cooling was then accelerated to 20-25°. The microcapsules were filtered off, washed three times each with 150 ml of fresh cyclohexane at 10 ° and allowed to dry in air over night. 2 : 1, 1 : 1 and 1 : 2, drug : polymer, ratios were prepared.

Preparation of NF-SA microcapsules:

NF was suspended in a 2 % solution of sodium alginate in water. This suspension was then forced in a thin stream through a capillary tube into a beaker containing 100 ml of 5 % W/V of calcium chloride solution. The prepared microcapsules were then separated by filtration, washed and allowed to dry for three days in a vacuum desiccator at ambient temperature and away from light. The amount of NF was varied to prepare 1 : 2, 2 : 2 and 3 : 2, core : coat ratios.

Evaluation of the prepared microcapsules :

Photomicrography

Photomicrographs were taken and examined using photomicroscope (Lietz Laborlux D 513558, Lietz Wetzlar, Germany).

Scanning electron microscopic investigation:

Samples of NF-EC (1 : 1) and NF-SA (1 : 2) microcapsules were mounted onto stubs using double sided adhesive tape and vacuum-coated with gold film, approximately 30 nm in thickness.

Determination of drug content a-NF-ERS and NF-EC microcapsules :

An accurately weighed amount (20 mg) of microcapsules was sh ken with 10 ml of acetone. Distilled water (500 ml) was then added to dissolve the drug. After filtration, the amount of NF in the filterate was determined by measuring the absorbance at 367 nm. The content of NF was assessed using previously constructed calibration curve of NF in presence of either ERS or EC and 10 ml of acetone.

b-NF-SA microcapsules :

100 mg of the microcapsules were pulverised using a mortar and a pestle. 20 mg of the pulverised microcapsules were transferred to a 500 ml measuring flask containing 10 ml of dimethylformamide. The flask was completed to volume with distilled water being reasonabley shaken to dissolve the solids. The concentration of NF was determined spectrophotometrically at 367 nm. A previously constructed calibration curve of NF in presence of SA and dimethylformamide was used.

Dissolution characteristics study:

Accurately wighed samples (25 mg, each) of the prepared microcapsules were introduced into the

cups of the USP dissolution apparatus (Erweka DT-6, Germany). The dissolution medium was 900 ml of either 0.1 N HCl (pH 1.12) or phosphate buffer (pH 7.8). The temperature was kept constant at 37 ± 0.2 °C and the medium was continuously stirred at 100 rpm. Samples of 5 ml were withdrawn at suitable time intervals using a filter pipette and assayed spectrophotometrically at 367 nm. The withdrawn samples were replaced by equal volumes of the fresh dissolution medium at 37 °C.

Results and discussion

Photomicrography and scanning electron microscopy:

Fig. 1 shows the photomicrographs of NF-ERS microcapsules. They appear as irrigularly shaped particles with round edges. The yellow needle shaped NF particles could be difficultly distinguished inside the transparent coating of ERS. Fig. 2 shows the scanning electron micrographs of the ethyl cellulose walled NF microcapsules. They are seen as irrigularly shaped particles with round edges and a complete covering of ethyl cellulose. Few pores on the surface could be distinguished upon magnifying a segment of the surface of the microcapsules. Fig. 3 shows the scanning electron micrographs of NF-SA microcapsules (200 - 250 μ). They are irrigularly shaped with round edges and smooth surface completely covered with sodium alginate. On the other hand, the photomicrograph of a single microcapsule (Fig.4) showed yellow crystals of NF inside a transperent wall of sodium alginate.

Drug content:

Tables 1, 2 show the drug content of NF-ERS and NF-EC microcapsules, respectively. It could be seen that the amount of NF actually present in the microcapsules was less than the theoretical amount expected. This means that some of the drug was lost during the process. This could be due to the solubilization of about 12 % of NF in cyclohexane (the manufacturing vehicle). On the other hand, Table 3 shows the percent of drug content of NF-SA microcapsules where the loss of NF was higher (about 26 %) due to the solubility of NF in water (the manufacturing vehicle).

Release characteristics:

Fig. 5 shows the release profiles of NF-ERS microcapsules in comparison with that of NF powder. The release rate of NF was sustained for about 6 fold in case of 1 : 1 to 15 fold for 1 : 3 (drug : polymer) ratio microcapsules. This retardation in NF release could be also seen from the long T_{50} % and T_{80} % values shown in Table 4. The release of NF from the 1 : 2 (NF : ERS) formula in alkaline medium (pH 7.8) was faster than that in acidic medium (pH 1.12). This is propably due to the dependence of the solubility of ERS coating on the pH of the medium[6].

All the NF microcapsules coated with EC showed much more prolonged release of NF compared to the release from the unencapsulated drug particles as shown in Fig. 6 and the T_{50} % and T_{80} % values given in Table 5. A significant prolongation in the release of NF could be observed upon increasing the proportion of EC from 1 : 1 to 1 : 2 (NF : EC) which is in agreement with the results published by Chemtob et al[7].

