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Research Papers

Microencapsulation by ethylcellulose phase separation : microcapsule characteristics

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Summary

Microcapsules of metronidazole can be prepared for controlled drug release, prolonged dosage forms are obtained and 70–80% of metronidazole is released after 3 h. A linear relationship can be fitted with the square-root of time, and release is matrix type for all the different microcapsules obtained with various processes. Release is generally modified by increasing the stirring rate during the preparation and the addition of polyisobutylene, the modification of dissolution parameters may sometimes be attributed to a higher percentage of smaller microcapsules and at other times to a higher percentage of free drug. For prolonged dosage forms, matrix type microcapsules are interesting but their preparation must be controlled to keep release characteristics constant.

Introduction

Microencapsulation is actually used to modify and retard drug release. Many different coating materials and processes can be used. A procedure involving ethylcellulose coating by phase separation was described by Miller et al. (1967) and Jalsenjak et al. (1976), and used in several works. Most of them note that modifications in the method of preparation influences the microcapsule characteristics.

For some authors, microcapsules are aggregates of small microcapsules (Deasy et al, 1980; Oya Alpar and Walters, 1981) and the stirring rate modifies the size distribution. For others, the addition of a protective colloid such as polyisobutylene (Benita and Donbrow, 1977) or polyethylene (John et al., 1979) allows the formation of individual microcapsules with a thin coating of ethylcellulose. Regarding the characteristics studied, dissolution properties were observed on separated fractions but not on the whole batch and so it was not easy to correlate with the method of preparation. That is why we now tried to observe some parameters influencing the microencapsulation by ethylcellulose phase separation.

This paper reports the preparation of Metronidazole [1] microcapsules at different core:

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[1] Metronidazole, Laboratoire Specia.

wall ratios and attempts to observe the influence of the method of preparation (modification of stirring rate, use of polyisobutylene, modification of particle size of metronidazole) upon microcapsule size distribution, metronidazole contents and dissolution parameters.

Materials and Methods

Materials

Metronidazole[2] (1H-imidazole, 1-ethanol-2-methyl-5-nitro-), micronized (3 μm) and crystallized (200 μm).

Ethylcellulose [3], type N (ethoxy content 47.5–49%), viscosity 95 mPa (5% w/w solution in toluene–ethanol 80 : 20).

Polyisobutylene [4], molecular weight 400,000.

Cyclohexane, pure grade.

Methods

Preparation of microcapsules

The method was developed from that described by Jalsenjak et al. (1976). The coating vessel used had a 1 litre capacity fitted with a four-port cover. Through the center port was adjusted a 3-blade glass stirrer connected to the chuck of a variable speed motor. The other ports were used to insert a reflux condenser, a thermometer, and an entry point. The lower part of the vessel was immersed in a water bath.

To prepare a batch, 300 ml of cyclohexane was introduced into the vessel, heated at 50°C, ethylcellulose was added, and the temperature was raised to 70°C during 30 min; the metronidazole was added and the temperature was held at 80°C for 1 h. The system was allowed to cool at 40°C, maintaining it for 1 h between 50°C and 40°C and then cooled rapidly to 20°C. Microcapsules were separated by decantation, washed twice with cold cyclohexane (10°C), filtered off on paper, calibrated on a 1250 μm sieve before drying in air overnight. Four processes were used: process A (stirring rate 400 rpm); process B (stirring rate 700 rpm); process C (stirring rate 400 rpm, 7% polyisobutylene); and process D (same as C crystallized metronidazole instead of micronized).

TABLE 1

QUANTITIES USED FOR 100 ml OF CYCLOHEXANE

Core : wall ratio	Metronidazole (g)	Ethylcellulose (g)
2 : 1	6	3
4 : 3	4	3
1 : 1	3	3

Quantities of metronidazole and ethylcellulose used varied depending on the core : wall ratio required (Table 1).

Size distribution of microcapsules

The various batches were fractioned into three particle size ranges using 1250 μm, 800 μm and 315 μm sieves on a moving sieve shaker for 5 min.

Determination of microcapsule contents

To determine the total drug content in microcapsules, 200 mg were dissolved in 50 ml of chloroform, these samples were diluted and assayed spectrophotometrically at 317 nm. To determine the microcapsule free drug content, the quantities dissolved after 5 min in dissolution studies were considered as the free metronidazole.

