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RESEARCH PAPER

Methoxybutropate Microencapsulation by Gelatin-Acacia Complex Coacervation

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ABSTRACT

Microcapsules of methoxybutropate solid particles or of an oily saturated solution of the same drug were prepared by complex coacervation between gelatin and acacia and dried with three different methods: isopropanol addition, spray-drying, and freeze-drying. Successively, microparticles were analyzed by infrared thermobalance, ultraviolet (UV) spectroscopy, optical and scanning electron microscopy, and sieves to find out parameters such as yield, moisture content, encapsulation percentage, morphology of solid particles, and particle size. Results highlighted that the most appropriate drying method for industrial purposes was spray-drying, particularly for oil-containing microcapsule formulations.

Key Words: *Coacervation; Freeze-drying; Methoxybutropate; Microcapsules; Spray-drying.*

INTRODUCTION

Methoxybutropate is an analgesic, nonsteroidal, anti-inflammatory drug derived from the esterification reaction between ibuprofen and guaiacol. This water-insoluble molecule presents very good stability; being insensible to oxygen and ultraviolet (UV) radiation, it undergoes hydrolysis only at very low or very high pH values; it is absorbed from the gastrointestinal tract. Unfortunately, the drug possesses a very unpleasant bitter taste and is administered in a relatively high dosage (600 mg); this makes it difficult to formulate tablets as the final pharmaceutical dosage form. Thus, microencapsulation of the drug in a polymeric shell could offer a solution to this problem.

Many kinds of polymers have been used with a large number of procedures for the encapsulation of solid parti-

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cles or fluid droplets; these can be summarized and simplified as coacervation–phase separation, solvent evaporation, atomization, interfacial polymerization, and fluid bed technique (1–17). The choice of one method over another depends on drug chemical and physical characteristics and on the final aim.

In this case, as methoxybutropate is water insoluble and no modification of absorption kinetics is wanted, an appropriate microencapsulation method appears to be coacervation of colloidal polymers from an aqueous drug suspension.

This method has been widely studied (18–21), but it is not easy to reproduce on an industrial scale because of the difficulty of recovering single microcapsules and avoiding sticking phenomena at the end of the procedure.

The aim of this work was to microencapsulate methoxybutropate by a coacervation process with colloidal polymers using a method to avoid the sticking phenomena that normally occur during the drying phase, thus making the process reproducible on an industrial scale.

The drug, either as a powder or previously dissolved in an oily phase, was microencapsulated by complex coacervation between gelatin and arabic gum. The microcapsules were dried and recovered using three different methods: coacervate dehydration with isopropanol and subsequent filtration, spray-drying, and freeze-drying of the same coacervate.

MATERIALS AND METHODS

Gelatin Characterization

To determine the isoelectric point of the gelatin utilized (Nuova Astrochimica, Milan, Italy), isoelectrofocalization was performed with a Rotofor cell under the following experimental conditions: 50 ml of 1% gelatin and 2.5 ml of 40% Ampholines (I.P. 3–10) as a sample; 0.1 N NaOH as an anodic solution; 0.1 N H_3PO_4 as a cathodic solution; focalization room temperature 4°C; generator power 12 W; time course 5 hr.

Encapsulation Process

The two procedures used are presented in Figs. 1 and 2. For the encapsulation of the solid drug, a certain amount of methoxybutropate powder (ACRAF, Ancona, Italy) was put in a 10% (w/v) gelatin solution at 40°C, and the suspension was homogenized with an Ultraturrax (Janke and Kunkel Labortechnik, Staufen, Germany) at 10,000 rpm for 2 min. Then, an equal volume of a 10%

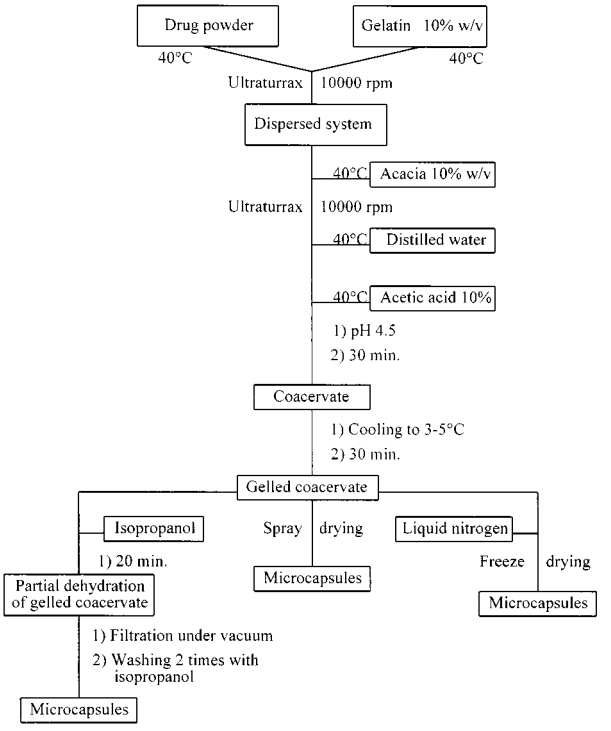

Figure 1. Coacervation procedure for solid drug encapsulation.

