Session : 2013—2018
Page: 1—5
N 5/19

materials takes place and it may be the only process suitable for this type of product.

Spheronizers/pelletizers

For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment above. Such pellets are used for controlled drug release products following coating with a suitable polymer coat and filling into hard gelatin capsules. Capsule filling with a mixture of coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule shell dissolves.

A commonly used process involves the separate processes of wet massing, followed by extrusion of this wet mass into rod-shaped granules and subsequent spheronization of these granules. Because this process is used so frequently to produce modified-release multiparticulates, this process will be discussed in some detail.

Extrusion/spheronization

Extrusion/spheronization is a multi-step process used to make uniformly sized spherical particles. It is primarily used as a method to produce multiparticulates for controlled drug release applications. The major advantage over other methods of producing drug-loaded spheres or pellets is the ability to incorporate high levels of active ingredients without producing excessively large particles (i.e. minimal excipients are necessary).

The main steps of the process are:

- *dry mixing of ingredients* to achieve a homogeneous powder dispersion
- *wet massing* to produce a sufficiently plastic wet mass
- *extrusion* to form rod-shaped particles of uniform diameter
- *spheronization* to round off these rods into spherical particles
- *drying* to achieve the desired final moisture content
- *screening* (optional) to achieve the desired narrow size distribution.

Applications of extrusion/spheronization

Potential applications are many but relate mainly to controlled drug release and improved processing.

Controlled drug release Both immediate-release and controlled-release pellets can be formed. In turn, these pellets can either be filled into hard gelatin capsule shells or compacted into tablets to form unit dosage forms. Pellets can contain two or more ingredients in the same individual unit or incompatible ingredients can be manufactured in separate pellets.

Pellets can be coated in sub-batches to give, say, rapid-, intermediate- and slow-release pellets in the same capsule shell. Dense multiparticulates disperse evenly within the GI tract and have less variable gastric emptying and intestinal transit times than single units, such as coated monolithic tablets.

Processing The process of extrusion/spheronization can be used to increase the bulk density, improve flow properties and reduce the problems of dust usually encountered with low-density, finely divided active and excipient powders.

Extrusion/spheronization is a more labour-intensive process than other forms of granulation and therefore should only be considered when other methods of granulation are either not satisfactory for that particular formulation or are inappropriate (i.e. when spheres are required).

Muhammad Qamar -Uz- Zaman
Assistant Professor
Department Of Pharmacy
The Islamia University Bahawalpur.

Desirable properties of pellets

Uncoated pellets have:

- uniform spherical shape
- uniform size
- good flow properties
- reproducible packing (into hard gelatin capsules)
- high strength
- low friability
- low dust
- smooth surface
- ease of coating

and once coated:

- maintain all of the above properties, and
- have desired drug release characteristics.

Process

Dry mixing of ingredients This uses normal powder mixing equipment.

Wet massing This stage also employs normal equipment and processes as used in wet granulation. There are two major differences in the granulation step compared with granulation for compaction:

- amount of granulation fluid, and
- the importance of achieving a uniform dispersion of fluid.

The amount of fluid needed to achieve spheres of uniform size and sphericity is likely to be greater than that for a similar tablet granulation. Poor liquid dispersion will produce a poor-quality product.

P1

Extrusion Extrusion produces rod-shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. The extrudate particles break at similar lengths under their own weight. Thus the extrudate must have enough plasticity to deform but not so much that the extruded particles adhere to other particles when collected or rolled in the spheronizer.

There are many designs of extruder but generally they can be divided into three classes, based on their feed mechanism:

- screw-feed extruders (axial or endplate, dome and radial)
- gravity-feed extruders (cylinder roll, gear roll, radial)
- piston-feed extruders (ram).

The first two categories (shown in Fig. 29.8) are used for both development and production but the latter is only used for experimental development work as it is easy to add instrumentation.

The primary extrusion process variables are:

- the feed rate of the wet mass
- the diameter of the die
- the length of the die
- water content of the wet mass. The properties of the extrudate, and thus the resulting spheres, are very dependent on the plasticity and cohesiveness of the wet mass. In general, an extrudable wet mass needs to be wetter than that appropriate for conventional granulation by wet massing.

