BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902017000400216

Review

Physical characterization of multiparticulate systems

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The search for new pharmaceutical dosage forms and different drug delivery systems already used in therapeutics is a global trend, serving as an opportunity to expand the portfolio for the pharmaceutical industry. In this context, multiparticulate systems, such as pellets, granules, and minitablets, represent an attractive alternative, given the range of possibilities they provide. Among the methods used in the production of these systems, we highlight the process of extrusion-spheronization for pellet manufacture, wet granulation and hot-melt extrusion for the obtention of granules, and direct compression for minitablets. Although highly versatile, depending on the technology chosen, many processes and formulation variables can influence the ensuing stages of manufacture, as well as the final product. Therefore, the characterization of these small units is of fundamental importance for achieving batch homogeneity and optimal product performance. Analyses, including particle size distribution, morphology, density, porosity, mechanical strength and disintegration, are example tests used in this characterization. The objective of this review was to address the most widely used tests for the physical evaluation of multiparticulate systems.

Keywords: Multiparticulate systems/physical characterization. Pellets. Granules. Minitablets.

INTRODUCTION

An innovation can be considered a positive contribution when it is beneficial to society. Examples include promoting the dissemination of knowledge created or offering differentiated products and services that have added value (Araújo *et al*., 2010; Johnstone, Pairaudeau, Pettersson, 2011). In the pharmaceutical field, innovation can be exemplified by a technology that translates to direct benefit for patients, such as the introduction of new therapeutic arsenals providing alternatives to conventional treatments (Johnstone, Pairaudeau, Pettersson, 2011).

However, the entry of new chemical products onto the market is a slow and costly process, making the reformulation of already established drugs with well-known effects an attractive option for the pharmaceutical industry (Issa *et al*., 2012a; Zerbini, Ferraz, 2011). Incorporation of drugs into new pharmaceutical dosage forms and different delivery systems have led to performance improvements in medications, resolving problems such as low absorption and lack of adherence to treatment, as well as providing business opportunities within existing portfolios that can be extended (Kulkarni *et al*., 2010; Sandner, Ziegelbauer, 2008).

Controlled-release, colonic release, pulsatile, oral disintegration and gastro-retentive systems are examples of alternatives that have been widely exploited. Among the pharmaceutical dosage forms, multiparticulates standout for the multitude of options they provide where, besides the above-mentioned systems, they can also be used in the production of immediate-release drugs and gastro-resistant systems (Cram, Bartlett, Heimlich, 2013; Dey, Majumdar, Rao, 2008; Greb, 2010; Zerbini, Ferraz, 2011).

Multiparticulates, whose size ranges from 0.05 mm to 5 mm, are mainly used in the form of pellets, granules or minitablets that can be delivered in capsules or tablets (Dey, Majumdar, Rao, 2008; Greb, 2010; Pezzini, Silva, Ferraz, 2007; Zerbini, Ferraz, 2011). In these dosage forms, the drug dose is divided into smaller subunits, which, when administered disperse in the gastrointestinal tract. This provides numerous advantages over monolithic systems including only minor irritation of the mucosa,

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reduced variability in absorption and, in the case of controlled-release formulations, a lower risk of dose dumping (Cram, Bartlett, Heimlich, 2013; Dey, Majumdar, Rao, 2008; Santos *et al*., 2004).

Additionally, technological advantages include the obtention of different doses using the same formulation and the possibility of incorporation of incompatible drugs into a single medication (Pezzini, Silva, Ferraz, 2007; Zerbini, Ferraz, 2011). Given their small size, flexible doses and the possibility of obtaining oral disintegration systems, the use of particulates in formulations for pediatric and elderly patients has proven attractive (Cram, Bartlett, Heimlich, 2013; Dey, Majumdar, Rao, 2008; Grycze *et al*., 2011; Stoltenberg, Breitkreutz, 2011).

