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Optimization of controlled drug release through interfacial polymerization

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Summary

Interfacial nylon polymerization was chosen from the different in situ polymerization techniques to assess its utilization for controlled release medication. Sulfadiazine sodium was selected for such investigation, and several polymerization factors were altered during the technique stated. The pharmaceutical properties of the resulting products were used to evaluate the factor under consideration. The total product yield, as well as the product flowability were decidedly superior in the presence of either cross-linked gelatin or calcium alginate as aqueous phase modifiers during polymerization. Particle size was shown to increase depending upon the type and concentration of the included modifier. Scanning electron micrographs have confirmed morphologically the porous nature of the polymer coat. The latter displayed some pronounced effects on the first-order medicament dissolution kinetics.

Introduction

Interfacial polymerization is one of the most feasible and convenient methods of in situ polymerization techniques utilized for controlled release medication. The technology of the polyamides (nylons) polycondensation has grown considerably in

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recent years and a number of variations have been reported (Florence and Jenkins, 1973, 1975; Watanabe and Hayashi, 1975; Madan, 1978). Since a number of different nylons can be formed, an excellent array of possibilities seems to exist for the microencapsulation of pharmaceuticals by this technique (Luzzi et al., 1970; McGinity et al., 1975, 1981; Kassem et al., 1985). Most of the cited literature dealing with the nylon in situ microencapsulation is restricted to the techniques adopted for its preparation. Further investigations into the pharmaceutical application of such products to optimize their utilization in sustained release medication were deemed necessary.

Experimental

Materials and methods

Sulfadiazine sodium (Sigma Chemicals), hexamethylenediamine and sebacoyl chloride (Eastman Organic Chemicals), Arlacel A (Atlas Chemical Industries), cyclohexane and chloroform (pure grades).

Scanning electron microscope (Hitachi 450, Japan), and optical microscope (Karl Zeiss) were used.

Using sulfadiazine sodium as model drug, drug-loaded nylon microcapsules were prepared. Different concentrations of either cross-linked gelatin or calcium alginate were utilized as aqueous phase modifiers. Both the plain drug–nylon microcapsules as well as those containing the aqueous phase modifiers were pharmaceutically investigated.

Preparation of sulfadiazine sodium–nylon microcapsules

Two grams of sulfadiazine sodium were mixed with 8 ml of 0.4 M hexamethylenediamine in 0.4 M aqueous solution of sodium carbonate in an Erlenmeyer flask stirring at 300 rpm on a magnetic stirrer. To the clear aqueous solution, 60 ml of 1% solution of Arlacel A in a 4 : 1 mixture of cyclohexane and chloroform was added and emulsified by further stirring for 1 min. Immediately thereafter, 100 ml of a 0.76% solution of sebacoyl chloride in cyclohexane/chloroform mixture was added, the stirring rate was rapidly raised to 1200 rpm for 1 min, then lowered to 300 rpm again for 3 min. The organic phase was then supplemented by a fresh solvent mixture, and the microcapsules formed were allowed to settle. The supernatant liquid was decanted and the microcapsules were washed twice, each with 50 ml of the organic solvent mixture, and left to dry in a desiccator over phosphorous pentoxide.

Two aqueous phase modifiers, namely cross-linked gelatin and calcium alginate were chosen in this study. The formalization of gelatin was conducted for 2, 8, 16, 24 and 48 h. Accordingly five products containing 5, 10, 15, 20 and 25% gelatin were prepared for investigation. For practical purposes, only three microencapsulated products containing 5, 10 and 15% calcium alginate were prepared.

Products containing different concentrations of gelatin were prepared by dissolving the specified concentration of gelatin in the aqueous phase before homogeniza-

tion of drug, and the process was continued as usual. Formalization of gelatin was affected by adding 2 ml of 37% formaldehyde solution to the polymerization medium just after polymerization was completed, stirring for 5 min, and then allowing the system to stand in the refrigerator for the specified time. Collection of the product, its washing, and its drying processes were carried out as previously mentioned.