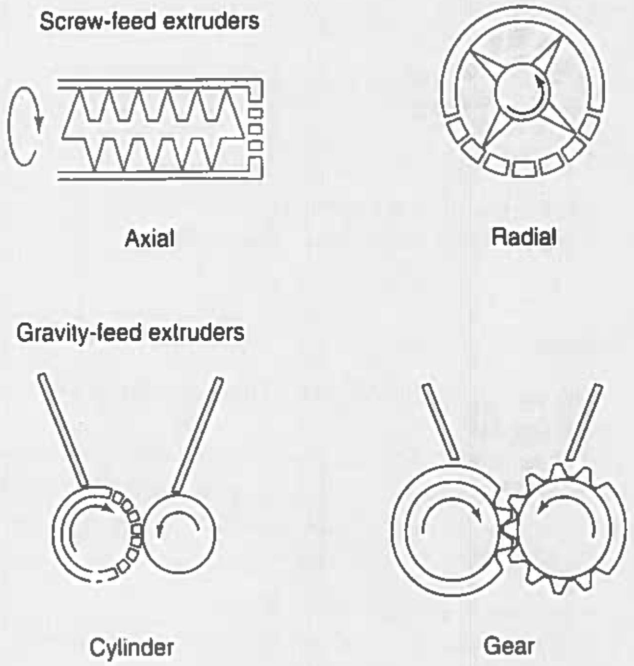

Fig. 29.8 Schematic representation of production extruders.

Spheronization The function of the fourth step in the process (i.e. spheronization) is to round off the rods produced by extrusion into spherical particles.

This process is carried out in a relatively simple piece of apparatus (Fig. 29.9). The working part consists of a bowl having fixed side walls, with a rapidly rotating bottom plate or disc. The rounding of the extrudate into spheres is dependent on frictional forces generated by particle–particle and particle–equipment collisions.

The bottom disc has a grooved surface to increase these forces. Two geometric patterns are generally used:

- a cross-hatched pattern with grooves running at right angles to one another, and
- a radial pattern with grooves running radially from the centre of the disc.

The transition from rods to spheres during spheronization occurs in various stages. These are best described by examining the diagrams in Figure 29.10.

If the moist mass is too dry spheres will not be formed; the rods will only transform as far as dumbbells.

Drying A drying stage is required in order to achieve the desired moisture content. Drying is often the final step in the process. Drying of the pellets can be accomplished in any dryer that can be used for conventional wet granulations, including tray dryers and fluidized-bed dryers. Both are used successfully for extrusion/spheronization. If solute migration (see Chapter 30) occurs during drying of the wet spheres, this may result in:

- increased initial rate of dissolution
- stronger pellets, and
- modified surfaces which might reduce the adhesion of any added film coats.

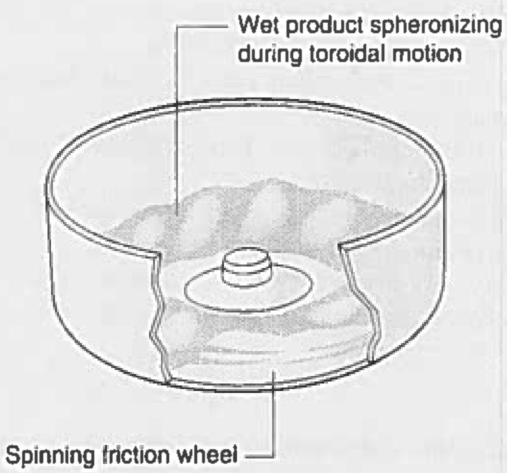

Fig. 29.9 A spheronizer showing the characteristic toroidal (rope-like) movement of the forming pellets in the spheronizer bowl during operation.

