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New-types of apparatus for producing microcapsules and microgranules

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Abstract

Two types of simple compact apparatuses for microencapsulation and microgranulation have been developed. The vibration-type apparatus is a better fit for producing gel-like microgranules of 1.5–3.0 mm in diameter to be used in production of food (fodder) products and additives and microgranulated cell culture. The spray apparatus is fit for operation in two modes: drop-forming (particles of 100–500 μm in diameter) and spray modes (particles of 10–50 μm in diameter). The apparatus is most efficient when used in the mode of forming the particles directly in the medium of liquid nitrogen with successive lyophilic drying (without preliminary defrosting). It is used for microgranulating the live virus materials with their virulence being preserved.

Keywords: Microgranulation; Vibration; Spray apparatus; Vaccines

1. Introduction

The last decade has been characterized by active development of research work in various areas such as:

- sustained action of drugs in peroral applications;
- search of potential peroral applications of such drugs (as the cheapest, simplest, and most easily available for mass administration, for example, immunization or antidote which need to be protected against acidity and proteolytic enzymes of gastric juice;
- search of sustained-action drugs for parenteral administration (ideally, sustained-action insulin);
- implantation of live cells and others.

They all are associated by a common methodology-development of microencapsulated or microgranulated (MIC) forms (Fig. 1) (Kissel and Koneberg, 1996). The nature of polymer shell or matrix, and a technology of microencapsulation

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should correspond to requirements for the safety of active component (drug, live virus, live cell, and others), non-toxicity for organism, and functional requirements to the shell (matrix) regarding its non-solubility, solubility in certain areas, swelling or degradation for the purpose of primary nutrient release. In connection with the above, the technologists in the microencapsulation field have been intensively working on the development of adequate apparatuses both for research and commercial purposes. Two types of rather advanced apparatuses are known:

An apparatus made by Inotech company (Inotech Encapsulation, 2001) based on vibration splitting of laminar jet, using electrostatic charging of particles to prevent their agglutination and to collect them in some appropriate liquid (for example, alginate-containing particles into solution of chitozan with $CaCl_2$). Mechanical separation of particles at the beginning and end of the process is provided for and allows us to ensure narrow size scattering. The narrow concentric spray nozzles are provided for and make it possible to produce both granules and capsules (the principle of "pipe in a pipe"), but shells produced are rather thick—the minimum particle size is 100 μm (as can be seen from the description).

The jet-cutter apparatus (Vorlop, 1998) is based on mechanical cutting of laminar jet with rapidly rotating string made of special material. It has very high efficiency. It can also be equipped with concentric spray nozzles.

Both apparatus have rather complex systems of control and are expensive.

We followed a simpler way, assuming that it is possible to allow certain statistic scattering of particle size if that scattering is stable, as it is not expected to affect the dosing and efficiency of MIC drug. Two types of apparatus have been developed to produce microgranules in the size range from 0.5 to 3.0 mm and from 10 to 100 μm. A number of solutions have been suggested to optimize particle formation and to introduce new principles of their processing after formation.

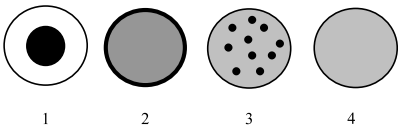

Fig. 1. Types of microcapsules–microgranules: 1, classical-reservoir type; 2, intermediate type—the shell is formed by cross-linking the matrix at the phase interface; 3, matrix type: suspensions or emulsions; 4, molecular solutions.

2. Materials

Serving as polymer matrix and objects to be microencapsulated, the following systems have been used:

2.1. Matrix

Matrix I, interpolymer complex polyacrylic acid (PAA) MM 310000, poly-*N*-vinylpyrrolidone (PVP) Kollidon 90F in proportion 1:1; aqueous solution concentration, 10%; pH 6.0–7.0.
Matrix II, esterified PAA; esterification agent, ethyl alcohol; replacement degree, 60%; aqueous solution concentration, 10%; pH 7.0–7.4.
Matrix III, esterified PAA; esterification agent, butyl alcohol; replacement degree, 60%; aqueous solution concentration, 10%; pH 7.0–7.4.
Matrix IV, gelatin with sodium alginate cross-linked with calcium glycerophosphate and tannin in proportion 4/1 by mass; aqueous solution concentration, 4%; pH 7.0–7.1; gel melting point, 32 °C.