Products containing, as modifier, calcium alginate were prepared by adding in the polymerization formula the indicated weight of sodium alginate, and the polymerization procedure was conducted as usual. Before the final collection of the microcapsular product, about two-thirds of the organic phase was decanted. To the remaining portion, containing the product, 1 ml of a saturated aqueous solution of calcium chloride was added and the mixture stirred at a low speed for about 1 min. The slurry of the microcapsules was frozen using a dry-ice/acetone mixture after which the product was freeze-dried overnight.

Investigation of the sulfadiazine sodium microcapsules

(a) Electron microscopic scanning. The microcapsules were fixed to a metallic plate by spraying the powdered product on a very thin adhesive layer attached to the metallic slide. The samples were coated with carbon-gold layers (about 50 nm thick) under vacuum before they were photomicrographed.

(b) Total yield. The microcapsular product was weighed accurately on successive days of standing in the open air until constant weight had been attained.

(c) Available medicament content. An accurately weighed 0.1 g of the dry microcapsules was transferred with the aid of 75 ml of phosphate buffer pH 7.2, into a 250 ml glass stoppered Erlenmeyer flask. The contents of the flask were left to stand for 24 h at 37°C with occasional shaking. The product was filtered off and washed with sufficient buffer solution into a 100-ml measuring flask, and then completed to volume with the same buffer. The sulfadiazine content of the solution was determined spectrophotometrically against a blank simultaneously prepared using plain polymerized nylon microcapsules.

(d) Flowability. The angle of repose (Harwood and Pilpel, 1968) was determined and was taken as a measure of flowability of the microcapsules, as well as the powdered drug. A clean dry funnel with a horizontally cut stem end was supported on a stand so that the horizontal end of its stem was held exactly 2 cm above graph paper. The drug microcapsules were gradually and continuously allowed to flow through the funnel stem thus forming a continuously growing heap over the graph paper below the funnel. The end point is attained when the apex of the heap just touches the lower end of the funnel stem. The coefficient of friction was computed, as tan θ, through the mean diameter of the powdered heap base.

(e) Particle size analysis. Optical microscopy was employed to determine the horizontal diameter of component particles, which ranged between 100 and 150 particles for each sample.

(f) In vitro dissolution. The in vitro release of the drug from the microcapsules was studied by the beaker method, in both 0.1 N HCl and phosphate buffer of pH 7.2. To avoid the effect of variation of the surface area exposed to the dissolution

media, specific microcapsule size range of the prepared products was utilized for the dissolution experiments, viz. 100–400 μm.

To 1000 ml of the dissolution medium in a beaker, maintained at 37°C, 500 mg of the medicated microcapsules were added. The system was magnetically stirred at a rate of 100 rpm. Aliquot samples were withdrawn at fixed time intervals for analysis. The samples withdrawn were replaced by the same volume of dissolution fluid. Total drug content was measured from the 24-h sample analysis. Dissolution results were computed from spectrophotometric calibration curve of the drug in the respective dissolution media (Stober and De Witte, 1982).

Results and Discussion

In our laboratory, extensive work has been carried out to utilize the nylon interfacial polymerization technique for the preparation of microcapsules of certain drugs (Mahmoud, 1983). Due to certain homogeneity and stability problems, this technique proved to be practically more valuable for the microencapsulation of weakly acidic drugs. Hence, sulfadiazine sodium was chosen, as a model drug, to study nylon interfacial microencapsulation, and to investigate the technique and conditions for optimal controlled release medication. In this study, 9 formulations were tried, namely sulfadiazine sodium microcapsules prepared by plain nylon interfacial polymerization, in addition to 5 products containing increasing concentrations of formalized gelatin, viz. 5, 10, 15, 20 and 25%, as well as three products containing 5, 10 and 15% of calcium alginate. Despite the high gelatin concentrations, the aqueous gels produced remained fluidy and emulsifiable due to the high alkalinity of the medium. Higher concentrations of sodium alginate were too viscous to be emulsified and displayed many difficulties during microencapsulation procedure.

