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The influence of drying method on the physical properties of some graft copolymers for drug delivery systems

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Graft copolymers of methyl methacrylate (MMA) on various natural substrates (carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl starch and hydroxypropyl starch) were prepared in aqueous medium by the ceric ion initiator method. Products were dried in two differents ways: in ovens (O products) and by lyophilization (L products). The extent of graft copolymerization was measured in terms of grafting efficiency (GE), grafting (G), total conversion (CT) and crude grafting (CG). As would be expected, by both drying methods almost identical values of grafting yields were obtained. Using scanning electron microscopy (SEM) some morphological particle size differences between O and L products were observed. These differences lead to different physical properties (particle size, moisture uptake, density and swelling capacity) of O and L products. Copyright © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

One of the more common methods of fabricating controlled-release dosage forms is by incorporating the drug in a matrix containing a hydrophilic rate-controlling polymer. A matrix is defined as a well-mixed composite of ingredients fixed into a shape by tableting or use of a hard-shell capsule. In the development of drug delivery devices, polysaccharides as cellulose derivatives (Alderman, 1984) and starch derivatives (Dumoulin *et al.*, 1994) have been widely used, as have synthetic polymers, e.g. methacrylates (Peppas & Peppas, 1989), acrylic acids (Pérez-Marcos *et al.*, 1991) and methacrylamides (Kopečková & Kopecek, 1990).

When a water-soluble polymer is formulated as a tablet and placed in a dissolution medium, a gelatinous layer is formed at the tablet surface that prolongs the release of drugs. Fast hydration would lead to a dispersion of the system, due to the internal polymer–penetrant interaction, and dissolution of water-soluble polymers, increasing drug release. Fast polymer hydration can be reduced by using less water-sensitive ingredients (Alderman, 1984). Many polysaccharides possess chemically active functional groups that can be used for further manipulation. Furthermore, our research work has dealt with making graft copolymers on polysaccharides (Goñi *et al.*, 1983) as a way of obtaining materials that profit from the particular properties of both natural and synthetic macromolecules. Thus, in this work we have synthesized graft copolymers of methyl methacrylate (MMA) on various cellulosic and starch derivatives using the Ce(IV) redox initiation method (Mino *et al.*, 1959). Graft copolymerization of vinyl monomers on some polysaccharides in the presence of the ceric ion is generally thought to result from radical sites generation on the carbohydrate backbone, by cericion oxidation (Mino *et al.*, 1959). We have chosen polymethyl methacrylate (PMMA) because of its known biocompatibility and non-toxic behavior (Andrade, 1976), together with its ease of polymerization.

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The aim of this study was to obtain products for controlled drug delivery devices, as was advanced in an earlier work (Velasco *et al.*, 1996), with different absorption capacities. In addition, some of the parameters that could influence grafting effectiveness and water content, e.g. drying method, chemical composition of carbohydrates (Doelker, 1990), chemical structure of the graft copolymers (Castellano *et al.*, 1995), particle size and size distribution (Kawashima *et al.*, 1993), and polymer densities (Perry & Chilton, 1973), are studied.

EXPERIMENTAL

Materials

Carboxymethyl starch (CS) (Avebe, Quicksolan, CMS), hydroxypropyl starch (HS) (Avebe, Perfectamyl A-5914), carboxymethyl cellulose (CC) (Aldrich, 19189-2) and hydroxypropyl cellulose (HC) (Aldrich, 32.306-3) were used as received.

The methyl methacrylate monomer (MMA) (Merck) was purified by distillation under previously described conditions (Goñi *et al.*, 1983). The initiator was ceric ammonium nitrate (Fluka). All the other products were reagent grade or the equivalent.

Synthesis and characterization

To make a more profitable process, from an industrial point of view, in this study we have increased the amount of reactives in each reaction with respect to the method used in our first work (Goñi *et al.*, 1983).

