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SPRAY DRYING AS A PROCESS FOR MICROENCAPSULATION AND THE EFFECT OF DIFFERENT COATING POLYMERS

Lucy S.C. Wan, Paul W.S. Heng, Cecilia G.H. Chia

Department of Pharmacy, National University of Singapore,
10 Kent Ridge Crescent, Singapore 0511.

ABSTRACT

Microencapsulation of theophylline drug particles was carried out by a spray drying technique using an aqueous system. Comparison was made between the use of a solution and a suspension feed. The spray dried products obtained from a suspension feed were encapsulated and have better flowability. Various polymers, hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (NaCMC) were studied to evaluate their spray-coating properties. The results showed that drug release from the coated products was dependent on the hydrophilicity of the polymer. NaCMC, which is more hydrophilic, gelled faster and retarded the drug release more effectively. HPMC and MC produced products with similar dissolution profiles and flow properties. Spray coating with HPMCAS was unsuccessful. The polymers also affect the size and cohesiveness of the products. Smaller size particles which are more cohesive cause agglomeration and delay release of the drug.

INTRODUCTION

Spray drying is a process describing the transformation of liquid feed into a dried particulate form by spraying the feed into a hot drying gaseous medium [1]. The process has been commonly used in the pharmaceutical industries for drying heat-sensitive materials and/or improving

(a) the solubility of poorly water-soluble substances [2],

(b) flow properties in the preparation of free-flowing granules for tablet production [3] and

(c) dispersibility as in the manufacture of spray dried methylcellulose [4].

Solid particles can also be prepared directly from liquid droplets by a chemical reaction during spray drying [5]. Recently, there has been a renewed interest in the use of spray drying to coat drugs with polymers to produce dust-free controlled release products [6-10]. The advantage of using this technique over other coating methods is that it is a one-step process applicable to heat-sensitive and sterile materials. Although there are a number of reports on the use of spray drying for encapsulation, many described spray drying techniques involving an organic solvent base. The purpose of this study is to utilise spray drying to coat theophylline particles with an aqueous polymeric solution. Products from spray drying a solution and a suspension feed and the coating efficiency were examined. Various polymers were also studied to ascertain their suitability and ability to produce well-formed coatings on the drug particles.

MATERIALS AND METHODS

Materials

The drug used was anhydrous theophylline (B.P.Grade, China). Coating polymers examined were hydroxypropylmethylcellulose (HPMC; 50 and 4000 cps, Shin-Etsu Chemical, Japan), sodium carboxymethylcellulose (NaCMC; Edifas B, ICI Ltd, UK), methylcellulose (MC; 4000 cps, Shin-Etsu Chemical, Japan) and hydroxypropylmethylcellulose acetate succinate (HPMCAS; grade AsHF, Shin-Etsu Chemical, Japan). Triethylcitrate and citric acid monohydrate (Merck, Germany) were the plasticizers used.

Preparation of Feed

The polymer was first hydrated in about 200 mL of distilled water until all the polymer was dissolved and the solution made up to 500 mL. For the insoluble HPMCAS, a dispersion of 500 mL was used. The required plasticizer and/or the drug, theophylline, previouly screened through a 150 um mesh sieve, was added to the solution. For the solution-feed, all the drug was dissolved while in the suspension feed, the drug was added to the polymer solution just before spraying. The formulations used were :

Feed-Type-	Theophylline	0.25%
	HPMC (50 cps)	1.25%
	Distilled water to	100%
Polymer Type-	Theophylline	2%
	Polymer	0.6%
	Plasticizer	0.18%
	Distilled water to	100%

Spray Drying Technique

The feed prepared was continuously stirred while being spray dried (Pulvis Minispray GA 32, Yamato Scientific, Japan) using a 2-fluid pressure nozzle and the product was collected in a cyclone separator. The flow of feed was concurrent with the direction of the inlet drying air. The operating conditions adopted after preliminary experiments were :