Fig. 7 illustrates the release profiles of NF-SA microcapsules. A marked retardation of the release rate of the drug from these microcapsules was achieved; about 24 fold compared with the unencapsulated drug. These microcapsules showed also long T_{50} % and T_{80} % values as demonestrated in Table 6. It was observed that no

significant effect on the dissolution rate was noticed upon changing the polymer proportion of these microcapsules. Furthermore, a very rapid release of NF from NF-SA microcapsules was observed at pH 7.8 (phosphate buffer). Complete release of the drug from these microcapsules (1 : 2 core/coat ratio) was achieved in less than 20 minutes. This may be due to the high solubility of calcium alginate in alkaline medium.

Release kinetics:

The release mechanism of NF from all the microcapsules tested was not according to zero order model, since the release profiles of the percent of the drug released against time was not linear (Figs. 5 - 7). Upon plotting the percentage of drug released as a function of the square root of time, Higuchi[8], linear correlations were obtained for the different microcapsules tested (Tables 4 - 6). Linear relationships could also be obtained upon plotting the logarithm of the percent drug remaining versus time (first order mechanism) with high correlation coefficients "r" for NF-ERS microcapsules but with lower "r" values for the other types of NF microcapsules (Tables 4 - 6). Since both Higuchi and first order models were found to be applicable for describing the release of NF from its microcapsules coated with ERS, a stringent test using the Kinetic exponent (n) of drug release proposed by Sinclaire and Peppas[9] was applied to distinguish between the two models as follows :

$$M_t / M_\infty = K^n t$$

Where "M_t / M_∞" is the fraction of drug released at time "t",
"k" is the rate constant and
"n" is the kinetic exponent of drug release.

The "n" value for each of the formulation tested was found to be about 0.2 as shown in Table 7. Thus, the release of NF from these microcapsules was proved not to follow Higuchi equation which requires an "n" value of 0.5 but follows preferably first order kinetics.

Another representaion of the release data was tried for testing NF-EC and NF-SA microcapsules by applying Baker and Lonsdale equation[10] as follows :

$$3/2 [1 - (1 - F)^{2/3}] - F = Kt$$

Where F, is the fraction of drug released at time t and k, is the release rate constant.

Interestingly, a linear relationship was found for each of the formulations tested (Figs. 8, 9 and Tables 5, 6). This finding indicated that Baker and Lonsdale model was the most suitable one describing the release behaviour of NF from EC and SA coated microcapsules.

Conclusion :

From the results obtained throughout this study, it could be concluded that :

-All the prepared microcapsules of ERS, EC and SA were found to be successful in sustaining the release of NF.

-The microcapsules of NF coated with EC in 1 : 2, core : coat ratio gave rise to the most prolonged release whereas, ERS coated microcapsules were found to be less effective in prolonging the release of NF.

-The release of NF from NF-ERS microcapsules was found to follow the first order kinetics whereas, Baker and Lonsdale equation was the most suitable model describing the release of NF from NF-EC and NF-SA microcapsules.

Table 1 : Drug Content of NF-Eudragit RS_{100} Microcapsules.

Drug : Polymer ratio	Theoretical % of drug	Actual % of drug	% of drug content	% of drug loss
1:1	50.0	43.8	87.5	12.5
1:2	33.3	29.4	88.1	11.9
1:3	25.0	22.1	88.3	11.7

Table 2 : Percentage of Drug Content for NF-Ethylcellulose Microcapsules:

NF : EC ratio	Theoretical % of drug content	Actual % of drug content	% of drug content	% of loss of drug
1:1	50.0	42.1	84.2	15.8
1:2	33.3	29.7	89.2	10.8
2:1	66.7	59.7	89.6	10.4

Table 3 : Percent of Drug Content of NF-SA Microcapsules.

Core :Coat (NF:SA)ratio	Theoretical % of drug	Actual % of drug	% of drug content	% of loss of drug
1:2	33.3	24.8	74.3	25.7
2:2	50.0	36.9	73.8	26.2
3:2	60.0	43.9	73.2	26.8

Table 4: Kinetic Data of Drug Release from NF-Eudragit TS[100] Microcapsules.

Parameter	pH of the dissolution medium							
	pH= 1.12						pH = 7.8	
	Core : Coat (NF : ERS) ratio							
	(1 : 1)		(1 : 2)		(1 : 3)		(1 : 2)	
	Higuchi	First order	Higuchi	First order	Higuchi	First order	Higuchi	First order
r	0.987	-0.998	0.991	-0.999	0.993	-0.996	0.995	1.000
B[a]	10.325	-0.010	7.994	-0.007	7.057	-0.005	11.289	-0.011
A	-12.266	2.039	- 6.108	2.001	-8.624	2.013	14.277	2.020
K_F^b (hr^{-1})		1.239		0.946		0.666		1.358
t_{50} (min)	33.559		43.953		62.432		30.619	
t_{80} (min)	77.950		102.101		145.027		71.134	

-$T_{50\%}$ and $t_{80\%}$ (min.) were calculated from the first order equation.
-r: correlation coefficient.
-B: the slope.
-A: the intercept.