The carbohydrate (40 g) was dispersed in 550 ml of bidistilled water and purged by passing purified nitrogen through it. The temperature was maintained at 30°C. 100 ml of MMA and, 15 min later, 50 ml of the initiator solution (0.1 M ceric ammonium nitrate in 1 N nitric acid) were added. Grafting was allowed to proceed for 4 h. Thus, the following graft copolymers were synthesized: HS–MMA, CS–MMA, HC–MMA and CC–MMA. The products obtained were filtered and the solid washed with nitric acid solution and bidistilled water.

Taking into account the great importance of powder particle characteristics in the pharmaceutical industry, in this work we compare the characteristics of powders obtained by two different drying methods: in an oven to constant weight under vacuum at 50°C (O products) or freeze-dried in a lyophilization apparatus (FD-154D, Varian) (L products). In both cases the same product is obtained but in two different states: as a glassy mass (O products) or as a powder (L products).

In order to identify and compare powder properties, the results obtained were analyzed by ANOVA.

Characterization of graft copolymers

In order to characterize the graft copolymerization reaction, the PMMA homopolymer was removed from the total reaction product, with tetrahydrofuran (THF), by soxhlet extraction for 72 h. Afterwards, the grafted PMMA was isolated from carbohydrate chains by acid hydrolysis with perchloric acid (60% vol.) in a glacial acetic acid medium (Gurruchaga *et al.*, 1984).

Grafting yields

The following parameters were calculated: percent grafting efficiency (%GE = percent weight of graft copolymer with respect to total polymer), percent crude grafting (%CG = percent weight of total acrylic polymer with respect to total carbohydrate), percent grafting (%G = percent weight of grafted acrylic polymer with respect to grafted carbohydrate) and percent total conversion (%CT = percent weight of total acrylic polymer with respect to initial monomer).

Characterization of powders

In order to investigate the suitability of a product for a specific application, for example as a controlled drug delivery system, it is necessary to gather information about its physical properties.

The oven-dried copolymers were previously crushed in a hand mill to get powdery products.

True density

The density of the polymers can significantly influence the average gastrointestinal transit time of the drug delivery devices because if the polymer density is lower than the gastric juice density the product floats for an extended period. For example, an increase in density from 1.0 to 1.6 decreased the average transit time from 7 to 25 h (Ranade, 1991). Therefore, the true density of each powder was determined using a pycnometer (Model SPY-3 Quantachrome). The gas used was helium.

Moisture uptake capacity

Products can retain large amounts of water. This influences the flowability of the powder during the manufacturing process or storage. Enscore *et al.* (1977) reported that the mechanism of moisture sorption is affected by the particle size of the powder. In this study, the moisture uptake capacity (MU) of dried products was calculated by an IR moisture analyzer (Sartorious) at 50°C for 20 min. Previously samples were conditioned in closed chambers with a relative humidity (RH) of 75.5% (Nyquist, 1983) at room temperature for a week.

SEM

For a better understanding of the differences between the products obtained by each drying method, the

morphology of particles was studied by means of a scanning electron microscope (SEM HITACHI-S-2700). The surface of the powders was previously gilded.

Water content

Some authors suggest that the drug release rate of tablets of hydroxypropyl cellulose can be predicted from the water uptake characteristics. Before the contents of the tablet can dissolve, quick formation of a protective gelatinous layer is necessary to achieve controlled drug release from a hydrophilic matrix (Alderman, 1984). Therefore, the relative rates of hydration of the polymer must be considered. The water content of products (%WC = weight of water content in hydrated products with respect to the weight of hydrated products) was determined gravimetrically after placing the products in bidistilled water at 37°C and the equilibrium was attained.

