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Note

Preparation of monodisperse controlled release microcapsules

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Abstract

Since the handling of many active agents in its pure form has many problems, microencapsulation is used to have better properties in the product. With the patented BRACE-Processes it is possible to encapsulate a very wide range of materials in monodisperse Microspheres or Microcapsules in a diameter range of 50–6000 μm with a very narrow size distribution. The Microsphere Units from BRACE can be customer tailored to the materials and all necessary specifications as FDA, GMP/GLP, EX, CIP, WIP etc. The throughput of the BRACE Microsphere Units ranges between 10 ml per h (small laboratory scale) up to over 1000 l per h (production scale) while the production cost are very low, especially if compared directly to competitive processes as spray-drying or fluidized bed coating. © 2002 Elsevier Science B.V. All rights reserved.

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The most technically or industrial available products are handled as grains, flakes, blocks or powders. With this granulometry many disadvantages are at hand. Especially when handling of active agents is required, the difficulties are enormous. Not only the application itself is in many cases trouble-loaded, e.g. due to instabilities of the active agent in air, but also the dosage with potent or expensive agents or the handling with oily ones leads to expensive machinery with many problems.

The solution of these problems can be done by microencapsulation with BRACE Microspheres and Microcapsules. The Microspheres are solid spheres with a matrix encapsulated active agent while the Microcapsules consist of a solid shell with a liquid or solidificated core (Fig. 1).

Fig. 1. Schematic drawing of Microcapsules and Microspheres. From left to right: Microcapsule with solution as core, Microcapsule with cell suspension as core, Microsphere with matrix encapsulated active agent.

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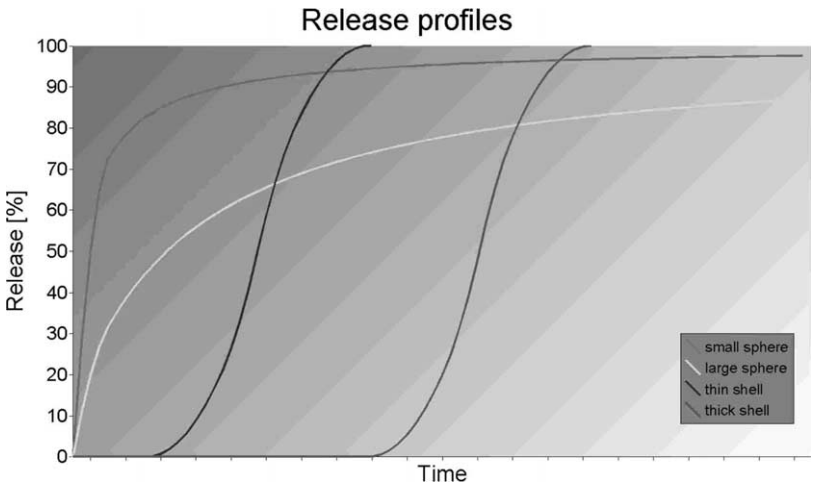

Fig. 2. Release profiles of different types of Microspheres and Microcapsules. While small Microspheres have a fast release profile (bright red), larger Microspheres have slower release rates (bright green). The burst time of Microcapsules depend on the thickness of their shell (dark red and dark green).

The main difference between these two types of microgranules is in the release profile. While Microspheres usually have diffusion controlled release profiles with a permanent release rate which is kinetically controlled by the particle size, Microcapsules expel their content by a single high burst as the shell breaks (Fig. 2).

The patented BRACE-Processes for producing Microspheres and Microcapsules are basically vibrating nozzle processes. These processes produce particles with monomodal grain size distributions with a single sharp maximum. d_{min}/d_{max}-values lower 1.10, 1.05 or even 1.01 are common for spherical granules produced with the BRACE Microsphere Units. It is possible to obtain Microspheres or Microcapsules in a diameter range of about 30–8000 μm. A wide range of shell materials are usable with this highly scalable process. All installations can be customer tailored to meet all necessary requirements like GMP/GLP, FDA, Pharma-, Food-, Nuclear-, Chemistry- or other Industrial-Standards.