According to the type of system employed, different technologies may be used in the production of multiparticulates (Zerbini, Ferraz, 2011). In the case of pellets, extrusion-spheronization (Abdalla, Mader, 2007; Beringhs *et al*., 2012; Kulkarni *et al*., 2010) and coating inert core (Abdalla, Mader, 2007; Kulkarni *et al*., 2010) are the most commonly used processes. For the obtention of granules, wet granulation (Cai *et al*., 2013), melt granulation and hot-melt extrusion processes are used (Crowley et al., 2007; Gryczke *et al*., 2011; Mašic *et al*., 2012). In the case of minitablets, the granulation methods mentioned above and direct compression are used, where this process is carried out using a conventional machine equipped with multiple punches (Lopes *et al*., 2006; Zerbini, Ferraz, 2011).

Depending on the chosen technology, several variables (formulation, equipment, process) can influence the physical and physicochemical properties of the multiparticulates. These properties can impact coating, compression and the filling of gelatin capsules, as well as the behavior of the final product (Gómez-Carracedo *et al*., 2009; Mangwandi *et al*., 2012; Pund *et al*., 2010; Santos *et al*., 2002; Sonaglio *et al*., 2012).

Thus, the characterization of these systems is crucial to gaining a better understanding of the mechanisms that govern the release of the drug for further absorption and of aspects related to production.

Therefore, the objective of the present review was to address the most widely used tests and parameters for physical characterization of multiparticulate systems as a source of information for those who need to characterize these types of formulations.

MULTIPARTICULATE DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

By using a variety of processes, different multiparticulate delivery systems can be produced resulting in a wide range of applications. Among these, the viability of drug association is important (Patel, Dhake, 2011).

Some example applications reported in the literature for pellets, granules and minitablets include:

Pellets

- ✓ Obtention of immediate-release systems, with a focus on masking drug flavor (Hamedelniel, Bajdik, Pintye-Hódi, 2010; Issa *et al*., 2012b; Patel, Patel, Patel, 2010);
- ✓ Controlled-release (Abbaspour, Sadeghi, Garekani, 2008; Bialleck, Rein, 2011; Cantor, Hoag, Augsburger, 2009a; Cantor, Hoag, Augsburger, 2009b; Franc *et al*., 2015; Ghanam, Kleinebudde, 2011; Ghosh, Chakraborty, 2013; Han *et al*., 2013; Heckötter *et al*., 2011; Hung *et al*., 2015; Pezzini, Ferraz, 2007; Ríos, Ghaly, 2015; Roblegg *et al*., 2011; Szkutnik-Fiedler *et al*., 2014; Wang *et al*., 2015; Xu, Liew, Heng, 2015; You *et al*., 2014);
- ✓ Improvement in dissolution of poorly soluble drugs (Abdalla, Mader, 2007; Abdalla, Klein, Mader, 2008; Chopra, Venkatesan, Betageri, 2013; Ibrahim, El-Badry, 2014; Lu *et al*., 2009; Patel *et al*., 2016);
- ✓ Gastro-retentive systems/ floating systems (Amrutkar, Chaudhari, Patil, 2012; Li *et al*., 2014; Pagariya, Patil, 2013; Qi *et al*., 2015; Zhang *et al*., 2012);
- ✓ Enteric release/gastro-resistant systems (Andreo-Filho *et al*., 2009; Ghanam, Kleinebudde, 2011; Pund *et al*., 2010);
- ✓ Improvement of plant extract or active ingredient stability (Araújo-Junior *et al*., 2013; Beringhs *et al*., 2012; Burke *et al*., 2013);
- ✓ Combination of different delivery systems (Bialleck, Rein, 2011; Liu *et al*., 2013);
- ✓ High drug loading (Di Pretoro *et al*., 2010; Pund *et al*., 2010);
- ✓ Colonic release (Di Pretoro *et al*., 2010; Ferrari *et al*., 2013; Omwancha *et al*., 2013; Rabiskova *et al*., 2012);
- ✓ Bio-adhesive formulation for vaginal application (Hiorth *et al*., 2013).