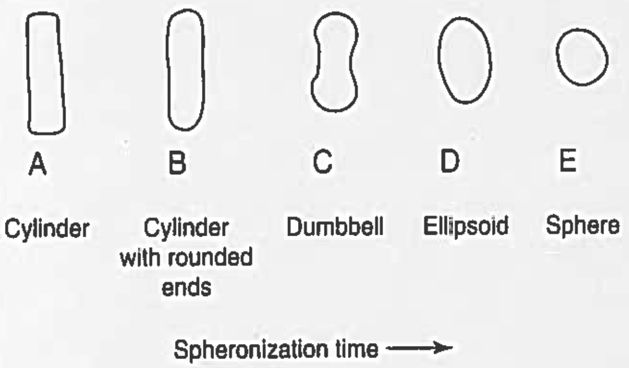

Fig. 29.10 Representation of a mechanism of spheronization. The diagram shows a transition from cylindrical particles (a) into cylindrical particles with rounded edges (b), then dumbbells (c), to ellipsoids (d) and finally spheres (e).

Screening (optional) Screening may be necessary in order to achieve the desired narrow size distribution. Normal sieves are used. If all the previous stages are performed efficiently and with careful development of process and formulation conditions, this step may not be necessary.

Formulation variables

The composition of the wet mass is critical in determining the properties of the particles produced. During the granulation step a wet mass is produced which must be plastic, deform when extruded and break off to form uniformly sized cylindrical particles which are easily deformed into spherical particles. Thus the process has a complex set of requirements that are strongly influenced by the ingredients of the pellet formulation.

Summary

Extrusion/spheronization is a versatile process capable of producing spherical granules having very useful properties. Because it is more labour intensive than more common wet massing techniques, its use should be limited to those applications where a sphere is required and other granulation techniques are unsuitable.

The most common application of the process is to produce spherical pellets for controlled drug release.

Care must be taken to understand the required properties of the pellets and the manner in which the process and formulation influence the ability to achieve these aims.

Developments of the standard extrusion/spheronization process allow heated extrusion of formulations containing excipients which melt and bind the ingredients together. This is *melt granulation*. Low melting point waxes are used in the process.

Rotorgranulation

This process allows the direct manufacture of spheres suitable for controlled-release solid dosage forms from dry powder in one process. The powder mix is added to the bowl and wetted with granulating liquid from a spray or multiple sprays (Fig. 29.11). The base plate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor. Here the velocity difference

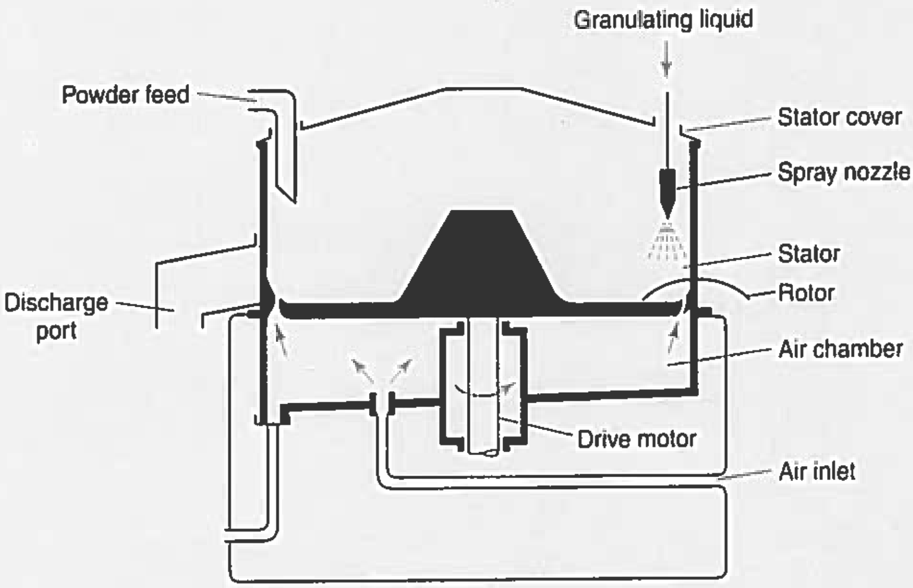

Fig. 29.11 Rotorgranulator.