(w/v) acacia (Nuova Astrochimica, Milan, Italy) solution at 40°C was added to the suspension, and the system was rehomogenized under the already described conditions. The final weight ratio of the methoxybutropate and the two polymers together was 1 : 1. This new suspension was next diluted with distilled water (prewarmed at 40°C) to reach a concentration of 1.5% (w/v) for each colloidal polymer. Finally, the addition of a volume of a 10% acetic acid solution (always prewarmed at 40°C) necessary to reduce the pH value to 4.5 gave rise to the coacervation process. After 30 min, the system was cooled to 5°C and left for 1 hr at this temperature before drying and recovering the free-flowing microcapsules. During the process, the system was continuously stirred at 150 rpm except during homogenization with the Ultraturrax.

For the encapsulation of the oily phase, an amount of solid drug was previously dissolved, at room temperature, in the lowest necessary volume of soybean oil to obtain a saturated solution (25 g/100 ml). Then, a certain volume of this solution was added to an equal volume of a 10% (w/v) gelatin solution at 40°C, and the emulsion was homogenized with the Ultraturrax at 10,000 rpm for 2 min. Finally, a volume of 10% (w/v) acacia solution

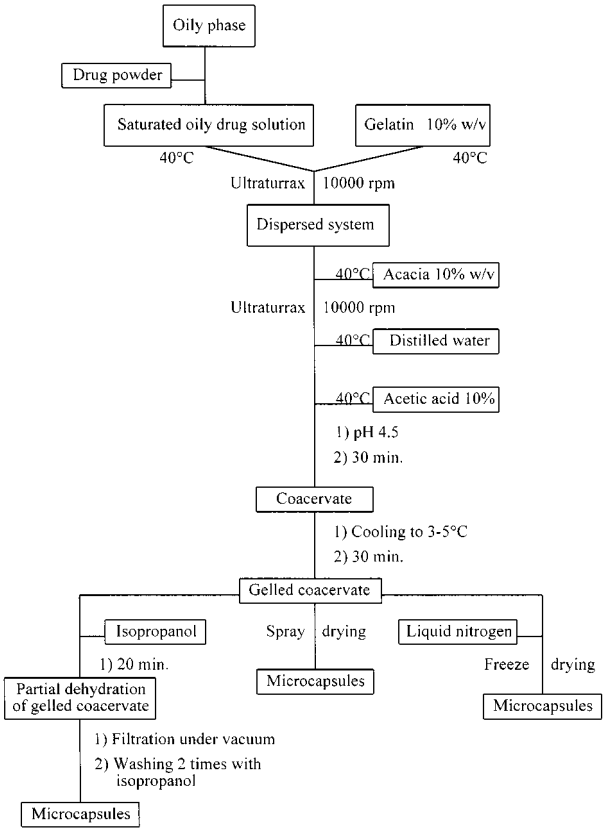

Figure 2. Coacervation procedure for encapsulation of oily drug solution.

at 40°C, exactly equivalent to the already used volume of gelatin, was added to the emulsion, and the system was rehomogenized. The remaining encapsulation process was identical to that described above.

In both cases, microcapsules were recovered using the methods described next.

Dehydration with Isopropanol

An equal volume of previously cold isopropanol (5°C) was added to the system (maintained at 5°C), which was filtered under vacuum 20 min later. Then, the partially dehydrated microcapsules were resuspended twice in fresh isopropanol, filtered again, and finally air dried overnight before analysis.

Spray-Drying

The gelled system was directly spray-dried using a Niro Atomizer (Denmark) under the following conditions: inlet temperature 150°C, outlet temperature 85°C, feed rate 20 ml/min, pressure 4 kg/cm^2. The obtained powder was then collected and analyzed.

