ISSN : 2249 - 8877 Volume 3 Issue 2

Trade Science Inc.

Research & Reviews On Polymer

Review

RRPL, 3(2), 2012 [55-63]

Pellets as a drug delivery system: Formulation and evaluation aspects

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Received: 12th November, 2011 ; Accepted: 12th December, 2011

ABSTRACT

The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. The advantages offered by pellets as a drug delivery system are discussed in this work. Methods of manufacturing pellets (as spray drying, spray congealing, fluidized bed and extrusion/spheronization techniques) are presented. Moreover, evaluation of pellets shapes, sizes, surfaces, friability, porosity, disintegration, and dissolution is reviewed. Several formulation variables which might impact the pellet attributes will be also briefly discussed.

KEYWORDS

Pellets;
Manufacturing techniques;
Evaluation;
Formulation variables.

INTRODUCTION

Multiple-unit dosage forms have several advantages compared with single-unit dosage forms including more stable plasma profiles and little risk of local side effects[1]. Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 □m for pharmaceutical applications[2]. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. Pellets as a drug delivery system offer therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping[3].

The use of pellets as a vehicle for drug delivery 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[4].

Advantages of pellets as a drug delivery system

There are numerous advantages offered by multiple unit dosage forms:

1- 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[5].

2- 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[3].

3- High local concentration of bioactive agents, which may inherently be irritative or anesthetic, can be avoided[6].

4- When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type, single unit formulations[6].

5- Better flow properties, narrow particle size distribution, less friable dosage form and uniform packing[7].

6- 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[6].

7- 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[8].

METHODS OF PELLETS MANUFACTURING

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

Spay drying

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[9].

Spay congealing

In spray congealing, 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[6].

Fluidized bed technology

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[10, 11], prepared and characterized pellets of Salbutamol and Chlorpheniramine maleate, respectively.

Rotary spheronization

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[12] prepared acetaminophen pellets and, in a comparison with extrusion–spheronization, they demonstrated that acceptable, immediate release pellets could be produced.

Rotary shaker pelletization

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[13].

Layer building method

A further technique used to prepare pellets is the layer building method, in which a solution or suspension of binder and a 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[6].

Extrusion/ 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, Figure 1[14].

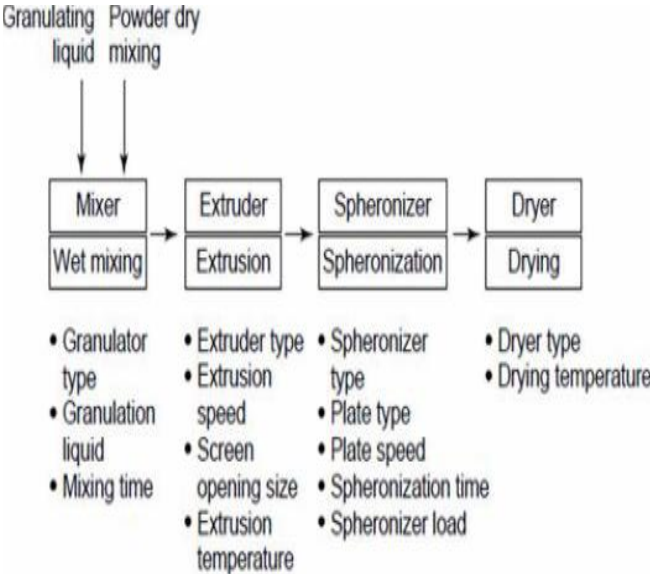

Figure 1 : Flow diagram showing different steps, process parameters and equipment involved in extrusion and spheronization to produce spherical pellets.

EVALUATION OF PELLETS

Size distribution

The sizing of pellets is necessary because it has significant influence on the release kinetics[15]. Particle size distribution, mean ferret diameter, geometric mean diameter, mean particle width and length, are the parameters by which size of pellets can be determined. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker[16-19]. Wiwattaapatapee et al.[20] reported the use of vernier calipers to determine the size of pellets. In other studies the particle size of pellets could be determined using the mastersizer laser diffractometry[21].

Pellets shape

Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference[19, 22]. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity[13, 23]. Visual inspection of pellets by microscope and stereomicroscope is another method to determine shape of pellets[24, 25].

One plane critical stability, which an angle at which a plane has to be tilted before a particle begins to roll, is one of the important methods used for determining shape[26, 27]. The angle of repose is an indirect indication of the circularity of pellets[28] and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to fall from a given height through a specific orifice.