The process itself can be described schematically as follows (Fig. 3): a liquid feed is pumped from a feed tank (Brandau, 1993) to the nozzle head (Brandau, 1995b) where the vibrating device (Brandau, 1995a) induces the breakup of the flow into uniform droplets. These are formed into spheres by the surface tension of the feed. The

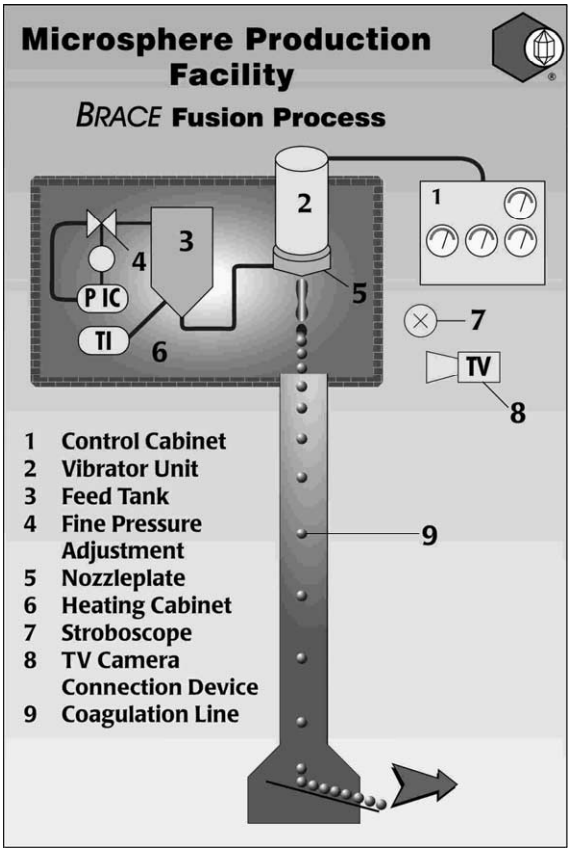

Fig. 3. BRACE Microsphere Process (Fusion Process).

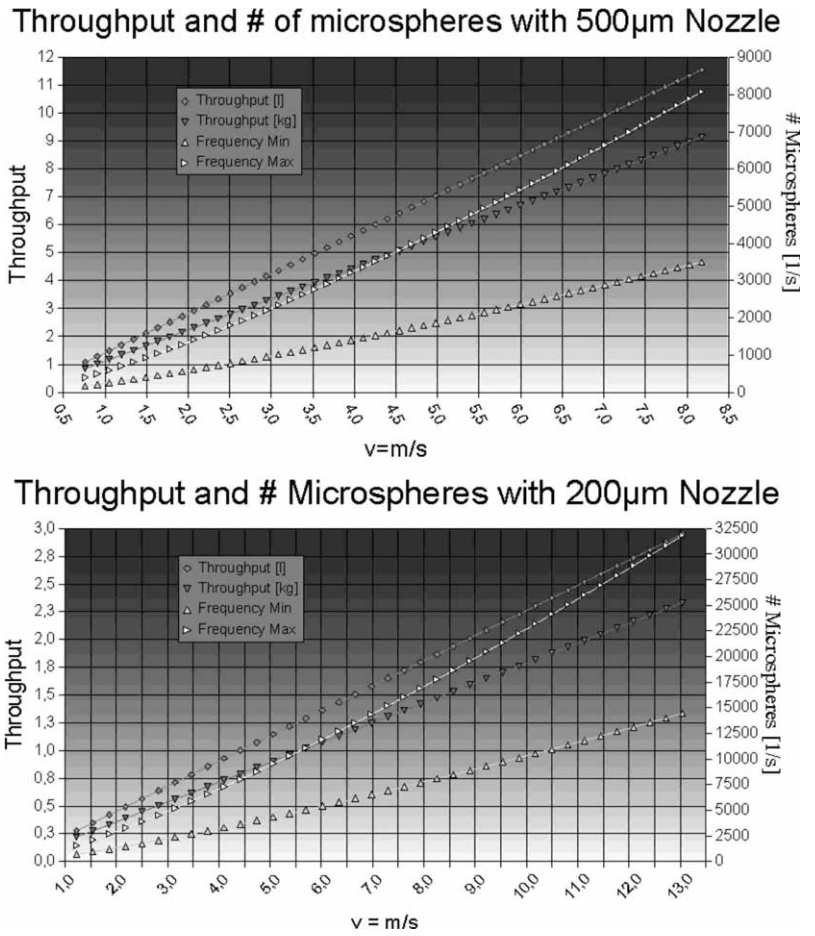

Fig. 4. Comparison of throughput and Number of Microspheres per s to the nozzle diameter. As a calculation base a thermoplastic with a melting point of 80 °C has been chosen.

droplets are solidificated during falling (Brandau, 2001). This can be realized depending on the materials and/or coagulation system used by cooling, chemical reaction or drying. The head of the Microsphere unit can be placed in a heating chamber (Brandau, 1995c), the visual control of the process can be either done by a stroboscopic lamp or with a camera set for remote control. The electronic cabinet (Brandau, 2002) controls the microsphere unit and can be integrated in existing control systems.