2.2. Active excipients

I, drug, Pyracetam;
II, live measles vaccine in form of lyophilized virus material on a stabilizer (gelatose, peptone, saccharose);
III, live cell cultures of pancreas or adrenal gland;
IV, food ingredients: dry milk, egg powder, taste flavors, pigments.

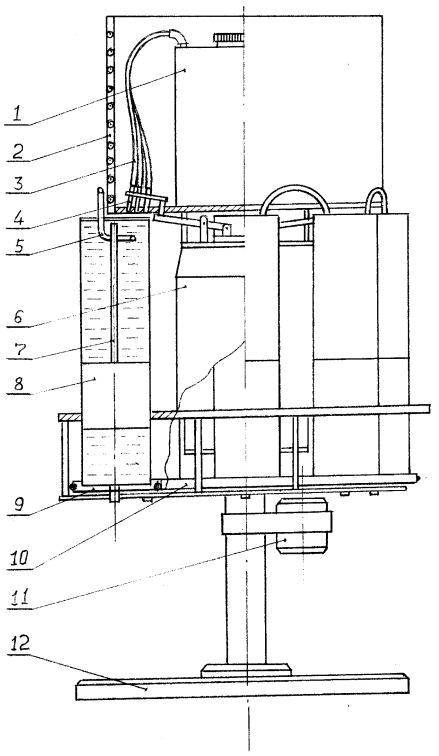

Fig. 2. Layout of vibration-type apparatus (cross-section). 1, container; 2, thermal chamber; 3, flexible pipes; 4, draw plates; 5, cooling element; 6, vibrator of electrodynamic type; 7, drain pipe; 8, 9, receiving containers (cylinders); 10, common drive; 11, electric motor; 12, base.

3. Results and discussion

3.1. Vibration apparatus

The first type of apparatus based on the vibration splitting of laminar jet is designed for production of gel-like granules (Figs. 2 and 3) (Vilesov et al., 2000b). Fig. 2 shows the design of the proposed device (cross-section). The device used for producing granulated product is made of two parts. In the upper part there is a container 1 into which the initial mixture for granule formation is loaded. The container (1) is placed inside thermal chamber (2) and connected with draw plates (4) through a system of flexible pipes (3). The initial mixture for granule formation is supplied to the draw plates under pressure of compressed air. The draw plates are mechanically connected with vibrator (6) of electrodynamic type. The lower part of the device is made as a planetary gear with common drive and sockets which house receiving containers (cylinders) (8, 9), each consisting of upper and lower vessels. Inside the upper vessel (in its upper part) there is installed cooling elements (5). The upper vessel is connected with the lower one with drain pipe (7) for draining the excess forming liquid forced out by the mass of finished granules. The receiving containers through the sockets are rotated (independently of each other) by the drive from electric motor (11). The planetary gear is installed in such a way as to allow it to rotate around its own axis independently of receiving container rotation. The entire device is mounted on base (12).

The device operates in the following way. Container (1) is loaded with initial mixture for granule formation. Container (1) with pipe system (3) is placed into the thermal chamber where the tem-