Granules

- ✓ Controlled-release (Almeida *et al*., 2011; Grassi *et al*., 2003; Phaechamud, Thongpin, Choncheewa, 2012; Sharma, Amin, 2013; Tran *et al*., 2011; Verhoeven, Vervaet, Remon, 2006);
- ✓ Gastro-retentive/floating systems (Malode, Paradkar, Devarajan, 2015);

- ✓ High drug loading in immediate-release systems (Cai *et al*., 2013);
- ✓ Combination of different delivery systems (Dierickx *et al*., 2012; Dierickx, Remon, Vervaet, 2013);
- ✓ Obtention of immediate-release systems, with a focus on masking drug flavor (Gryczke *et al*., 2011; Issa *et al*., 2012b);
- ✓ Improvement in dissolution of poorly soluble drugs (Deng *et al*., 2012; Kalidova, Fischbach, Kleinebudde, 2012);
- ✓ Enteric release/gastro-resistant systems (Del Gaudio *et al*., 2015);
- ✓ Bio-adhesive system/increased gastric residence time (Pal *et al*., 2013);

Minitablets

- ✓ Orally disintegrating/fast dissolving tablets (Stoltenberg, Breitkreutz, 2011);
- ✓ Controlled-release (Aleksovski *et al*., 2015; Lopes *et al*., 2006; Tomuta, Leucuta, 2007);
- ✓ Combination of different delivery systems (Souza, Goebel, Andreazza, 2013);
- ✓ Colonic release (Vemula, 2015);
- ✓ Ocular bio-adhesives (Bozdag *et al*., 2010; Weyenberg *et al*., 2003; Weyenberg *et al*., 2006);
- ✓ Gastro-retentive/floating systems (Goole *et al*., 2008; Hauptstein *et al*., 2013; Katakam *et al*., 2014);
- ✓ Obtention of immediate-release systems, with a focus on masking drug flavor (Eckert, Pein, Breitkreutz, 2014);

Regarding the technologies employed in the obtention of these delivery systems (Figure 1) for pellets, extrusion followed by spheronization are the most exploited. For granules, the hot melt extrusion process is the most recently studied approach, whereas for the production of minitablets, direct compression is a widely used option.

Although multiparticulates provide many opportunities, their manufacture can involve a host of unit operations and variables. Additionally, they are inherently higher-cost processes because of their reliance on advanced technology. For example, obtaining pellets requires equipment such as extruders, a spheronizer and fluidized bed, whereas hot-melt extrusion requires screw extruders or co-extruders (Dey, Majumdar, Rao, 2008; Dierickx *et al*., 2012; Patel, Dhake, 2011; Zerbini, Ferraz, 2011).

