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Controlled release salbutamol sulphate microcapsules prepared by emulsion solvent-evaporation technique and study on the release affected parameters

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Abstract

Microcapsules of salbutamol sulphate with ethylcellulose were prepared using an emulsion-solvent evaporation technique and by the use of two different stirrer types, propeller and magnet. Different amounts of drug were added in order to obtain various drug to polymer ratios. The physical properties, loading efficiency and dissolution rate depended on the emulsion-solvent evaporation technique and on the drug to polymer ratio. Tween 80 was used as a dispersing agent. For a given drug to polymer ratio the percentage amount of Tween 80 affected the release of salbutamol sulphate and the size distribution of microcapsules. In order to further investigate the type of drug release mechanism taking place, the dissolution data were plotted according to the four different kinetic models. In vitro dissolution studies showed that first-order and square-root of time (Higuchi model) release characteristics were exhibited.

Keywords: Controlled release; Salbutamol sulfate microcapsule; Microencapsulation; Emulsion solvent-evaporation technique; Ethylcellulose

1. Introduction

Salbutamol sulphate, an adrenergic agonist, is an effective bronchodilator following peroral administration (Gardikas and Papadatos, 1987). In acute asthmatic conditions, salbutamol is given orally four times daily in a dose of 2.4 mg to maintain a therapeutic blood level. The biologigal half-life is about 4.5 h. Salbutamol sulphate is suitable for construction in an oral sustained release dosage form for 12–24 h duration of action.

Salbutamol sulphate is fairly soluble in water, and therefore the construction of a sustained release product in microcapsules is more convenient (Khalil and Elgamal, 1971).

Microencapsulation is used to modify and retard drug release. In pharmaceutical sustained release preparations, the uniqueness of microcapsules lies in the wide distribution throughout the gastrointestinal tract. This potentially improves drug adsorption and reduces side effects related

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to localized build-up of irritating drugs against the gastrointestinal mucosa (Li et al., 1988).

Many different coating materials and microencapsulation processes can be used. The emulsion-solvent evaporation technique has been described in the literature, and has been applied to polymers like ethylcellulose (Ismail et al., 1984; Nixon and Meleka, 1984) and Eudragit (Kawashima et al., 1989).

The purpose of this investigation was: (a) to prepare salbutamol sulphate microcapsules using ethylcellulose as wall material by the emulsion-solvent evaporation technique; (b) to study the effect of the manner of stirring (propeller and magnetic stirring) on the microcapsule quality; (c) to determine the effect of the polymer to drug ratio on in vitro dissolution; (d) to study the effect of the various percentages (w/w) of the dispersing agent on the microcapsules' physicochemical properties and on in vitro dissolution; and (e) to fit the data to various postulated drug release models.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (Glaxo, batch no. WC 50175), ethylcellulose (Ethocel 7, lot no. MM 900803, Dow Benelux), paraffin (DAB 7, NF XIV, Merck, Darmstadt), and dispersing agent (Tween 80, art. 822187 Merck-Schuchardt, acetone zur analyse Ferak, Laborat GmbH, Berlin) were obtained from the indicated sources.

2.2. Preparation of microcapsules

Microcapsules were prepared by the emulsion solvent evaporation technique. Acetone was used as the polymer solvent, light mineral oil as the microcapsulating vehicle and *n*-hexane as the decanter of paraffin oil. To prepare microcapsules with various drug to polymer ratios such as 1:1, 1:1.5 and 1:3, an amount of 1.8 g of polymer (EC) was weighed and either 1.8, 1.2 or 0.6 g of salbutamol sulphate was added respectively. The drug to polymer ratio was varied keeping the amount of polymer and solvent constant in all cases and decreasing the amount of drug used.

An amount of 1.8 g of polymer ethylcellulose (EC) was dissolved in 30 ml of acetone. Weighed amounts of salbutamol sulphate, depending on the desired ratio, were dispersed in this solution and stirred for 20 min. The dispersion was poured into 100 ml of light mineral oil containing 1.3% Tween 80 and stirred for 5 h at 1100 rpm at room temperature.

Stirring was carried out using two stirrer types, i.e., a propeller and a magnet stirrer. During the 5 h stirring period, acetone, used as a solvent for EC, was completely removed by evaporation. The light mineral oil was decanted and the collected microcapsules were washed twice with 100 ml of *n*-hexane at room temperature, after which the microcapsules were separated by filtration and air dried for 12 h.