Dissolution studies

250 mg of microcapsules were introduced in a French Pharmacopeia dissolution paddle assembly containing 1 litre of water adjusted to pH 1.2 at 37 ± 1°C, stirring rate was standardized at 100 rpm. At periodic intervals (5, 10, 15, 30, 45, 60, 120 and 180 min), 2 ml were removed, filtered (0.22 μm Millipore membrane), diluted and assayed at 317 nm.

Results and Discussion

The microcapsules are irregularly shaped. They are aggregates of small ones, about 2 at 10 μm for the processes A and B (Photo 1) and they consist

[2] Société Specia.

[3] Hercules.

[4] B.A.S.F. Oppanol B 50.

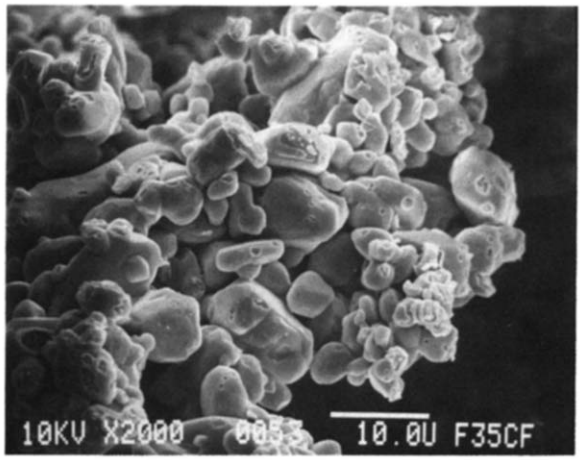

Photo 1. ×2000.

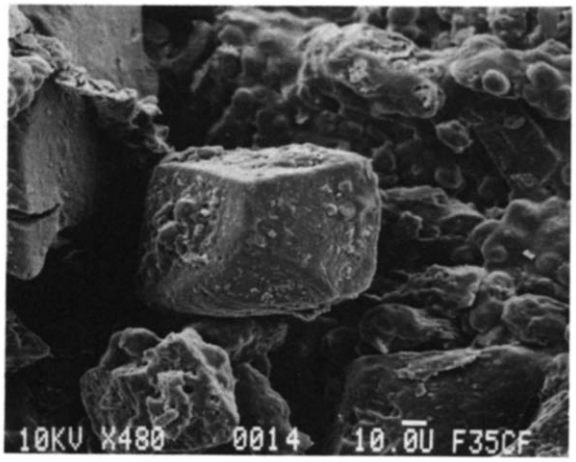

Photo 2. ×480.

of an ethylcellulose coating around metronidazole particles for the crystallized product (Photo 2).

The sieving analysis results obtained from the mean of two batches show the influence of different parameters on microcapsule size distribution. With every process used, size distribution depends on the core : wall ratio (Table 2), higher percentages of large microcapsules (> 800 μm) and lower percentages of small microcapsules (< 315 μm) are observed when it decreases, but this observation does not agree for microcapsules obtained with process B. With processes A, C and D for the 2 : 1 and 4 : 3 core : wall ratios, there is enough ethylcellulose in the medium preparation for the microencapsulation of drug particles, but with the 1 : 1 core : wall ratio even if drug particles are coated with ethylcellulose coacervates, more microcapsules remain attached to one another by linkages due to the quantity of ethylcellulose present which is more important for the quantity of drug particles.

The stirring rate during microcapsule preparation influences their size distribution, and if we compare with process A, a higher speed (process B) gives less aggregates; we noted lower percentages of larger microcapsules and higher percentages of smaller microcapsules at a higher stirring rate as Jalsenjak et al. (1976) and Deasy et al. (1980) observed. But this observation depends on the core : wall ratio and it is more evident for the 1 : 1 core : wall ratio. With the 1 : 1 core : wall ratio, the same quantity of ethylcellulose is solubilized in the preparation medium for a lower quantity of drug particles but by increasing the stirring rate, a

TABLE 2

SIZE DISTRIBUTION OF MICROCAPSULES OBTAINED BY DIFFERENT PROCESSES

Size range (μm)	% sieve fraction for a given core : wall ratio											
	2 : 1				4 : 3				1 : 1			
	A	B	C	D	A	B	C	D	A	B	C	D
1 250 > x > 800	21.8	19.3	17.0	13.7	22.8	18	20.5	14.8	25.5	14.5	29.0	23.7
800 > x > 315	65.9	69.7	53.5	52.5	68.9	68	50.5	56.3	68.5	74.0	54.6	55.2
< 315	12.3	11.0	29.5	33.7	8.53	14	29.0	28.6	6.0	11.5	15.4	21.0

better deposit of the coacervates results and prevents the bridging of microcapsules.