Table 5 : Kinetic Data of Drug Release from NF-EC Microcapsules

core:coat ratio	pH of the medium	Higuchi			First order K_F ($h r^{-1}$)	Lonsdale K_L (hr^{-1})	$t_{50\%}$	$t_{80\%}$
		Parameter	Initial stage	Terminal stage *				
1:1	1.12	K_H	6.720	2.686	0.341	0.033	100.00	340.00
		r	0.997	0.982	-0.980	0.991		
		A	-18.023	28.280				
1:2		K_H	5.206	2.912	0.300	0.023	143.48	487.83
		r	0.996	0.997	-0.989	0.998		
		A	- 0.770	16.428				
2:1		K_H	6.441	3.084	0.331	0.032	103.13	350.63
		r	0.997	0.992	-0.992	0.998		
		A	-17.220	21.399				
2:1	7.8	K_H	8.910	2.638	0.786	0.068	48.53	165.00
		r	0.993	0.990	-0.990	0.993		
		A	-14.360	51.478				

-K_H, K_F and K_L are the release rate constants of Higuchi, first order and Baker-Lonsdale respectively.
-$t_{50\%}$ and $t_{80\%}$ min) were calculated from Bsker and Lonsdale equation.
-r is the correlation coefficient;
-A is the intercept.
-Terminal stage* starts after nearly 100 minutes.

Table 6 : Kinetics of NF Release from Sodium Alginate Coated Microcapsules

Drug: polymer ratio	Lonsdale				Higuchi				Zero order			First order		
	K_L	$t_{50\%}$	$t_{80\%}$	r	Stage	K_H slope	A	r	r	B	A	r	B	A
1:2	0.028	117.86	400.71	0.999	first	4.947	- 1.829	0.990	0.960	0.375	12.799	-0.994	-0.002	1.911
					second	2.979	20.183	0.999	0.993	0.090	43.575			
2:2	0.028	117.86	400.71	0.999	first	4.887	- 0.698	0.975	0.932	0.365	13.978	-0.994	0.002	1.901
					second	3.149	16.508	0.996	0.988	0.095	41.302			
3:2	0.033	100.00	340.00	0.999	first	5.122	- 0.312	0.987	0.953	0.380	14.890	-0.997	0.002	1.911
					second	3.282	19.563	0.999	0.993	0.099	45.350			

K_L[(a)] and K_H[(b)] are the release rate constants of Baker-Lonsdale and Higuchi respectively

Table 7 : Correlation Coefficient "r" for Plots of Release Rate (dQ'/dt) vs Amount (Q') and Reciprocal Amount (1/Q') of Drug Release from NF-Eudragit RS_{100} Microcapsules.

Core : coat ratio	vs (Q')	vs (1/Q')	"n"
1:1	-0.970	0.754	0.203
1:2	-0.982	0.904	0.214
1:3	-0.932	0.815	0.203

"n" is the kinetic exponent of release.

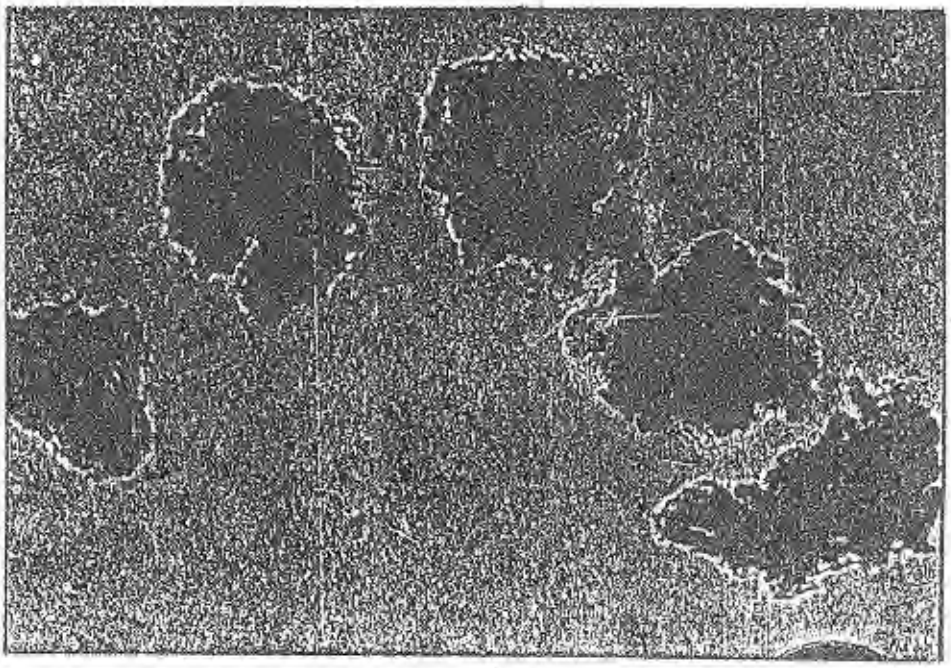
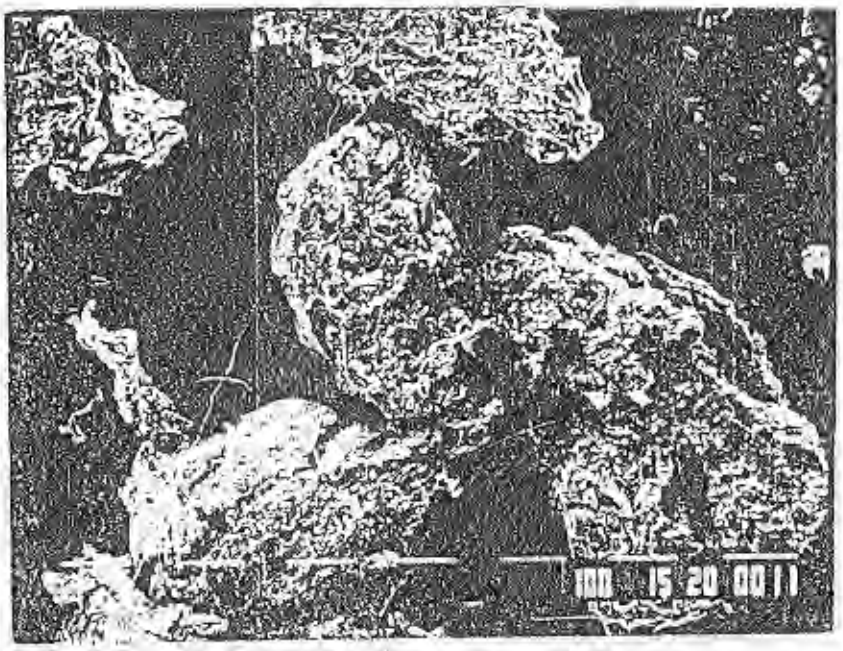


