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INFLUENCE OF POLYISOBUTYLENE ON MICROENCAPSULATION OF METRONIDAZOLE

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ABSTRACT

Metronidazole was microencapsulated with ethylcellulose by a phase separation method to develop a sustained release dosage form. Polyisobutylene (PIB) was used as a protective colloïd to control the particule size and the drug release of the microcapsules. The influence of PIB on microcapsules characteristics depends on the core-wall ratio, the molecular weight of PIB and the concentration of PIB.

INTRODUCTION

Ethylcellulose is widely used in many works to prepare microcapsules by a phase separation method to improve the bioavailability and to develop a sustained

release dosage forms. The process was first described by Miller, Fanger and Mc Niff[1]. Experimental results have demonstrated that changes in the method of preparation (stirring rate, drug particule size) influence the microcapsule characteristics (Jalsenjak[2], Oya Alpar[3], Chemtob[4]). Some authors propose to add during the preparation a protective colloid such as polyisobutylene (PIB) to control the particule size and to obtain individual microcapsules. Benita and Donbrow[5] used PIB of molecular weight of $3.8.10^5$, Samejima and coll.[6] and Kawashima and coll.[7] PIB of molecular weight of $1.12.10^6$, to stabilize individual microcapsules during the preparation. In the present study, various quantities of those two PIB were used to elucidate the effect of PIB on microscopic aspect, size distribution, drug content, drug release of metronidazole microcapsules with various core-wall ratios.

EXPERIMENTAL

Materials - Ethylcellulose, type N (ethoxy content 47.5% 49%), viscosity 95 mPa (5% w/w solution in toluene-ethanol 80:20), Hercules . Polyisobutylene, Oppanol 50 (molecular weight $3.8.10^5$) and Oppanol 150 (molecular weight $1.12.10^6$), B.A.S.F. Cyclohexane pure grade. Metronidazole micronized 3 µm, Rhône Poulenc, France.

Methods - For the preparation of microcapsules, various quantities of PIB_{50} and PIB_{150} were dissolved in 600 ml of cyclohexane at 70°C under stirring (700 rpm), 1 per cent ethylcellulose was added and the temperature was raised at 80°C during 30 minutes. The metronidazole was added and the temperature was held at 80°C for one hour. The quantities of metronidazole used depend on the core-wall ratio 1-1 or 2-1. The microcapsules were formed by cooling between 50°C and 45°C during one hour and then quickly to 20°C in a water bath with ice. 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.

- Optical microscopy with a calibrated scale was used to observe microcapsules in cyclohexane. Size distribution was determined using 1250 µm, 800 µm and 315 µm sieves. The assay for metronidazole in the microcapsules (total drug content) was performed by dissolving 200 mg of microcapsules in 50 ml of chloroform, by diluting and determining the absorbance at 317 nm. The free drug content of microcapsules was estimated in dissolution studies by the quantities dissolved after 5 min.

- Dissolution studies were determined by placing 250 mg of microcapsules in a French Pharmacopoeia dissolution

paddle assembly containing 1 l of water adjusted to pH 1.2 at 37°C ± 1°C, stirring rate was standardized at 100 rpm and metronidazole in the sample was assayed spectrophotometrically at 276 nm.

RESULTS AND DISCUSSION

- Microscopic studies of metronidazole microcapsules allow to do some observations for the both core-wall ratios.Without PIB, microcapsules of 5 to 10 µm form agglomerats of 40 to 250 µm. With 1.5 % of PIB_{50} or PIB_{150} individual elongated shape microcapsules are obtained. When the quantity of PIB is increased, 6 % of PIB_{50}, spherical shape microcapsules of 40 to 50 µm are recovered, but with 10 % of PIB_{150} many small empty microcapsules are formed. Benita and Donbrow[5] noted that a quantity of 3 % of PIB_{50} is a minimum to obtain the formation of individual microcapsules of cristallized theophyllin, but when the quantity of PIB is too much increased the number of empty microcapsules is higher too. With PIB of high molecular weight (PIB_{150}), 3 % give the microcapsules the less aggregated. Koida[8] observed also that 3 % of PIB_{150} gives microcapsules with smooth surface with a few small holes and not aggregated.

- Size distribution of microcapsules.

