DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(11), 1339-1346 (1995)

PREPARATION AND CHARACTERIZATION OF ETHYLCELLULOSE-WALLED THEOPHYLLINE MICROCAPSULES USING THE EMULSION-SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Ethylcellulose microcapsules containing theophylline are prepared by emulsification of a organic ethylcellulose solution in a oil phase containing a surfactant. The preparation is based on dispersion of acetone containing the drug in liquid paraffin. Tween 80 was used as a dispersing agent. Good reproducibility in microcapsule preparation was observed. The microcapsules obtained were uniform and free-flowing particles. The type of the stirring-manner (propella - and magnet - stirring), and the drug to polymer ratios have an important influence on the in vitro dissolution and release of theophylline from microcapsules.

INTRODUCTION

Theophylline, which is a recognized treatment for bronchical asthma, has a short half-life and narrow therapeutic range and has therefore received a considerable amount of attention in sustained release formulations (1).

Microencapsulation is used to modify and retard drug release. In pharmaceutical sustained release preparations, the microcapsules offer the advantage that the coated particles can be widely distributed throughout the gastrointestinal tract. This potentially improves drug adsorption and reduces side

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[1] Part of Thesis
[2] Correspondence

effects related to localized buildup of irritating drugs against the gastrointestinal mucosa (2).

Many techniques for the preparation of microcapsules have been developed and the techniques have been comprehensively reviewed (3),(4).

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 (5),(6) and regins (7).

The purpose of this study was a.) to prepare theophylline microcapsules using ethulcellulose as wall-material by the emulsion-solvent evaporation technique b.) to study the effect of the stirring-manner (propella-stirring and magnet-stirring) on the microcapsules quality c.) to study the effect of polymer to drug ratio on the in vitro dissolution and d.) fitwhe data to various postulated drug release models.

MATERIALS AND METHODS

1. Materials

Theophylline, Courtesy of Bristol, Hellas. Ethylcellulose, Ethocel 7,lot No: MM 900803, Dow Benelux, Paraffin DAB 7, NF XIV, Merck Darmstadt. Dispersing agent, Tween 80, Art. 822187 Merck-Schuchardt. Acetone zur analyse Ferak, Laborat GMBH: Berlin.

2. Preparation of microcapsules.

Microcapsules were prepared by the emulsion solvent evaporation technique. Acetone was used as the polymer solvent and light mineral oil as the microcapsulating vehicle and n-hexane as the decanter of paraffin oil. To prepare a batch with a 1:1 polymer to drug ratio 1.8 grams of ethylcellulose (EC) were dissolved in 30 ml of acetone. 1.8 grams of theophylline were dispersed in this solution and stirred for 20 minutes. This dispersion was poured into 100 ml of light mineral oil containing 1.3% Tween 80 and stirred for 5 hours at 1100 r.p.m. at room temperature.

The polymer to drug ratio (1:2, 1:1, 3:2, or corresponting to 0.5, 1, 1.5) was varied keeping the amount of polymer and solvent constant in all cases and decreasing the amount of drug used.

The stirring is carried out with two stirrer types, with propella-stirrer and with magnet-stirrer. After the 5 hours and during this time, acetone, used as a solvent of EC, is 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, thereafter the microcapsules were separated by filtration and air dried for 12 hours.

3. Evaluation of microcapsules

3.1 Density and Porosity determination: The true density (ρg) of the microcapsules was determined with the aid of an air comparison pycnometer (Beckman,Model 930). The loose bulk density (ρb) and the tap density (ρt) were measured in a 25 ml cylinder Eberhard Bauer by 100 taps with a rate of 240 taps/min. Each determination was carried out in triplicate. The changes which could occure in packing arrangement for microcapsules subjected to the tapping procedure are expressed as the Compressibility index = [(ρt-ρb)/ρt]*100 and the percentage of porosity was calculated as:e=[1-(ρt/ρg)]*100%.

3.2 Determination of microcapsules size: The determination of arithmetical diameter was measured by a special system, where a simple microscope is combined with a video and with a computer. Using the computer the size of the microcapsules was measured by an specific computer program,the ImageAnalysis.

3.3 Drug Content determination: The total drug content of EC microcapsules is determined after each dissolution test. This means that the solution from the in vitro dissolution test with the microcapsules samples was stirred in an ultra Turrax by ultrasounds in order to obtain the complete bracking of the microcapsules wall and to release the total drug content. Thereafter the samples were analyzed by measuring the UV absorbance at 270 nm.