Usable materials for the BRACE Microsphere processes have to be liquid, the viscosity has to be lower than 10 000 mPa·s, emulsions and dispersions have to be stable over the duration of the process, dispersed particles should have diameters lower than 1/4th of the nozzle size to be used and the coagulation system used should be a fast process so that the particles are not deformed. Suitable materials are for example alginates, gelatines, agar–Agar, wax/thermoplastics, metal oxides, PEG, PVA, Polyacrylate, -methacrylate and Polystyrene.

Suitable active agents depend on the encapsulation technique. For matrix-encapsulation (Microspheres) the active agent can be dispersed, dissolved or emulsified into the shell material. For Microcapsules the core material can consist of a liquid like a solution, an emulsion, a dispersion or a fusion/melt. The only restriction is, that the core

material should not react with the shell material (i.e. to weaken it).

All Microsphere Units from BRACE are customer tailored to the specific needs of the customer. Depending on the application they are build conform to GMP/GLP, FDA, CIP, WIP, as continuous or batch wise installations, fully automatic or semi automatic. They can be adapted into existing production facilities and scaled from laboratory scale up to large production scale.

The production capacity of a BRACE Microsphere installation ranges from about 10 ml per h up to over 1000 l per h. A comparison of different nozzle sizes to throughput are shown in Fig. 4. The example is calculated for a thermoplastic but can be transferred to other materials. With a 500 μm nozzle a throughput of 11 l per h with about 8000 Microspheres per second of 1 mm diameter can be produced. With a 200 μm nozzle (resulting in about 400 μm Microspheres) it is only about 2.8 l per h but with 30 000 Microspheres per s.

The manufacturing cost depends on the material and the production capacities. For industrial scale production the manufacturing cost start at €2.66 per kg for a production of 50 tons/year and reach €0.31 per kg at 1000 tons per year (Table 1). This calculation is based on a thermoplastic with a melting point of about 80 °C including a turn-key installation with building, storage and packing facilities, quality control and operator cost.

The BRACE-Processes are widely used in the chemical, pharmaceutical and food industries. For example, waxes are used in cosmetic (Fig. 5) or dental application or as catalysts with active ingredients. Agar–Agar is used to encapsulate oils or other volatile ingredients for cosmetic applications (Figure 6), gelatine or alginates are used to encapsulate oils, fragrances or flavors for food technology applications. Polymer beads (Figure 7) are used in combinatorical synthesis since the BRACE-Process produces monomodal grains of high quality polystyrene Microspheres with

Table 1
Manufacturing cost for different production scales. A thermoplastic with a melting point of about 80 °C is assumed

Investment, description (Tons per year)	Manufacturing capacity, 1 shift, 2000 h/a				
	50	100	300	500	1000
kg per h	25	50	150	250	500
Nr of Nozzles	12	24	72	120	240
Feed preparation	20 000 €	25 000 €	40 000 €	50 000 €	80 000 €
Microsphere unit	150 000 €	180 000 €	240 000 €	290 000 €	380 000 €
Storage and packing	10 000 €	15 000 €	20 000 €	30 000 €	50 000 €
Total I	180 000 €	220 000 €	300 000 €	370 000 €	510 000 €
Laboratory, quality control	10 000 €	12 000 €	16 000 €	24 000 €	30 000 €
Total II	190 000 €	232 000 €	316 000 €	394 000 €	540 000 €
Building (rent)	15 000 €	15 000 €	20 000 €	20 000 €	25 000 €
Raw material €1/kg	50 000 €	100 000 €	300 000 €	500 000 €	1 000 000 €
Operators per shift	2	2	2	3	3
Operator cost per shift	80 000.00 €	80 000.00 €	80 000.00 €	120 000.00 €	120 000.00 €
Maintenance 5% of Total II	9,500.00 €	11 600.00 €	15 800.00 €	19 700.00 €	27 000.00 €
Amortisation 5a, 8% (0,2505)	47,595 €	58 116 €	79 158 €	98 697 €	135,270 €
Amortisation 10 a, 8 % (0,14903)	28,316 €	34 575 €	47 093 €	58 718 €	80 476 €
Manufacturing cost per kg (5a)	3.04 €	1.65 €	0.65 €	0.52 €	0.31 €
Cost including material	4.04 €	2.65 €	1.65 €	1.52 €	1.31 €
Manufacturing cost per kg (10a)	2.66 €	1.41 €	0.54 €	0.44 €	0.25 €
Cost including material	3.66 €	2.41 €	1.54 €	1.44 €	1.25 €