Inlet Air Temperature : 140 ± 2 °C
Feed Spray Rate : 9 ± 0.5 mL/min
Drying Air Rate : 0.5 ± 0.05 m^3/min
Atomizing Air Pressure : 1 kgf/cm^2

Dissolution Studies

The rate of release of theophylline from the spray dried products was determined using a dissolution apparatus (Method 1, USPXXI, Model 72RL, Hanson Research, USA) with the base of the rotating basket lined with a circular disc to hold the spray dried product. The basket was rotated at 50 rpm. The dissolution medium was 900 mL of deaerated distilled water maintained at 37 ± 0.5 °C. At specified intervals of time over a period of 4 hours, 4 mL samples were collected using an automated sampler (Dissoette, Model 27-6A,

Hanson Research, USA). The samples were then assayed spectrophotometrically at 274 nm (HP8451A, Hewlett Packard, USA). At least 3 replicates were carried out for each batch of product and the results averaged.

Flow Properties

The experiments to assess the flow properties of the product were carried out in a humidity-controlled environment with a relative humidity of 50-60%. Kawakita's constants, a and 1/b, were then determined by the method modified from Yamashiro *et al.* [11] with a 10 mL measuring cylinder. The change in volume was measured after every 2 taps for 40 taps. Constants, *a and 1/b*, are related to compactibility or fluidity and cohesion of the particles respectively in Kawakita's equation.

$$N/C = (1/a)N + 1/ab$$

where N is the number of taps, $C = (V_o - V_n)/V_o$ is the degree of volume reduction, V_o is the initial volume and V_n is the bulk volume which was measured at every 2 taps. Kawakita's constants obtained were the mean values of 4 replicates.

Hausner ratio is a measure of the interparticulate friction and can be used to predict powder flowability [12]. A higher Hausner ratio indicates greater cohesion between particles while a high Carr Index is indicative of the tendency of the powder to form bridges. The methods used to determine Hausner ratio and Carr index were similar to that described by Wan *et al.* [13]. The product was tapped (STAV2003, Stampfvolumeter, Germany) for 1000 taps in a filled 10 mL cylinder. Preliminary investigations have shown that volumetric change after 1000 taps was negligible. An average of 4 determinations was taken.

Microscopy

The spray dried particles were examined under a scanning electron microscope (SEM; JSM5200, Jeol Ltd, Japan).

RESULTS AND DISCUSSION

Feed Types

In order to optimize the production of the microcapsules and the efficiency of the spray dryer, a suitable feed-type must be used. It is imperative,

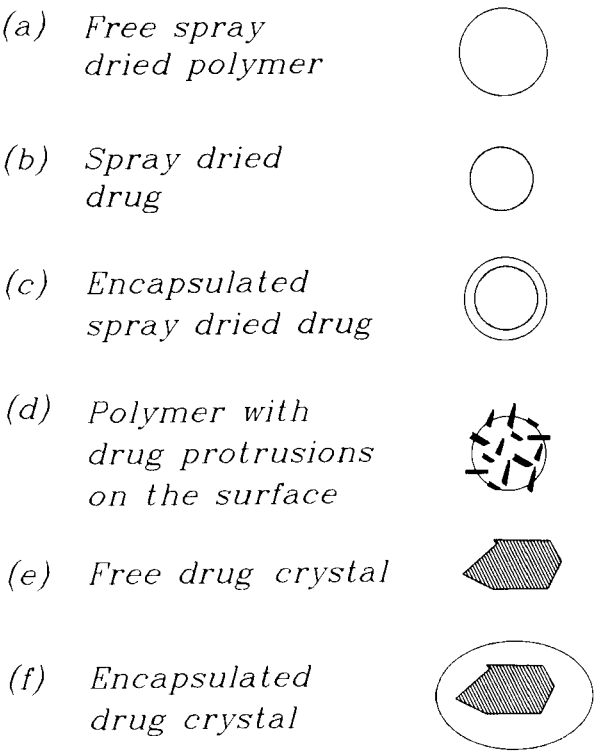


FIGURE 1
Possible types of products obtained by spray drying a solution-feed (a)-(d) and a suspension-feed (a)-(f).

therefore, to compare the type of product formed from a solution feed with a suspension feed. The different types of spray dried products obtainable from a solution-feed and a suspension-feed observed from the SEM are diagrammatically depicted in Figures 1(a)-(f). Different spray or formulation conditions affect the predominance of the type of product formed.