RESULTS AND DISCUSSION

Synthesis and characterization

The results obtained on grafting MMA on the different carbohydrates are shown in Table 1. In this table are listed the yields obtained for the products obtained by oven and lyophilization drying methods. Although, obviously, the drying method does not influence the grafting yields, it should be noted that the values obtained for HS–MMAO and HS–MMAL showed statistically significant differences ($\alpha < 0.01$). The different aspect of the powders obtained in each case makes us think that in some cases removal of a good homopolymer removing is prevented, giving rise to a higher %GE and so to a higher %G in L products, but not varying the %CT.

Comparing the grafted backbone, the lowest values of %GE and %G are obtained for CS–MMA graft copolymers. This indicates a lower reactivity of this carbohydrate, with respect to the others, with MMA. We observed that hydroxypropyl carbohydrates show a higher statistically significant %G than their corresponding carboxymethyl carbohydrate and only CC–MMA copolymers (O and L), show statistically significant %CT differences ($\alpha < 0.01$) with respect to the other copolymers.

Owing to the complexity and heterogeneity of particle size distributions, and in order to be able to justify our results, we calculated the average radius ($1/R = \Sigma X_i/R_i$, where X_i is the weight fraction) (Buchholz, 1990) of the graft copolymer particles (Table 2). Only HC–MMA copolymers show no statistically significant average radius differences ($\alpha < 0.05$) between the O and L copolymers. Hydroxypropyl carbohydrates showed statistically significant lower radius values ($F = 7.83$, $\alpha < 0.05$) than carboxymethyl copolymers and there are no statistically significant differences between starch and cellulose copolymers.

These different particle sizes influence the later compaction process and drug delivery (Nokhodchi *et al.*, 1995).

Taking into account that the PMMA density is lower ($1.218\,g\,cm^{-3}$) than that of each of the carbohydrates used, it would be expected that the density of MMA graft copolymers would be lower than that of the pure carbohydrates (Table 2). In addition, when a grafting reaction takes place polymer chains wrap the carbohydrate's backbone, increasing the free volume of the total product and consequently decreasing its density. However, it should be noted that HC copolymers do not show a density decrease with respect to the departing HC carbohydrate density value, possibly because of the similar density values of HC and PMMA polymers.

Table 1. Yields of the graft copolymerization of MMA on different carbohydrates

	%CG	%GE	%G	%CT
HS–MMAO	184.6 ±2.5	81.6 ±1.2	125.5 ±8.1	2.6 ±7.1
HS–MMAL	170.8 ±1.3	73.1 ±2.1	83.7 ±9.8	70.8 ±3.6
CS–MMAO	182.8 ±1.7	36.7 ±2.1	29.4 ±1.4	82.9 ±0.9
CS–MMAL	176.0 ±0.9	37.2 ±2.8	25.1 ±3.5	82.5 ±1.9
HC–MMAO	181.1 ±1.5	57.0 ±0.45	127.3 ±7.6	89.6 ±1.1
HC–MMAL	182.3 ±2.7	60.5 ±4.8	132.5 ±4.4	88.9 ±6.6
CC–MMAO	175.0 ±2.3	84.6 ±5.9	66.6 ±19.6	57.9 ±6.8
CC–MMAL	166.5 ±3.6	88.9 ±3.2	57.6 ±10.4	5.3 ±3.7

Table 2. Physical characteristics of the different graft copolymer powders

		Density(g cm^{-3})	MU(%)	R(μm)
HS	—	1.490±0.017	13.32±0.56	14.75±0.29
	MMAO	1.288±0.007	4.85±0.19	32.64±0.65
	MMAL	1.358±0.012	5.01±0.06	45.85±0.86
CS	—	1.531±0.006	12.14±0.62	102.83±2.04
	MMAO	1.314±0.009	4.28±0.09	51.22±1.02
	MMAL	1.361±0.010	4.52±0.11	92.30±1.80
HC	—	1.263±0.018	6.56±0.25	81.75±1.63
	MMAO	1.239±0.006	4.00±0.05	58.93±0.88
	MMAL	1.261±0.008	4.56±0.13	57.92±0.95
CC	—	1.581±0.004	17.47±0.34	24.36±0.48
	MMAO	1.375±0.003	8.22±0.12	60.79±1.60
	MMAL	1.399±0.004	8.89±0.42	74.34±0.99