Fig. 1 : Photomicrograph of NF-Eudragit RS100 Microcapsules (1:2, core : coat ratio).

(A)



(B)

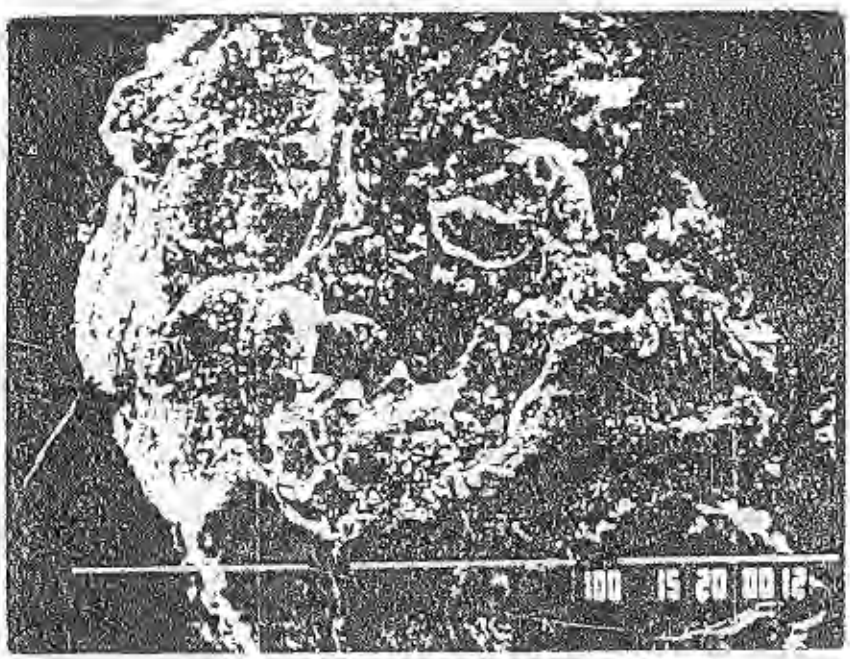
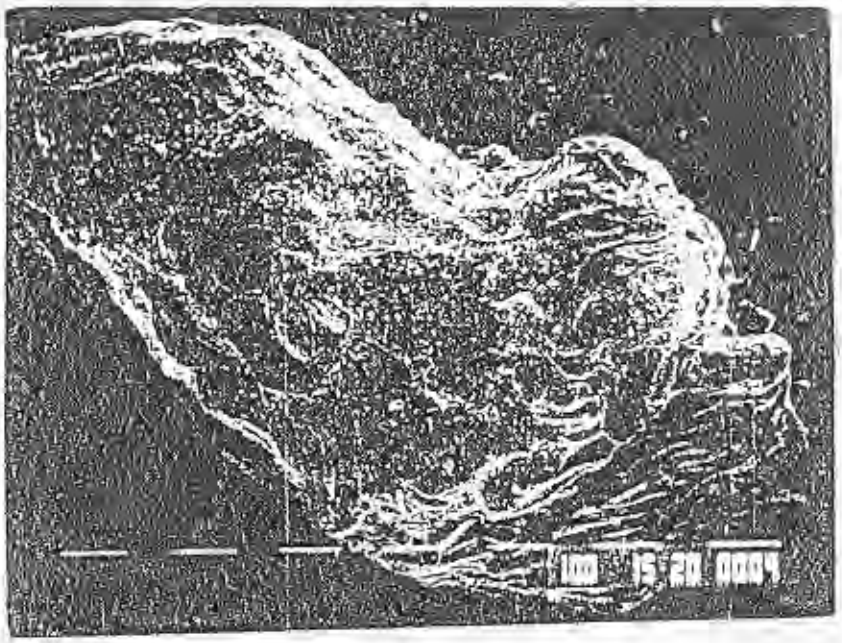


Fig. 2 : Scanning Electron Micrographs of NF-EC (1:1) Microcapsules [A] and Magnified Part of the Surface of a Microcapsule [B].