On drying a droplet atomized from a solution feed, the products formed include spray dried polymer and theophylline without any coating (Fig. 1 (a,b)). It is also possible for some of the spray dried drug to be coated with a thin polymeric film (Fig. 1(c)). The predominant product has drug protrusions on the surface of the polymer (Fig. 1(d)). These particles were obtained by the initial formation of a polymeric solid crust, followed by the diffusion of water within

Table 1

The Dissolution $T_{50\%}$ and Flow Property Parameters of the Spray Dried Product from a Suspension and a Solution Feedtype.

Feed-type	Suspension	Solution
Dissolution $T_{50\%}$ (min)	64.7	33.4
Hausner Ratio	1.44	1.49
Carr Index	30.3	32.8
Kawakita's Constants, a	0.22	0.23
1/b	23.3	19.2

the crust to the surface, carrying dissolved drug. On evaporation, rod-like drug crystals were deposited on the surface of the microcapsules [14].

With a suspension-feed, the undissolved drug remained as large crystals. Some of these drug crystals appeared not to be coated after spray drying (Fig. 1(e)). However, for majority of the drug, the polymer forms an envelope round the drug crystal (Fig. 1(f)). The dried products are microencapsulated drug crystals with fairly smooth surfaces compared to the solution-feed spray dried product which has a higher degree of roughness due to drug deposition. These encapsulated products from a suspension-feed showed better flow properties and slower drug dissolution than the solution-feed spray dried product (Table 1). Two factors could contribute to this slower drug release, the coating round the drug crystals and the larger size of the drug crystals of the suspension-feed spray dried product.

Similar results were obtained by Bodmeier and Chang [9] where spray drying with a solution-feed caused precipitation of both drug and polymer. For a suspension-feed with micronized theophylline, encapsulation occurred by the deposition of the polymer enclosing the dispersed drug particles. Drug release was thus slower from these encapsulated particles. Since suspension-feed