The use of polyisobutylene (7%) increases the percentages of small microcapsules much more than the modification of stirring rate. But, they are still aggregates of small ones and they are matrix type microcapsules. The addition of 7% of polyisobutylene does not allow the production of individual microcapsules, film type, as Benita and Donbrow (1982a) obtained with 9% of the same product. For us, the percentage of polyisobutylene in the preparation medium was limited by the high viscosity produced by polyisobutylene and the impossibility to collect the whole batch.

Nixon and Agyilirah (1982) have used polyisobutylene of a lower molecular weight (1000) and noted that polyisobutylene affects the size distribution of microcapsules which are still matrix type. They noted that the addition of polyisobutylene led to an increase in the microcapsule size for the high core : wall ratios (3 : 1 and 1 : 1), while in our study, we observed more smaller microcapsules at high core : wall ratios, 2 : 1 and 4 : 3 than at 1 : 1. This may be explained by the high viscosity of the polyisobutylene used in our work. For the high core : wall ratios, the viscosity of the preparation medium may prevent the empty coacervates or the swollen ethylcellulose to interact with microcapsules and to give larger aggregates.

When we compare microcapsules prepared with polyisobutylene in preparation medium, we noted that the modification of particle size of metronidazole (process D) does not influence microcapsule size distribution. The same observation was noted by Jalsenjack et al. (1980) with drug particles of 62.5 μm and 282.5 μm.

Drug contents

Microcapsule contents, total drug contents and free drug contents are compared in Table 3. The total drug content is essentially the same for the different processes, and the free drug content does not really depend on the core : wall ratio, but on the process followed during the microcapsule preparation. When a higher stirring rate is used during microcapsule preparation, more free drug is noted for the 2 : 1 core : wall ratio and we observed no modification for the other ratios. The same remark can be made when polyisobutylene is added during preparation; more free drug is recovered only for the 2 : 1 core : wall ratio. The higher quantity of free drug with the 2 : 1 core : wall ratio may be attributed to an ethylcellulose quantity being too low to ensure complete microencapsulation when stirring rate is increased and when polyisobutylene is added, this decreases the ethylcellulose solubility.

When crystallized metronidazole is used instead of the micronized form, high percentages of free drug are observed for all the different core : wall ratios. Benita and Donbrow (1982b) noted more free drug too, with microcapsules film type when particle size of the drug is increased.

Dissolution studies

Studies of in vitro dissolution allow a comparison to be made between the different microcapsules prepared with the various core : wall ratios

TABLE 3

MICROCAPSULES DRUG CONTENTS

Quantities for 100 mg of microcapsules	core : wall ratios											
	2 : 1				4 : 3				1 : 1			
	A	B	C	D	A	B	C	D	A	B	C	D
Theoretical total drug content	66.6	66.6	66.6	66.6	57.1	57.1	57.1	57.1	50.0	50.0	50.0	50.0
Recovery total drug content	66.0	67.3	67.0	70.0	58.0	57.2	57.0	63.4	51.7	50.0	51.4	55.0
Free drug content	9.8	16.6	24.8	26.8	13.3	15.8	14.9	27.8	12.9	11.7	14.8	25.9

TABLE 4

RESULTS OF IN VITRO DISSOLUTION FROM MICROCAPSULES OBTAINED BY DIFFERENT PROCESSES

	core : wall ratios											
	2 : 1				4 : 3				1 : 1			
	A	B	C	D	A	B	C	D	A	B	C	D
Percentage of drug released after 3 h	73	82	80	78.1	76	78	78.5	75.7	73	82	75	70
Efficiency of dissolution	0.565	0.582	0.652	0.663	0.581	0.603	0.597	0.613	0.519	0.556	0.536	0.562
$T_{50\%}$ (min)	45	45	30	30	45	35	35	30	70	60	60	45

and the various processes. For each sample, we noted percentages of drug released during 3 h, efficiencies of dissolution, time for 50% drug released and dissolution rates (Tables 4 and 5).