Surface morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets[29-31]. Reported the use of optical microscopy to examine the microstructure of pellet surface. Eurrkainea and Lindqvist[32] took SEM pictures to observe the influence of different fillers and concluded that MCC and corn- starch gives best quality pellets with smooth surface. Prieto *et al.*[33] took SEM pictures of pellets to show the influence of Starch-Dextrin mixtures, a base excipient for extrusion spheronization technique while Wiwaattarapatapee and Pengno[20] took SEM pictures to detect antagonistic bacteria both on the surface and inside of the pellets. Santosh *et al.*,[23] analyzed surface roughness of pellets by applying a non-contracting laser profilometer.

Specific surface area

Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area[15]. Specific surface area of pellets is determined by gas adsorption technique[23].

Friability

The mechanical properties of pellets are important

for processing. Pellets flake off during handling and coating process resulting in formation of dust. In the case of subsequent coating it is desirable to have pellets with low friability. Friability of pellets are determined by using Erkewa type tablet friabiliator[33] or turbula mixer[34] for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with Wurster insert by using stream of air[35].

Tensile strength

The tensile strength of the pellets are determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the Tensile strength is calculated applying the value for the failure load and the radius of the pellets[36].

Density

Density of pellets (bulk and tapped) can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression, and is determined simply by USP density apparatus[37, 38].

Porosity

The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry[39]. The porosity of the pellets can also be determined quantitatively by using optical microscopy and SEM together with image analysis[40].

Disintegration time

Disintegration of pellets is one of the main characteristics for immediate release pellets. Huyghebaert *et al.*, 2005[30] reported disintegration test using the reciprocating cylinder method (USP Apparatus 3). While Thommes and kleinbudde, 2006[24] performed it in a tablet disintegration tester specially designed by inserting special transparent tubes of certain diameter and length with sieve of 710 μm mesh size at the top and bottom of the tube.

In vitro dissolution studies

In vitro dissolution has been recognized for the past four decades as an important element both in drug development and quality assessment, especially in controlled released formulation[41]. Release of drug from solid dosage form often constitute a determining step in the *in vivo* absorption process and used in conjunction with *in vivo*/*in vitro* correlation to establish quality control parameter. Release of the drug from pellet mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I[42] or by USP Apparatus II[43]. The drug release profiles from pellets also depended on the nature of the carrier solid, aqueous solubility of the drug, physical state of the drug in the matrix, drug load and the presence of additives such as surfactants. The influence of pellet composition by incorporating citric acid in the formulation on retarding the release of highly water soluble drug from enteric coated pellets in 0.1 N HCl was investigated by Bruce *et al.*, 2003[35].

FORMULATION VARIABLES

Wet mass composition

The composition of the wet mass is critical in determining the properties of the particles produced. This is clearly understood if we look at what material behaviors are required during each of the process steps. During the granulation step, a plastic mass is produced a simple enough task if ended there. The materials must form a plastic mass, deform when extruded and break off to form uniformly sized cylindrical particles. A minimal amount of granulating fluid should migrate to the surface during extrusion and the particles should stay discrete during collection. During Spheronization, the particles must round off to form uniformly sized spheres. They must not dry out due to temperature or air volume or grow in size due to agglomeration.

The fact is that a lot is expected from materials used in this process.

This is especially true of formulations containing high percentages of active where low levels of excipients are used to impart the desired properties to the mass.

The use of sphere forming excipients

The importance of using sphere-forming excipients

was noted early on. Conine and Hadley[44] cited the necessity of using microcrystalline cellulose. Reynolds went on to indicate the need for either adhesive or capillary type binders[7]. He cited cellulose gums, natural gums, and synthetic polymers as adhesives and microcrystalline cellulose, talc, and kaolin as capillary type binders. Since then much work has been conducted in an attempt to understand the significance of material properties. Some of the studies are discussed in the following text. O'Connor et al.[45] studied the behavior of some common excipients in extrusion/spheronization. The materials were studied as single components using water as the granulating fluid in an attempt to understand their application in the process. Of the materials tested, only MCC or MCC with Na-CMC (Na-caboxymethyl cellulose) was capable of being processed. Others including dicalcium phosphate, lactose, starch, and modified starch did not process adequately. In an additional study, they investigated the effect of varying drug, excipient, and excipient:drug ratios. At low drug levels they found the spheronizing excipient played the most significant role in determining sphere properties. They found that, for low dose applications, MCC was the best excipient to use since it formed the most spherical particles. At moderate drug loading (50%), MCC as well as the two products consisting of MCC coprocessed with Na-CMC (Avicel_ RC-581 and Avicel CL-611) resulted in acceptable spheres. At higher loading levels, however, the MCC did not yield acceptable spheres and the coprocessed materials did. The spheres produced using Avicel CL-611 were the most spherical. In addition, they found dissolution to be dependent on the type of excipient used, the solubility, and concentration of the active. Spheres containing MCC remained intact and behaved as inert matrix systems, while those containing the coprocessed products formed a gel plug in the dissolution basket and were described as water-swellable hydrogel matrix systems.