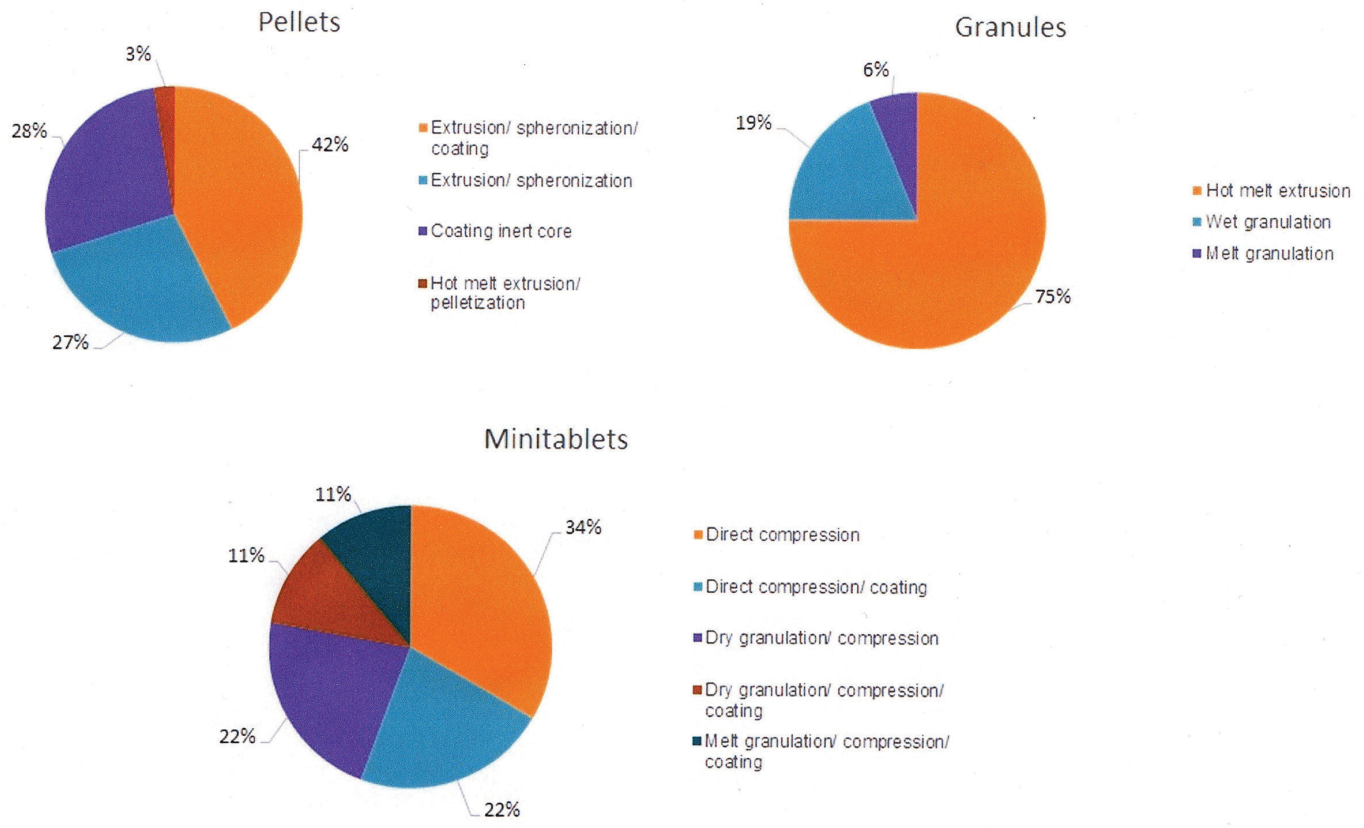

FIGURE 1 - Technologies used in production of pellets, granules and minitablets. The information for charts was based on 65 articles on multiparticulate systems published in the 2003-2015 period and retrieved from the Science Direct and SciFinder databases.

Nevertheless, assessment of the possibilities provided by these systems, such as the launch of new products and acceptance by patients, indicates that multiparticulate formulations are set to gain market space in the coming years (Greb, 2010).

ASSAYS FOR PHYSICAL CHARACTERIZATION OF MULTIPARTICULATE SYSTEMS

The goal of a system constituted by multiparticulate dosage forms is that their small functional units can release the drug in a reproducible way. Thus, the homogeneity of physical characteristics such as particle size, morphology, surface area, porosity and density, among others, is essential for the drug to perform as expected (Kulkarni *et al*., 2010; Mehta, 1989).

Besides the release effect, these properties may also exert an influence at some stages during processing, such as coating, compression and encapsulation (Almeida-Prieto, Blanco-Mendez; Otero-Espinar, 2007; Santos *et al*., 2002; Sousa *et al*., 2002a).

Thus, together with tests evaluating a drug, suitable physical characterization of these small units must be performed at the product development stage, so that some properties are also considered in process control testing (Mehta, 1989). The knowledge generated and monitoring during production contribute to the reliability and yield of the batch, ultimately saving resources.

Pellets and granules are conventional systems studied for some time, while minitablets, melt granulation and hot melt extrusion are relatively new. The most common assays and parameters reported in the literature for physical characterization of multiparticulates are listed below. Some characterization tests are applied to all multiparticulate dosage forms, whereas others are specific to the process and or release system.