(A)



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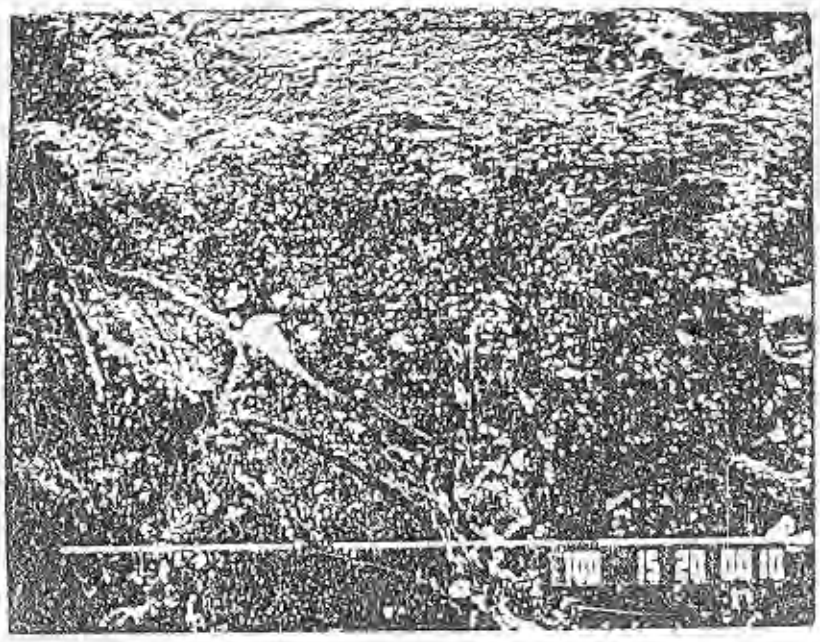

Fig. 3 : Scanning Electron Micrographs of NF-SA (1:2) Microcapsules [A] and a Part of the Upon Magnification [B].

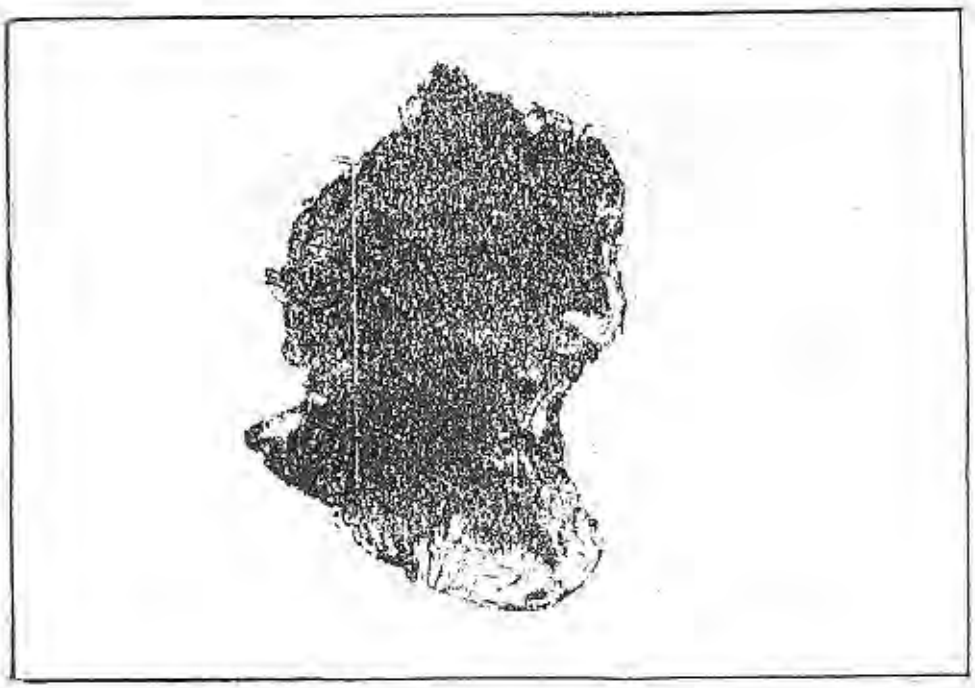

Fig. 4 : Photomicrograph of NF-SA (1:2) Microcapsules.

