PSTT Vol. 2, No. 4 April 1999

Extrusion and spheronization in the development of oral controlled-release dosage forms

Rajesh Gandhi, Chaman Lal Kaul and Ramesh Panchagnula

The concept of multiparticulate dosage forms was introduced in the 1950s. With the increasing use of multiparticulate controlled release (CR) oral dosage forms, in recent times there has been a rise in interest in the methods of preparing these dosage forms. A method that has gained increased usage over the past few years is that of extrusion and spheronization. It has been extensively explored as a potential technique and also as a future method of choice for preparation of multiparticulate CR dosage forms. In this review an attempt is made to outline the general process of extrusion and spheronization and to assess its importance in the development of multiparticulate CR oral dosage forms.

Rajesh Gandhi, Chaman Lal Kaul and Ramesh Panchagnula*
Department of Pharmaceutics
National Institute of Pharmaceutical Education and Research
Sector 67, S.A.S. Nagar
Punjab 160 062
India
*tel: +91 172 673048
fax: +91 172 677185
e-mail: niper@chd.nic.in

Conventional medication systems that require multi-dose therapy are not without problems. With a view to overcoming these problems, the current trend in pharmaceutical research is to design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Moreover, the impetus for research into drug delivery can be attributed to the exorbitant cost and large development period involved in 'new drug development' with concomitant recognition of the therapeutic advantages of controlled drug delivery.

Controlled release (CR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into systemic circulation at a predetermined rate. The choice of drug to be delivered, clinical needs, and drug pharmacokinetics are some of the important considerations in the development of CR formulations, in addition to the relationship between the rate of drug release from the delivery system to the maximum achievable rate of drug absorption into the systemic circulation. By achieving a predictable and reproducible bioactive agent release rate for an extended period of time, CR formulation can achieve optimum therapeutic responses, prolonged efficacy, and also decreased toxicity[1].

The therapeutic advantages of CR systems over conventional dosage forms have been amply documented in the literature[2,3]. One of the important advantages is the reduced dosing frequency, thereby improving patient compliance and therapeutic efficacy. In addition, the constant blood levels of the drug, unlike in conventional dosage forms, leads to a minimization of drug-related side effects.

Although a variety of dosage forms have been developed for the preparation of oral CR formulations, they broadly fall into two categories: single unit dosage forms and multiple (multiparticulate) dosage forms.

Single unit dosage forms

Single unit dosage forms are defined as oral dosage forms that consist of single units, with each unit containing one dose of the drug and intended to be administered singularly. There are several such dosage forms that have been developed for the CR of various bioactive materials, as has been reported in the literature and of which monolithic matrix-based tablets are the most common single unit dosage form used for controlled drug delivery[4,5]. Advantages associated with such dosage forms include high drug loading, simple and cost-effective manufacturing operations, the availability of a wide range of excipients and polymers for controlling drug release

1461-5347/99/$ – see front matter PII: S1461-5347(99)00136-4

and the possibility of using different mechanisms for drug release control (such as diffusion controlled, swelling controlled, erosion controlled or a combination of all of these). Single unit dosage forms that have been used for controlled drug delivery include drug-release controlling polymer membrane-coated tablets and osmogen-controlled formulations[6,7].

Multiple unit dosage forms

The concept of the multiple unit dosage form was initially introduced in the early 1950s. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. Together, these characteristic units provide the overall desired CR of the dose. These multiple units are also referred to as pellets, spherical granules or spheroids. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5–1.5 mm and in some applications may be as large as 3.0 mm (Ref. 8).

The use of pellets as a vehicle for drug delivery at a controlled rate has recently received significant attention. Applications are found not only in the pharmaceutical industry but also in the agribusiness (such as in fertilizer and fish food) and in the polymer industry[9]. There are numerous advantages offered by multiple unit dosage forms.