However, assays are commonly adapted according to the experience of the researchers and the results used to compare formulations. Further studies evaluating analytical variables of assays for multiparticulate systems are necessary.

Particle size distribution

Sieving is the most commonly employed method for particle size determination of particulate materials. Various sieve stirrers are available on the market whose movement can be mechanically induced, electromagnetic by airstream or ultrasonic pulses at different orientations. The meshes used, amount of material, equipment, as well as the intensity and duration of stirring, are key variables to be considered in this type of assay (European Pharmacopeia, 2008; Mehta, 1989; United States Pharmacopeia, 2015; Wan, 1994).

Mass used, sieves and stirring time are the parameters most commonly cited in the literature. In some cases, data relating to the intensity, frequency and amplitude are also described (Table I). However, assay conditions must be selected based on the configuration of the equipment and the material to be submitted to analyses. American and European pharmacopeia suggest determining the test endpoint as when there is no significant weight change between the sieves.

Although a very informative and accessible method, complementation with other assays such as microscopy (optical and electronic) can aid the interpretation of inconclusive results, since sieving is unable to detect variation in the particle shape (Mehta, 1989).

Apart from these techniques, particle size analyses by laser diffraction equipment is also cited in the literature for more accurate determination of average pellet diameter (Bialleck, Rein, 2011; Pund *et al*., 2010) and granules (Cai *et al*., 2013; Tissen *et al*., 2011).

As shown in Table I, the dry method is the most used technique for evaluating multiparticulate systems by laser diffraction (Ibrahim, El-Badry, 2014; Lin *et al*., 2011; Yeung, Rein, 2015). Using compressed air as the dispersing agent can be a better alternative than the wet method since liquid can partially dissolve the formulation, reducing the original size of the material.

Morphology

The quantity, type of drug and processing conditions, as well as the excipients used in the formulation, are factors that contribute to defining the morphology of multiparticulate materials. The shape of the linked units can significantly influence the physical and chemical properties of the dosage form (Almeida-Prieto, Blanco-Mendez, Otero-Espinar, 2007; Crowley *et al*., 2007; Gomez-Carracedo *et al*., 2009).

The particle size distribution based on sieving in combination with microscopic analyses techniques were originally used for morphological evaluation. Currently, analyses are based on geometric parameters calculated from the optical microscopic images derived (Almeida-Prieto, Blanco-Mendez, Otero-Espinar, 2007; Mehta, 1989), including Feret diameters, circularity and aspect ratio (Figure 2). However, the result is highly dependent on the image analyses software used, as the same parameter can be calculated by different equations generating disparate results, thereby hindering the comparison of

TABLE I - Example descriptions of parameters used for particle size distribution in multiparticulate systems

Multiparticulate system	Assay conditions	Reference
Granules	Laser diffractometer, wet module, ethanol as dispersing agent, 10-12% obscuration and Franhoufer Theory	Auriemma *et al*., 2013; Del Gaudio *et al*., 2015
Granules	Electromagnetic agitator sieves, 5 minutes of stirring and amplitude of 6.0 mm	Cai *et al*., 2013
Granules	Electromagnetic agitator sieves, 700 g of material, 12 minutes of stirring, amplitude of 0.7 mm and range of 8 seconds	Rahmanian, Naji, Ghadiri, 2011
Granules (HME*)	Laser diffractometer, dry module and Franhoufer Theory	Yeung, Rein, 2015
Pellets	Sonic sifter, 5 minutes of stirring, amplitude of 6.0 mm and pulse of 5 seconds	Cantor, Hoag, Augsburger, 2009a
Pellets	Electromagnetic agitator sieves, 2 minutes of stirring, 50 Hz frequency, amplitude of 2.0 mm	Ferrari *et al*., 2013
Pellets	Mechanical sieve shaker and 5 minutes of stirring	Heckötter *et al*., 2011
Pellets	Laser diffractometer, dry method and 300 mg of material	Ibrahim, El-Badry, 2014
Pellets	Electromagnetic agitator sieves, 2 minutes of shaking, amplitude of 1.0 mm and range of 10 seconds	Issa *et al*., 2012b
Pellets	Mechanical agitator sieves, 25 g of material and 15 minutes of agitation	Keen *et al*., 2015
Pellets	Laser diffractometer, dry module, 4-7% of obscuration and 60 seconds of measurement time	Lin *et al*., 2011
Pellets	Electromagnetic agitator sieves, 30 g of material and 5 minutes of agitation	Omwancha *et al*., 2013
Pellets	Electromagnetic agitator sieves, 5 minutes of agitation, 50 Hz of frequency, amplitude of 1.0 mm	Pund *et al*., 2010
Pellets	Electromagnetic agitator sieves, 50 g of material, 10 minutes of agitation and amplitude of 1.0 mm	Xu, Liew, Heng, 2015

