DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(2&3), 353-376 (1988)

RECENT ADVANCES IN MICROENCAPSULATION TECHNOLOGY AND EQUIPMENT

Shun Por Li[1,2], Chana R. Kowarski,[2], Kenneth M. Feld[1] and Wayne M. Grim[1]

[1]Pharmaceutical Research and Development Division, Rorer Central Research, Rorer Group, Inc., Fort Washington, PA 19034

[2]Department of Pharmacy, School of Pharmacy, Temple University, Philadelphia, PA 19140

INTRODUCTION

Microencapsulation is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation is arbitrarily differentiated from macroencapsulation in that the former involves the coating of particles ranging dimensionally from several tenths of a micrometer to about 5000 m (1,2). Microencapsulation may be of use for a number of reasons. (3,4). These include:

1. protection of reactive materials from their environments,
2. safe and convenient handling of materials which are otherwise toxic or noxious,
3. means of providing controlled and/or sustained release of materials following application,
4. means of handling a liquid as a solid,
5. taste masking of bitter drugs,
6. masking of unpleasant odors,
7. preparation of free-flowing powder, and
8. modification of physical properties of drugs.

In pharmaceutical preparations, the uniqueness of microcapsules lies in the size of the coated particles and their subsequent use and adaption to a wide variety of dosage forms. Due to the use of these discrete particles, drug moieties can be widely distributed throughout the gastrointestinal tract. This potentially improves drug adsorption and reduces side effects related to localized buildup of irritating drugs against the gastrointestinal mucosa.

Preparation of Microcapsules

The microcapsules have been prepared by a variety of methods. The methods of preparation and the techniques employed for microencapsulation overlap considerably. For the sake of simplicity, the various microencapsulation techniques may be catergorized as follows:

1. Phase separation, or coacervation,
2. Interfacial polymerization,
3. Electrostatic methods,
4. Mechanical methods.

Phase Separation or Coacervation

The term "coacervation" has been used by chemists to describe the salting out of or phase separation of lyophilic solids into liquid droplets rather than into solid aggregates (5). Coacervation has been classified into two categories: simple coacervation and complex coacervation.

Simple Coacervation

Simple coacervation is a process involving the addition of a strongly hydrophilic substance to a solution of a colloid. This added substance causes two phases to be formed, one phase rich in colloidal droplets and the other poor in such droplets. This process depends primarily on the degree of hydration produced, and its prinicipal requirement is the creation of an insufficiency of water in part of the total system. Figure 1 illustrates the preparation of microcapsules by simple coacervation (4,6).

Complex Coacervation

Complex coacervation is primarily a pH - dependent process. The acidic or basic nature of the system is manipulated to produce microcapsules. Above a certain critical pH value, the system, depending on its acidic or basic nature, may produce microcapsules. Below that pH value, they will not form. Usually complex coacervation deals with systems containing more than one colloid, e.g., in gum arabic/gelatin systems. Figure 2 is a flow diagram of micro-encapsulation by complex coacervation using Type A gelatin and gum arabic. Complex coacervation occurred and microcapsules formed at pH values below the isoelectric point of the gelatin, but would not occur above this pH. At pH values below the isoelectric point of gelatin, the gelatin becomes positively charged while acacia particles retain their negative charge regardless of pH (4,7).

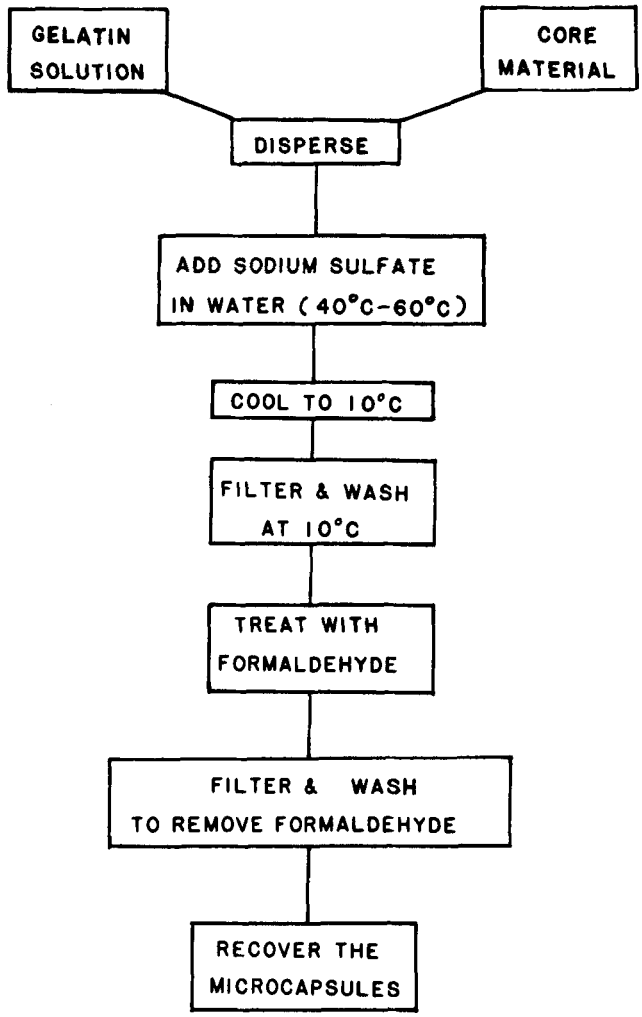

FIGURE 1 Microencapsulation by simple coacervation

Interfacial Polymerization

Microencapsulation by this method is a process whereby a monomer is made to polymerize at the interface of two immiscible substances. If the internal phase is a liquid, it is possible to disperse or solubilize the monomer in this phase and emulsify the mixture in the external phase until the desired particle size is reached. At this point, a cross-linking agent may be added to the external phase. Since there is usually some migration of the monomer from the internal to the external