- Pellets disperse freely in the gastrointestinal (GI) tract, and so they invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability[10].
- Pellets also reduce variations in gastric emptying rates and overall transit times. Thus inter- and intra-subject variability of plasma profiles, which is common with single unit regimens, is minimized[11].
- High local concentration of bioactive agents, which may inherently be irritative or anesthetic, can be avoided[12].
- When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type, single unit formulations[12].
- Better flow properties, narrow particle size distribution, less friable dosage form and uniform packing[13,14].
- The pellets offer advantages to the manufacturer because they provide an ideal shape [low surface area to volume ratio] for the application of film coating. They can also be made attractive because of the various shades of colour that can be easily imparted to them during the manufacturing process, thus enhancing the product elegance and organoleptic properties[12].
- Pellets also offer the advantage of flexibility for further modifications, such as compression to form tablets or coating to achieve the desired dosage-form characteristics[15].

Methods of pellet preparation

Pellets are spheres of varying diameter and they may be manufactured by using different methods according to the application and the choice of producer.

In a spray-drying process, aqueous solution of core materials and hot solution of polymer is atomized into hot air, the water then evaporates and the dry solid is separated in the form of pellets, usually by air suspension. In general, a spray-drying process produces hollow pellets if the liquid evaporates at a rate faster than the diffusion of the dissolved substances back into the droplet interior or if due to capillary action dissolved substances migrate out with the liquid to the droplet surface, leaving behind a void[12,16].

In spray congealing a slurry of drug material that is insoluble in a molten mass is spray congealed to obtain discrete particles of the insoluble materials coated with congealed substances. A critical requirement for this process is that the substance should have a well-defined melting point or small melting zone[12].

In fluidized bed technology a dry drug form is suspended in a stream of hot air to form a constantly agitated fluidized bed. An amount of binder or granulating liquid is then introduced in a finely dispersed form to cause a momentary reaction prior to vaporization. This causes the ingredients to react to a limited extent, thereby forming pellets of active components. Using this process Govender and Dangor[13] and Mathir et al.[17] prepared and characterized pellets of Salbutamol and Chlorpheniramine maleate, respectively.

In the rotary processor (rotogranulator) the whole cycle is performed in a closed system. The binder solution and powder mix are added at a fixed rate on the plate of the spheronizer so that the particles are stuck together and spheronized at the same time. Using this process Robinson and Hollenbeck[18] prepared acetaminophen pellets and, in a comparison with extrusion–spheronization, they demonstrated that acceptable, immediate release pellets could be produced.

A novel method involving the use of a rotary shaker pelletizer has been developed for making pharmaceutical spheres. It is essentially based on a laboratory shaker in which a cylindrical bowl is attached to the platform of a rotary shaker. Spiral particle motion combined with a high degree of particle bowl bottom friction and interparticulate collision in the bowl (feed with plastic extrudates) results in plastic deformation of extrudate and the granule surface to form the spheres[19].

A further technique used to prepare pellets is the layer building method, in which a solution or suspension of binder and a

PSTT Vol. 2, No. 4 April 1999

drug is sprayed onto an inert core and the pellets are built layer after layer. However, use of this technique is limited because of the smaller drug loading that can be layered effectively onto the core material, thus making this technique unsuitable for drugs with large doses[20].

Extrusion and spheronization

Extrusion and spheronization is currently one of the techniques used to produce pharmaceutical pellets. With each production technique, pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established method because of its advantages over the other methods[18,21] (Box 1), and the technique will now be described in detail.

Box 1. Advantages of the extrusion and spheronization process

Ease of operation
High throughput with low wastage
Narrower particle size distribution
Production of pellets with low friability
Production of pellets that are suited for film coating
More sustained and better controlled drug-release profile when compared with other techniques

Spheronization is a technique of Japanese origin that is sometimes referred to as Merumerization, after the trademark of the Fuji Denki Kogyo Company (Osaka, Japan). Although originally invented in 1964 by Nakahara[22], it wasn't until 1970 and the publication of the process by Reynolds (Lilly Research, UK)[14] and Conine and Hadley (Eli Lilly, Indianapolis, IN, USA)[23] that the technique became widely known. In subsequent years the detailed process of spheronization, including the individual processing variables based on extrusion and spheronization, was published by J.B. Schwartz's group and the whole process was reduced to a series of pharmaceutical operations, each of which is associated with a number of individual parameters[24,25].