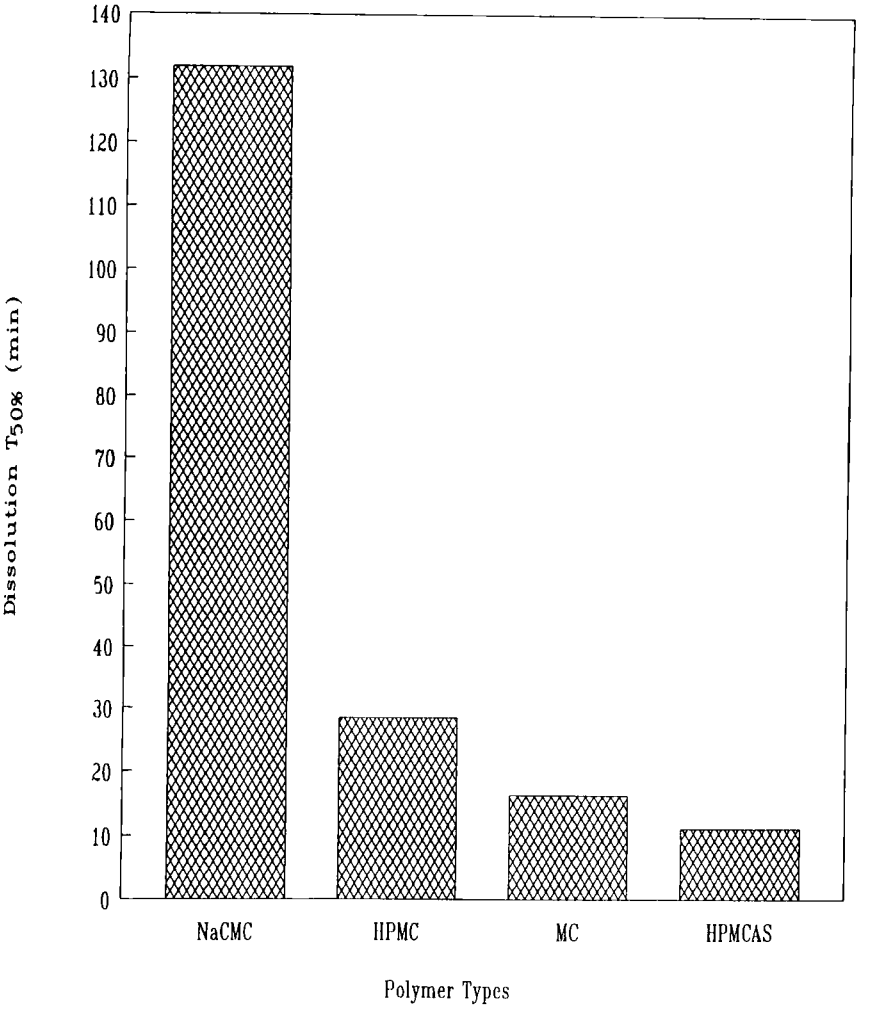


FIGURE 2

Influence of polymer types on the dissolution $T_{50\%}$ of the spray dried microcapsules.

produced well encapsulated particles, Seagar [15] recommended that in coating by spray drying, it is preferable for the drug to be of low solubility in the feed medium so that a suspension-feed can be used. Further experiments on the various polymer types were carried out using a suspension-feed.

Polymer Types

The polymers investigated were HPMC, MC, NaCMC and HPMCAS. The dissolution $T_{50\%}$ of the spray dried products with the respective polymers (Fig. 2) show the following trend: NaCMC > HPMC > MC > HPMCAS. For polymeric systems, it is essential that the polymer hydrates rapidly to form a gel. It is this gel formation that prevents initial dissolution of surface particles and retards the release of the enclosed drug. An initial small burst effect is expected due to the dissolution of the drug crystals present on the surface of the spray dried particles [16]. The water penetrates and gelling of the polymer film takes place, increasing the thickness of the gel as the water moves inwards. The rate of penetration is dependent on the nature of the polymer, especially its hydrophilicity. Drug release would be dependent on the rate of drug diffusion through the gel layer. If no gelling occurs, water penetrates through the pores and drug release will then be determined by the rate of drug transfer through these pores.

The spray dried microcapsules prepared in this study tended to form aggregates and on contact with water formed multi-particulate gelatinous masses. Polymer gelling, together with swelling can block up pores and set up a diffusional barrier. The hydrophilicity of the polymer could play a major role in determining the dissolution properties of the spray dried microcapsules since it controls the rate of wetting/hydration. The hydrophilicity, which is a measure of the affinity for water, of the polymers in descending order is [16] : NaCMC > HPMC > MC > HPMCAS. The same order was also obtained with the dissolution $T_{50\%}$ values (Fig. 2). NaCMC, being more hydrophilic, swelled faster, blocked up the pores and hindered the dissolution of the theophylline, resulting in a prolonged dissolution $T_{50\%}$. The sustained release (Fig. 3) suggested that rapid gelation immediately retarded the release of surface drug particles.