Although, as has been said before, there are no compositional differences between the O and L products of each copolymer, there are statistically different densities ($\alpha < 0.01$) between them. When the gel obtained in the reaction is dried in an oven, on deswelling a 'surface skin' layer is formed, trapping water inside the gel (Okano *et al.*, 1993). The skin formation leads to the build up of hydrostatic pressure within the gels (Kaneko *et al.*, 1995). When the shrinking force in the network bulk becomes large, the surface portion of the gel exhibits a bubble-like structure and the trapped water is squeezed from the interior by way of bubble formation (Kaneko *et al.*, 1995). When the gel obtained is dried by lyophilization, the water is removed by a sublimation process, preventing bubble formation. This means that water molecules are removed as solid particles from L products. This different way of removing water could be responsible for the slightly lower density of O products compared with the corresponding L products.

Generally, polysaccharides can absorb and retain large amounts of water in their amorphous portions

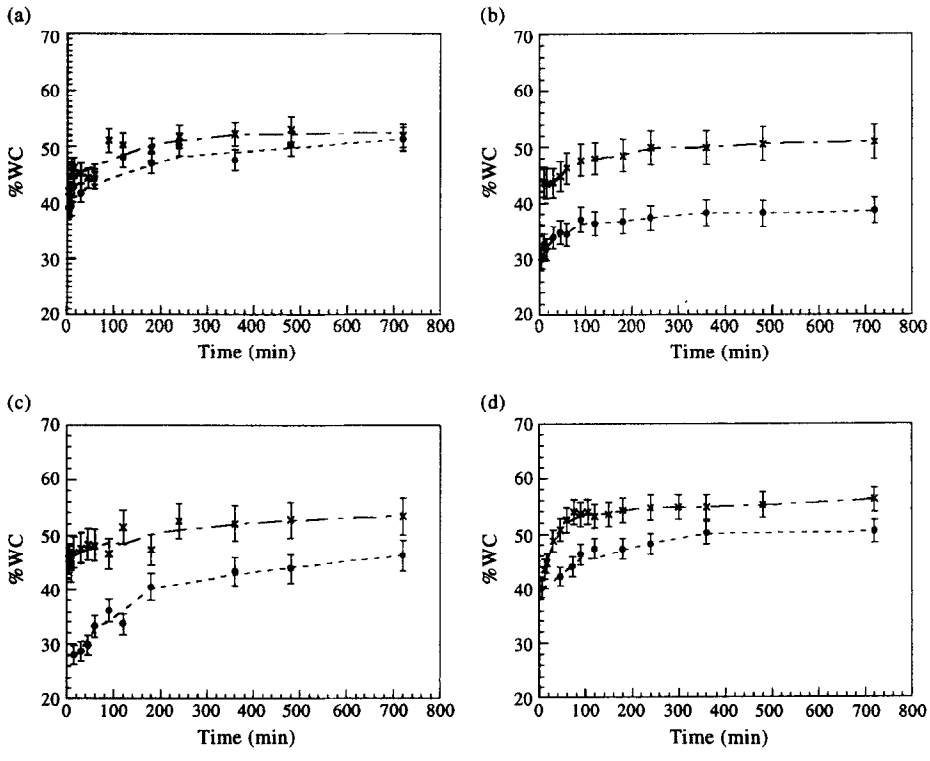

Fig. 1. Water content (%WC) of O (•) and L (x) products: (a) HS–MMA, (b) CS–MMA, (c) HC–MMA and (d) CC–MMA in bidistilled water at 37°C as a function of time.

when exposed to water vapor at various relative humidities (Aoki *et al.*, 1992). At high humidities the flowability of the hydrogel powders deteriorates in relation to the gradual moisture uptake in the hydrogel. This means that it is difficult to obtain tablets by direct compression. Table 2 shows the values of moisture uptake (at 75.5% of RH) of carbohydrates and O and L graft copolymers. Obviously the addition of a hydrophobic polymer, as the PMMA, to the carbohydrate gives rise to fewer hydrophilic products, leading to lower MU values.