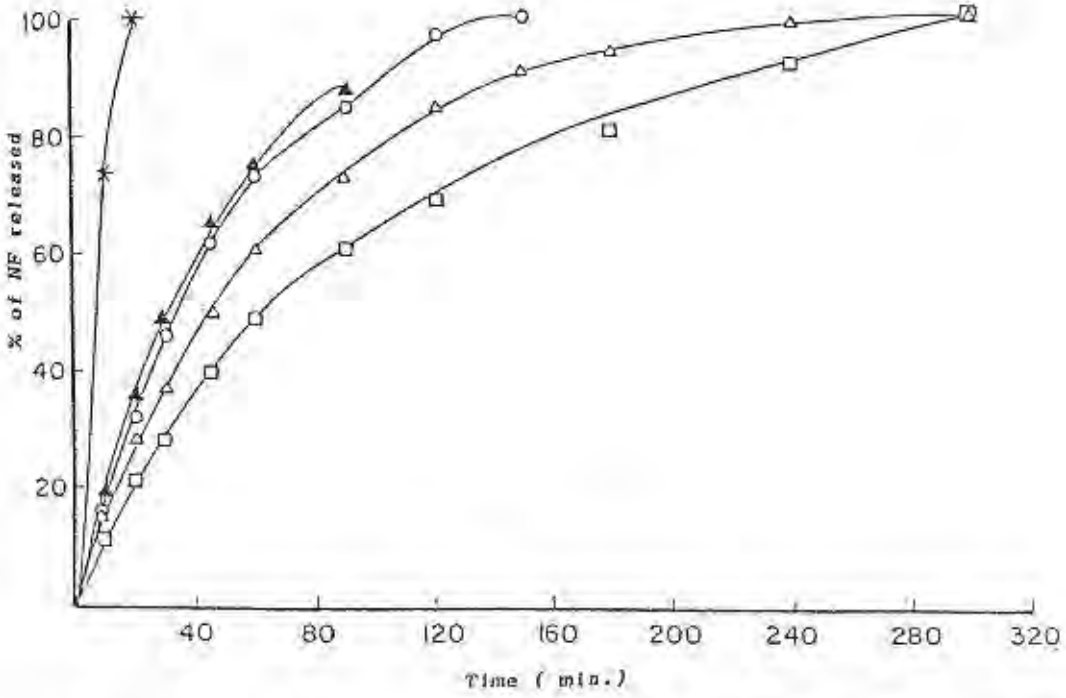

Fig. 5 : The Release Profiles of NF-ERS Microcapsules.
Key : NF powder (*). NF : ERS Ratios of 1:1(O) 1:2 (Δ), 1:3 (□) at pH = 1.12 and 1:2 (▲) at pH = 7.8.

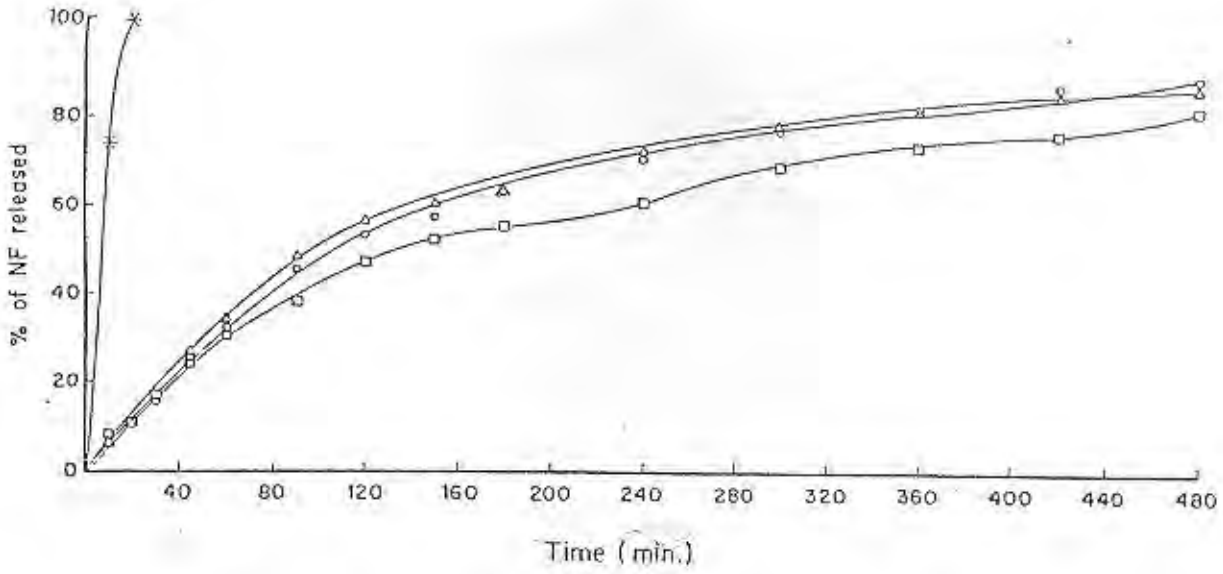

Fig. 6 : The Release Profiles of NF-EC Microcapsules (at pH=1.12). Key : NF powder(*), Ratio of 1:1 (O), 1:2(□), and 2:1(Δ).