Freeze-Drying

An FTS Dura-Dry FD-14-84 freeze-drying apparatus (New York) was used for this process. The gelled system was put in borosilicate glass containers that were plunged in liquid N_2 for a while and then put inside the freeze-dryer chamber previously cooled to −30°C. When the ice temperature was stabilized, the condenser temperature was set to −90°C, and the vacuum pump was switched on. After the process had set out, the freeze-drying room was heated in the right proportion to avoid further cooling of the congealed mass (which could slow or stop the sublimation process). When primary drying was finished, the temperature of the freeze-dryer chamber was increased to 20°C, which was maintained for 30 min before stopping the process. The obtained powder was then collected and analyzed.

Moisture Content

Humidity of the obtained powders was verified using a Mettler PJ 300 infrared thermobalance.

Ultraviolet Analysis

The UV analyses of the microcapsules were performed to determine the percentage of encapsulated drug. An amount of each powder was extracted with 50 ml of ethanol for 12 hr under continuous stirring at room temperature. Then, the suspension was filtered with a 0.45-μm membrane filter (Millipore), and the drug content of the ethanol solution was determined spectrophotometrically at 255 nm with a UV-2101 PC UV-Vis (visible) scanning spectrophotometer (Shimadzu, Japan) connected to an AT 386 computer.

Optical and Scanning Electron Microscopy

Optical Microscopy

An Olympus 234682 microscope (Japan) was used to observe particle transformation during the coacervation process.

Scanning Electron Microscopy

A Stereoscan 360 electron scanning microscope (Cambridge Instruments Limited) was used to point out morphology and surface structure of the microcapsules obtained with the three different drying methods.

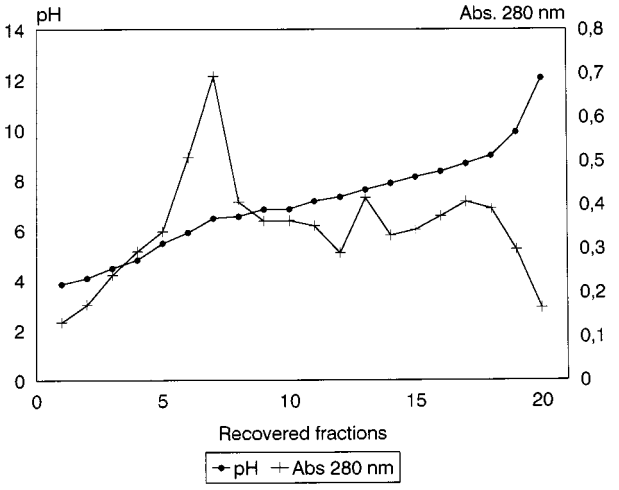

Figure 3. Gelatin isoelectrofocalization.

Sieve Analysis

Particle size distribution and mean diameter of microcapsules were determined by sieving 100 g of each powder with a Vibrotronic VE1 (Retsch, Germany) using sieves of the following aperture size: 40, 80, 125, 160, 200, 250, 400, 500, 630, and 1000 μm.

RESULTS AND DISCUSSION

Gelatin Isoelectric Point

Gelatin used the for microencapsulation process was composed of several fractions (Fig. 3) with isoelectric points that ranged between pH 6.46 and pH 8.64. Particularly, the isoelectric point of the predominant fraction was 6.46.

Yield of Microencapsulation Procedures

The yield for the three drying methods has been calculated for both encapsulation procedures from the difference between the amount of material used and that recovered at the end of the process (Table 1). For the encapsulation of solid drug, the yield was only 76.1% when the microcapsules were dried with isopropanol, while the best results were obtained by freeze-drying (99%). Spray-drying gave intermediate results (89.5%); in fact, a small amount of the microcapsules adhered to the spray-dryer chamber. On the other hand, when the drug was previously dissolved in soybean oil and then encapsulated, the yield was remarkably lower (66%) using the isopropanol drying method and a little higher (93%) with the spray-drying method. These results highlighted the advantage of using spray-drying or freeze-drying to recover solid and dry microcapsules to obtain good yields, particularly in the encapsulation of an oily phase.

Table 1

Yield of Microencapsulation Procedures

	Yield (%)	
Drying method	Solid Core	Oily Core
Isopropanol	76.1	66
Spray-drying	89.5	93
Freeze-drying	99	99.5

Table 2

Moisture Content of Dried Microcapsules with Solid Core

	Humidity (%)	
Drying Method	10 min After Drying	2 Days After Drying
Isopropanol	4.53	5.6
Spray-drying	1.15	4.13
Freeze-drying	1	4.15

Moisture Content

Residual humidity of dried microcapsules with solid cores and oily cores are reported in Tables 2 and 3, respectively. Microcapsules dried with isopropanol possessed a certain residual humidity, while those dried by spray-drying and freeze-drying had considerably lower values. This difference in moisture content fell if powders were exposed to air. After 2 days, all values were similar, with a humidity increase more sensible in microcapsules dried by spray-drying or freeze-drying.