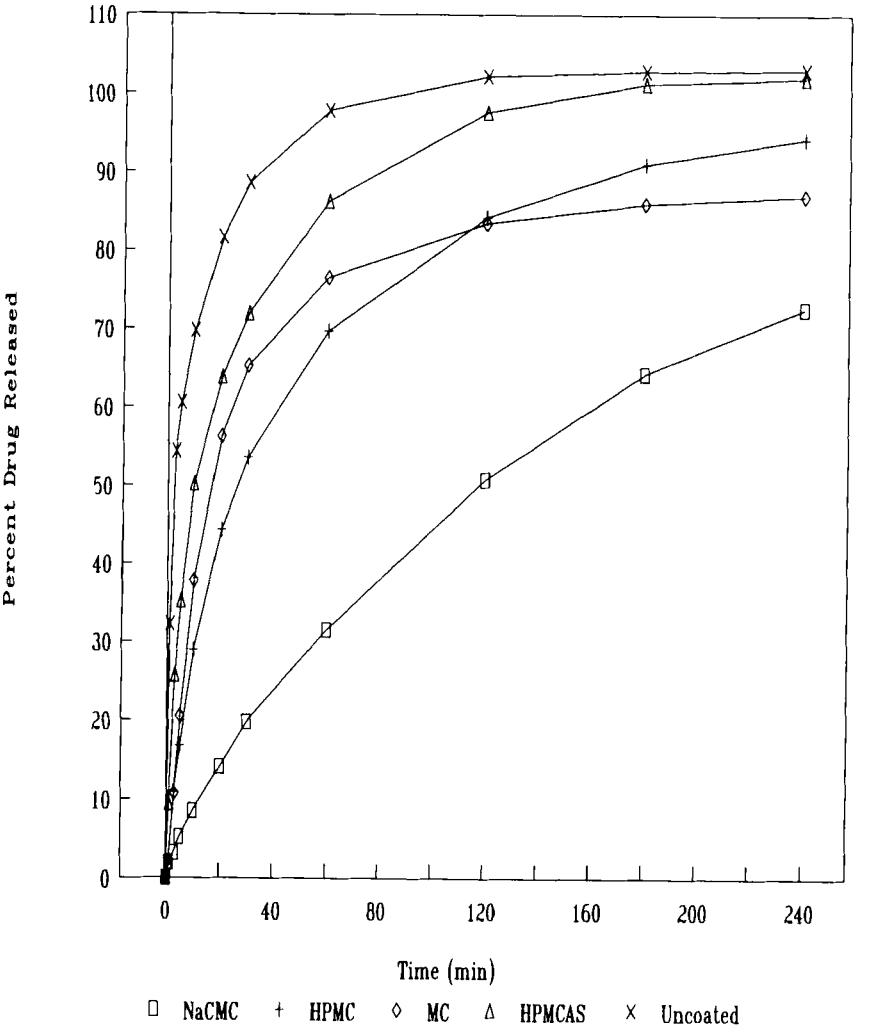


FIGURE 3

Effect of polymer types on the release profiles of theophylline from the spray dried product.