For all microcapsules, release occurs by a diffusion controlled process as described by Higuchi (1963) for the release of drug from insoluble porous matrices. Release profiles are described by the linear square-root of time dependance. Just as Jalsensak et al. (1976, 1980), Oya Alpar and Walters (1981) and Öner et al. (1983), we find that the Higuchi equation is a good fitting equation to define the release from ethylcellulose microcapsules. The linear relationship can be observed (Figs. 1–3) during 60 min or 45 min (process B), then the release becomes slower but stays linear. For the 1 : 1 core : wall ratios, the first linear relationship is noted during 2 h (process A) or 3 h (process B).

The drug dissolution from microcapsules depends on the core : wall ratio, the efficiencies of dissolution and dissolution rates decrease when the core : wall ratio decreases and with processes C and D we can note a linear relationship between total drug recovered in microcapsules and efficiencies of dissolution (Figs. 4 and 5).

If we compare dissolution parameters of microcapsules prepared with different stirring rates, we observe higher dissolutions with process B. This can be attributed to a higher percentage of smaller microcapsules and to a higher percentage of free drug content; but it also depends on the core : wall ratio considered. For the 2 : 1 core : wall ratio, there is more free drug and for the 1 : 1 core : wall ratio, there are more smaller microcapsules.

TABLE 5

VALUES OF SLOPES AND INTERCEPTS FROM PLOTS OF PERCENTAGE OF DRUG RELEASED VERSUS $(TIME)^{1/2}$
KEY: A = FIRST FITTING; B = SECOND FITTING

		core : wall ratios											
		2 : 1				4 : 3				1 : 1			
		A	B	C	D	A	B	C	D	A	B	C	D
A	Slope	8.0	8.4	6.5	4.6	8.9	7.6	8.7	5.5	6.8 *	5.7 **	6.2	5.0
	Intercept	−6.0	−5.6	+15.8	+28.0	−8.4	+4.5	+4.2	+20.0	−6.5	+0.7	+2.7	+18.8
	r^2	0.999	0.997	0.986	0.987	0.998	0.998	0.987	0.997	0.989	0.997	0.996	0.990
B	Slope	3.2	4.6	2.39	2.31	2.9	3.3	2.8	2.2			3.9	2.2
	Intercept	+32	+20	+48	+46	+37	+33	+39	+45			+21.5	+40
	r^2	0.998	0.997	0.967	0.987	0.987	0.993	0.991	0.998			0.996	0.998

* Over 2 h.
** Over 3 h.

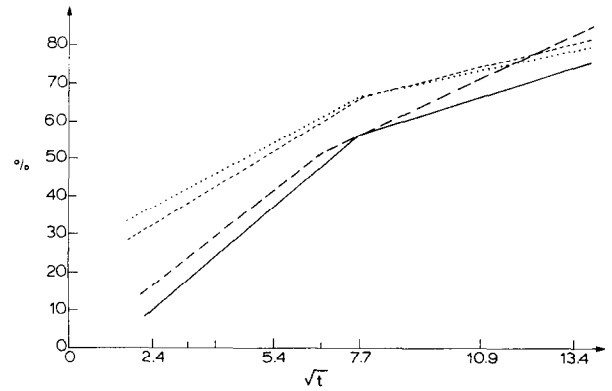

Fig. 1. Percentages of drug released against (time)$^{1/2}$, core : wall ratio of 2 : 1. Key: process A, ———; process B, — — —; process C, - - - - - -; process D, · · · · · · ·.

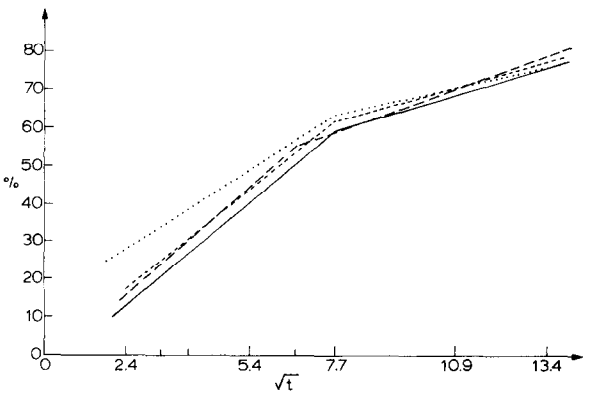

Fig. 2. Percentages of drug released against (time)$^{1/2}$, core : wall ratio 4 : 3. Key process A, ———; process B, — — —; process C, - - - - - -; process D, · · · · · · ·.