Table 3

Moisture Content of Dried Microcapsules with Oily Core

	Humidity (%)	
Drying Method	10 min After Drying	2 Days After Drying
Isopropanol	4.25	5.1
Spray-drying	0.9	3.15
Freeze-drying	1	3.1

Table 4

Microencapsulation Percentages of Microcapsules with Solid Core

Drying Method	Methoxybutropate (%)	Encapsulation (%)
Isopropanol	40	80
Spray-drying	46.7	93.4
Freeze-drying	49.2	98.4

Ultraviolet Analysis

Tables 4 and 5 show the percentages of drug recovered in the powders and the consequent microencapsulation percentages (confirmed by microscopic analysis) for microcapsules with solid cores and oily cores, respectively. All powders presented a very good percentage of microencapsulation even if differences in values had been remarked. The lowest percentage was obtained when coacervate was dried with isopropanol because this solvent partially extracted the drug from the core of the microcapsules. However, on the other hand, for microcapsules with a solid core, after freeze-drying with the same coacervate, nearly 100% of the drug was found in the powder. Also, spray-drying presented very good efficiency, with 93.4% of the drug encapsulated. For microcapsules with an oily core, this efficiency was further improved; in fact, both spray-drying and freeze-drying gave nearly 100% encapsulation.

Optical Microscopy

Figures 4 and 5 show images of solid methoxybutropate particles suspended in the colloidal dispersion and of the gelled microcapsules, respectively, as visible by optical microscopy (magnification 400). Irregularly shaped drug particles (Fig. 4) were transformed, after coacervation and coacervate gelling, into spheroidal agglomerates that constituted the core of the microcapsules (Fig. 5). Around this core, it was very visible that the colloidal layer of coacervate made the particles completely spherical.

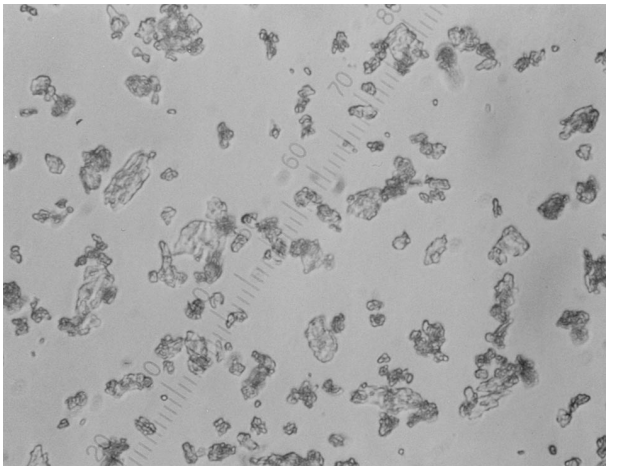

Figure 4. Solid methoxybutropate particles suspended in the colloidal dispersion (optical microscope).

Figures 6 and 7 show the initial (oil-in-water, o/w) emulsion and the gelled oil-containing microcapsules, respectively, as visible by optical microscopy (magnification 400). Emulsified oily droplets (Fig. 6) were attracted after coacervation and coacervate gelling to form a polynucleated core. Around this core, the polymer layer of coacervate was visible (Fig. 7).

Table 5

Microencapsulation Percentages of Microcapsules with Oily Core

Drying Method	Methoxybutropate (%)	Encapsulation (%)
Isopropanol	13	70
Spray-drying	18.3	99
Freeze-drying	18.1	98

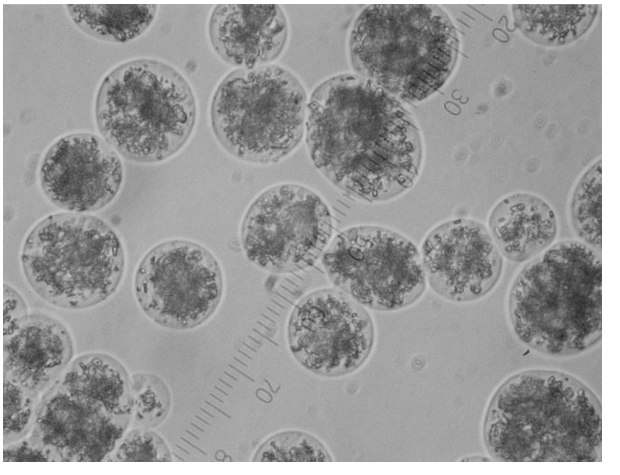

Figure 5. Gelled microcapsules with solid core (optical microscope).