P3

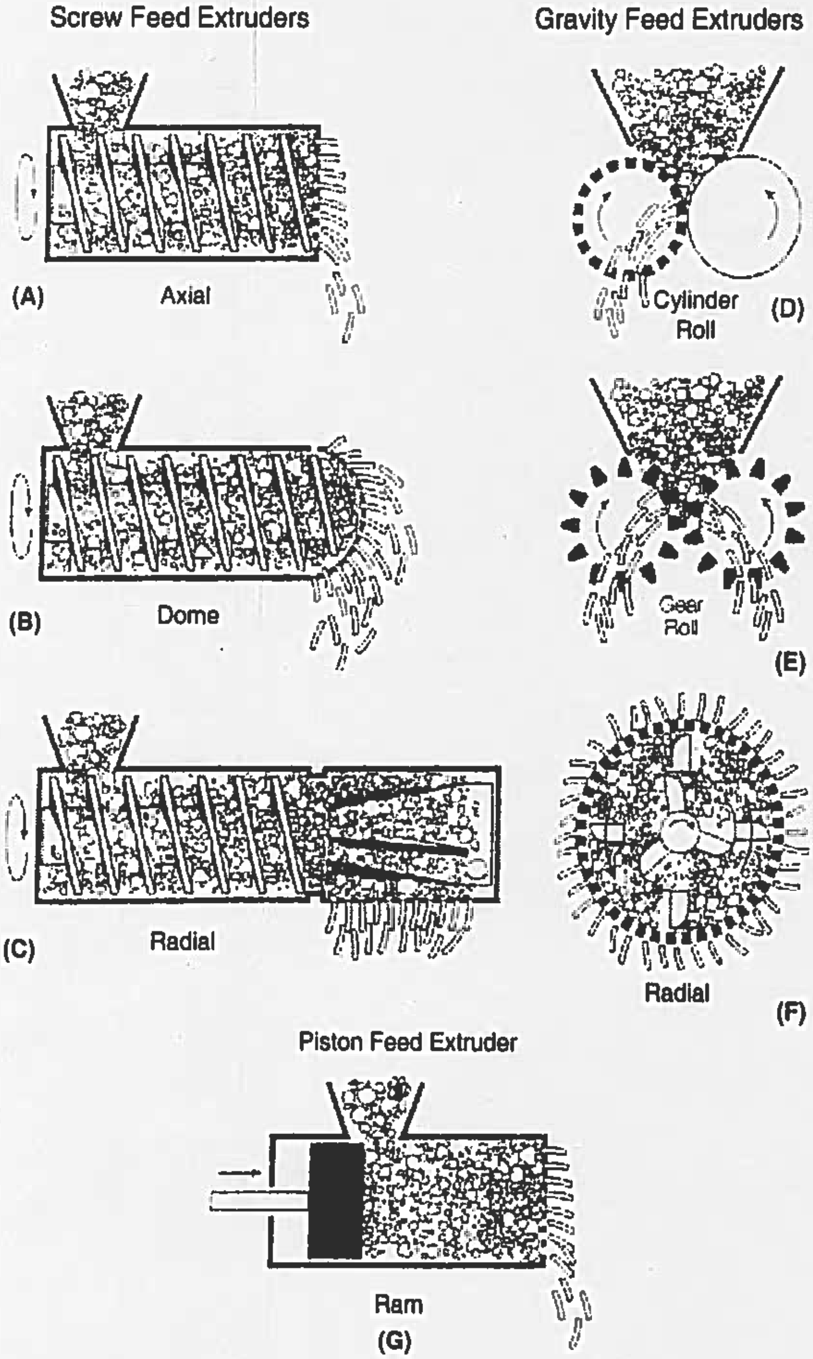

Figure 5 Schematic diagrams of extruder types used in extrusion/spheronization.

their own weight. The extrudate must have enough plasticity to deform but not so much to adhere to other particles when collected or rolled in the spheronizer.

Extruders come in many varieties but can generally be divided into three classes based on their feed mechanism. They include those that rely on a screw, gravity or a piston to feed the wet mass into the extrusion zone (35). Examples of extruders from each class are shown in Figure 5. Screw feed extruders include the (a) axial or end plate, (b) dome, and (c) radial type, while gravity-feed extruders include (d) cylinder, (e) gear, and (f) radial types. The screw and gravity-feed types are used for development and manufacturing with the radial varieties being the most popular for pharmaceutical applications. The piston feed or ram extruder is primarily used in research as an analytical tool.