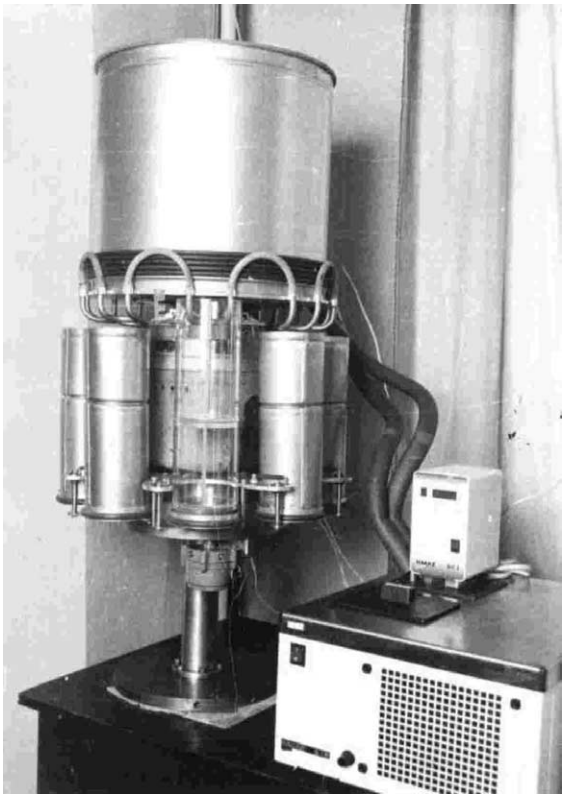

Fig. 3. General view of vibration-type apparatus.

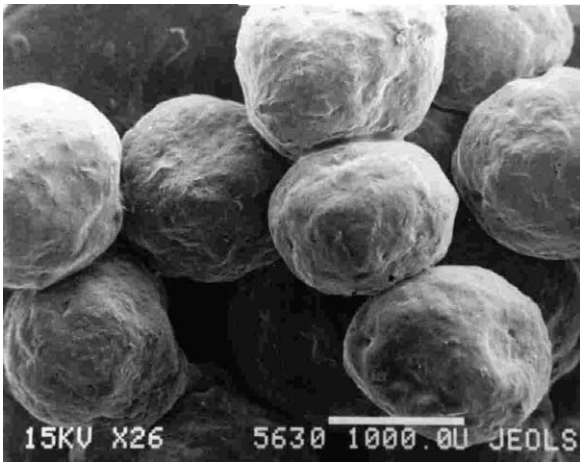

Fig. 4. Electron microphotograph of granules on the basis of gelatin.

perature is maintained in the range of 30–60 °C. The granule formation method is based on dynamic splitting of initial mixture laminar jets coming out of draw plates (4) of certain diameter driven by the compressed air pressure. Vibrator (6) controls the frequency of splitting of laminar jets coming out of draw plates (4). The drops being formed fall into rotating receiving cylinders filled with forming liquid. The liquid upper layer is cooled down to 5–10 °C. The surface tension forces make the drops take shape of spherical granules which are deposited on the bottom of the upper vessel of receiving container (8) forcing out the liquid into the lower vessel through draining pipe (7). The cooling of liquid upper layer is accomplished with the help of cooling elements (5), located inside the upper vessel of the receiving container. As soon as the upper vessel is filled with granules, its rotation is stopped and the cylinder is replaced with an empty one. The device can simultaneously fill from one to several cylinders. The upper vessels filled with granules are coming for filtration to separate granules from the forming liquid.

The proposed device possesses a number of advantages:

- due to the fact that drops fall into uniformly rotating forming liquid, their path length is increased and in so doing the quality of granule formation is improved without increasing the device size;
- due to the fact that the forming liquid is cooled only in the place where drops fall, the power consumption for cooling can be considerably reduced; and
- the use of planetary gear and the design providing for installation of containers on each other make it possible to save pay space and to facilitate servicing.

The apparatus characteristics are given below:

Production capacity, kg h^{-1}	8–10
Granules diameter, mm	0.5–3
Raw stuff viscosity 100 s^{-1}, Pa s^{-1}	0.5–10
Power consumption (not greater), V A^{-1}	3000
Main unit overall dimensions, mm	$520 \times 520 \times 1000$
Main unit weight (not greater), kg	50

The vibration apparatus is used at present to produce a new food product-alternative black caviar. Granules (caviar grains) are produced on the basis of matrix IV and excipient IV. The forming liquid is vegetable oil (Fig. 4) (Vilesov et al., 2000a). In terms of experiment, matrix IV has been used as a base for producing MIC-suspensions of live cells of pancreas and adrenal gland. We have also checked on a possibility of producing known alginate–chitozan microcapsules where the liquid for shell formation is $CaCl_2$ solution.