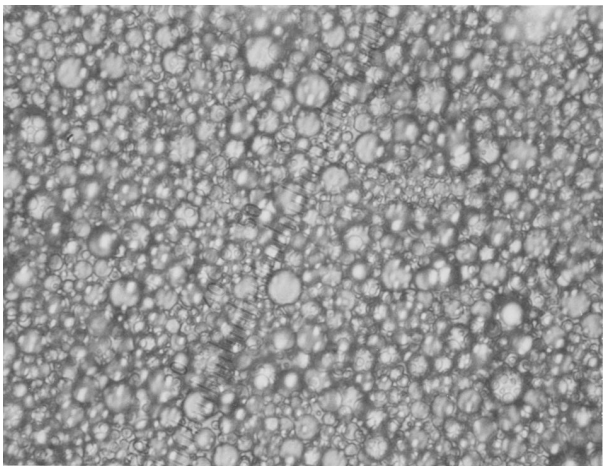

Figure 6. Initial oil-in-water emulsion (optical microscope).

Scanning Electron Microscopy

Figures 8, 9, and 10 show the final shape of solid-core microcapsules dried with isopropanol, by spray-drying, and by freeze-drying, respectively, as visible by electron scanning microscopy. Particles obtained by treatment with isopropanol were formed by agglomerates of single microcapsules (Fig. 8) and were greater than those obtained by atomization (Fig. 9). As expected, the spraying device of the atomizer broke every particle cluster so that single microcapsules were recovered. On the contrary, single microparticles could not be recovered using freeze-drying (Fig. 10) because the uncoacervated excess

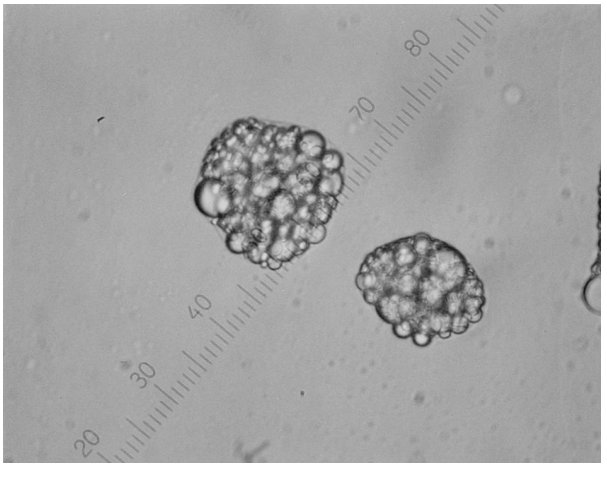

Figure 7. Gelled microcapsules with oily core (optical microscope).

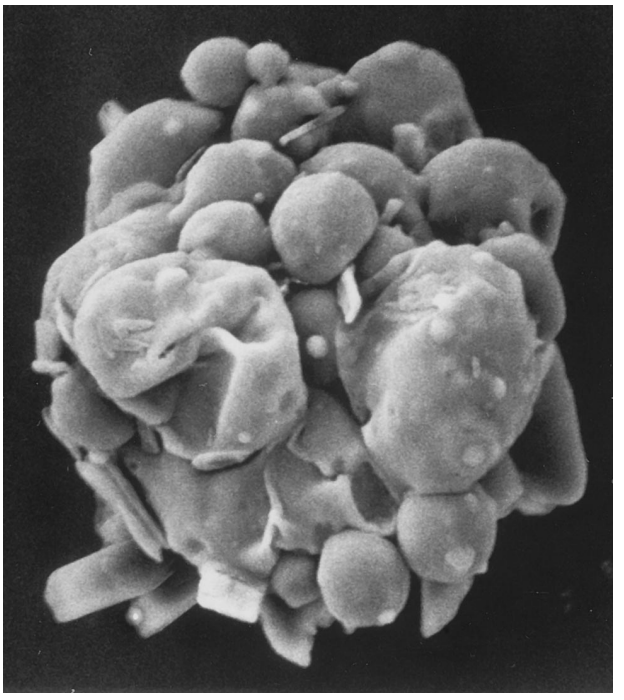

Figure 8. Final shape of microcapsules with solid core dried with isopropanol (scanning electron microscope).