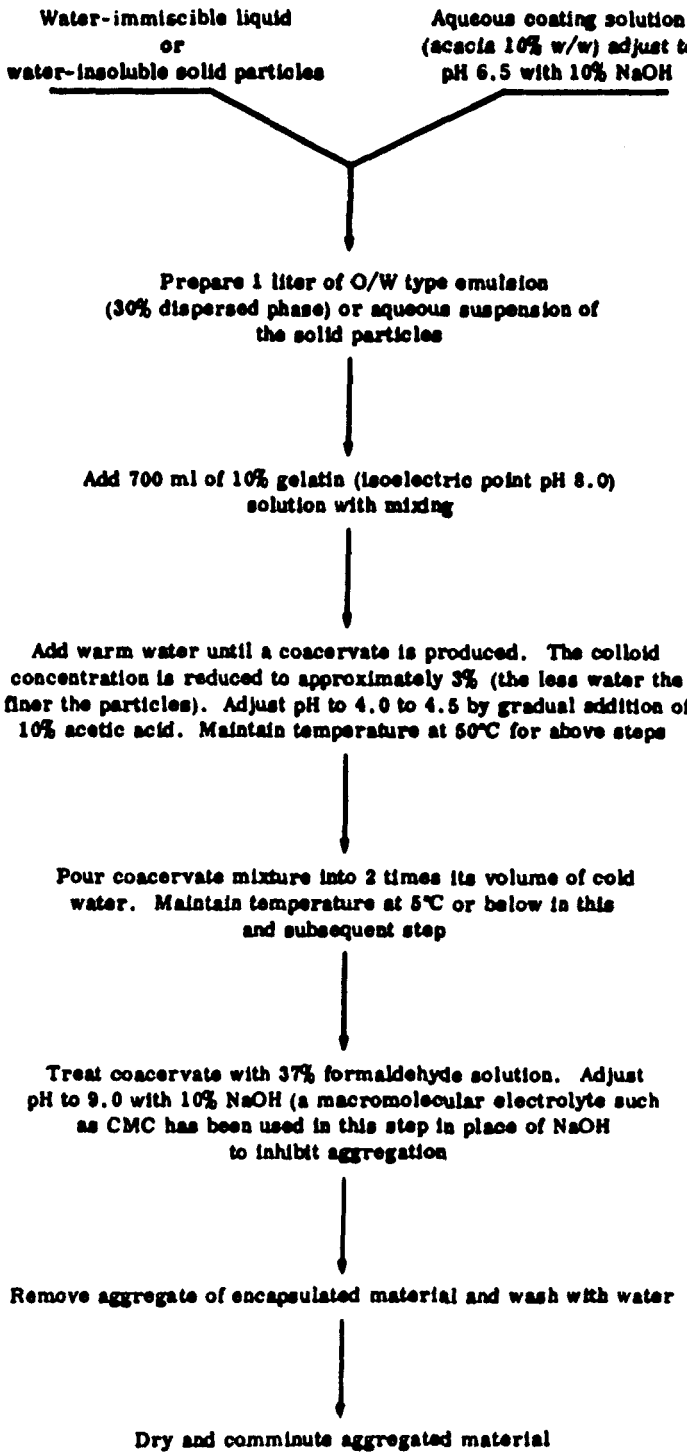

FIGURE 2 Microencapsulation by complex coacervation. (From H. A. Lieberman and L. Lackman, eds. Vol. 3, p. 143, Marcel Dekker, Inc., N.Y., 1982. By courtesy of Marcel Dekker, Inc.)

phase, and since it is preferred that the crosslinking agent does not transfer to the internal phase, the bulk of any polymerization will take place at the interface (6).

Electrostatic Methods

Preparation of microcapsules by these methods involves bringing together the wall material and the material to be encapsulated when both are aerosolized. The wall material must be liquid during the encapsulation stage and must be capable of surrounding the core material. The aerosols produced must be oppositely charged. Three chambers are used for the process, two for atomization of wall and core material and the third for mixing. Oppositely charged ions are generated and deposited on the liquid drops while they are being atomized (6,7).

Mechanical Methods

All of the mechanical methods used for microencapsulation employ special equipment. The microcapsules produced result from mechanical procedures rather than from a well-defined physical or chemical phenomenon.

Since the last decade, there have been tremendous technological advances in different types of microencapsulation coating equipment. The remaining portions of this presentation will discuss how this new equipment has affected the preparation of microcapsules.

Mechanical Methods: Available Technologies for the Preparation of Microcapsules

Multiorifice - Centrifugal Process

The Southwest Research Institute (SWRI) has developed a mechanical process for producing microcapsules which utilizes centrifugal forces to hurl a core material particle into an enveloping microencapsulation membrane (Figure 3). In a device for capsule production with this method, concentric feed tubes enter a seal arrangement at the center of a rotary head. The filler, flowing through the inner tube, enters a central chamber from which tubes radiate outward and penetrate orifices about the periphery of the head. The shell formulation flows through the annulus of the concentric feed tubes, into the rotating head, and finally through the annuli created by the radial tubes and orifices. As the multiorifice centrifugal extrusion head rotates, a compound fluid rod of filler and shell materials emerges from each orifice continually breaking up at the end to form a series of individual capsules. This new method brought about a dramatic increase in production capabilities. It has produced capsules with a diameter of 350 microns at a rate of more than 300,000 per second per orifice (8).

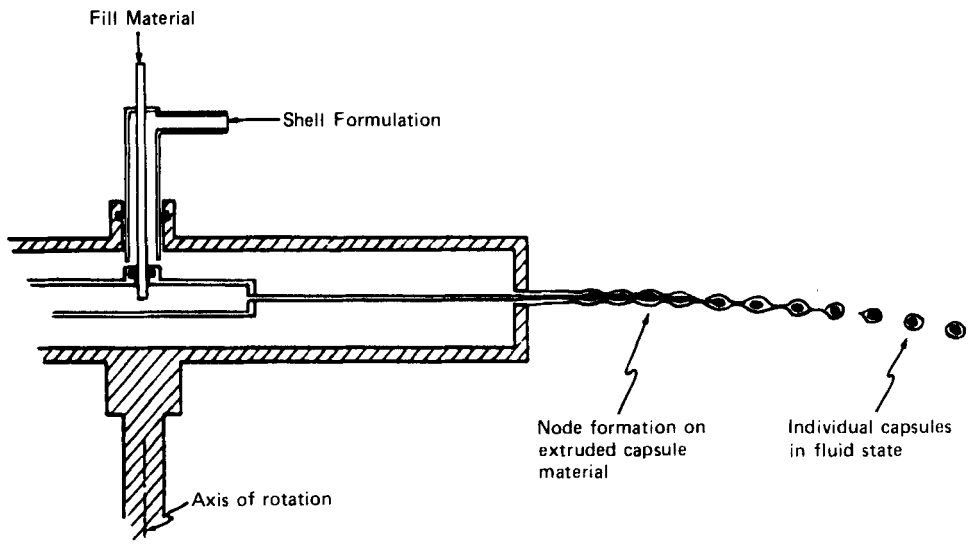

FIGURE 3 Schematic drawing of multiorifice centrifugal extrusion head. (From Goodwin, J. T. and Somerville, G. R., Microencapsulation Processes and Applications, Vandegner, J. E., Ed., Plenum Press, New York, 1974, p. 155. With permission.)

Spray Drying

Microencapsulation by spray drying is conducted by dispersing a core material in a coating solution which contains the dissolved coating substance. This dispersion is then atomized into an air stream. The air, usually heated, supplies the latent heat of vaporization required to remove the solvent from the coating material. This forms the micro-encapsulated product. The equipment components of a standard spray dryer include an air heater, atomizer, main spray chamber, blower or fan, cyclone and product collector (Figure 4). Process control variables include feed material (properties such as viscosity, uniformity, and concentration of core and coating material), feed rate (which is normally controlled by the inlet and outlet temperature) and the air stream solvent concentration. The process produces microcapsules approaching a spherical structure in the size range of 5 to 600 microns in diameter (2).