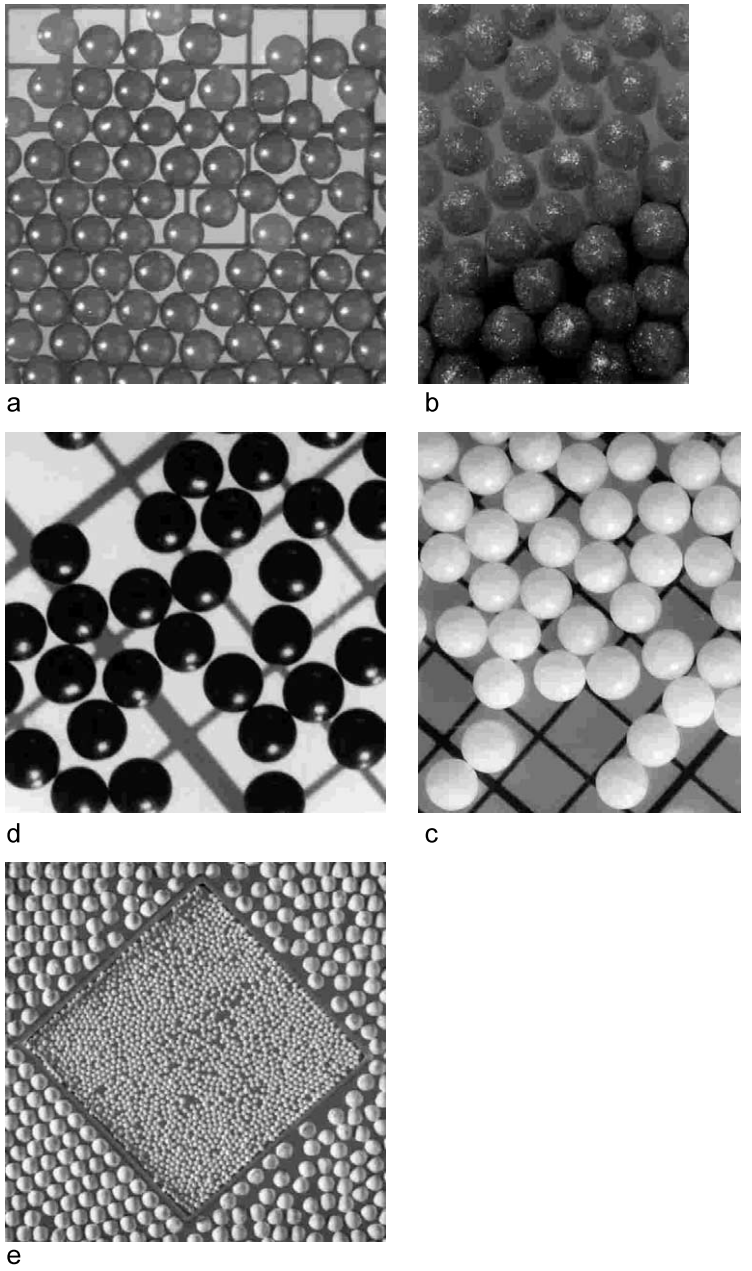

Fig. 5. Different Microsphere: (a) Cosmetic Waxes, (b) Agar-Agar with oils, (c) Polymer beads for combinatorical synthesis, (d) Pharmaceutics encapsulated in wax, (e) Inorganic Microspheres as catalyst carriers.

defined binding capacities. In the pharmaceutical industry the BRACE-Process is used to encapsulate active agents either against the destructive forces in the digestive system or as taste masking for very bitter materials (Figure 8). The adjustable size of the Microspheres is used to produce defined release profiles. Chemical and petrochemical industries use catalyst carriers (Figure 9) and

grinding balls produced by the BRACE-Processes to obtain maximum performance and low wear and tear in process. Medical industries use inorganic Microspheres in bone surgery applications while food technologist prepare toothpaste with 'crunch'.

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