3.2. Spray apparatus

The second type of apparatus is based on the principle of splitting the liquid laminar jet coming out of a draw plate with the help of an air jet (excess pressure is 0.05–0.3 atm). Depending on the design of the module being used which directs the air jet (two variants of forming modules), the apparatus is capable of operating in drop-forming mode (particle size is in the range of 500–100 μm) and spray mode (particle size is in the range of 10–50 μm).

Figs. 5–7 give the layout and general view of apparatus, and the characteristic cone of spray. Microcapsules or microgranules are formed in the following way: container (15) is filled with composition (solution or suspension) for microencapsulation. The container is connected through a flexible pipe (11) with a nozzle of forming module (6) into which the composition is supplied driven by compressed air. Thermal chamber (8) ensures keeping the composition in container at a given temperature. Receiver (9) is used for heating the air supplied for splitting the jet of composition. The particles of composition being formed fall into rotating receiving container which is additionally equipped with a magnetic stirrer. Here the particles acquire a spherical form. In case of

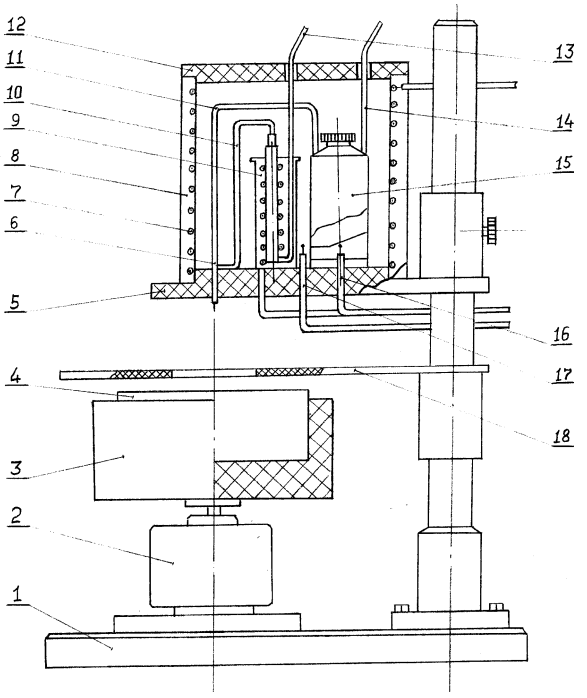

Fig. 5. Layout of spray apparatus. 1, base; 2, electric motor; 3, heat-insulating jacket; 4, receiving container; 5, movable base; 6, forming device; 7, heater; 8, thermal chamber; 9, receiver for heating the air; 10, pipe system for heated air supply; 11, pipe system for composition supply; 12, cover; 13, input pipe system to supply air for spraying; 14, pipe system for building up excess pressure in container; 15, container for composition; 16, measuring thermocouple; 17, controlling thermocouple; 18, protective glass.

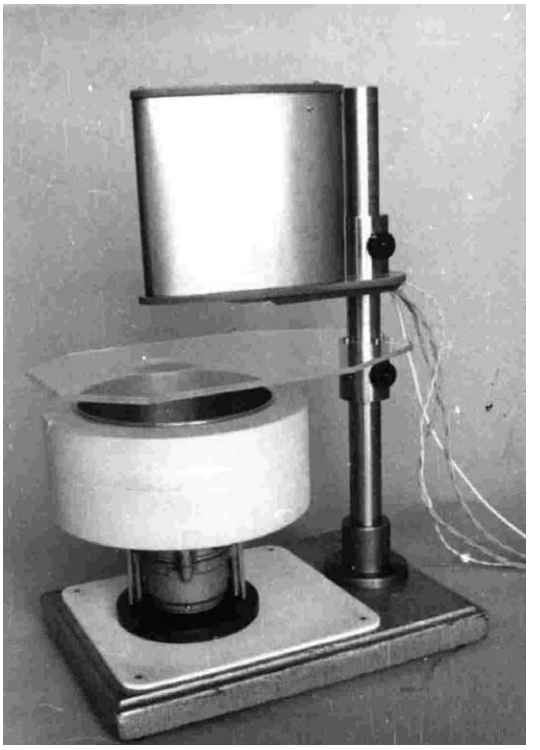

Fig. 6. General view of spray apparatus.