2.3. Evaluation of microcapsules

2.3.1. Density and porosity determination

The true density (ρ_g) of the microcapsules was determined with the aid of an air comparison pycnometer (Beckman, model 930). The loose bulk density (ρ_b) and the tap density (ρ_t) were measured in a 25 ml Eberhard Bauer cylinder by carrying out 100 taps at a rate of 240 taps/min. Each determination was carried out in triplicate and densities were calculated from the mean of the three determinations. The changes which could occur in the packing arrangement of microcapsules subjected to the tapping procedure were expressed as the compressibility index:

$$\text{Compressibility index} = [(\rho_t - \rho_b)/\rho_t]^*100$$

and the percentage of porosity was calculated as:

$$e = [1(\rho_t/\rho_g)] \times 100\%$$

2.3.2. Determination of microcapsules size

The determination of arithmetical diameter was performed using a special system, where a simple microscope is combined with a video and a computer. The size of the microcapsules was measured by a specific computer program, the Image Analysis.

2.3.3. Drug content determination

The total drug content of EC microcapsules was determined after each dissolution test. This means that the solution from the in vitro dissolution test with the microcapsule samples was subjected to ultrasonication in an Ultra Turrax in order to achieve the complete breakage of the microcapsule wall and to release the total drug content. Thereafter, the samples were analyzed by measuring the UV absorbance at 276 nm.

2.3.4. In vitro dissolution

The USP paddle method was used to determine release of salbutamol sulphate from the microcapsules (USP XXI, 1985). As dissolution medium, 250 ml distilled water at 37 ± 0.1°C was used with stirring at 50 rpm (Murthy et al., 1991). Samples were taken at appropriate intervals up to 8 h and then filtered. Salbutamol sulphate content was determined spectrophotometrically at $\lambda_{max} = 276$ nm. Each release determination was carried in triplicate.

2.4. Kinetic models

The goodness of fit of the release data was initially tested with the following mathematical models: (1) zero-order kinetics (Eq. 1); (2) first-order kinetics (Eq. 2); (3) Hixson-Growell's cube-root equation (Eq. 3); and (4) square-root of time equation (Eq. 4) (Alvarez et al., 1991):

$$w = w_o - k_o t \text{ (zero-order)} \quad (1)$$

$$\ln w = \ln w_o - k_1 t \text{ (first-order)} \quad (2)$$

$$\sqrt[3]{w} = \sqrt[3]{w}_o - k_2 t \text{ (cube-root of time)} \quad (3)$$

$$Q = k\sqrt{t} \text{ (square-root of time)} \quad (4)$$

3. Results and discussion

The physical properties, namely, arithmetical diameter with the standard deviation, drug loading efficiency (%) of microcapsules, as well as the density (true, bulk and tap), porosity (e%) and compressibility index (%) are listed in Table 1.

As the drug to polymer ratio increased the microcapsules' mean size decreased (Table 1). This was observed with both stirring types. The drug to polymer ratio was varied, maintaining the amount of polymer and solvent constant in all cases and decreasing the amount of drug used. The reduction in microcapsule size with increase in drug to polymer ratio may be due to a decrease in the viscosity of the internal phase as a result of a decrease in the concentration of solids in the polymer solution.

Table 1
Physical properties of salbutamol sulphate microcapsules prepared by the solvent evaporation technique with the two stirring types (magnetic and propeller)

Drug/polymer ratio	Size: arithmetic diameter (d) (μm) (±S.D.)	Loading efficiency (%)		Density (g/ml)			Porosity (e%)	Compressibility index (%)
		Theoretical	Experimental	True (ρ_g)	Bulk (ρ_b)	Tap (ρ_t)		
Magnet								
1:1	912.1 ± 437	50	47	1.137	0.412	0.429	62.2	3.96
1:1.5	878.9 ± 28	40	39	1.183	0.418	0.473	60.0	11.52
1:3	695.4 ± 175	25	22	1.225	0.430	0.514	58.0	16.34
Propeller								
1:1	578.2 ± 146	50	48	1.10	0.405	0.421	61.83	3.28
1:1.5	484.6 ± 201	40	34	1.12	0.466	0.481	57.05	4.15
1:3	436.2 ± 102	25	23	1.21,	0.470	0.530	55.62	12.47