Mehta et al.[46, 47] demonstrated the use of polymethacrylate type polymers such as Eudragit L 100–55 and Eudragit S 100 via extrusion/Spheronization in the development of controlled release pellets. They theorized that for the development of zero-order controlled release pellets of a poorly soluble drug, MCC would not be a good choice to form a pellet system via extrusion/spheronization. This would be due to the fact that MCC being insoluble would form a nondisintegrating matrix from which it would be difficult for an insoluble drug to be released. In their work they showed that Eudragit L100–55 and Eudragit S 100 can be used as pellet forming and release rate governing polymers for developing a controlled release drug delivery system with out the use of MCC in the matrix.

Zhou and Vervaet[48] produced matrix pellets by combining microcrystalline waxes, pregelatinized starches, and hydrolyzed starches with model drugs such as Ibuprofen, chloroquin phosphate, and others. They concluded that the combination of microcrystalline waxes and pregelatinized starches or maltodextrins is a flexible system for the production of matrix pellets, even with a high drug concentration. Additionally, they concluded that the drug release with such a system could be modeled by varying the type and the concentration of the wax and the starch.

Granulating liquid

Kleinebudde and Jumaa[49] concluded that during the extrusion process, water content in the extrudate and pellet porosity were increased as the degree of polymerization of MCC and powder cellulose in the matrix was increased. Millili and Schwartz[50] demonstrated the effect of granulating with water and ethanol at various ratios. The physical properties of the spheres changed significantly as the ratio of the two fluids was varied. Spheres could not be formed with absolute ethanol but were possible with 5: 95 water: ethanol. An increase in the water fraction resulted in a decrease in porosity, friability, dissolution, and compressibility and an increase in density. The porosity of spheres granulated with 95% ethanol was 54% while the water granulated product had a porosity of 14%. When greater than 30% water was used, spheres remained intact throughout the dissolution test. As previously discussed, water granulated spheres were very difficult to compress while spheres granulated with 95% ethanol were significantly more compressible than those prepared using water. In contrast, Mehta et al.[51] showed that an increase in granulation water level increased the total number of pores in the pellet matrix without changing the pore diameters. Additionally they concluded that this direct increase in porosity increased the dissolution

contact angle due to which dissolution of the poorly soluble drug was increased. Jerwanska et al.[52] concluded that the rate of drug release increased with increased levels of granulation liquid because of a greater degree of porosity obtained after drying. They also correlated these results with differences in hardness of the pellets. Jerwanska et al.[52] proposed that for a continuous extrusion process, adequate water is required to bridge the particles together until liquid saturation in the granulation is achieved. This strategy is necessary to deform the granulation to form extrudates and consequently shape them into spheres by spheronization. If the granulation water level is below the liquid saturation point, then the spheres obtained will be hard and less porous, thereby leading to decreased drug release rates. Above the liquid saturation point, the hardness and porosity of the pellets are not significantly decreased.

In a later study, Millili et al.[50] proposed a bonding mechanism, referred to as autohesion, to explain the differences in the properties of spheres granulated with water and ethanol. Autohesion is a term used to describe the strong bonds formed by the interdiffusion of free polymer chain ends across particle–particle interfaces.

Excipients solubility in the granulating fluid

Baert et al.[53] used mixtures of microcrystalline cellulose and coexcipients at various ratios to demonstrate the effect of solubility and the total fluid on extrusion forces. They showed that if the coexcipient was insoluble, such as dicalcium phosphate, the force required to extrude increased with increasing levels of coexcipient. When a soluble excipient such as lactose was used, the force required to extrude decreased with the addition of the initial amounts of lactose. After a certain level, however, the reduction in force stopped and began to increase. This was due to the initial solubilization of lactose and the resulting increase in the total fluid level. Once the fluid was saturated the remaining lactose was not soluble and the force began to increase. The increase began at about 10% lactose level for a-lactose and 20% for b-lactose. This was due to the difference in solubility between the two materials.

Effect of binder level

Funck et al.[54] showed that low levels of common binders could be used to produce high drug loaded spheres with microcrystalline cellulose. Materials such as carbomer, Na-CMC, hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), povidone (PVP), and pregelatinized starch were used. All materials were capable of producing spheres of acceptable quality. Dissolution testing showed spheres containing HPC and HPMC remained intact during testing while spheres containing starch, PVP, and Na-CMC disintegrated.

Effect of cellulose type

Lender and Kleinebudde[55] reported that spheres produced with powdered cellulose had higher porosity and faster dissolution than those made using microcrystalline cellulose. Spheres could not be produced using only powdered cellulose and drug; a binder was required. The higher porosity of the spheres prepared from powdered cellulose may be beneficial for applications requiring compression.