3.4 In vitro dissolution: The USP Paddle Method was used to determine the release of theophylline from the microcapsules (8). An amount of 900 ml distilled water at 37±0.1°C was used as dissolution medium and it was stirred at 100 rpm. Samples were taken at appropriate intervals up to 8 hours and filtered. The samples were analyzed by measuring the UV absorbance at 270 nm. Drug concentration in each sample solution was calculated from a standard curve. The in vitro dissolution of theophylline from the microcapsules was reported as the mean of 6 determinations.

3.5 Kinetic models: The goodness of fit of the release-data was initially tested with the mathematical models as the following : zero-order kinetic $w = w_o - k_o t$, first-order kinetic $\ln w = \ln w_o - k_1 t$, Hixson-Growell's cube-root of time $\sqrt[3]{w} = \sqrt[3]{w_o} - k_2 t$, and square-root of time $Q = k\sqrt{t}$ (9).

RESULTS AND DISCUSSION

The physical properties, namely arithmetical diameter with the standard deviation, the drug loading efficiency (%) of microcapsules, as well as the density (true,bulk and tap),porosity (e%) and compressibility index (%) are listed in Table1. As the polymer to drug ratio increased the microcapsules mean size decreased. This was observed in both types of stirring. The polymer to drug ratio was varied keeping the amount of polymer and solvent constant in all cases and decreasing the amount of drug used. The reduction in microcapsules size while increasing the polymer to drug ratio may be due to a decrease in the viscosity of

TABLE 1.
Physicochemical Properties of Theophylline Microcapsules

Polymer: Drug ratio	Mean Arithm. diameter d(μm)±sd	%Loading eff/cy	DENSITY TRUE (ρg)	DENSITY BULK (ρb)	DENSITY TAP (ρt)	Porosity e%	Comps indx %
MAGNET							
0.5	892±48	87.5	1.23	0.55	0.59	52	6.78
1	870±52	76.4	1.19	0.48	0.53	55	9.43
1.5	819±38	70.1	1.12	0.40	0.45	60	11.1
PROPELLA							
0.5	806±28	85.5	1.29	0.58	0.61	53	4.92
1	680±25	72.6	1.18	0.49	0.52	56	5.78
1.5	646±21	68.2	1.14	0.45	0.48	58	6.25

the internal phase as a result of a decrease in concentration of solids in the polymer solution. The stirring speed was kept constant (10).

When the microcapsules were prepared using propella-stirrer the particles size was smaller since when the microcapsules were prepared using magnet-stirrer was observed a big particles size. This was due probably to the different stirring manner. The propella stirrer provides a strong stirring in the total volume of the emulsification preventing the aggregation of microcapsules whereas the magnet stirrer used at the same r.p.m. allows microcapsules aggregation.

As a result microcapsules produced using the magnet stirrer end up being larger because they are aggregates of smaller microcapsules as it is evident from the photographs, from Figure 1.

The curves of dissolution rate profiles as Figure 2 shows, indicate that increasing the polymer to drug ratio resulted in thicker coated walls and a greater impeding at the release of theophylline(11).

Increasing the polymer to drug 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 workers.(12) It was observed that the dissolution

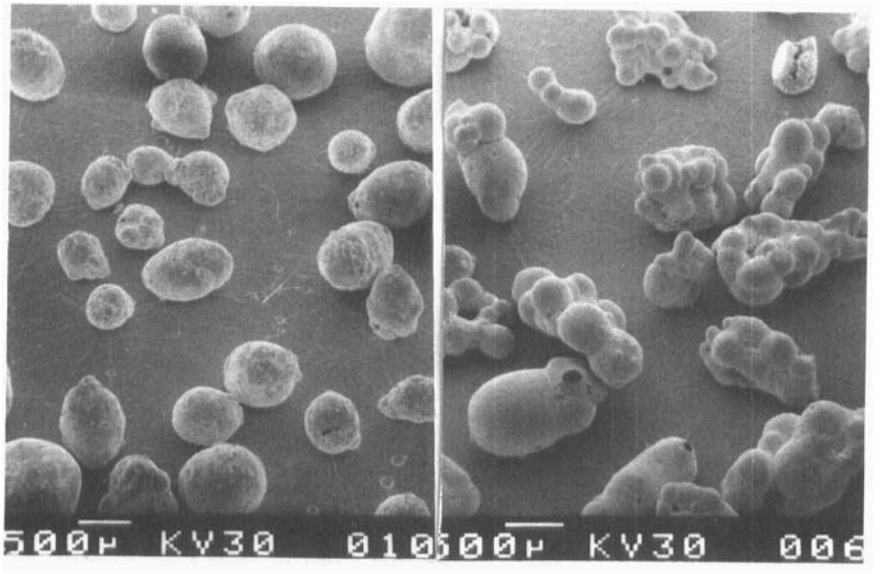

FIGURE 1.