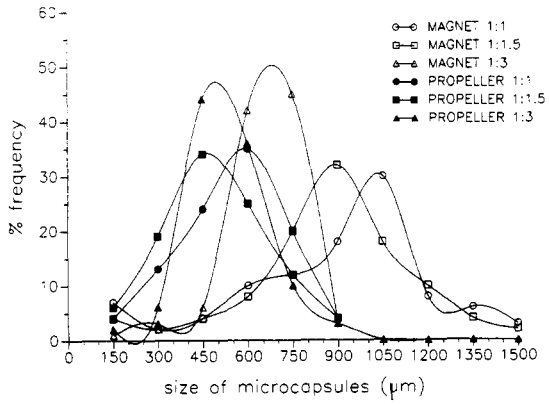

Fig. 1. Curves showing the size distribution of microcapsules prepared with the two types of stirrer, propeller and magnetic, at different drug to polymer ratios.

Fig. 1 shows the influence of variation in drug to polymer ratio on the size distribution of microcapsules: the greater the drug to polymer ratio the smaller the size of microcapsules. This was due to the fact that the lower ratios produced a more viscous internal phase which was more difficult to disperse in the external phase during emulsification, resulting in larger microcapsules. The stirring speed was kept constant (Pongpaibul et al., 1989).

The curves of size distribution of the microcapsules in Fig. 1 also show that when the microcapsules were prepared using the propeller stirrer the particle size distribution was smaller than that of microcapsules prepared using the magnet stirrer where a broader particle size distribution