Process and equipment

In basic terms, the extrusion and spheronization process involves four steps:

- granulation – preparation of the wet mass;
- extrusion – shaping the wet mass into cylinders;
- spheronization – breaking up the extrudate and rounding off the particles into spheres;
- drying – drying of the pellets.

Different steps, parameters and equipment used in the process are summarized in Fig. 1.

The first step of the extrusion and spheronization cycle consists of the preparation of the wet mass. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. There are three types of processors used to mix different constituents of the powder blend. The most commonly used granulator is a planetary mixer[18], although in various cases use of a high shear mixer, sigma blade mixer[26] and a continuous granulator[27] has also been reported. However, it is important to note that high shear mixers introduce a large amount of heat into the mass during granulation, which may cause evaporation of the granulation liquid because of a rise in temperature, thereby influencing the extrusion behaviour of the wet mass. This may be avoided by cooling the granulation bowl[28].

Extrusion

Extrusion is the second step of the process and consists of shaping the wet mass into long rods, which are more commonly termed 'extrudate'. The extrusion process is used not only in the pharmaceutical industry but also in the food, ceramic and polymer industries. The extrusion process is currently used as an alternative method for the manufacture of completely water-soluble tablets[29].

Types of extrusion devices have been grouped into four main classes; that is, screw, sieve and basket, roll and ram extruders. A screw extruder, as the name implies, utilizes a screw to develop the necessary pressure to force the material to flow through the uniform openings, producing uniform extrudates[30]. In the sieve and basket extruders the granulate is fed by a screw or by gravity into the extrusion chamber in which a rotating or oscillating device processes the plastic mass through the screen. The basket type extruder is similar to the sieve extruder except that the sieve or screen is part of a vertical, cylindrical wall[31]. The third class of extruders are the roll extruders and these are also known as 'pellet mills'. Two types of roll extruders are available[31,32]. One extruder is equipped with two contrarotating wheels, of which one or both are perforated, and the second type of roll extruder has a perforated cylinder that rotates around one or more rollers that discharge the materials to the outside of the cylinder. The final type of extruder is an experimental device called the ram extruder. The ram extruder is believed to be the oldest type of extruder and features a piston riding inside a cylinder or channel that is used to compress material and force it through an orifice on the forward stroke. Fielden et al.[32] compared the extrusion and spheronization behaviour of wet mass processed by a ram extruder and a cylinder extruder and concluded that they are not always equivalent.

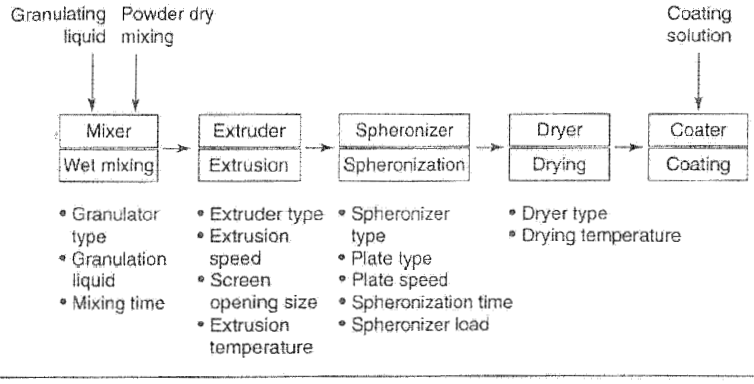

Figure 1. Flow diagram showing different steps, process parameters and equipment involved in extrusion and spheronization to produce spherical controlled release pellets.