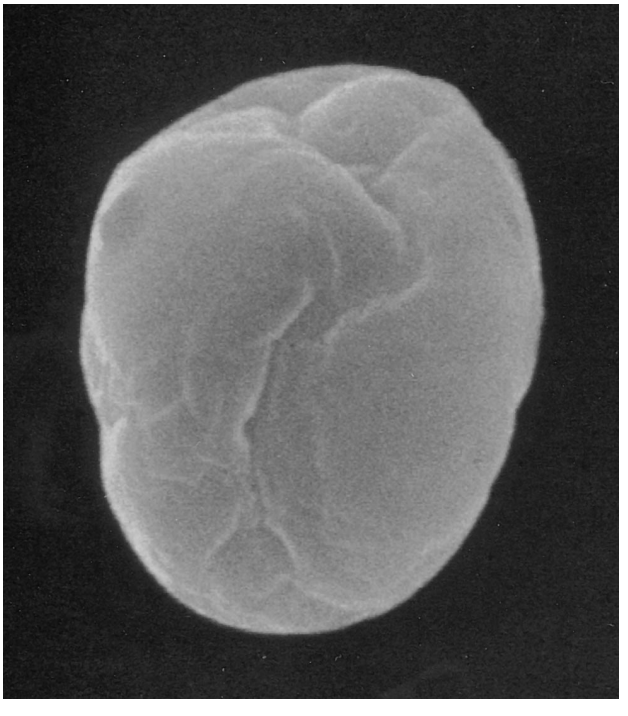

Figure 9. Final shape of microcapsules with spray-dried solid core (scanning electron microscope).

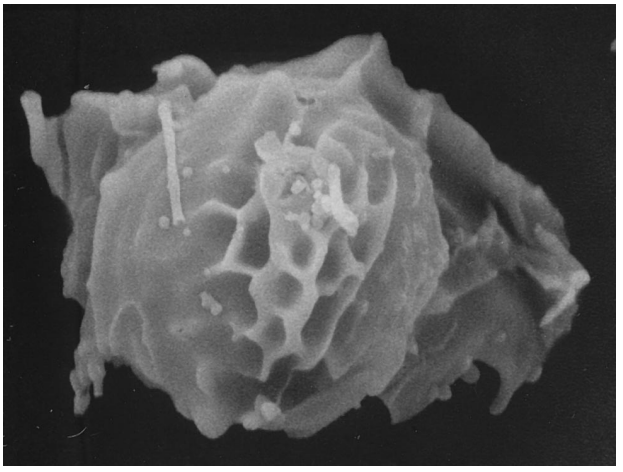

Figure 10. Final shape of microcapsules with freeze-dried solid core (scanning electron microscope).

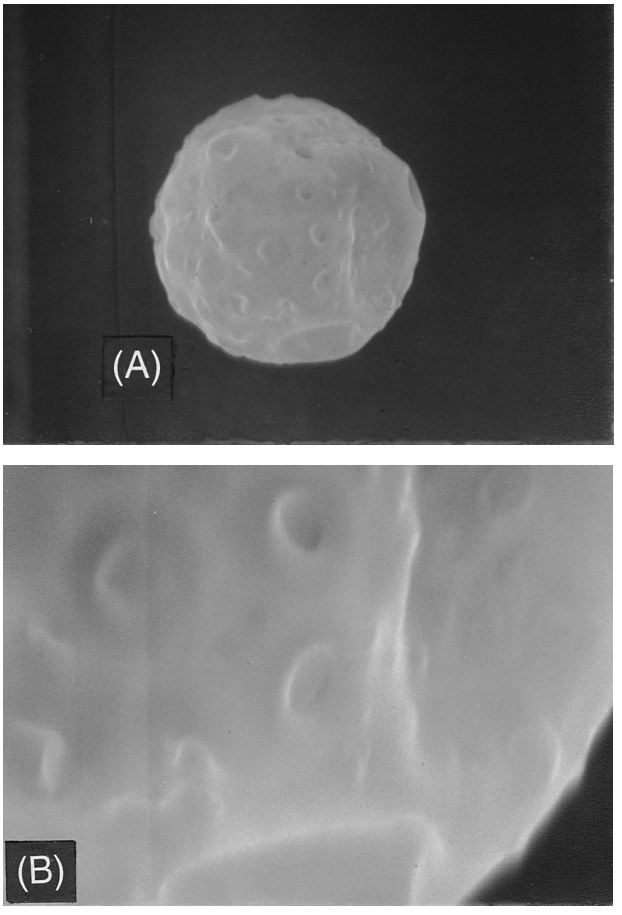

Figure 11. A. Final shape of microcapsules with spray-dried oily core (scanning electron microscope). B. Surface of microcapsules with spray-dried oily core (scanning electron microscope).