Spray Congealing

This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spary dryer in which cold air is circulated. The slurry droplets congeal on coming into contact with the air and are collected in

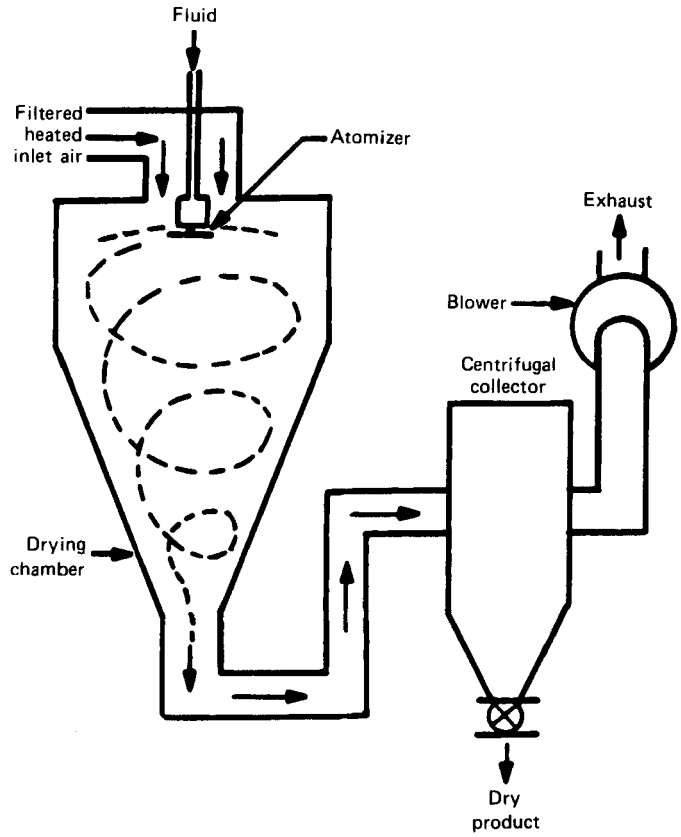

FIGURE 4 Schematic diagram of spray-drying apparatus. (From H. A. Liberman and L. Lackman, eds. Vol. 3, p. 140, Marcel Dekker, Inc., N.Y., 1982. By courtesy of Marcel Dekker, Inc.)

the same manner as the spray dried product. The coating agents normally employed are low melting materials such as waxes. The congealing process requires a much higher ratio of coating agent to active material than does spray drying, because only the molten coating agent constitutes the liquid phase. Spray congealed coatings are used mainly for taste masking and for sustained release formulations (9).

Pan Coating

The "traditional" , i.e. oldest, way of building up cores for controlled release is by the use of conventional sugar coating pans. Therefore, this method suffers from the same limitations as the sugar coating of tablets. These limitations

include requiring manual intervention and the utilization of the skills of an operator. It is a slow process, taking several days or weeks to prepare a single batch of material. A typical pan coating method is as follows:

> The non-pareil seeds are placed in a conventional coating pan and are wetted with a binder/alcohol mixture. When the mixture becomes tacky, the drug powder is added to the rotating seeds. Then the drying step is initiated. These steps are repeated until the desired product is obtained. For sustained-release preparation, a polymer solution (e.g. ethylcellulose solution) is applied onto the coated pellets in order to retard the release rate of the drug from the finished pellets. With the advance of spray systems, the drug powder could be suspended into the binder/alcohol mixture. The drug/binder/alcohol slurry then is sprayed onto the non-pareil seeds through either an airless or air atomization system to prepare drug pellets.

The major drawback of this coating system is the inefficiency of drying in the entire coating process. The drying air and the exhaust air both enter and exit at approximately the same place. A portion of the drying air may be exhausted before it ever reaches the pellets bed surface. Thus, it may never have an opportunity to remove any solvent before it exits from the pan. Since the drying air only contacts the pellets at the surface of the tumbling bed the drying rate is generally slow with a resultant long coating time.

The drying efficiency in conventional coating pans can be improved by the use of two recent developments. One, developed by Strunck, introduced drying air into the pan by means of a tube immersed in the pellet bed. The air is then exhausted through a plenum above the pellet surface while the coating solution is introduced through a nozzle in the inlet air duct (Figure 5). The second utilizes the immersed sword made by Glatt Air Techniques, Inc., Ramsey, New Jersey. Again, the intention is to introduce more efficient drying to the pellet mass. Although in this latter case the coating solution is applied in a conventional manner to the surface of the pellet bed (10,11).

The DriaCoater® represents a variation of the pan coating systems described above. Drying air is introduced through hollow ribs on both the conical and cylindrical portions of the pan. The movement of drying air is from beneath the pellet bed to the surface, where it is exhausted through a rear vent. This has the effect of partially fluidizing the pellet mass. It improves drying efficiency and aids pellet mixing while minimizing the pellet damage attributed to harsh baffle systems in other types of equipment.

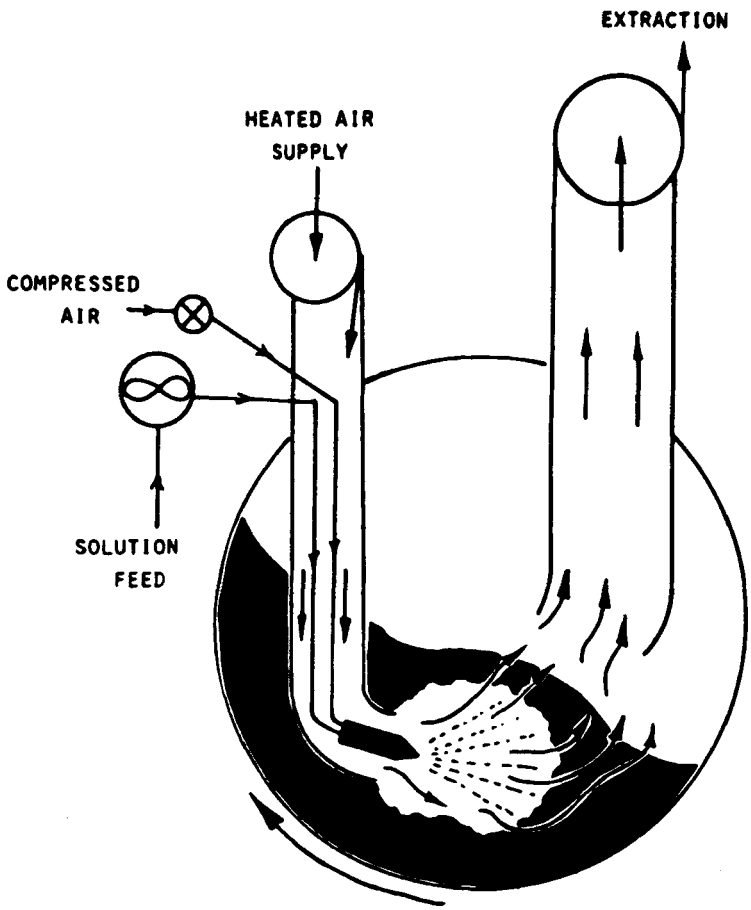

FIGURE 5 Schematic diagram of strunch immersed-tube apparatus. (From H. A. Liberman and L. Lackman, eds. Vol. 3, p. 83, Marcel Dekker, Inc., N.Y., 1982. By courtesy of Marcel Dekker, Inc.)

Figure 6 schematically shows the air flow in the DriaCoater® (10,11). The perforated pan section of the DriaCoater® is covered with #40 mesh wire screen. The reverse air flow drying system of the DriaCoater® provides excellent drying efficiency. As such, the DriaCoater® is ideal equipment for the manufacturing of pellets via an air atomization system.