Regarding those products containing formalized gelatin, as an aqueous phase modifier, the effect of cross-linking time (2, 8, 16, 24 and 48 h) was investigated using the microcapsules containing 5% gelatin. The products were subjected to dissolution measurements and the computed first-order dissolution rate constants in the sequence stated were found to be 0.0823, 0.0361, 0.0146, 0.0139 and 0.0141 min^{-1} in acid medium, and 0.0911, 0.0608, 0.0555, 0.0503 and 0.0493 min^{-1} in phosphate buffer. It is apparent that formalization of the products for 16 h was feasible, hence exposure of the products to longer cross-linking has little value and would lead to loss of drug stability. Accordingly, the effect of the aqueous phase modifier concentration was followed after 16 h formalization.

Free flowable, nearly spherical homogeneous products were obtained in each of the microencapsulation procedures adopted. The scanning electron micrographs in Fig. 1 show in different magnifications the microcapsules prepared using 10% cross-linked gelatin. It is apparent that the microcapsules are generally spherical with corrugated surfaces (Fig. 1A, B and C). Such corrugations were mainly formed during the drying stage, a finding which could be verified during the dissolution study, where the empty microcapsules could be finally detected as intact spherical

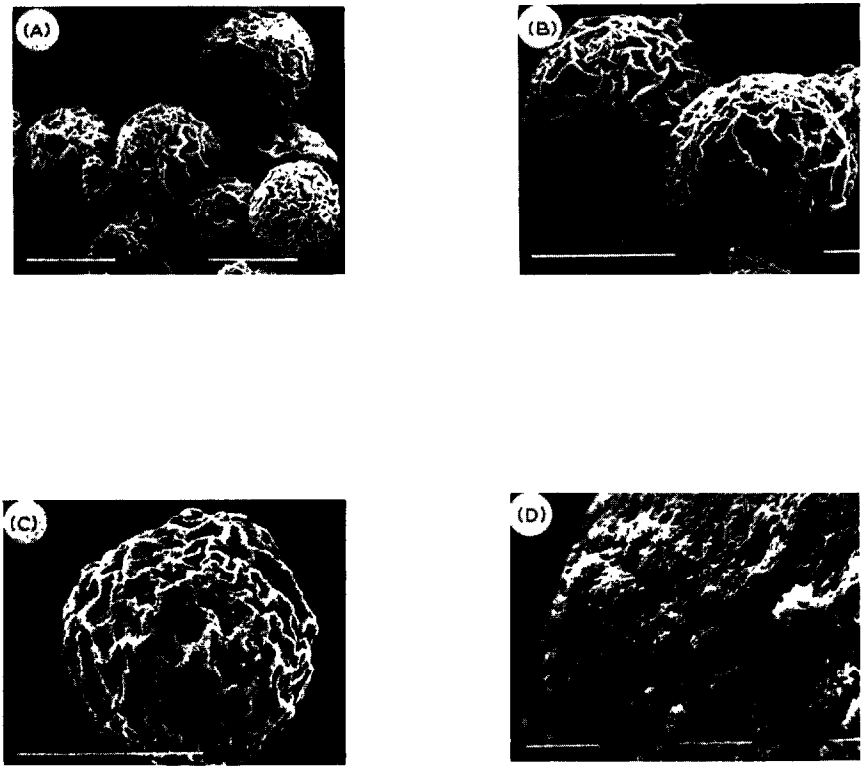

Fig. 1. Scanning electron micrographs of nylon microcapsules of sulfadiazine containing 10% cross-linked gelatin. ×125 (A), ×300 (B), ×625 (C) and ×2500 (D).

bubbles. Higher magnification of the microcapsules containing cross-linked gelatin (Fig. 1D) illustrated the highly irregular rough surface with rare minute drug particles and fine surface pores. Fig. 2 shows the almost spherical and clearly porous microcapsules containing 10% calcium alginate. Its higher magnification clearly showed the well-defined porosity and the thick and sharp edge threading around these pores.