The modification of the core-wall ratio influences the aggregation of microcapsules (Table 1).Without PIB

Table 1 : Influence of polyisobutylene on percentage of sieve fraction < 315 µm

Percentage of PIB w/v	Polyisobutylene 50				Polyisobutylene 150		
	0	1.5%	6%	10%	1.5%	2%	3%
Core-wall ratio 1-1	8.2	33.3	56.1	94.7	20.1	59.5	47.1
Core-wall ratio 2-1	20.4	14.3	65.3	97.5	24.7	33.5	34.0

the sieve fraction < 315 µm is lower for microcapsules of core wall ratio 1-1 than for microcapsules of core-wall ration 2-1. With the two core-wall ratios, there is the same quantity of ethylcellulose but less metronidazole for the core-wall ratio 1-1, and may be some ethylcellulose coacervates which are not used to coat metronidazole interacts with microcapsules inducing linkages and agglomerats. The percentage of sieve fraction < 315 µm is generally increased when PIB is added during the microcapsules preparation and when the quantities are higher. For the core-wall ratio 2-1 and PIB_{50}, a linear relation is established between percentage of sieve fraction < 315 µm and percentage of PIB_{50} used during the preparation.

The formation of aggregated microcapsules is lower with PIB_{50} than with PIB_{150}. Many authors concluded in their works[5,6,8], that there is an optimum concentration of PIB to prevent the agglomeration of microcapsules which depends on the PIB molecular weight, with the core-wall ratio 1-1 in this work, 6 % of PIB_{50} and 2 % of PIB_{150} have the same effect to prevent microcapsules aggregation.

- Percentages of free drug content as we defined, percentages of immediatly dissolved drug, are not very influenced by the addition of PIB of low molecular weight or high molecular weight except for high quantities of PIB_{50} such as 10 % (Table 2). For the core-wall ratio

Table 2 : Influence of polyisobutylene on microcapsules drug contents.

Percentage of PIB w/v		Polyisobutylene 50				Polyisobutylene 150		
		0	1.5%	6%	10%	1.5%	2%	3%
Core wall ratio 1-1	Free drug content %	6.3	6.7	6	73	4.3	7.9	3.8
	Total drug content %	55.0	46.9	47.5	48	59.0	56.0	60.0
Core-wall ration 2-1	Free drug content %	7.8	9.7	26.9	54	9.1	9.4	12.4
	Total drug content %	68.2	81.2	82.0	81.2	65.6	65.0	71.9

2-1, more free drug content is recovered with 6 % of PIB_{50} ; we already observed in an another study (Chemtob[4]) that an appropriate core-wall ratio may be necessary and that the excess of drug for the quantity of ethylcellulose is recovered as free drug.

- The total drug contents of microcapsules are generally not influenced by the addition of PIB and the quantities used during the preparation. However, for the core-wall ratio 2-1 and with the PIB_{50}, total drug contents are higher than without PIB, but they are not modified when the concentration of PIB is increased. Some authors have noted that the addition of PIB may modify total drug contents of microcapsules. Benita and Donbrow[5] observed with PIB_{50} too, but with a core-wall ratio of 1-1 and 5 % of ethylcellulose that the quantities of ethylcellulose recovered in microcapsules decrease when the concentration of PIB is increased. However, Koïda and coll.[8] noted no modification of total drug content with 3 % of PIB_{50}, but noted one with 3 % of PIB_{150}. For various core-wall ratios, different molecular weights of PIB and different quantities of PIB, the whole ethylcellulose is not used in the coacervation process to form the film coating ; It may produce empty microcapsules or aggregats which are recovered in the middle of preparation, and drug micro-

capsules which are obtained are coated with a thin film of ethylcellulose and contained more drug.

- Studies of in vitro dissolution show an influence of PIB on percentages of drug released after 3 hours and on time for 50 % drug released (Table 3). When PIB is used and when the quantities are increased the percentages of dissolved metronidazole are higher and $t_{50\%}$ are lowered. With PIB_{50} and for the two core-wall ratios, we noted a linear relationship between percentages of released metronidazole and quantities of PIB used during the preparation (Figure 1). With this PIB of low molecular weight and only for the core-wall ratio 1-1, we observed a linear relationship between $t_{50\%}$ and quantities of PIB_{50}. With PIB_{50}, $t_{50\%}$ from metronidazole microcapsules of core-wall 2-1 are shorter than those from microcapsules of core-wall 1-1 because there is less ethylcellulose and an higher drug content. Results of in vitro dissolution are similar with 1.5 % of PIB_{50} or PIB_{150} for a same core-wall ratio.