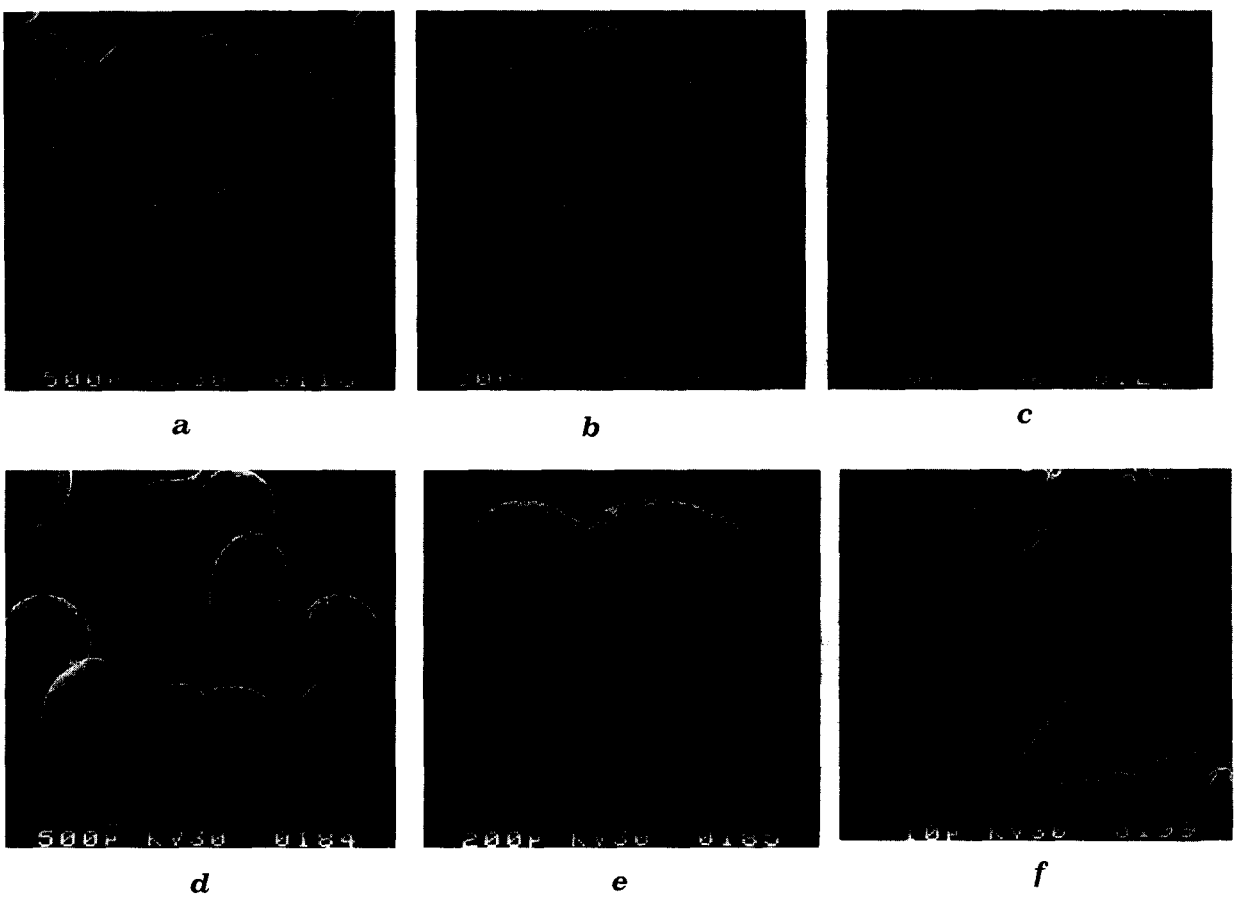

Fig. 2. Scanning electron migrographs of salbutamol sulphate microcapsules prepared at the same drug to polymer ratio 1:1.5: propeller stirring (a–c) and magnetic stirring (d–f).

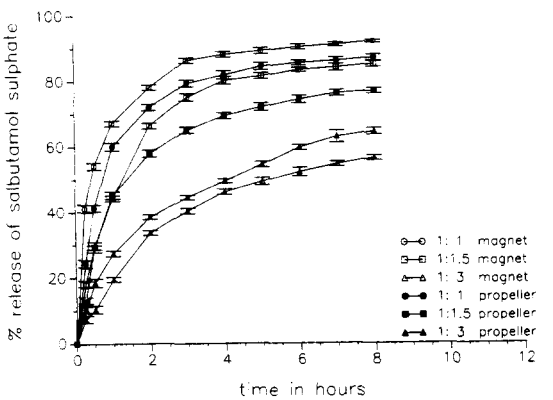

Fig. 3. Dissolution test curves for propeller stirring and magnetic stirring.

was observed. This was due probably to the different manner of stirring. The propeller stirrer with a strong stirring in the total volume of the emulsification prevents aggregates of smaller microcapsules forming. During stirring with the magnet type, larger microcapsules are composed of aggregates of smaller capsules rather than single capsules with thicker walls as manifested by the photographic evidence in Fig. 2. This results in larger microcapsules with a wide particle size distribution.

The curves of dissolution rate profiles in Fig. 3 indicate that increasing the drug to polymer ratio resulted in thicker coated walls and greater impeding of the release of salbutamol sulphate (Jansenjak et al., 1976). Comparison of the dissolution rate of all formulations indicated a sustained effect due to the encapsulation of the drug. This effect is dependent on the drug to polymer ratio. Increasing the drug to polymer ratio resulted in a decrease in dissolution rate as a result of increase in coat thickness surrounding the drug particles, thereby increasing the distance travelled by the drug through the coat. These findings are in agreement with previous work (Al Gohary and El Gamal, 1991). It was observed that the dissolution profiles of microcapsules prepared with the two different stirring types and with varying drug to polymer ratios were affected in the same way as shown in Fig. 3. A difference was found in the drug to polymer ratio 1:3, where the microcapsules prepared by magnetic stirring released the drug more slowly than those prepared by propeller stirring. This occurred because the microcapsules with greater particle size are aggregates of smaller microcapsules. This would appear to suggest that dissolution was confined to the outer surface, possibly due to incomplete wetting or the formation of static concentrated films of dissolution material towards the centre of the aggregate, which would lower the local concentration gradient and thus inhibit further release of the drug from the centre of the aggregate (Jansenjak et al., 1980).

Thus, it is concluded that aggregates of smaller microcapsules cannot be created by propeller stirring whereas this is possible by magnetic stirring, as demonstrated for the ratio 1:3 shown in

Table 2
Correlation coefficient (r) and constant (K) for drug to polymer ratios 1:1, 1:1.5, and 1:3 for the two types of stirring (magnetic and propeller stirring), after fitting of dissolution results to the different kinetic models

Drug/polymer ratio	Kinetic models							
	Zero-order		First-order		Hixson-Growell		Higuchi	
	r	K	r	K	r	K	r	K
Magnet								
1:1	0.8451	5.43	0.9705	62.52	0.9084	1.17	0.9277	42.62
1:1.5	0.8661	7.79	0.9701	40.20	0.9132	0.65	0.9428	14.69
1:3	0.9854	5.59	0.9991	16.09	0.9928	0.15	0.9995	2.84
Propeller								
1:1	0.8318	6.51	0.9472	49.58	0.8954	0.89	0.9174	27.89
1:1.5	0.8707	6.88	0.9475	35.44	0.9181	0.57	0.9446	13.97
1:3	0.9561	6.53	0.9993	24.75	0.9771	0.29	0.9930	3.06