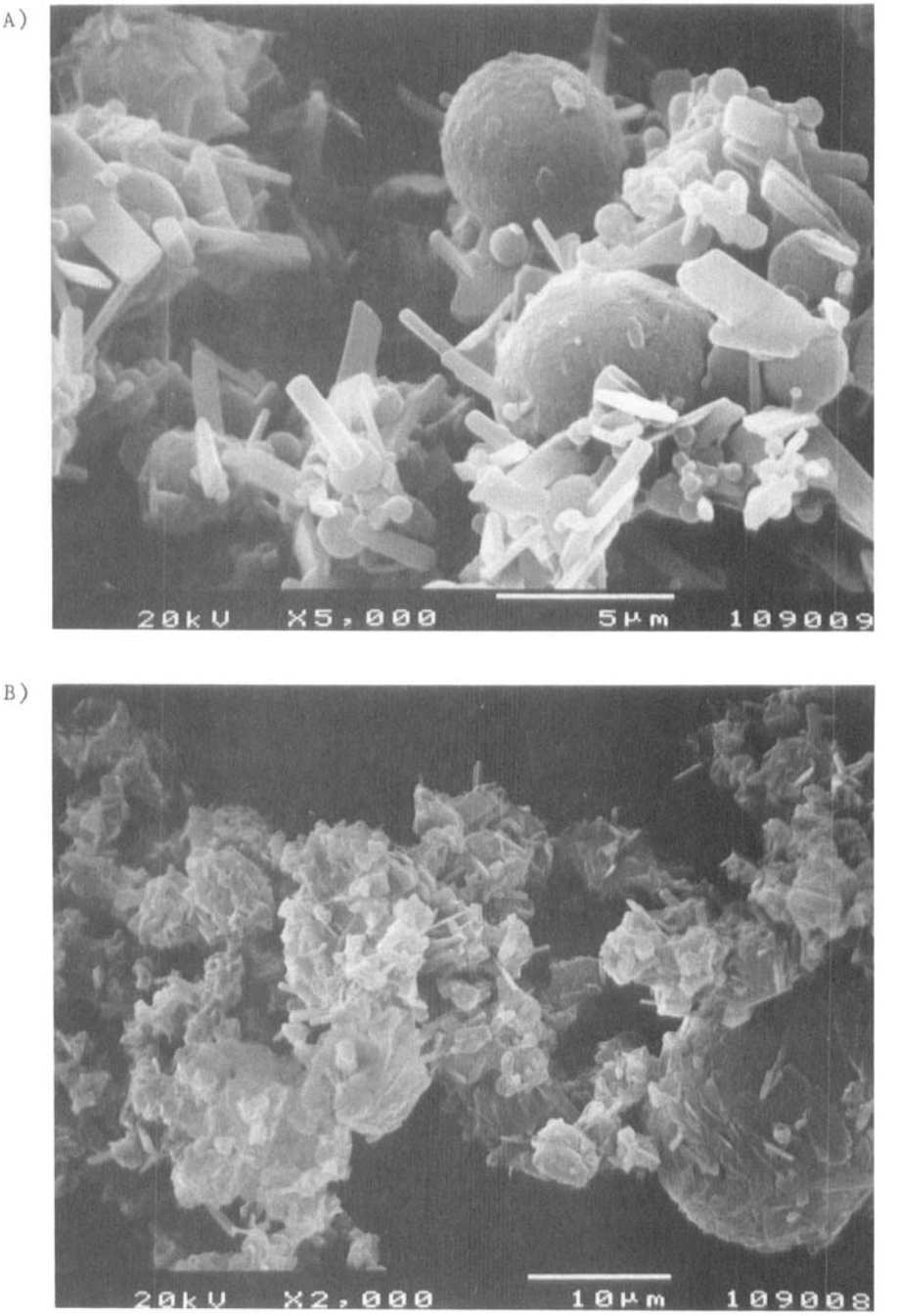
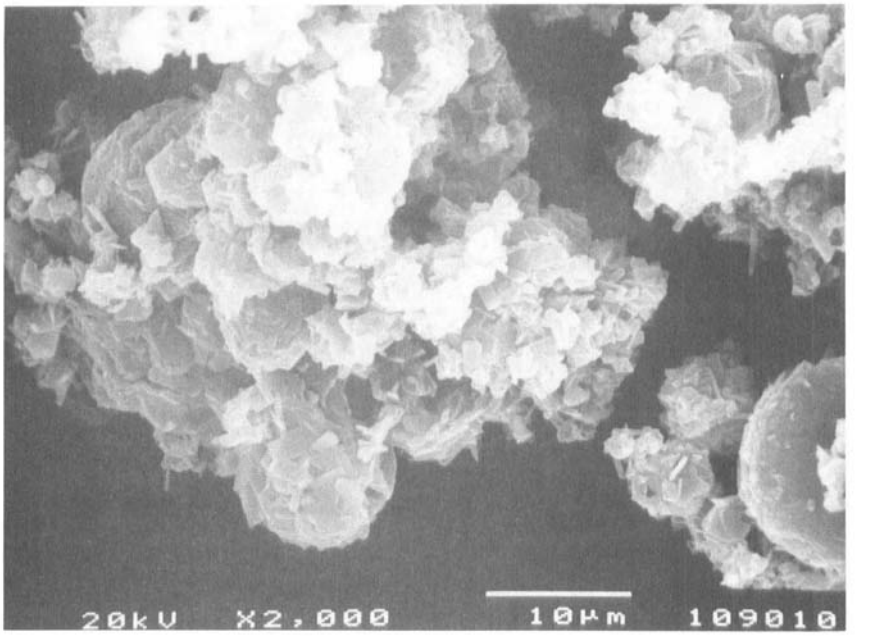


FIGURE 4

SEM photomicrographs of the products obtained by spray drying with different polymers - (a) NaCMC, (b) HPMC, (c) MC and (d) HPMCAS.