Spheronization

The third step of the extrusion and spheronization process involves the dumping of the cylinders onto the spheronizer's spinning plate, known as the friction plate, upon which the extrudate is broken up into smaller cylinders with a length equal to their diameter. A spheronizer is a device that consists of a vertical hollow cylinder (bowl) with a horizontal rotating disk (friction plate) located inside. The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist; more common is the cross-hatch geometry in which the grooves intersect each other at 90° angles, whereas the other pattern is radial geometry in which grooves emanate from the centre like the spokes of a bicycle wheel. The spheronization of a product usually takes 2–10 minutes, and a rotational speed of between 200–400 rpm for the friction plate is satisfactory to obtain highly spherical pellets[9,23]. A special type of spheronizer, designed by NICA systems, features a lip around the rim of the friction plate that is claimed to reduce the milling effect of the plate in order to produce a smaller amount of fines[30].

The fourth and final step of the process is the drying of the pellets. The pellets can be dried at room temperature[32] or at an elevated temperature in the fluidized-bed drier[18], in an oven[33], in a forced circulation oven[13] or in a microwave oven[34]. Pellet quality is dependent on the type of dryer used. According to Bataille *et al.*[34], oven drying provides less porous and harder minigranules and a more homogenous surface than those dried by a microwave oven. Dyer *et al.*[35] prepared ibuprofen pellets that were dried either by tray drying or fluidized-bed drying, and they showed that the drying technique has a quantifiable effect on the diametral crushing strength and elasticity of the pellets, their *in vitro* release, and a qualitative effect on the surface characteristics of ibuprofen pellets.

Pellet formation

Numerous mechanisms of pellet formation have been suggested. The overall process of spheronization can be divided into various stages in terms of the changes in the shape of the extrudate. According to Rowe[36], extruded plastic cylinders are rounded in the form of pellets because of frictional forces. Cylinders transform into cylinders with rounded edges then to dumb-bells and elliptical particles and eventually to perfect spheres. Baert and Remon[28] suggested that another pellet-forming mechanism might also exist that is based on frictional forces as well as rotational forces. In this mechanism a twisting of the cylinder occurs after the formation of a cylinder with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts with both parts featuring a round and a flat side. Because of the rotational and the frictional forces involved in the spheronization process, the edges of the flat side fold together like a flower, forming the cavity observed in certain pellets. Figure 2 shows both pellet-forming mechanisms.

The process of extrusion and spheronizaton is a multi-step process that involves a number of parameters that have a final bearing on the characteristics of the obtained pellets. Moisture content is an extremely important parameter in the extrusion and spheronization process. It is necessary to give the powder mass its plasticity so that it can be extruded and shaped afterwards. It was

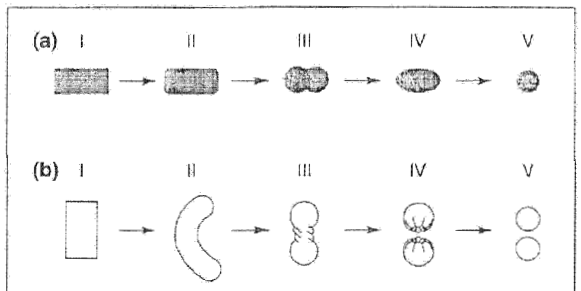

Figure 2. Pellet-forming mechanism according to: (a) Rowe[36] – I. Cylinder; II. Cylinder with rounded edges; III. Dumb-bell; IV. Ellipse; V. Sphere. (b) Baert – I. Cylinder; II. Rope; III. Dumb-bell; IV. Sphere with a cavity outside; V. Sphere. [Reproduced with permission from Ref. 9.]

shown that there is a certain limit of moisture content at which pellets of an acceptable quality are produced. If the moisture content is less than a certain lower limit, a lot of dust will be introduced during spheronization which will result in a large yield of fines. If moisture content is more than a certain upper limit then an overweighed mass and agglomeration of individual pellets during spheronization are caused because of an excess of water at the surface of pellet[32]. The extent of moisture content also influences the mechanical strength, friability, internal porosity and the particle-size distribution of pellets.