Fluid-Bed Coating

Still another method for the mechanical coating of small particles is the Wurster fluidized bed coating technique. The

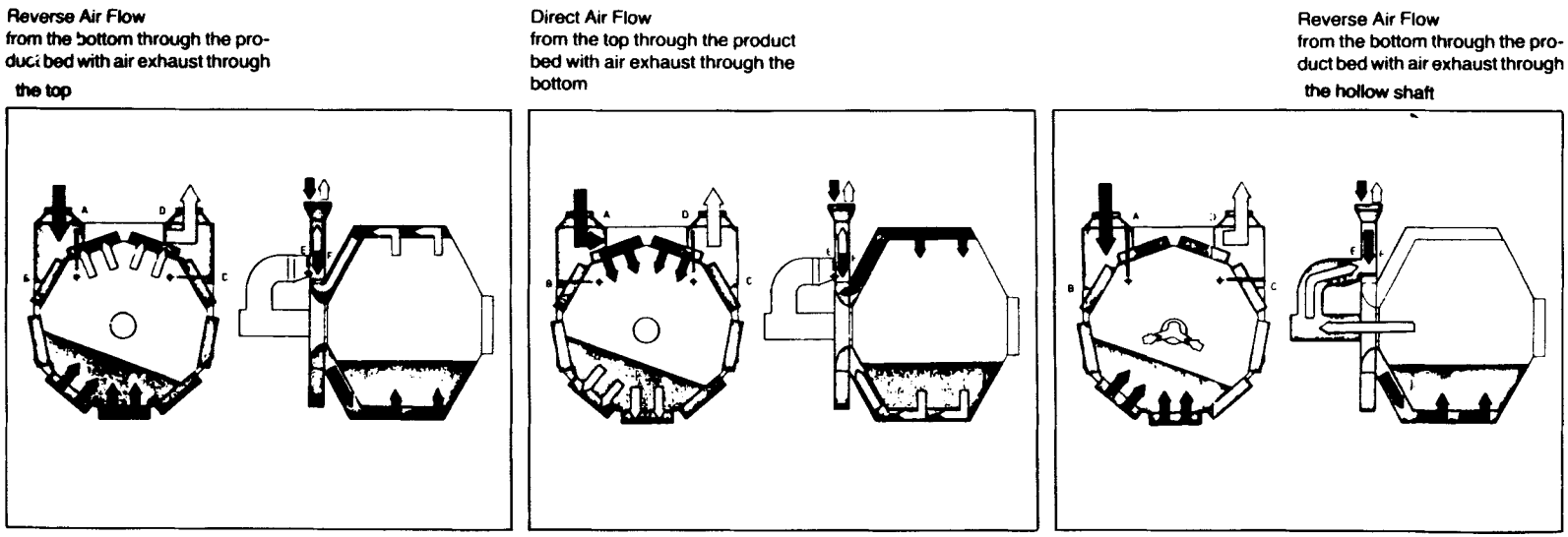

FIGURE 6 Air-flow in the Driacoater

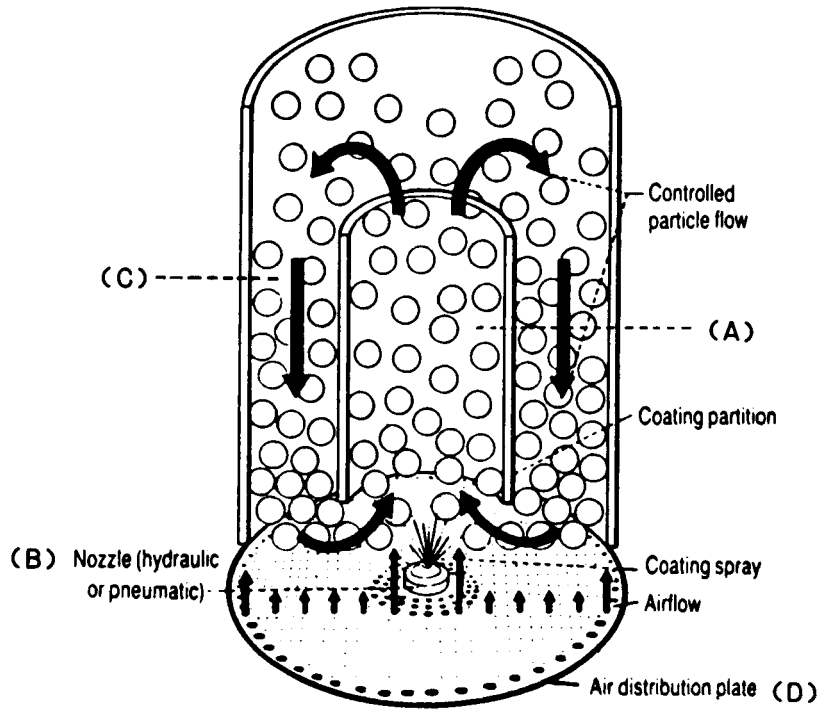

FIGURE 7 Schematic diagram of a Wurster coating chamber

air suspension coating process can appropriately be described as an upward moving, expanding fluidized bed in the central portion of the coating chamber coupled with a downward-moving, fluidized bed on the periphery of the column. Figure 7 is a schematic drawing of the equipment. Particles to be coated are pneumatically conveyed upward through the central tube (A) of the coating chamber. As the particles pass the atomizer (B), they are wetted by the coating fluid and then immediately subjected to a drying process due to the heated support air moving upwardly in the column. Partially coated particles move downward in a near - weightless condition along the periphery of the tube (C) where further drying occurs.

When the particles reach the lower end of the column they are directed back into the upward moving bed and the entire process is repeated. The air pump and heater provide the heated support air for the process and the distribution plate (D) directs the proper volume of air to the central and peripheral regions of the column. The proper adjustment of the air flow, the temperature, and the fluid application rate are critical to the operation of the process (12,13).

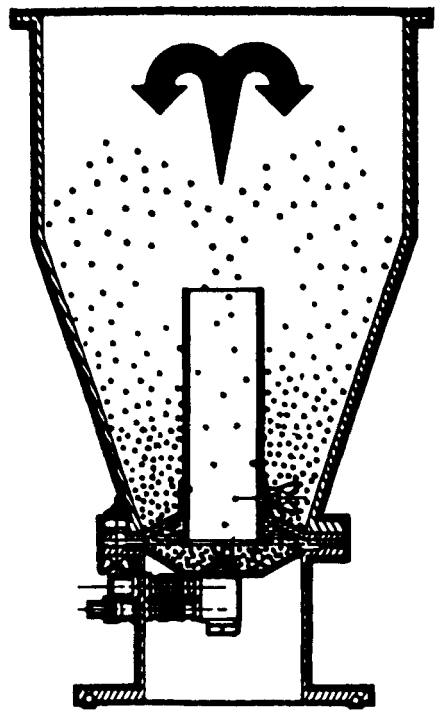

FIGURE 8 Schematic diagram of Aeromatic Aerocoater

Spherical particles of near-theoretical density can be prepared using a Wurster Column process by coating particles (e.g., non-pareil seeds) with a slurry which contains both suspended solids and binder. The drug coat is then overcoated with a barrier material. The Wurster column offered significant advantages over conventional coating pans in preparing non-pareil coating system. In terms of absolute drying potential, the Wurster column offers the best drying efficiency. Furthermore, the coating efficiency of the Wurster column (bottom-spray technique) is much superior to the top-spray method (14).