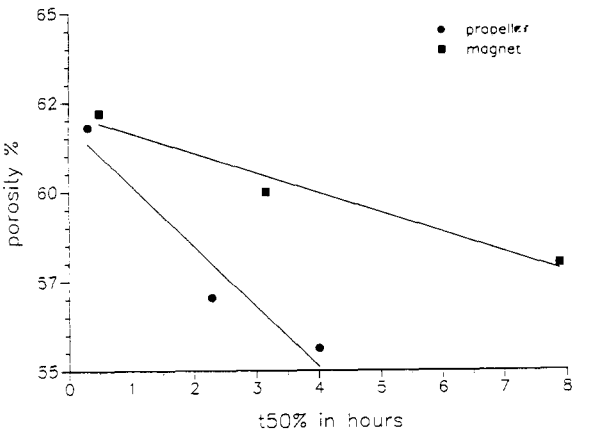

Fig. 4. $t_{50\%}$ in vitro, in relation to the microcapsule porosity.

Fig. 3. The proportion of polymer present at this ratio is much greater than that of drug and this is the reason why aggregates of smaller capsules are created.

In order to obtain meaningful information for the release models, the drug release profiles were fitted to the four different kinetic models mentioned above and the goodness of fit of the release data was assessed. Table 2 summarizes the correlation coefficients for the different release kinetic models for EC microcapsules formulated at 1:1, 1:1.5 and 1:3 drug to polymer ratios using the propeller and magnet stirrers. Models with higher correlation coefficients were judged to be a more appropriate model for the dissolution data.

As shown in Table 2 for a 1:1 drug to polymer ratio and for the two stirrer types, the best linear fitting parameter was the first-order equation (exponential model), since for the ratio 1:1.5 there was no significant difference between the square-root of time (Higuchi model) and first-order release models.

For microcapsules formulated at a drug to polymer ratio of 1:3 by the propeller stirrer there was no difference between the square-root of time (Higuchi model) and first-order release models, whereas for those microcapsules formulated at the same drug to polymer ratio of 1:3 using the magnet stirrer the model with the best linear fitting parameters was that of the Higuchi equation, suggesting that drug release is controlled by the diffusion of drug through the pores and not through the swollen polymer.

The in vitro $t_{50\%}$ is the time required for 50% of drug to be released from the microcapsules and has been suggested to be the best in vitro variable for correlation of the in vitro activity (Pongpaibul et al., 1984; Al Gohary and El Gamal, 1991).

Fig. 4 shows the $t_{50\%}$ for various batches of microcapsules prepared with both stirrer types

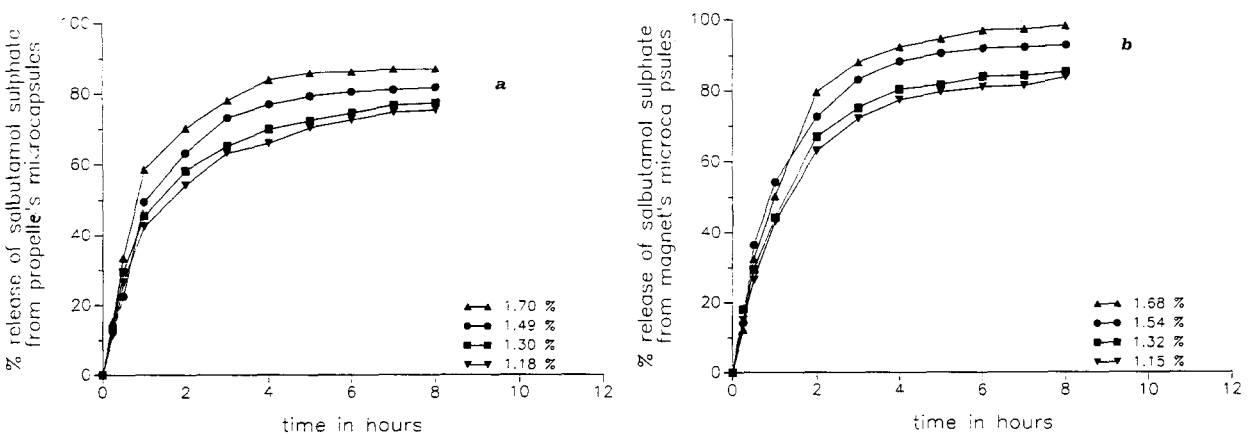

Fig. 5. Dissolution test curves: magnetic stirring (a), and propeller stirring (b) at 1:1.5 drug to polymer ratio, with different emulsifier quantities.

and for all three formulations. In Fig. 4, $t_{50\%}$ is plotted as a function of porosity. A nearly linear relationship is evident.