Ostuka *et al.*[37] reported that the internal porosity of spherical granules decreases with increasing water concentration, weight loss after the friability test increases with a decreasing amount of water and the quantity of water influences the mechanical strength of granules. Moisture content also affects the shape and size of granules[38]. Gazzaniga *et al.*[39] found differences in the friability and particle size of pellets when the powder mass was wetted with different quantities of water.

Starting material

The physical nature of the starting material influences the particle size, hardness, and sphericity as well as the release rate of the included drug. There is not only the obvious difference in pellet quality produced from different compositions but also the difference when different types of the same product are used[25]. The use of similar products but from different suppliers has also been found to change the characteristics of the pellet[40,41]. Pellets prepared with three types of microcrystalline cellulose (MCC) – Avicel® PH-101, Emcocel®, Unimac® – MG from different manufacturers featured differences in size and roundness when processed under the same conditions[40]. The physical properties of two types of commercial MCC, Avicel PH-101 and Microcel MC show differences during the step of moistening, thereby affecting the particle size and hardness of the pellets obtained[42]. The difference in release rate in different types of dissolution medium has been observed between pellets containing only MCC and those containig MCC with sodium carboxymethyl cellulose (NaCMC). This difference is because a gel-like structure was formed in water through the presence of NaCMC with MCC, whereas the pellets containing only MCC remain unchanged in aqueous medium resulting in a greater rate of release[43].

Granulation liquid

The use of different amounts of water as a granulation liquid alone or in combination with alcohol affects the hardness and particle size distribution of the final pellets. The most commonly used granulating liquid is water, although in some cases the use of alcohol or a water–alcohol mixture has also been reported[9]. The effect of the alcohol content in a water–alcohol mixture has been extensively studied by Millili and Schwartz[44]. Binary mixtures of theophylline and Avicel PH-101 (10:90 w/w) were found to form pellets when granulated with 90% ethylalcohol in water–alcohol mixture. Differences in friability and dissolution were observed between water granulated- and 95% ethylalcohol in water–alcohol mixture-granulated pellets. Increasing the water content in the granulation liquid leads to an increase in the hardness of the pellets. The increase in the hardness was correlated with a slower *in vitro* release rate of theophylline. Gazzaniga *et al.*[39] reported that when β-Cyclodextrin (β-CD) was used to form pellets using water as the granulating liquid, the poor quality of the extrudates, in terms of plasticity and sticking, invariably lead to irregularly shaped pellets and agglomerates with broad size distribution. In this respect, preliminary promising results were obtained by lowering the solubility of β-CD in the wetting liquid through the use of water–alcohol mixtures. This probably improves the plasticity of the wetted mass and thus the feasibility of the overall process.

Extruders

Several studies appear in the literature regarding the influence of the type of extruder on the size distribution, sphericity and density of pellets[14,36,41]. The studies have shown that pellets obtained from two types of extruder had differed in sphericity and in particle size distribution because of a shift in the optimal amount of granulation liquid needed with each extruder or because of the difference in the length-to-radius ratio of the extrusion screen used[45,46]. According to Reynolds[14] and Rowe[36], an axial screw extruder produces a more dense material compared with the radial screw extruder; the latter has a higher output but also produces a greater rise in the temperature of the mass during processing.

Extrusion screen properties

Pellet quality is dependent on the extrusion screen, which is characterized by two parameters: the thickness of the screen and the diameter of the perforations. Changing one of these two parameters influences the quality of the extrudate and hence the pellets. Baert *et al.*[46] reported the difference in extrudate quality when they were obtained by extrusion with different screen thicknesses. The screen with low thickness formed a rough and loosely bound extrudate, whereas the screen with high thickness formed smooth and well-bound extrudate because of the higher densification of the wet mass in the screen with the greatest thickness.

Similarly, the diameter of the perforations determines the size of pellets, and a larger diameter in the perforations will produce pellets with a larger diameter when processed under the same conditions[47,48]. An increase in the extruder screen

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.