There are several manufacturers of fluidized bed coating units; Lakso Company, Glatt Air Techniques, and Aeromatic, Inc. In terms of design of the Wurster column, Lakso and Glatt columns are quite similar. However, the Aeromatic Aerocoater® offers a different design from the other companies. The difference lies in the designs of the distribution plate and coating chamber (Figures 8, 9). Since there are differences in design of the column among various manufacturers, one should conduct trials to determine which column is the most suitable in meeting specific needs.

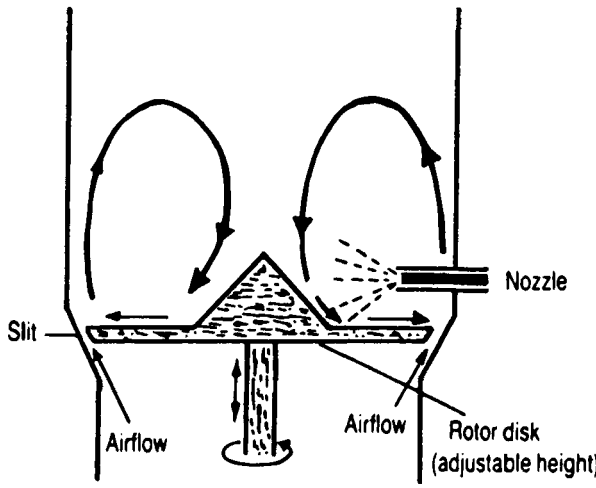

FIGURE 9 Schematic diagram of Rotogranulator. (From Pharmaceutical Technology, Vol. 9, No. 4, 1985, p. 55. With permission.)

Rotary Fluidized-Bed Granulator

A rotating-disk granulator, as shown in Figure 10 (Glatt Roto-Granulator®) combines centrifugal, high-intensity mixing with the efficiency of fluid-bed drying. Material produced by this technique contains fewer fine particles, is less friable, and is more spherical in shape than the techniques mentioned above. Due to the unique design of this type of granulator, an increase in spray rates of the drug/binder slurry can be achieved. This allows for the formation of spherical granules of rather high densities. This new rotating-disk granulator is a one-step apparatus that combines many advantages of mixing, pelletizing, and fluidized-bed agglomeration units (15,16).

There are three manufacturers of Rotary Fluidized-Bed Granulators: Glatt Air Technique, Aeromatic, Inc. and Vector/Freund Corporation. The design of these units is quite different among the various manufacturers. It is important that the formulator carry out trials with this equipment in order to determine the optimum unit. The major differences among these units are summarized as follows:

1. Glatt Rotor Granulator®: As can be seen from Figure 10, this equipment is ideal for non-pareil seed coating. The Rotor-Granulator®'s high air velocity through the slit and the centrifugal forces of its rotating disk create a dense, helical, doughnut-shaped pattern. High percentages

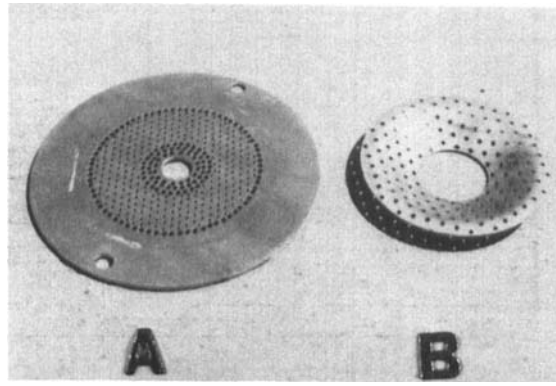

FIGURE 10 Air Distribution plates from two different manufacturers (A) Lakso, and (B) Aeromatic

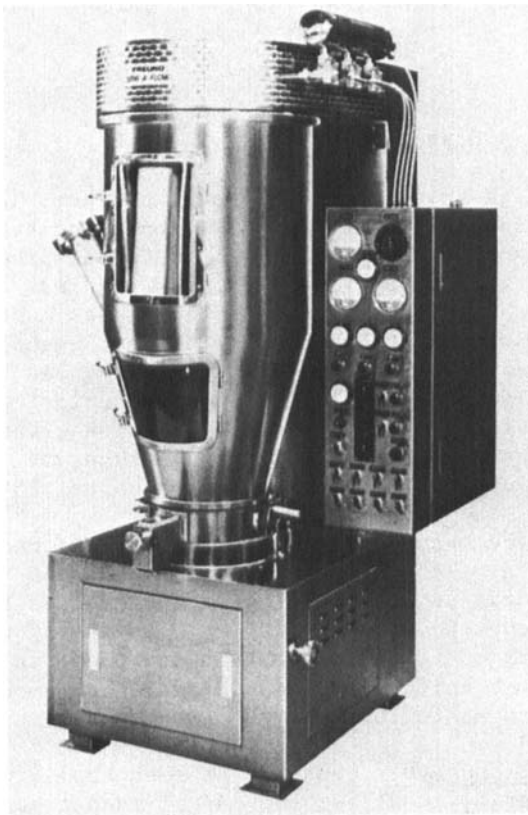

FIGURE 11 Spir-A-Flow Model SFC-15

of coating can be applied through a nozzle onto flowable powders, granules, and non-pariel seeds. In many applications, the coatings need not be dissolved or dispersed in a liquid, but may be applied directly as a micronized powder with the wetting agent dispensed through a separate nozzle.

2. Vector Spir-A-Flow® and C-F Granulator®: The appearance of the Vector/Freund Spir-A-Flow (Figure 11) is similar to that of a conventional fluid-bed granulator. However, that's where the similarity ends. The lower portion of the Spir-A-Flow® processing chamber consists of a rotor through which heated air is introduced for fluidization of the product bed. Air is also fed into the chamber through the narrow opening between the rotor and stator (Figure 12). As a result of the rotor/stator influence on the process air in the chamber, a unique spiral and twisting air pattern develps. When powder is introduced into this pattern, it is held in suspension longer and more evenly than in conventional fluid-bed systems.

The rotor is equipped with high speed mixer blades to prevent product lumping. A removeable agitator is also provided when processing materials with high moisture content.

It should be pointed out that this equipment has a unique spiral and twisting air pattern (not as smooth as the air pattern of the Rotor-Granulator®). This air-flow results in non-pareil coatings that have rough, irregular characteristics when compared to pellets prepared from the Glatt Rotor-Granulator®.

The CF Granulator® (Figure 13) is manufactured by Freund of Japan. It offers significant advantages over conventional coating pans in preparing non-pareil coating systems. The drying efficiency in the CF Granulator® is far superior to coating pans in that the CF Granulator® can be used for a continuous spraying process. A charge of non-pareil seeds is fluidized by the air stream flowing through an air gap between the place edge and the pan wall. On one side of the pan, a mixture of drug and starch is added by a vibrating powder feed, while diametrically opposite the powder feed, binding liquid is sprayed onto the bed. In this system the rate of addition of the liquid and solid are highly critical. If the liquid is added too quickly, or the solid is added too slowly, then the system overwets irretrievably.