For all microcapsules, drug release occurs by a diffusion controlled process as described by Higuchi for the release of drug from insoluble porous matrix (Figures 2, 3, 4, 5). Without PIB, the relation is linear during 3 hours, when PIB is added two linear relationships are generally observed, one during 90 min. and the release is faster than

Table 3 : Results of in vitro dissolution

Percentage of PIB w/v		Polyisobutylene 50				Polyisobutylene 150		
		0	1.5%	6%	10%	1.5%	2%	3%
Core-wall ratio 1-1	Percentage of drug released after 3 h	53.8	60	78.5	97.3	60.8	67.5	55.8
	$T_{50\%}$ min	163	142	65	3	143	75	154
Core-wall ration 2-1	Percentage of drug released after 3 h	55	61.8	68	78.1	68	57.7	85.3
	$T_{50\%}$ min	135	72	40	4	91	120	27

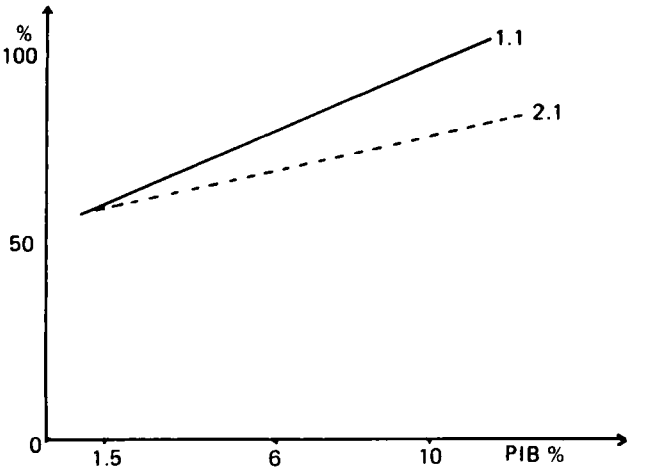

Figure 1

Plot of the percentages of drug released as a function of PIB concentration.

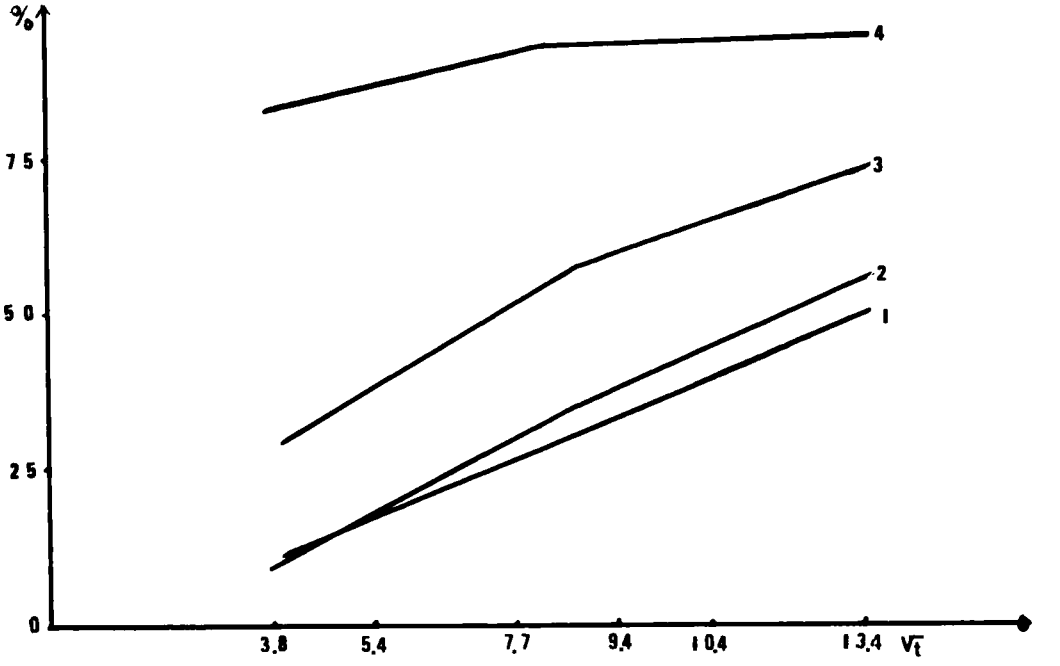

Figure 2

Percentages of drug released againts $(time)^{1/2}$ core-wall ratio 1-1, PIB_{50}.