Effect of particle size

Feilden et al.[56] showed that increasing the particle size of lactose resulted in forced flow and high extrusion forces, which resulted in poor quality extrudate and spheres having a wide size distribution. This was attributed to the increased pore diameter of the mixture containing the coarse lactose which allowed greater movement of water.

The use of surfactants

Chien and Nuessle[57] showed the use of a surfactant, such as sodium lauryl sulfate, reduced the migration of drug to the surface of the sphere during drying by reducing the surface tension of the granulating fluid. The reduction in surface tension also made it difficult to produce a cohesive extrudate in some cases.

Some miscellaneous observations include the following. Reynolds[7] reported that excess extrudate friability can be overcome by incorporating more MCC, binder, or water in the granulation. Erkoboni et al.[58] indicated that sphere hardness was most affected by the level of MCC in the formulation and the level of granulating fluid used. Hileman et al.[59] showed that MCC had a narrower water range over which quality spheres could be made than MCC coprocessed Na-

CMC. Helle´n et al.[60] showed that the surface characteristics were influenced by the water level with higher water levels giving smoother surfaces. Mehta et al.[47] showed that when concentrations of pellet forming and release rate governing polymers in the matrix were changed, it altered the dissolution kinetics of a poorly soluble drug.

MIX TORQUE RHEOMETRY FOR CHARACTERIZATION OF WET MASSES

It has been shown that the rheological properties of wet masses can be successfully monitored by a mixer torque rheometer[61, 62].

The use of the mixer torque rheometer (MTR) as an upfront analytical tool can greatly reduce the number of development batches. This equipment has been shown to be an excellent tool for the evaluation of wet granulated systems and as a scale-up tool for high shear granulations[63]. Several authors have compared the rheological properties of different microcrystalline cellulose (MCC) systems[64, 65]. The results obtained revealed that the amount of water added at the maximum torque should be comparable with that found for the optimum production of pellets during spheronization[64].

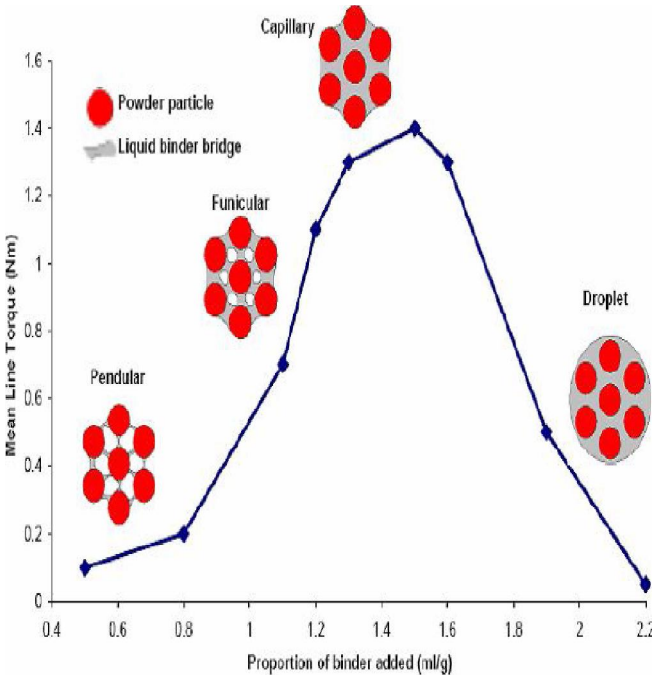

Figure 2 : Variation in measured torque value with increasing binder content.

Basic investigation of the granulation process

All materials studied using the MTR have exhibited changes in torque values with increasing water content. This rises to a maximum and then begins to decrease as more fluid is added. An explanation of this is shown below in Figure 2.

According to Rowe and Parker[66], the degree of liquid spreading and wetting as well as the substrate binder interaction will determine the relative positions of the peak values of mean line torque. An increase in the mean torque with the increase in the binder level at different concentrations either a sharp or an extended peak followed by a drop in the torque as over-wetting of the powder mass occurred. In addition, the pendular and funicular states are characterized by a progressively increasing network of liquid bridges. Both of these stages will cause an increase in cohesiveness of the powder mass and hence an increased torque on the mixer[61]. The capillary state which is reached when all the air spaces in the granular material are filled with liquid occurs at the maximum on the curve.

With further dispersed in liquid is formed. In addition, by increasing liquid content, the number and extent of the liquid bridges increases and a funicular state is formed. A further addition of liquid fills all the interparticulate voids, and the torque reaches a peak (capillary state). Prolonged mixing is assumed to cause a densification of the mass, and this should increase the liquid saturation causing a peak torque at a lower liquid amount. However, prolonged mixing will cause an increased absorption of water giving rise to a lower liquid saturation causing a peak torque at a higher liquid amount[67].

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