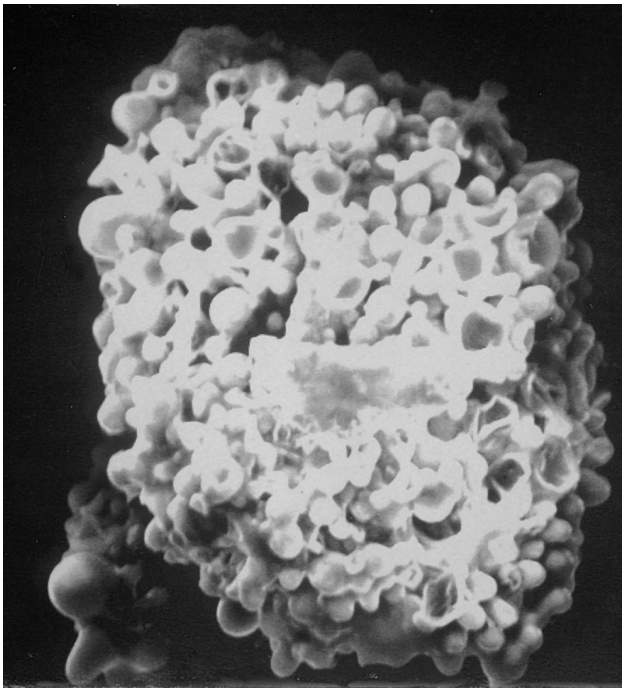

Figure 12. Final shape of microcapsules with freeze-dried oily core (scanning electron microscope).

of colloidal polymers formed bridges between particles after water sublimation.

Figures 11 and 12 show the final shape of oily core microcapsules dried by spray-drying and freeze-drying, respectively. In this case, freeze-drying gave clusters (Fig. 12), while single particles were recovered by spray-drying (Fig. 11A). The external surface of these microcapsules was not smooth, but presented many small craters, probably derived from water evaporation, in the shell pores, which disappeared at the end of the evaporation (Fig. 11B).

Oil-containing microcapsules dried with isopropanol could not be analyzed because, after complete drying, the soybean oil partially came out, causing particle agglomeration and making this kind of analysis impossible to perform.

Sieve Analysis

In Figs. 13, 14, and 15, the granulometric distributions (weight of powder retained by each sieve) of solid core microcapsules dried with isopropanol, by spray-drying, and by freeze-drying, respectively, are reported in percentages. The mean diameters of these powders calculated from the data shown in the three figures were 330

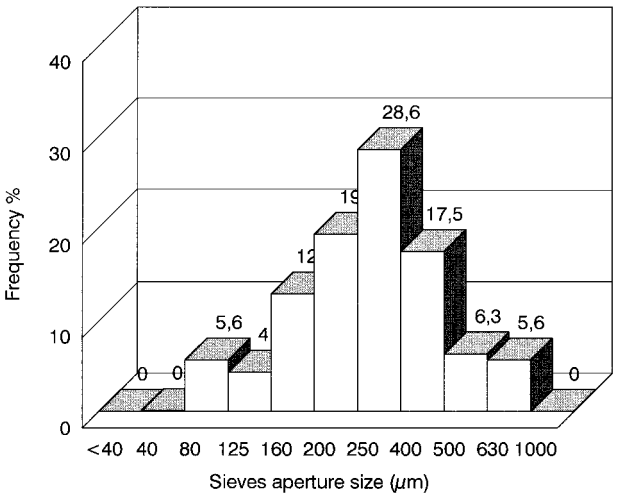

Figure 13. Granulometric distribution of solid-core microcapsules dried with isopropanol.

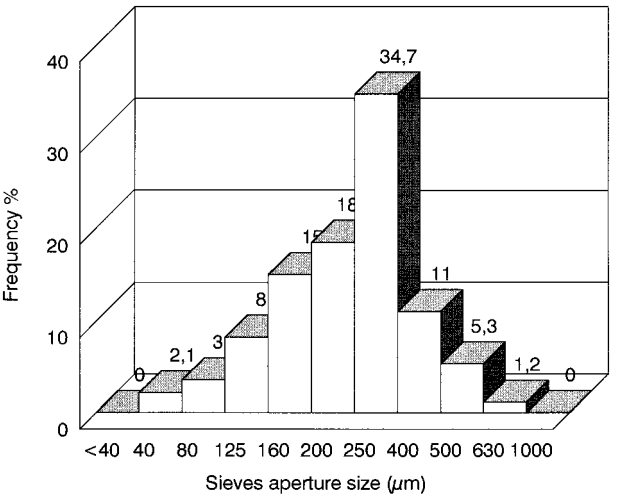

Figure 15. Granulometric distribution of freeze-dried solid-core microcapsules.