C)



D)

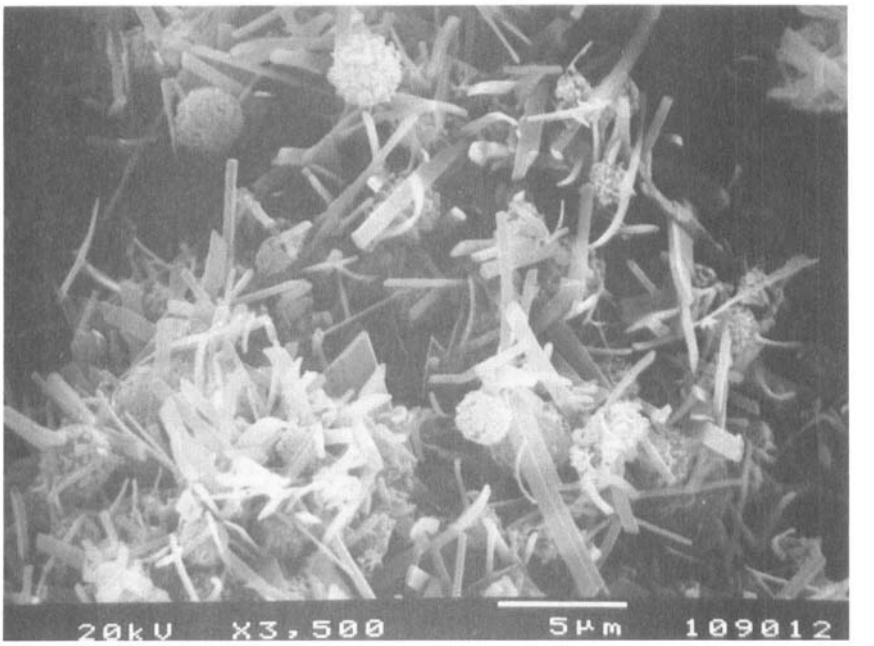


Figure 4 Continued

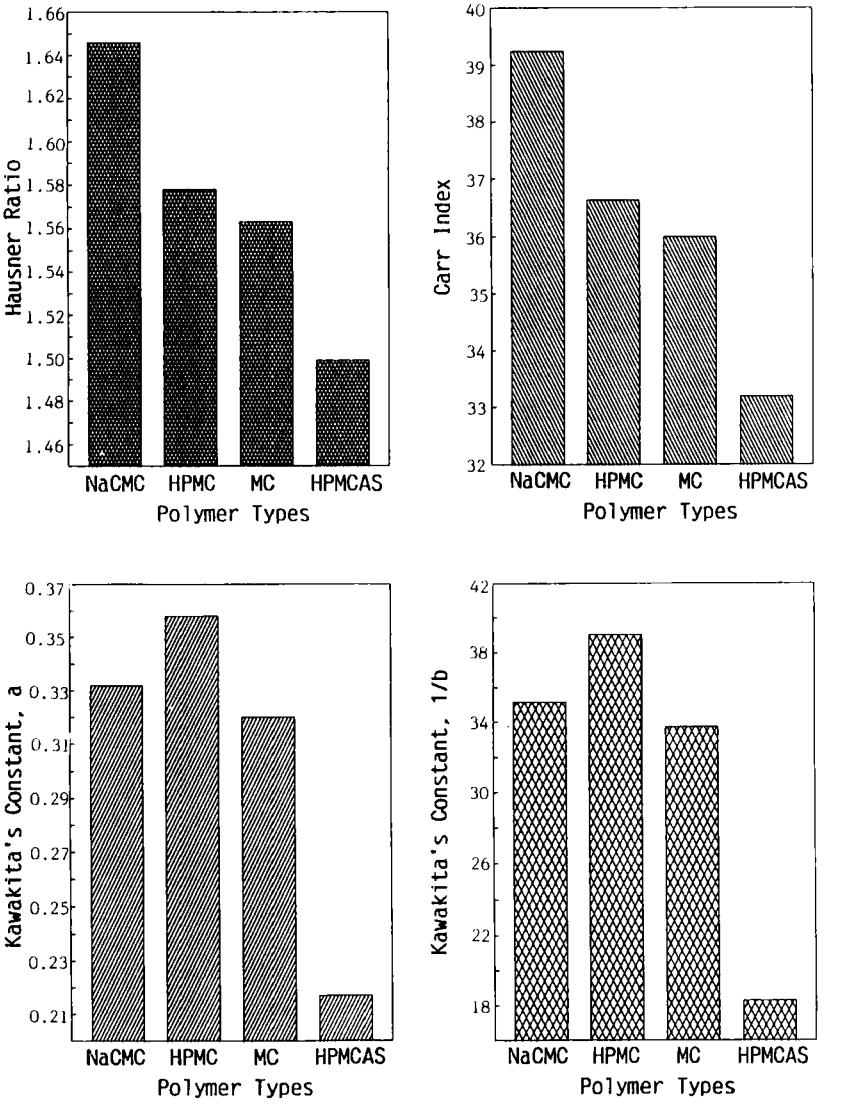


FIGURE 5

Type of polymer affecting the flowability parameters of the spray dried products.

The type of product formed was also different with different coating polymers shown in Figures 4(a)-(d). NaCMC produced smooth surfaced particles (Fig. 4(a)). The complete coating of the drug may also account for the delayed drug release. However, there were many surface crystals which appeared smooth, indicating that these crystals may be coated with a thin polymeric film unlike those with HPMCAS. Products with HPMC and MC have flake-like drug particles embedded in the polymer (Fig. 4(b-c)). These particles showed faster release rate than NaCMC coated particles (Fig. 3) due to initial loss of the surface and core drug before the complete formation of a gel layer. HPMCAS does not hydrate on wetting. The product spray dried with HPMCAS consisting of long thin needle-like theophylline with scattered HPMCAS particles (Fig. 4(d)) indicated that as an encapsulating agent for spray drying, HPMCAS does not appear to have suitable coat-forming and encapsulating properties with theophylline. Although the products containing HPMCAS have a rapid drug release, they show good flow properties (Fig. 5) because the long strands tended to align, this, coupled with the spherical polymeric materials, allow them to flow smoothly. According to Neumann [17], anisometric particles with high elongation to flatness ratio, tended to flow with their long axes oriented in the direction of the flow. In such an orientation, they showed less friction than isometric particles. The products with HPMC and MC appeared similar (Fig. 4(b-c)) and therefore showed more or less similar flow properties.