1. without PIB_{50}
2. 1.5 % of PIB_{50}
3. 6 % of PIB_{50}
4. 10 % of PIB_{50}

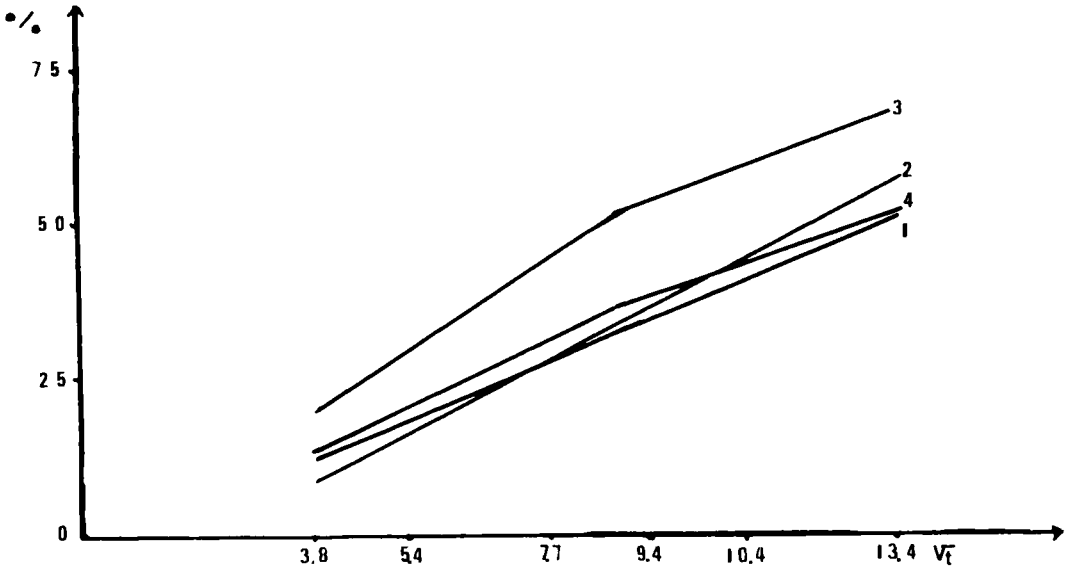

Figure 3

Percentages of drug released against (time)$^{1/2}$ core-wall ratio 1-1, PIB_{150}

1. without PIB_{150}
2. 1.5 % of PIB_{150}
3. 2 % of PIB_{150}
4. 3 % of PIB_{150}