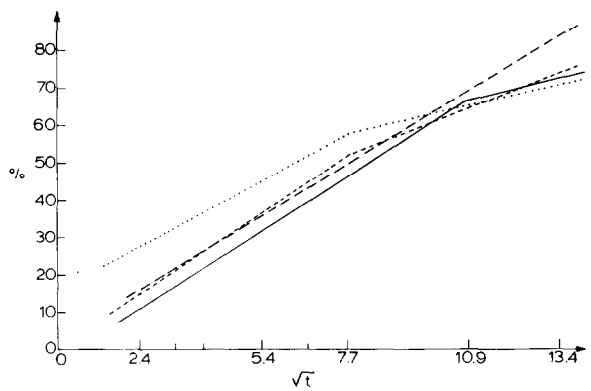

Fig. 3. Percentages of drug released against (time)$^{1/2}$, core : wall ratio 1 : 1. Key: process A, ———; process B, — — —; process C, - - - - - -; process D, · · · · · · ·.

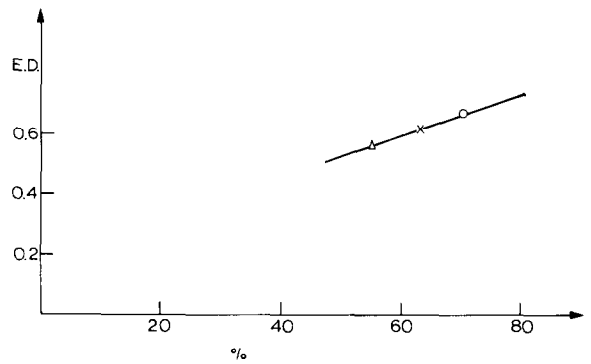

Fig. 4. Plot of the efficiency of dissolution of metronidazole as a function of microcapsule drug content. Process C. Key: core : wall ratios 2 : 1 (○); 4 : 3 (×); 1 : 1 (△).

The addition of polyisobutylene during microcapsule preparation modifies the metronidazole release from microcapsules. The increased release can be attributed to a higher percentage of smaller microcapsules for the three core : wall ratios and to the high percentage of free drug for the 2 : 1 core : wall ratio. When crystallized metronidazole is used instead of the micronized form, the percentages of drug released after 3 h decreased because dissolution is slower with the largest drug particles, but the efficiencies of dissolution are increased and times for 50% released are lowered; this can be the result of the high percentage of free metronidazole which dissolved quickly.

The modifications in the microcapsule preparation influence their size distribution, their drug

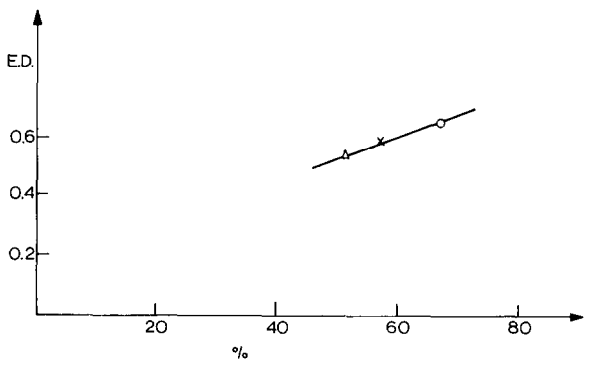

Fig. 5. Plot of the efficiency of dissolution of metronidazole as a function of microcapsule drug content. Process D. Key: core : wall ratios 2 : 1 (○); 4 : 3 (×); 1 : 1 (△).

contents and their dissolution characteristics. Jalsenjak et al. (1976) and Öner et al. (1984) report that release is faster from smaller microcapsules because of the corresponding thinner wall, but Oya Alpar and Walters (1981) and Nixon and Agyilirah (1982) find that the largest microcapsules release their content more rapidly since they are aggregates of small ones and their asymmetric structures are more important as well as their surface areas being increased. That is why it is not easy to predict the influence of the modification of stirring rate, or of the addition of polyisobutylene on dissolution parameters of matrix type microcapsules even if smaller microcapsules are obtained, because the free drug contents, the surface areas, the porosity of aggregates depend on the drug to be encapsulated and on the core : wall ratio.

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