Total yield determinations (Table 1) revealed that the inclusion of formalized gelatin resulted in decreasing drug content, over that recorded in the plain drug–nylon product, with higher modifier content. In relation to the theoretically expected yield, the plain drug–nylon microcapsules showed a yield loss of 10.34% which decreased to 5.76% in presence of 5% formalized gelatin. The total yield loss increased gradually by increasing aqueous phase modifier up to 20.20% loss at 25% gelatin concentration. In the presence of calcium alginate, the total yield displayed higher yield loss in comparison to the respective gelatin concentration (Table 1). The recorded total yield loss in presence of either of the two modifiers was presumably due to part of the modifier escaping collection into the product, but adhering instead, to the polymerization vessel. Such an adherance property, which appeared

TABLE 1

TOTAL YIELDS, AVAILABLE DRUG CONTENT, FLOWABILITY DATA AND PARTICLE SIZE MEASUREMENTS OF SULFADIAZINE SODIUM MICROCAPSULES PREPARED BY DIFFERENT FORMULATIONS

Item	Nylon microcapsules	Nylon microcapsules containing:							
		Gelatin					Calcium alginate		
		5%	10%	15%	20%	25%	5%	10%	15%
Total yield (g)	2.60	3.11	3.41	3.68	3.85	3.91	2.76	3.04	3.24
Yield loss (%)	10.34	5.76	7.84	10.24	14.44	20.20	16.36	17.84	20.97
Available drug content (%)	57.00	35.00	31.93	28.24	26.00	23.00	28.90	25.50	22.80
Drug loss (%)	17.34	42.54	40.52	42.11	41.49	43.65	52.31	52.83	53.26
Coeff. of friction ($\tan\theta$)	0.532	0.589	0.615	0.625	0.612	0.585	0.761	0.795	0.814
Angle of repose (θ)	28.01	30.50	31.59	32.00	31.47	30.33	37.27	38.48	39.14
Mean particle size (μm)	96.2	102.0	140.0	177.6	236.8	323.6	211.2	276.0	356.6
$\pm$S.D.	28.62	31.05	32.03	31.82	30.58	31.96	24.02	27.42	27.58

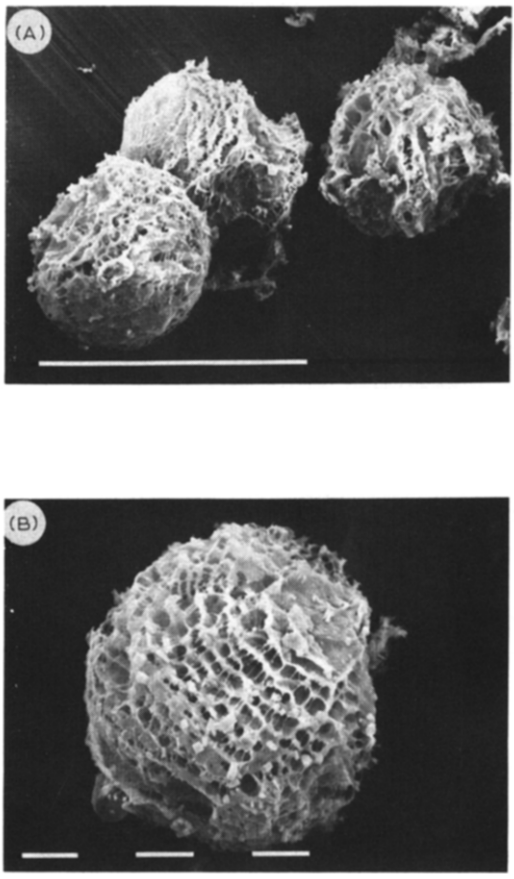

Fig. 2. Scanning electron micrographs of nylon microcapsules of sulfadiazine containing 10% calcium alginate. ×65 (A), and ×125 (B).

to be more appreciable at higher modifier content, was shown to affect the available medicament content in a similar pattern (Table 1). Parallel computation showed 17.34% loss in available medicament content in sulfadiazine sodium–nylon microcapsules, while the loss was around 42% in all products containing different gelatin concentrations. Drug microcapsules containing different calcium alginate concentrations showed nearly the same available medicament loss, namely around 53% (Table 1).