The degree of cohesiveness, as indicated in Figure 5, shows a similar relation to the data obtained for dissolution $T_{50\%}$ (Fig. 2). The possible reason for the product with NaCMC to have high values of Hausner ratio and Carr index was either due to the cohesiveness of the surface imparted by the polymer or the size of the particles which were much smaller than those with the other polymers. Particles which are more cohesive tend to aggregate and form larger agglomerates. These agglomerates have a comparatively reduced area exposed to the dissolution medium, thus delaying drug release.

CONCLUSIONS

The results showed that a suspension-feed produced microcapsules with better flow properties and slower drug dissolution than the products from a solution-feed. Most of the product from the solution-feed contain drug particles

on the polymer surface, resulting in a rapid drug release. The dissolution profiles of the spray dried product was dependent on the type of polymer and its hydrophilicity. NaCMC, which is more hydrophilic, gelled faster and retarded the release of the drug more effectively. HPMC and MC do not form smooth surface particles unlike those coated with NaCMC. Of the polymers studied, only HPMCAS was found unsuitable for this process. There seems to be a direct relationship between cohesiveness and dissolution $T_{50\%}$. The cohesiveness imparted by the polymer causes agglomeration of the microcapsules and affect drug release. This study shows that the spray drying process can be a very useful technique for the microencapsulation of drug materials. The method is simple and applicable with aqueous formulations.

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