Tween 80 is used as a dispersing agent in the preparation of water in oil (w/o) emulsions. As illustrated in Fig. 5, the percentage (w/w) amount of Tween 80 affected the dissolution rate of drug for the given formulation ratio of 1 : 1.5 of drug to polymer. With increasing percentage amount of Tween 80 added to the microcapsules it is also evident from Fig. 5 that the release of salbutamol sulphate from microcapsules increased.

As shown in Fig. 6, the size distribution of the microcapsules prepared using the two stirrer types and formulated with the same drug to polymer ratio of 1 : 1.5 when various percentage amounts of emulsifier are used became smaller and the size distribution of moved toward a narrower range when the amount of Tween 80 was increased. When Tween 80 was increased to 1.18–1.70% the particle size was greater as compared with that at 1.15–1.68%. This appeared to be the result of accelerated dispersion of microcapsules in the microencapsulation system by addition of excess Tween 80 (Kawata et al., 1986).

The above results can be satisfactorily explained in terms of reduced particle size of microcapsules, producing a greater surface area per unit of microcapsules, with increasing percentage of Tween 80.

From the present results, the following conclusions can be drawn:

(1) Sustained release for salbutamol sulphate was succesfully achieved by microencapsulation using an emulsion-solvent evaporation technique.

(2) Two stirrer types, propeller and magnet, can be used succesfully to prepare various batches of microcapsules by the emulsion-solvent evaporation technique.

(3) Higher drug to polymer ratios decrease the microcapsules size and the drug release for both stirrer type techniques.

(4) Smaller propeller stirrer microcapsules released salbutamol sulphate faster, whereas smaller magnet stirrer microcapsules released salbutamol sulphate slower. This is most evident at the same 1 : 3 drug to polymer ratio.

(5) The amount of emulsifying agent affect the microcapsules prepared using the two stirrer types in the same way. That is, as the amount of emulsifier increased, the particle size of microcapsules decreased and the release rate of the drug increased for both types of stirring techniques.

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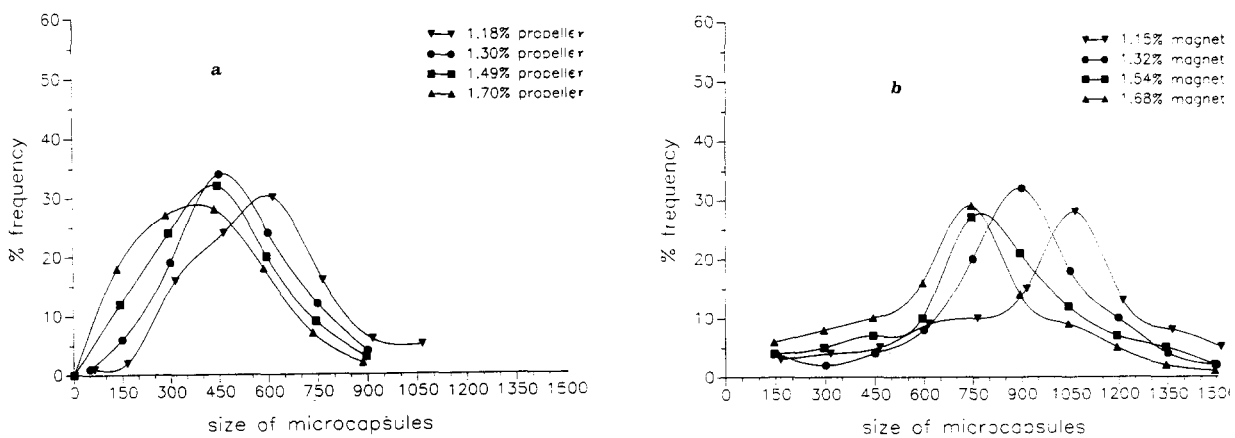

Fig. 6. Size distribution curves of microcapsules prepared with magnetic stirrer (a) and propeller stirrer (b) at 1 : 1.5 drug to polymer ratio, with different emulsifier quantities.

nology Institut, Westfahlische Wilhelms University, Munster, Germany, for technical assistance.

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