To explain the moisture uptake value sequence shown in Table 2 (CCMMA > HSMMA > CSMMA > HCMMA), we must take into account the ratio of MMA to carbohydrate in the final grafted products. A higher ratio would lead to a higher hydrophobicity and consequently to a lower moisture uptake. The ratios of the products are 0.97, 1.77, 2.44 and 2.92, respectively, i.e. they are in agreement with the sequence of moisture uptake values obtained. This behaviour is reinforced by the moisture uptake tendency of the carbohydrates. No statistically significant differences were found between starch and cellulose copolymers, although hydroxypropyl copolymers showed lower statistically significant MU values ($F = 5.23, \alpha < 0.01$) than carboxymethyl copolymers.

In order to relate moisture uptake and particle size, two copolymers, HS–MMAL and HC–MMAL, were fractionated by size and the moisture uptake of each fraction was determined. As expected, the higher the particle size, the lower the percentage moisture uptake, due to the higher surface area of small particles. In line with this, one would expect that O products will be able to retain more water molecules than L products. However, although no statistically significant differences were observed, O products gave lower moisture uptake values than L products.

Another interesting parameter in the formulation of hydrophilic matrices for drug delivery systems is the penetration rate of water or the swelling ability. The polymer selected must be hydrated quickly enough to form a gel layer before the contents of the tablets can dissolve (Alderman, 1984).

The %WC of powders was calculated at 37°C (Fig. 1). All the products reached the equilibrium before 4 h and had a similar water content, in the range 35–55%, but in general L products absorbed more

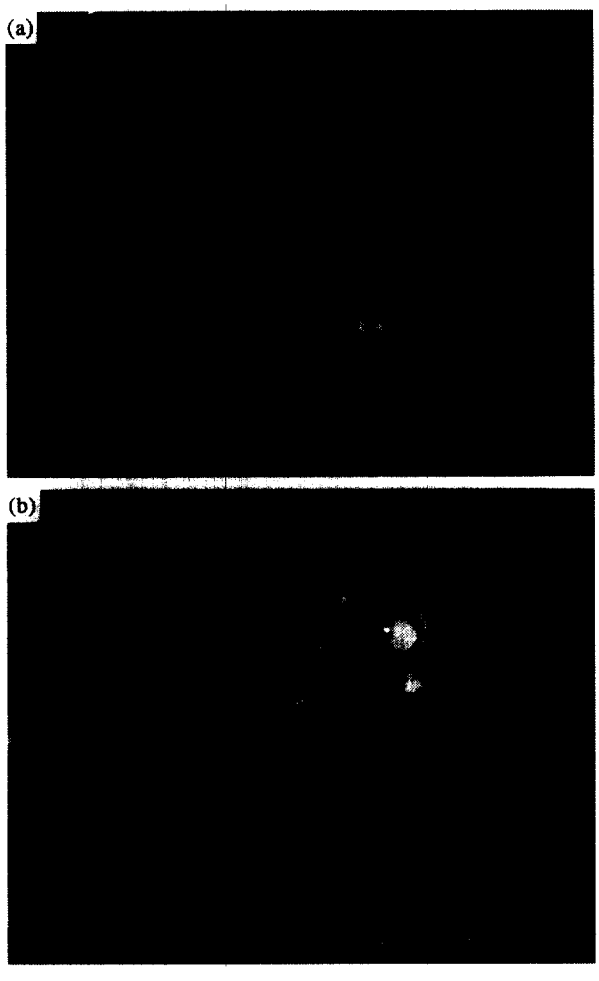

Fig. 2. SEM micrographs of (a) HS–MMAO and (b) HS–MMAL.