Flowability determinations have proved that any of the nylon microcapsular products has a better flowability than the pure uncoated sulfadiazine powder (Table 1). Drug–nylon microcapsule powder possessed the best flowability, illustrated by the lowest value of the angle of repose. Inclusion of different concentrations of formalized gelatin induced slight irregular decreases of flowability irrespective of the aqueous phase modifier concentration. Microcapsules containing calcium alginate

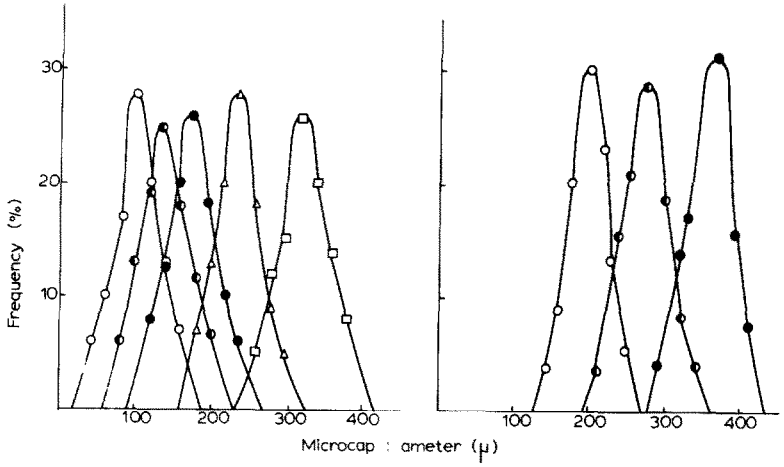

Fig. 3. Particle size distribution of nylon microcapsules of sulfadiazine containing cross-linked gelatin (A), and calcium alginate (B) as aqueous phase modifiers. ○——○, 5%; ◐——◐, 10%; ●——●, 15%; △——△, 20%, □——□, 25%.

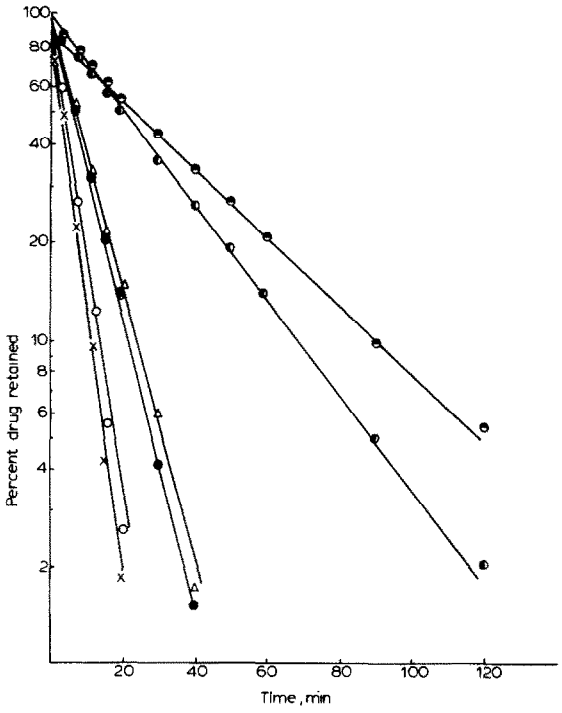

Fig. 4. First-order plot of sulfadiazine sodium dissolution in 0.1 N HCl at 37°C by the beaker method from nylon microcapsules containing different concentrations of cross-linked gelatin. ×——×, 0%; ○——○, 5%; ◐——◐, 10%; ◓——◓, 15%; ●——●, 20%; △——△, 25%.

acquired lower flowability than that of plain nylon product, but still slightly better than that of powdered drug.

The results of particle size analysis are demonstrated in Fig. 3, where the mean particle size values are apparent in Table 1. It is obvious that each product comprised particles of normal frequency distribution within limited particle size range. The mean particle size diameter of the plain drug–nylon microcapsules was estimated to be 96.2 μm in a range of 100 μm wide. The inclusion of gelatin, as an aqueous phase modifier, in different concentrations produced an increase in the mean microcapsule diameter with increasing gelatin concentration. Within the products containing calcium alginate, a 5% rise in concentration induced a particle size increase between 65 and 80 μm (Fig. 1B and Table 1).