This process is slow in that the addition of the solid and the liquid components to the seed material has to be stopped periodically to remove over - and under - size fractions. These are subsequently processed

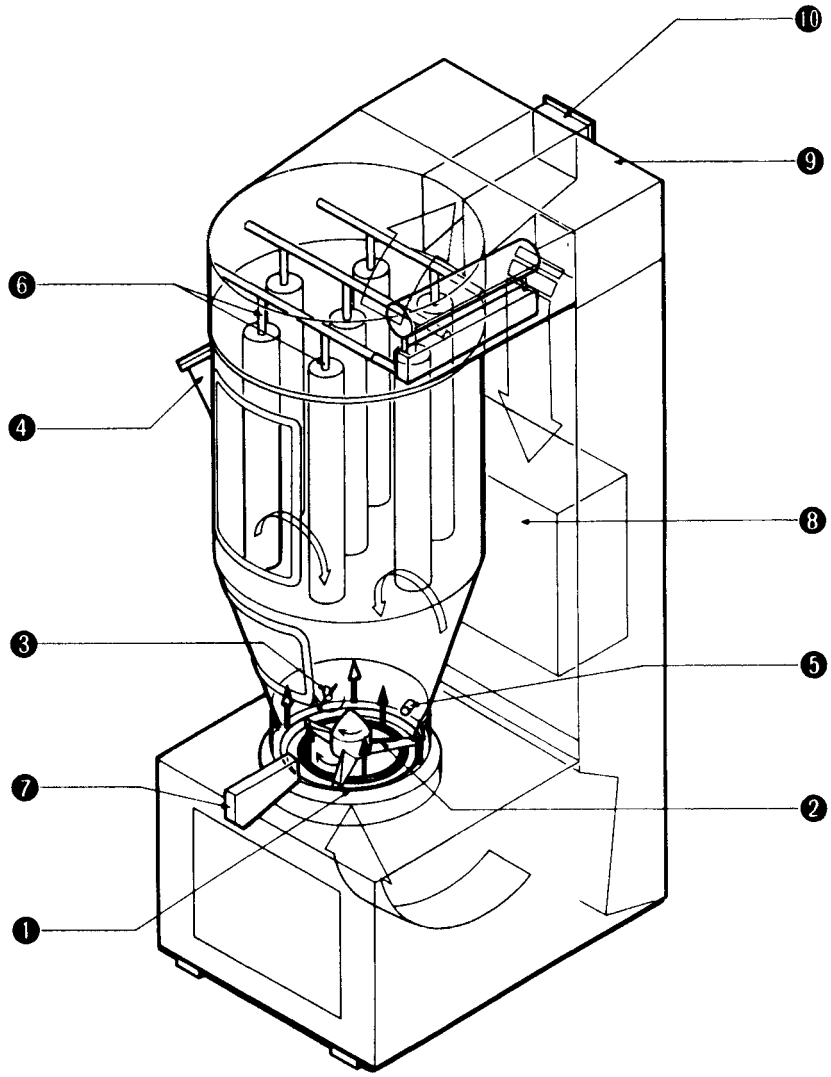

FIGURE 12 **Spir-A-Flow rotor/stator arrangement - located at the bottom of the expansion chamber. Heated process air is introduced into the chamner through 300-500 micron openings in the rotor as well as around the rotor's perimeter.**

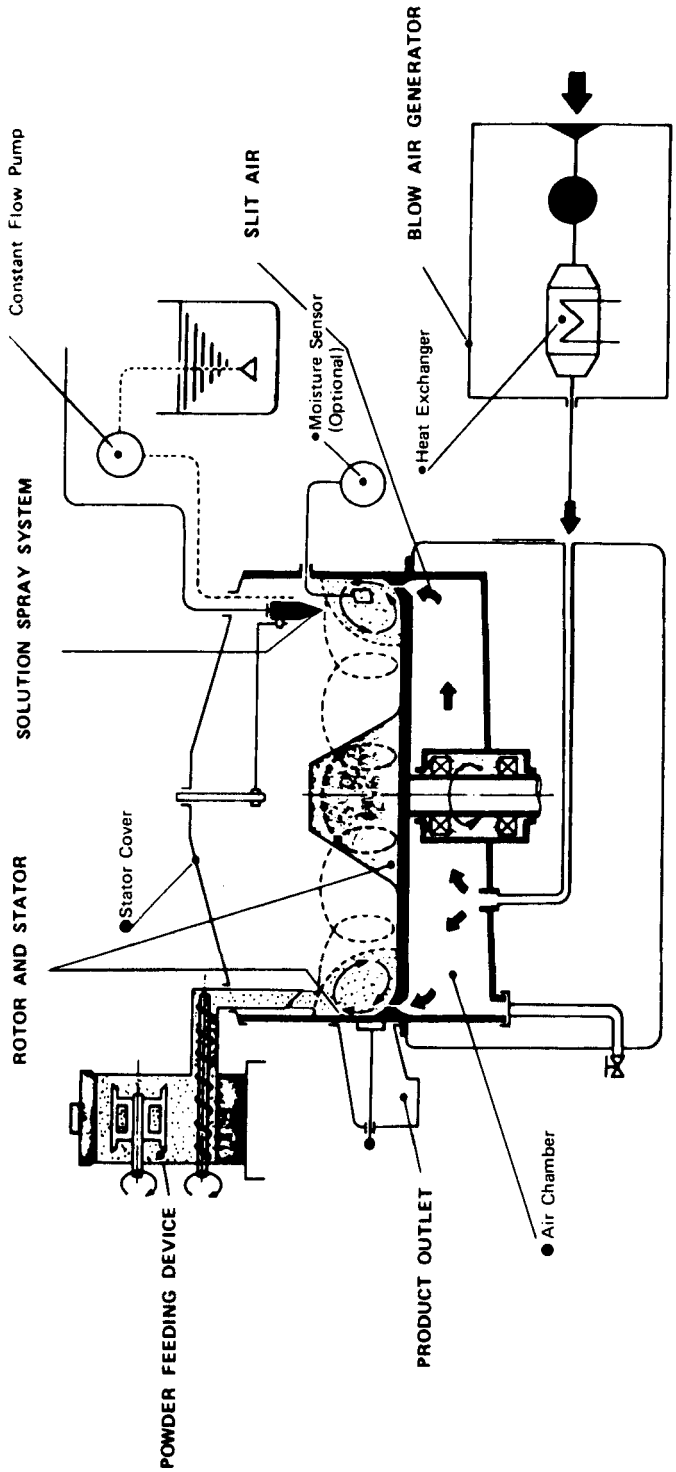

FIGURE 13 Schematic diagram of a CF-Granulator

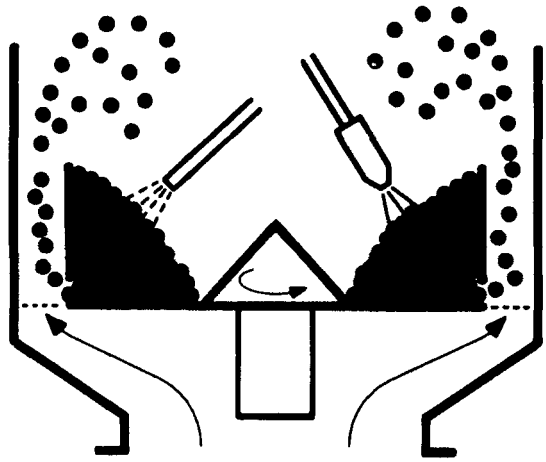

FIGURE 14 Schematic diagram of a Rotor-Processor

separately, leading to longer processing time and significant material losses (17, 18).