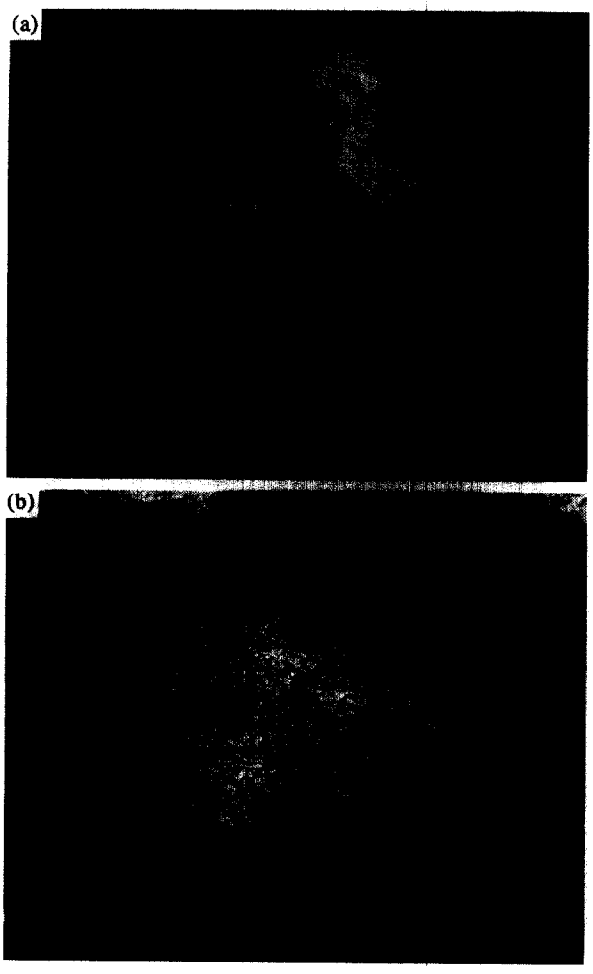

Fig. 3. SEM micrographs of (a) CS–MMAO and (b) CS–MMAL.

water than O products. These results are in agreement with the moisture uptake values obtained, which showed higher values for L products.

This fact can be explained if we observe by SEM the morphology of particles (Fig. 2, Fig. 3, Fig. 4 and Fig. 5). In Fig. 3, Fig. 4 and Fig. 5a, cracked O particles can be seen that suggest a spherical shape at origin, showing a smooth internal surface. In Fig. 2, Fig. 3, Fig. 4 and Fig. 5b, non-damaged L particles can be seen. The crushing process, necessary to obtain powders from O products, produces scar faces that lead to particles with lower surface areas with respect to their corresponding L products. The bigger the particles, the higher the mechanical degradation of particles; that is why some particles have all faces cut while others have only one or none. In all cases, the increase in scar faces and the less wrinkled topography of O products is enough to explain their slightly smaller hydrophilicity, MU and water absorption capacity values. The morphological differences are less evident in HS products (Fig. 2+ <2> b). HS–MMAO is more powdery than the other O products, thus the crushing applied is lowest and only a few particles appear cracked.

From this study we can conclude that different carbohydrates give rise to products of different acrylic polymer content and different particle and size shapes. The drying method followed determines their morphology and consequently some of their physical characteristics. The aim of this work has been to identify all the products obtained and study the influence of the various characteristics of the products on water content. A previous work (Velazquez, 1996) corroborated that this type of graft copolymer fullfilled the requirements of good flow and compression characteristics. The next step, which will be reported in future publications, is to gather more extensive data on the swelling as well as on the drug release rate at different pHs of tablets obtained by direct compression.