Sulfadiazine sodium dissolution from nylon microencapsulation products was followed, and the overall order of their kinetic behaviour was determined by the least-squares method. The C.V.% values computed according to zero- and first-order and the square-root of time patterns were found to be 18.67, 3.76 and 11.39, respectively. From these values, it is evident that the drug dissolution has followed first-order patterns in both 0.1 N HCl, and phosphate buffer of pH 7.2 dissolution media.

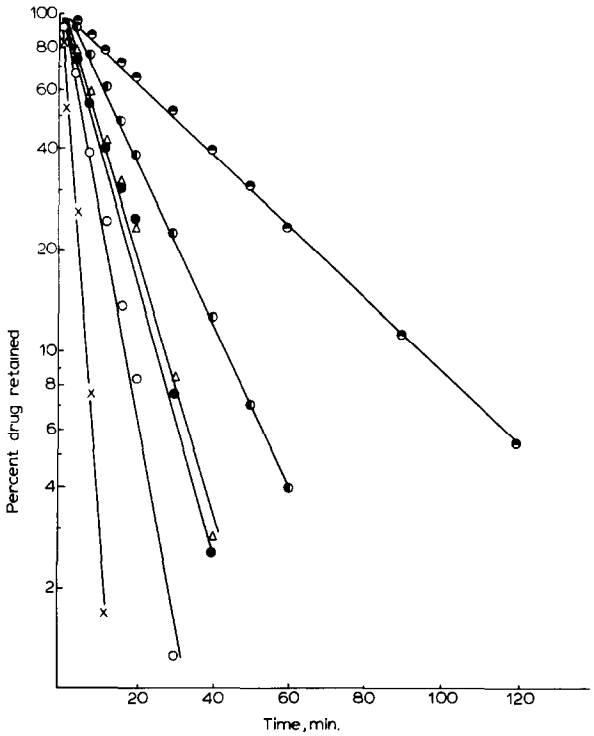

Fig. 5. First-order plot of sulfadiazine sodium dissolution in phosphate buffer of pH 7.2 at 37°C by the beaker method from its nylon microcapsules containing different concentrations of cross-linked gelatin. Key as in Fig. 4.

TABLE 2

KINETIC AND STATISTICAL DATA PERTINENT TO THE PERCENTAGE RETAINED DISSOLUTION OF SULFADIAZINE SODIUM FROM ITS MICROCAPSULES CONTAINING DIFFERENT ADDITIVES

pH		Nylon microcapsules	Nylon microcapsules containing:							
			Gelatin					Calcium alginate		
			5%	10%	15%	20%	25%	5%	10%	15%
1.2	Y-intercept (a)	2.054	2.097	2.016	1.898	2.069	2.078	1.944	2.048	1.879
	Slope $\times 10^3$ (b)	89.27	84.09	14.59	10.69	45.86	47.58	31.10	23.43	16.22
	$-K \times 10^3$ (min^{-1})	205.59	193.66	33.60	24.62	105.61	109.58	71.62	53.96	37.35
	$t_{50\%}$ (min)	3.37	3.58	20.62	28.15	6.56	6.32	9.68	12.84	18.55
7.2	Y-intercept (a)	2.007	2.032	2.067	2.024	2.106	2.105	1.884	1.941	1.965
	Slope $\times 10^3$ (b)	148.77	55.51	24.38	10.74	41.23	42.69	14.10	8.61	7.64
	$-K \times 10^3$ (min^{-1})	342.62	127.84	56.15	24.73	94.95	98.31	32.47	19.83	17.59
	$t_{50\%}$ (min)	2.02	5.42	12.34	28.02	7.30	7.05	21.34	34.95	39.40