3. Aeromatic Roto-Processor®: As can be seen from Figure 14, the design of this equipment is quite different from both the Glatt Rotor-granulator® and the Vector Spir-O-Flow®. The non-pareil seeds are filled into the interior section of the product container which is equipped with a rotating disc. The product inside the container is pressed against the wall of the jacket by the movement of the rotating disc and set in angular motion. Particles of high density are obtained by finely atomizing a suitable granulation liquid with the simultaneous addition of a powdery active substance. A slight upward movement along the wall allows a portion of the product to pass into the fluidizing area where it is dried by means of warm air. At the same time the product is deposited into the inner section of the product container.

The location of the spraying nozzle in the Roto-Processor® is different from the other units. The spraying nozzle in the Roto-Processor® is located at the top of the container (Figure 14), while the nozzle in both the Roto-granulator® and Spir-O-Flow® is immersed in the fluid bed. This difference in the location of the spraying nozzle will lead to differences in morphology of the finished pellets.

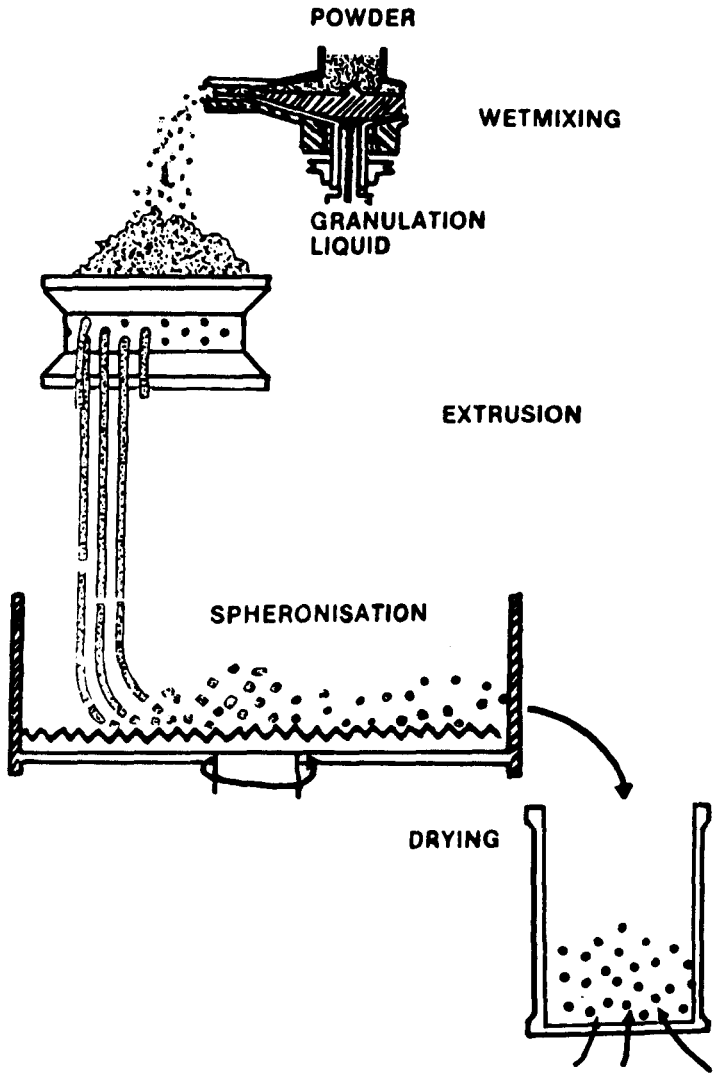

FIGURE 15 The extrusion/disc spheronisation process

Spheronization

Spheronization is a form of pelletization which refers to the formation of spherical particles from wet granulations (19). Spherization equipment generally operates by extruding wetted material into cylindrical segments, breaking the segments and then rolling them into solid spheres. The extrusion/disc spheronization process is given in Figure 15 (20).The spheronization process has the following features. It allows manufacture of

granules with high loading of active substances, spherical granules with a smooth surface, and granules of a narrow size distribution. The main processing steps are (21):

1. Blending: The medicaments and excipients are mixed with suitable binders and water to form a heavy "plastic" mass.

2. Extrusion: The mass is shaped into cylinders of uniform diameter and the cylinders are then cut into equal lengths.

3. Spheronization: The cut cylinders are rolled into spheres. In the spheronizer the extrudate is further broken down into short equal lengths. These are then transported by centrifugal forces to the periphery of the plate where their residual motion causes them to rise up the stationary wall and then fall as their momentum is dissipated. This movement, along with the angular motion, causes the moving mass to appear as a moving rope. The broken extrudates then form cylinders with rounded ends before forming dumb-bells and ellipses, and finally spheres. Three critical factors that have been found to affect the spheronization process are:

    1. the peripheral velocity of the spheronization disc,
    2. the process time of spheronization, and
    3. the geometry of the grooves on the plate.

4. Drying: After spheronizing, the spheres are emptied either into a fluid bed dryer or a tray-dryer for drying. Once dry, these spheres can be coated with a barrier coating utilizing fluid-bed technology for sustained-release preparations.

There are four manufacturers of spheronizing equipment: G.B. Caleva Ltd., Ascot, UK; Fuji Paudel Co. Ltd., Oaska, Japan; Lejus Medical AB, Molndal, Sweden; and Wyss and Probst Engineering, Altdorf, Switzerland. The design of the equipment has altered little since the original invention, and basically consists of a grooved horizontal plate rotating at high speed within a stationary vertical cylinder fitted with a door to allow the discharge of the spheroids.

Recently, a new piece of equipment, Roto-Coil® (Figure 16) supplied by Aeromatic Inc., has become available for the manufacturing of spheres. The Roto-Coil® can be used to form spheres from extrudates of various sizes. The processing method consists of passing the extrudate through a spiral-shaped