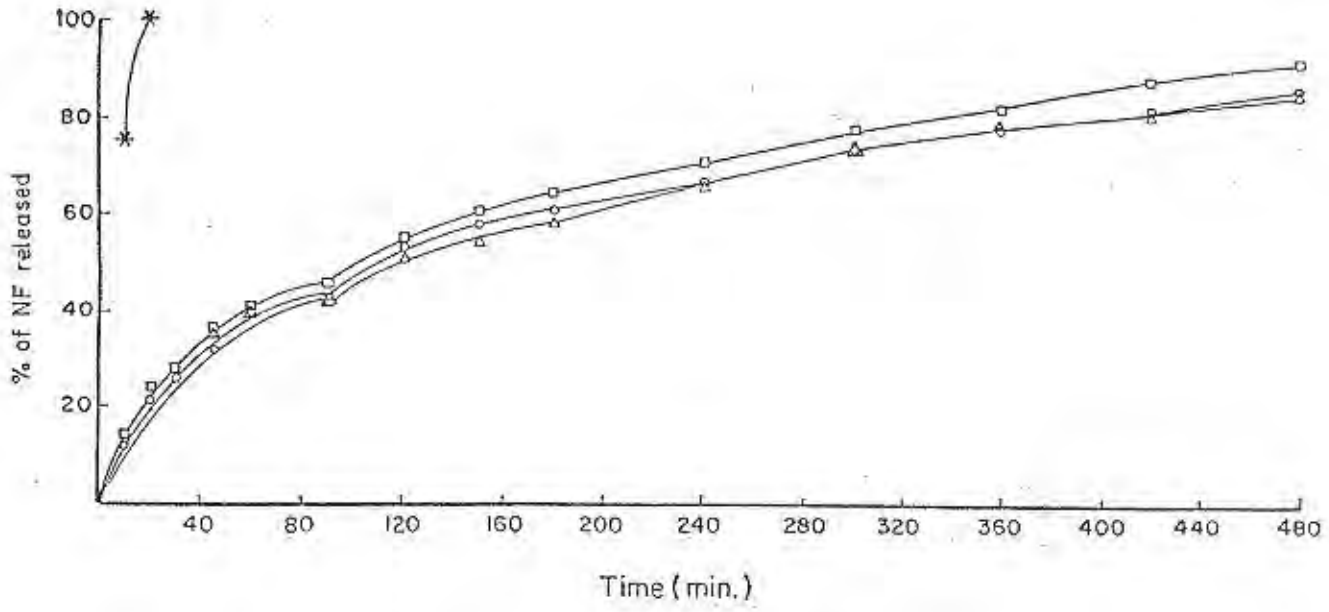

Fig. 7 : The Release Profiles of NF-Sodium Alginate Microcapsules of Different core : coat ratios : 1:2 (O), 2:2 (Δ) and 3:2(□) and NF Powder (*). at pH=1.12).