Relative to the pure medicament (100% dissolution was attained in 2 min), all the microencapsulated products have shown retarded first-order dissolutions in both media, but to variable extents, as may be seen in Figs. 4 and 5. It is obvious that drug dissolution in both media was delayed in relation to formalized gelatin concentration up to 15%, then began to increase gradually with increasing aqueous phase modifier concentration. Such a striking phenomenon could be attributed to increasing pore size in the nylon network of the microcapsules, in addition to the high channelling effect of gelatin in phosphate buffer. However, expansion of the formalized gelatin bodies inside the microcapsules may exert an expansion in the nylon membrane leading to higher drug release through such expanded surface, especially at higher gelatin concentrations. It is of interest also to note that the dissolution rates of sulfadiazine sodium, from its microcapsules containing formalized gelatin, were higher in acid medium than in alkaline phosphate buffer. Such an anomalous behaviour, which had been stated before (McGinity et al., 1975; Mahmoud, 1983), was attributed to the assumption that an inter-cross-linking between gelatin and the nylon network had occurred. Such bonding may not be sensitive to the action of higher pH as the normal intra-cross-linked gelatin. The

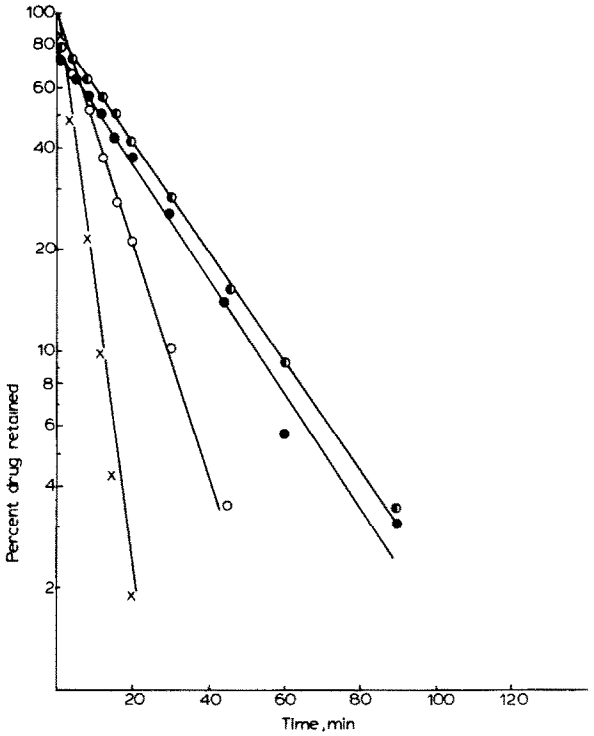

Fig. 6. First-order plot of sulfadiazine sodium dissolution in 0.1 N HCl at 37°C by the beaker method from its nylon microcapsules containing different concentrations of calcium alginate, × ——— ×, 0%; ○ ——— ○, 5%; ◐ ——— ◐, 10%; ● ——— ●, 15%.

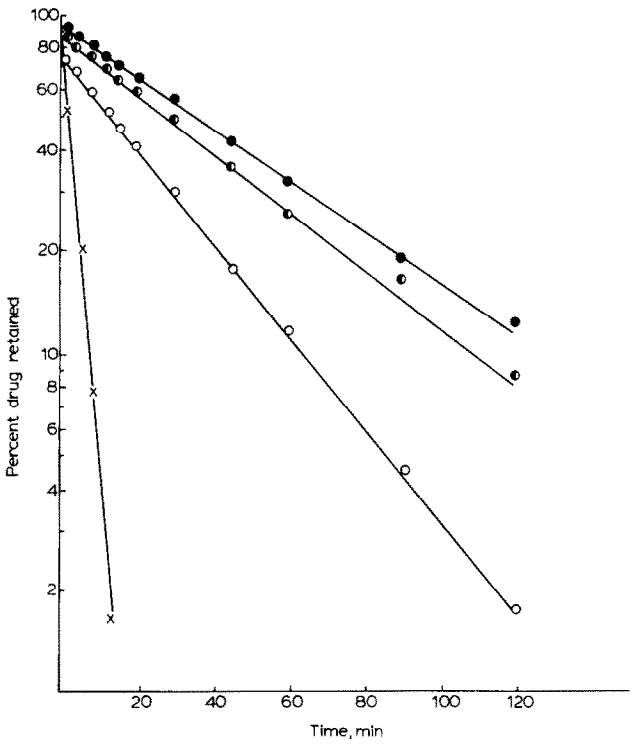

Fig. 7. First-order plot of sulfadiazine sodium dissolution in phosphate buffer of pH 7.2 at 37°C by the beaker method from its nylon microcapsules containing different concentrations of calcium alginate. Key as in Fig. 6.