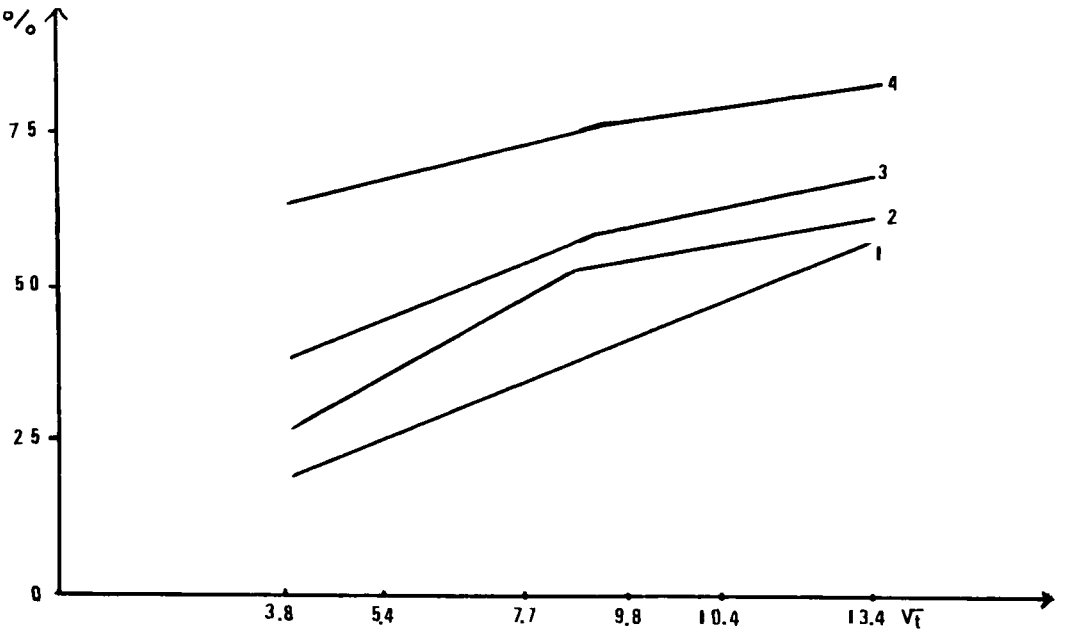

Figure 4

Percentages of drug released againts (time)$^{1/2}$ core-wall ratio 2-1, PIB_{50}

1. without PIB_{50}
2. 1.5 % of PIB_{50}
3. 6 % of PIB_{50}
4. 10 % of PIB_{50}

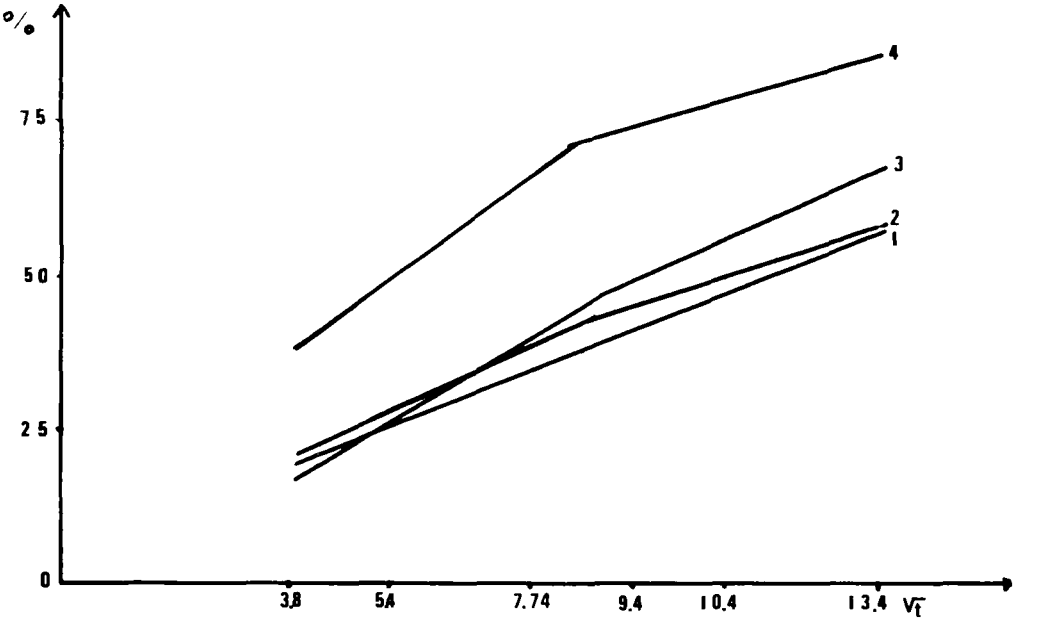

Figure 5

Percentages of drug released against (time)$^{1/2}$ core-wall ratio 2-1, PIB_{150}

1. without PIB_{150}
2. 1.5 % of PIB_{150}
3. 2 % of PIB_{150}
4. 3 % of PIB_{150}

the one noted without PIB, one from 90 min. to 180 min. and the release is slower than the one noted without PIB.

Drug release rate are not very different when 6 % of PIB_{50} or 2 % of PIB_{150} are used to prepare microcapsules of core-wall ratio 1-1.

For microcapsules prepared with PIB_{150}, drug release follows first-order kinetic too and the log of the amount remaining in the microcapsules decrease linearly with time.

In conclusion, a core-wall ratio 1-1, 6 % of PIB_{50} or 2 % of PIB_{150} allow to obtain the best results to microencapsulate micronized metronidazole. Percentage of agglomerated microcapsules are lowered, percentage of drug release after 6 hours are more important and release rate is not too fast. This work shows that the influence of PIB on microcapsules characteristics depend on the core-wall ratio used, the molecular weight of PIB and the concentration of PIB.

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