SEM - micrographs of EC - microcapsules prepared by propella (a) - and magnet (b) - stirring with the solvent evaporation technique.

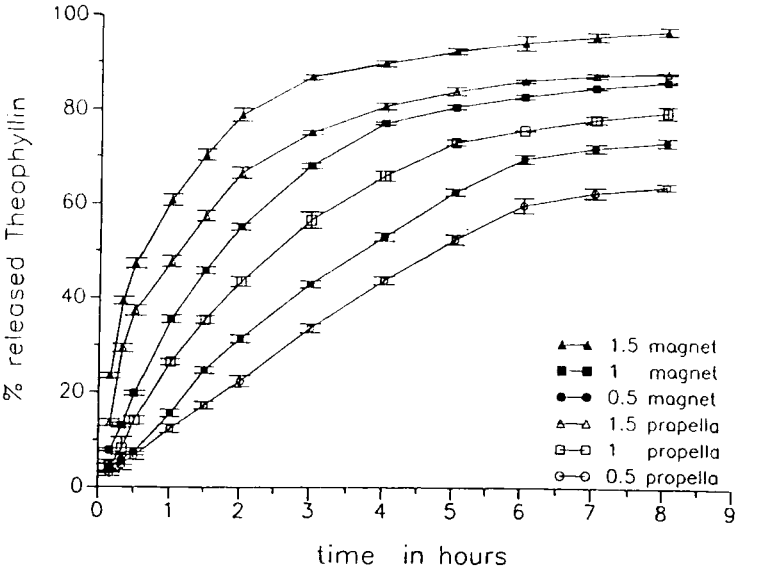

FIGURE 2.

In vitro dissolution curves of microcapsules prepared by two type - stirring (propella, magnet) by the solvent evaporation technique and with various polymer to drug ration.

TABLE 2.
Values of Correlation Coefficients (R) and Constands (K) for Kinetic models

Polymer: Drug ratio	ZERO ORDER corr. R ($K\ h^{-1}$)	FIRST ORDER corr. R ($K\ h^{-1}$)	HIXSON GROWELL ($\sqrt[3]{t}$) corr. R ($K\ h^{-1}$)	HIGUCHI ($\sqrt{t}$) corr. R ($K\ h^{-1/2}$)
MAGNET				
0.5	0.8590 (7.78)	0.9655 (55.01)	0.9536 (0.86)	0.9408 (28.15)
1	0.9147 (9.87)	0.9806 (29.57)	0.9591 (0.34)	0.9748 (0.43)
1.5	0.9362 (9.36)	0.9745 (19.82)	0.9623 (0.20)	0.9839 (6.62)
PROPELLA				
0.5	0.8823 (8.51)	0.9664 (41.10)	0.9405 (0.58)	0.9555 (13.37)
1	0.9435 (9.78)	0.9839 (21.52)	0.9739 (0.20)	0.9885 (7.2)
1.5	0.9849 (8.50)	0.9920 (12.46)	0.9925 (3.22)	0.9983 (13.25)

profiles of microcapsules prepared with the two different stirring types and with varying polymer to drug ratios compared to the dissolution rate of the drug are affected by the same way as it is shown in Figure 2.

In order to obtain meaningful information for the release models, the drug release profiles were fitted to the 4 different kinetic models mentioned above and the goodness of fit of the release data was tested.

As shown in Table 2 for the 0.5 (1:2) polymer to drug ratio and for both stirrer types the best linear fitting parameters was the first order kinetic and there is a good approach from the square-root of time (Higuchi model) and the cube-root of time (Hixson-Growell model). Since for the ratio 1 (1:1) there was no

significant difference between the square-root of time (Higuchi model) and the first order release model and cube-root of time for the propella- and magnet-stirring microcapsules respectively. For the microcapsules formulated with a 1.5 (3:2) polymer to drug ratio by both stirrer types the best linear fitting parameter was the square-root of time (Higuchi model), suggesting that the drug release is controlled by the drug diffusion through the pores and not through the swollen polymer.

CONCLUSION

-Two stirrer types propella and magnet can be used succesfully to obtain various batches of sustained release theophylline microcapsules by the emulsion-solvent evaporation technique.
-Higher polymer to drug ratios decrease the microcapsules size and the drug release for both stirrer types techniques.
-Smaller propella-stirrers microcapsules released theophylline faster, whereas smaller magnet-stirrers microcapsules released salbutamol sulphate slower.

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