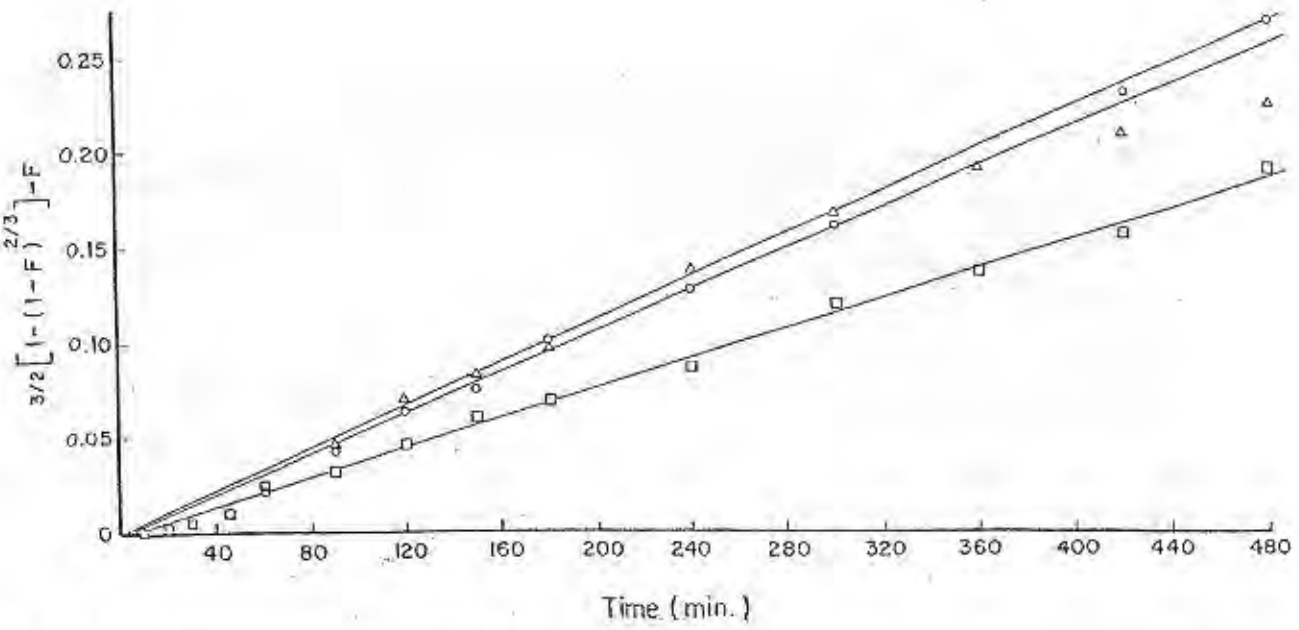

Fig. 8 : Plots of the Relation Between the Calculated Values of 3/2 $[1-(1-F)^{2/3}]-F$ and Time for NF-EC Microcapsules with core: coat ratios of 2:1(△), 1:1(O) and 1:2 (□) (at pH=1.12).

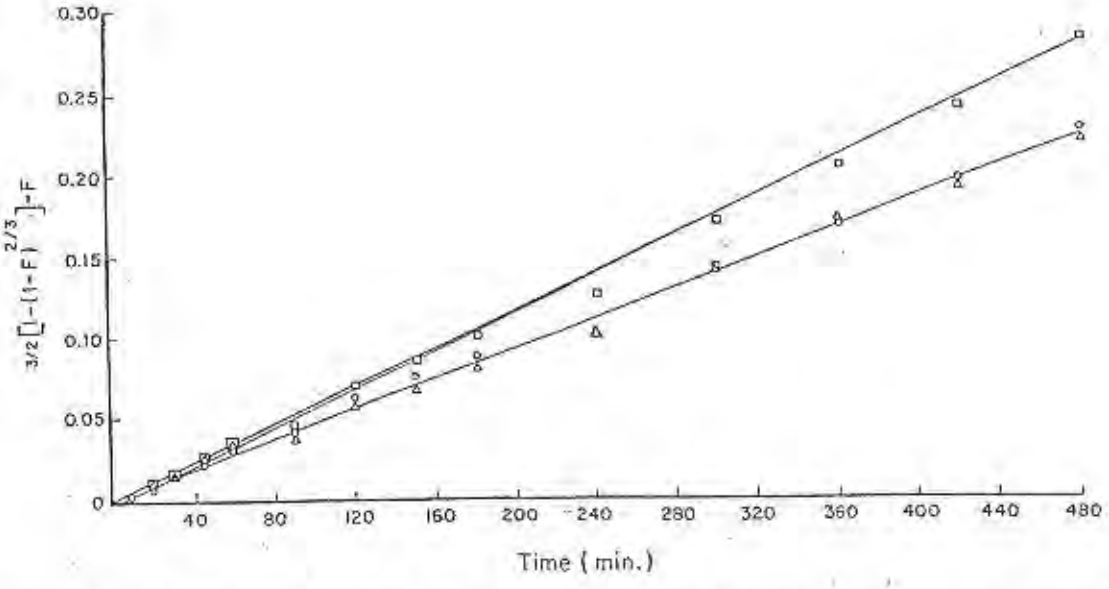

Fig. 9 : Plots of the Relationship Between the Calculated Values of 3/2 $[1-(1-F^{2/3}]-F$ and time for NF-Sodium Alginate Microcpsoles (at pH=1.12).
Key : NF:SA ratios of 1:2 (O), 2:2 (△) and 3:2(□).

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حوصلة النيتروفيورانتوين بطريقة انفصال الحوصلة باستخدام بوليمرات معينة

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تم فى هذا البحث حوصلة عقار النيتروفيورانتوين وذلك بغرض الحصول على حويصلات ممتدة المفعول وذات اعراض جانبية اقل وقد طبقت فى ذلك طريقة انفصال الحويصلة باستخدام ثلاث طرق مختلفة وثلاث بوليمرات كما يلى:

- طريقة اضافة سائل غير مذيب وذلك باستخدام ايدراجيت (رس ١٠٠).
- طريقة تغيير الحرارة وذلك باستخدام ايثيل السليولوز.
- طريقة اضافة الملح وذلك باستخدام الجينات الصوديوم.

وقد تم ايضا دراسة الصفات الطبيعية وكذا صفات الاتاحة للحويصلات المحضرة وقد أظهرت النتائج أن حويصلات النيتروفيورانتوين المحضرة لها معدل اتاحة بطىء فى محلول ذى أس هيدروجينى ١,١٢ وذلك مقارنة بالدواء غير المعامل وكذلك أظهرت حويصلات الايدراجيت معدل اتاحة اسرع نسبيا عن مثيلاتها فى حالة حويصلات الجينات الصوديوم او ايثيل السليولوز اما فيما يتعلق بميكانيكية الاتاحة فقد وجد ان معادلة باكرولونسدال هى اكثر النظم مطابقة لوصف اتاحة العقار من الحويصلات المحضرة باستخدام ايثيل السليولوز أو الجينات الصوديوم.

ومن ناحية أخرى فقد وجد أن معادلة الدرجة الأولى اكثر مناسبة لوصف ميكانيكية الاتاحة فى حالة الحويصلات المحضرة باستخدام الايدراجيت.

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