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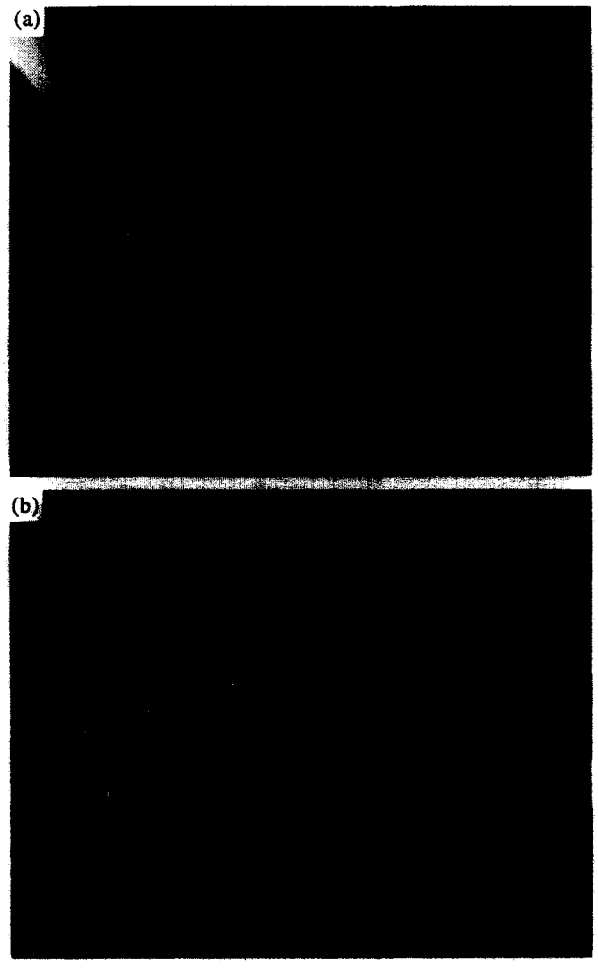

Fig. 4. SEM micrographs of (a) HS–MMAO and (b) HS–MMAL.

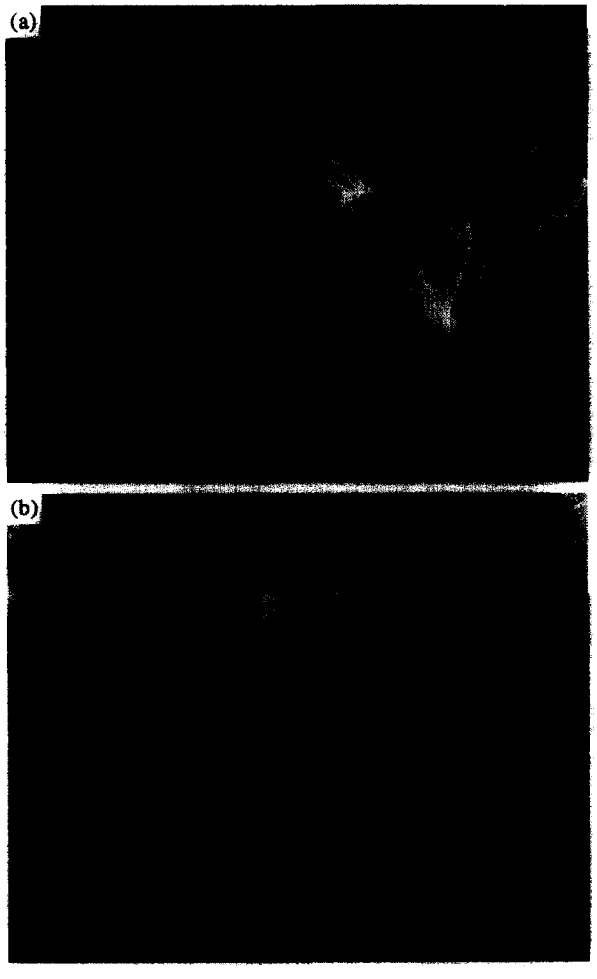

Fig. 5. SEM micrographs of (a) CC–MMAO and (b) CC–MMAL.

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