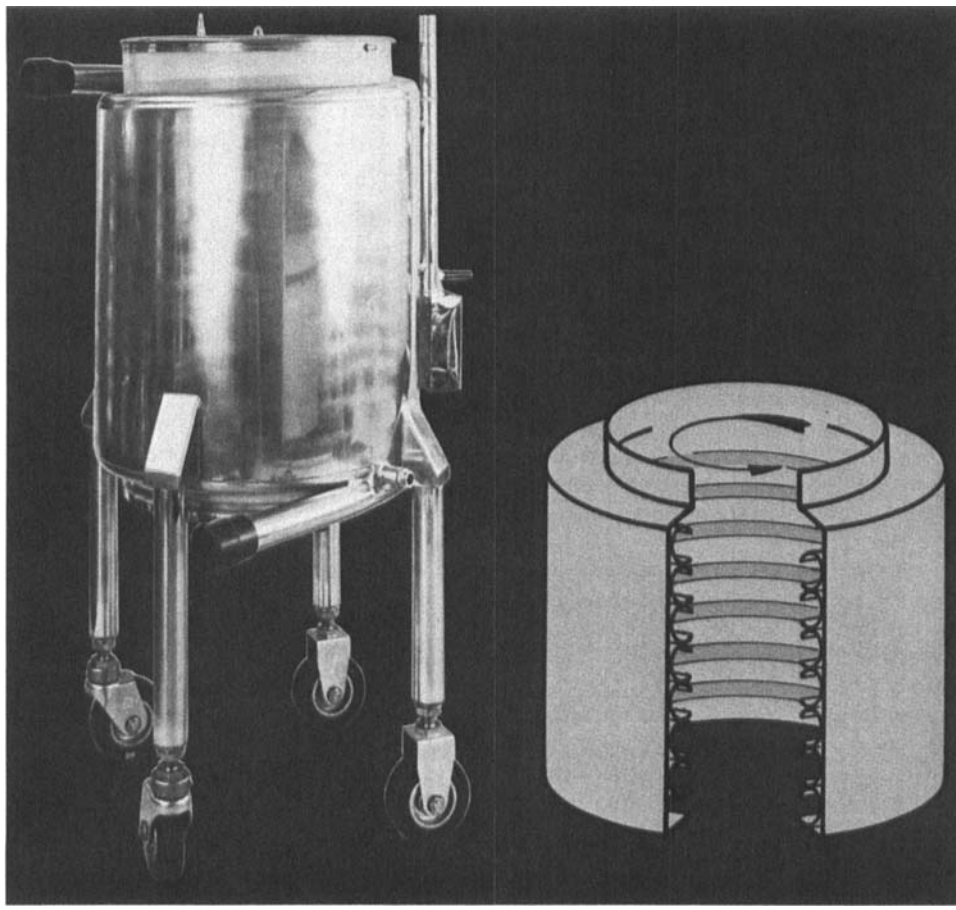

FIGURE 16 Diagram of a Roto-Coil

pipe with the aid of an air stream. Due to the rotational movement of the product, spheres are formed which can then be dried and coated in a fluid-bed unit. The difference between the Roto-Coil® and the spheronizer is that the former has no mechanical moving parts and it can be used for continuous processing.

SUMMARY

Microcapsules prepared by pan coating technologies usually are less elegant. Batch-to-batch reproducibility is always questionable, because processing parameters are much

more difficult to control. The yield of the pan coating process is rather low (~90%) because drug powder can be lost during either the dusting operation or the spraying operation. Furthermore, the quality of the barrier coatings on the pellets is less desirable due to difficulty in controlling processing parameters. The pan-coating process usually is time-consuming. Since the drying efficiency of this system is rather low, it will require a much longer time to evaporate or dry all the residual solvent from the microcapsules. Consequently, this system is not desirable for aqueous coating of pellets.

With the introduction of the air-suspension techniques, microcapsules were found to be much better both in quantity and quality than from the pan process. Processing parameters in the Wurster column are much easier to control than in the pan process. Batch-to-batch variability can be kept to a minimum. The quality of the barrier coating of the pellets is much more desirable than in the pan process.

When the Wurster bottom-spray method is used, it is possible to apply droplets to the substrate before much evaporation of solvent occurs, and the subsequent evaporation of solvent from the surface of the pellets is complete before the solvent can penetrate the pellet cores. Suspending the pellets in air keeps them discrete from one another and allows films to be applied to pellets with little or no agglomeration. In this system, the close proximity of the liquid nozzle to the fluidized particles and the rapid cycle times yield a more uniform distribution of the film. Consequently, the yield of the pellets is much higher in the Wurster column process than the pan process.

Due to the superior drying efficiency of this equipment, a continuous spraying process can be carried out. As such, a batch of pellets which may require days or weeks of preparation in the pan process can be manufactured in the Wurster column process in hours. The only drawback in the column process is that only low rate of drug application can be offered.

With the introductions of the Glatt Roto-granulator® and the Vector Spir-O-Flow®, pellets with superior quality are quaranteed. These systems offer significant advantages over Wurster columns. In particular, high rates of drug application can be achieved with significant reductions in drug losses. The equipment can be used with aqueous and organic solvents, and also can be used to apply drug-release controlling membranes. Furthermore, very high drug loading, up to 70%, can be achieved by utilizing these systems.

Spheronization is another process that can be used to prepare microcapsules or granules. The major advantage of this system is its suitability for use with a wide range of drug

concentrations, from 0 - 75%. In addition, a wide range of excipients can be utilized in this process to prepare pellets or granules with desired properties.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. Mary Pellak for typing this manuscript.

REFERENCES

1. T.J. Rosemand and S.Z. Mansdorf, "Controlled Release Delivery Systems," Marcel Dekker, Inc., New York, 1983, p. 177.

2. J.A. Bakan and J.L. Anderson, in "The Theory and Practice of Industrial Pharmacy," L. Lackman, H.A. Lieberman and J.L. Kanig, eds., 2nd ed., Lea & Febiger, Philadelphia, 1976, p. 420.

3. J.T. Goodwin and G.R. Somerville, in "Microencapsulation," R.E. Sparks, ed., The Center for Professional Advancement, 1974, p. 23.

4. P.L. Madan, Pharmaceutical Technology, Dec. 29 (1977).

5. "The Condensed Chemical Dictionary," 4th ed., Reinhold, New York, 1950, p. 178.

6. L.A. Luzzi, Journal of Pharmaceutical Sciences, 59, 1367 (1970).

7. J.M. Conrad and J.R. Robinson, in "Pharmaceutical Dosage Form: Tablets, " H.A. Lieberman and L. Lackman, eds., Vol. 3. Dekker, NY, 1982, p. 149.

8. J.T. Goodwin and G.R. Somerville, Chemtech, 4, 623 (1974).

9. A. Rankell and H.A. Lieberman, in "The Theory and Practice of Industrial Pharmacy, " L. Lackman, H.A. Lieberman and J.L. Kanig, eds., 2nd ed., Lea & Febiger, Philadelphia, 1976, p. 503.

10. S.C. Porter, C.H. Bruno and F.J. Jackson, in "Pharmaceutical Dosage Forms: Tablets," H.A. Lieberman and L. Lackman, eds. Vol. 3, Dekker, NY, 1982, p. 73.

11. S.C. Porter, Pharmaceutical Technology, Sept., 55 (1979).

12. D.E. Wurster, In "Pharmaceutical Dosage Forms: Tablets," H.A. Lieberman and L. Lackman eds., Vol. 3, Dekker, NY, 1982, p. 119.

13. H.S. Hall and R.E. Pondell, in "Controlled Release Technologies: Methods, Theory and Applications," Vol. II, CRS Press, Inc., Florida, 1980. p. 133.

14. A.M. Mehta, M.J. Vallazza and S.E. Abele, Pharmaceutical Technology, Apr., 46 (1986).

15. K.F. Tager and K.H. Bauer, Drug Mode in Germany, 25, 61 (1982).

16. D.M. Jones, Pharmaceutical Technology, Apr., 50 (1985).

17. M.J. Gamblen, Manufacturing Chemist, June, 56 (1985).

18. K.S. Murthy, R.V. Nesbitt and M.R. Harris, Pharmaceutical Engineering, July, 19 (1983).

19. E. King, in "Remington's Pharmaceutical Sciences", A. Owl, ed. 16th ed., 16th ed., Mack Publishing Co., Easton, 1980, p. 1565.

20. C. Eskilson, Manufacturing Chemist, March, 33 (1985).

21. R.C. Rowe, Pharmacy International, May, 119 (1985).