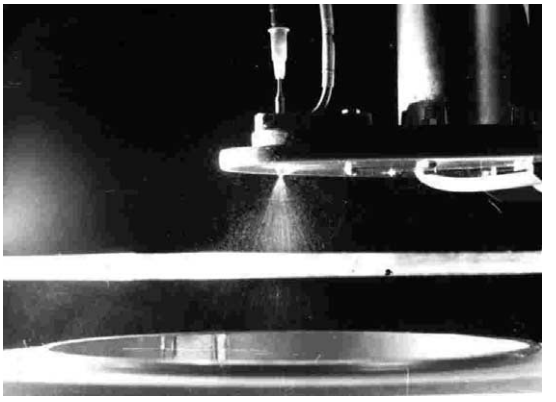

Fig. 7. Spray cone.

standard formation of microcapsules, for example alginate–chitozan type, the forming liquid is the solution of $CaCl_2$ and chitozan. The most interesting thing is formation of microgranules directly in the medium of liquid nitrogen with successive lyophilic drying without preliminary defrosting.

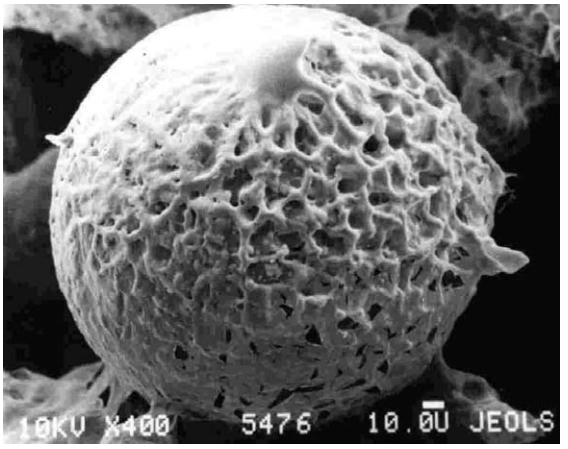

Fig. 8. Electron microphotograph of microgranule "matrix I, vaccine material".

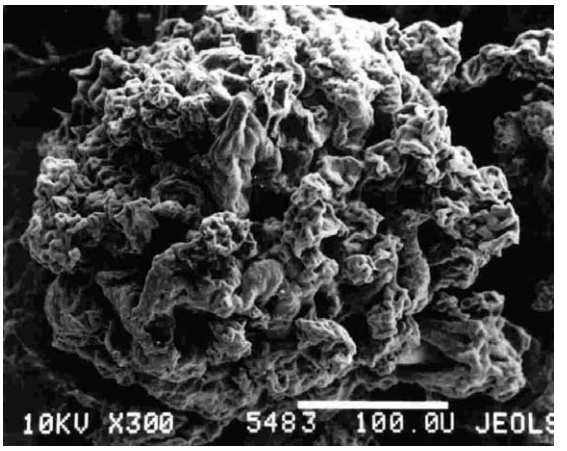

Fig. 9. Electron microphotograph of microgranule "matrix IV, vaccine material".

Microphotographs (Figs. 8 and 9) present dry microgranules on the basis of matrix I and matrix IV containing live virus of the measles in form of lyophilized virus material on a stabilizer.

At the State Research Center of Virology and Biotechnology "Vector" (Novosibirsk, Russia) it has been shown that live viruses in microgranules survive and an immune response has been received in case of their peroral administration (on guinea pigs).

Acknowledgements

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