μm for the isopropanol drying method (Fig. 13), 164 μm for the spray-drying method (Fig. 14), and 290 μm for the freeze-drying method (Fig. 15).

Figures 16 and 17 show granulometric distributions (%) of oily core microcapsules spray-dried and freeze-dried, respectively. The mean diameters calculated from these distributions were 155 μm for spray-dried powders (Fig. 16) and 423 μm for freeze-dried powders (Fig. 17).

In agreement with electron scanning microscopy, these results substantially confirmed the increased effectiveness of spray-drying in recovering single microparticles.

Granulometric distribution of oily core microcapsules dried with isopropanol could not be obtained because, as mentioned above, after complete drying, the soybean oil partially came out, causing particle agglomeration and making this kind of analysis impossible to perform.

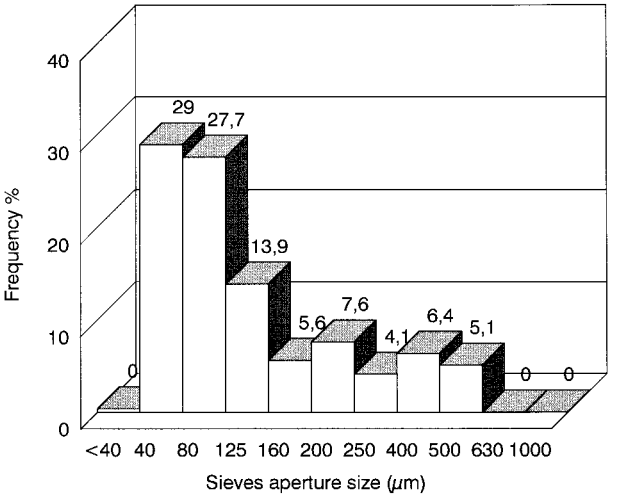

Figure 14. Granulometric distribution of spray-dried solid-core microcapsules.

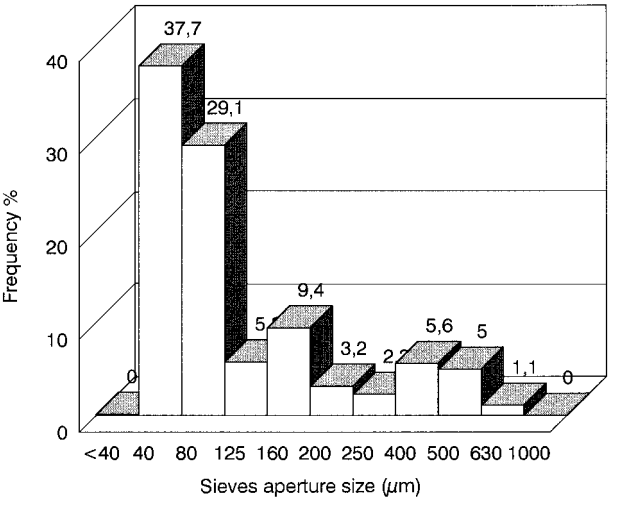

Figure 16. Granulometric distribution of spray-dried oily core microcapsules.

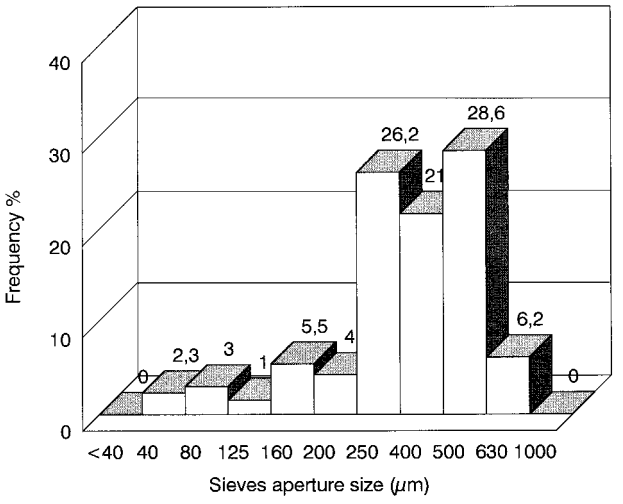

Figure 17. Granulometric distribution of freeze-dried oily core microcapsules.

CONCLUSION

Methoxybutropate microcapsules can be prepared from solid drug particles or from a saturated oily drug solution by gelatin-acacia complex coacervation, which forms a readily water-soluble shell. Independent of the nature of the core, a powder of single microcapsules is easily and quickly recovered using an atomizer as the drying method.

At the moment, the authors are carrying out an optimization of the spray-drying operating conditions to make the production of these microcapsules possible on an industrial scale.

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