statistical and kinetic data shown in Table 2 illustrate a parallel diminuation between the stated discussion and the first-order dissolution rate constants as well as the $t_{50\%}$ values computed.

Although calcium alginate-containing microcapsules showed irregular-sized particles with well-defined porosities, they displayed more delayed drug dissolution, in comparison to those containing gelatin (Figs. 6 and 7). It is again apparent that the drug dissolution in alkaline phosphate buffer was comparatively slower than that in acid medium. In 0.1 N HCl, drug microcapsules containing 10% calcium alginate showed the slowest dissolution pattern. Although drug product containing the higher calcium alginate concentration had the lower dissolution rate constant (Table 2), its dissolution data showed a high initial drug flux during the first 2 min. Such a finding may be attributed to larger porosity or to cracking which might have happened during freeze-drying due to high bulk content. This behaviour was not observed in the alkaline phosphate buffer dissolution data; nevertheless, very slight differences between the dissolution rate constants of products containing 10 and 15% calcium alginate had been seen.

In conclusion, sulfadiazine sodium–nylon microcapsules, with controlled particle

size range, could be prepared. Controlled dissolution of the drug from such products is determined by the concentrations of either of the aqueous phase modifiers used. Optimal concentrations of these were found to be 15% formalized gelatin or 10% calcium alginate.

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References

Florence, A.T. and Jenkins, A.W., In vitro assessment of microencapsulated drug systems and sustained released parenteral drug forms. In Nixon, J. (Ed.), Microencapsulation, Marcel Dekker, 1975, pp. 39–56.

Florence, A.T. and Jenkins, A.W., Scanning electron microscopy of nylon microcapsules. J. Pharm. Pharmacol., 25 (1973) 57–61.

Harwood, C.F. and Pilpel, N., Granulation of griseofulvin.. J. Pharm. Sci., 57 (1968) 478–481.

Kassem, A.A., Rohdewald, P., El-Samaligy, M.S., El-Miligi, M.F. and Mahmoud, H.A., Application of in-situ interfacial polymerization for the preparation of hydrochlorothiazide microcapsules. Bull. Fac. Pharm. Cairo Univ. (1985) in press.

Luzzi, L.A., Zoglio, M.A. and Maulding, H.V., Preparation and evaluation of prolonged release properties of nylon microcapsules. J. Pharm. Sci., 59 (1970) 338–341.

Madan, P., Microencapsulation. II. Interfacial reactions. Drug Dev. Ind. Pharm., 4 ((1978) 289–304.

Mahmoud, H.A., Application of In-Situ Polymerization Techniques in Pharmaceutical Formulation, Ph.D. Thesis, Faculty of Pharmacy, Cairo University, 1983, pp. 68–149.

McGinity, J.W., Martin, A.N., Cuff, G.W. and Combs, A.B., Influence of matrixes on nylon encapsulated pharmaceuticals. J. Pharm. Sci., 64 (1975) 889–890.

McGinity, J.W., Combs, A.B. and Martin, A.N., Improved method for microencapsulation of soluble pharmaceuticals. J. Pharm. Sci., 70 (1981) 372–375.

Stober, H. and De Witte, W., Sulfadiazine. Anal. Profiles of Drug Subs., 11 (1982) 523–551.

Watanabe, A. and Hayashi, T., Microencapsulation techniques of Fuji Photo Film Co. Ltd. and their applications. In Nixon, J., (Ed.), Microencapsulation, Marcel Dekker, 1975, pp. 13–38.