*Hot melt extrusion

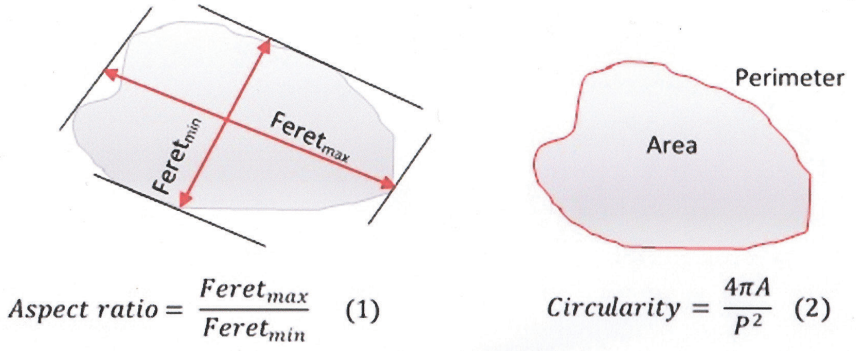

FIGURE 2 - Geometric parameters calculated in analyses of images of multiparticulate forms. Equations (1 and 2) are the most commonly employed - A = area and P = perimeter (Almeida-Prieto; Blanco-Mendez; Otero-Espinar, 2007).

data obtained by different laboratories (Almeida-Prieto, Blanco-Mendez,Otero-Espinar, 2007).

Another issue relates to a lack of standardization in terminology employed, where in some cases, different names can be assigned for the same parameter. For example, circularity that can also be denominated shape factor, sphericity index and surface factor, etc. (Almeida-Prieto, Blanco-Mendez, Otero-Espinar, 2007; Mehta, 1989).

Table II shows examples in the literature of shape parameters calculated of multiparticulate systems.

In general, besides optical microscopy, screening electron microscopy (SEM) is also performed, where images from the former are used to calculate the shape

TABLE II - Shape parameters calculated based on analyses of microscopic images in multiparticulate systems

Multiparticulate system	Parameters calculated/Units evaluated/Image analysis program	Reference
Granules	Sphericity/Image J	Auriemma *et al*., 2013
Granules	Sphericity and roughness/200/Image J	Del Gaudio *et al*., 2015
Granules (MG)*	Feret diameter, aspect ratio, circularity and projection of sphericity/ AnalySIS®	Mašić *et al*., 2012
Pellets	Circularity and radius ratio/50/Image-Pro® Plus 4.5.0.29	Cespi *et al*., 2007
Pellets	Aspect, average diameter, Feret diameter and sphericity/Image-Pro® Plus 4.5.0.29	Andréo-Filho *et al*., 2009
Pellets	Circularity and Aspect ratio/Image J	Chopra, Venkatesan, Betageri, 2013
Pellets	Sphericity and aspect ratio/Leco IA	Franc *et al*., 2015
Pellets	Aspect and circularity/Motic Images Advanced 3.2	Ferrari *et al*., 2013
Pellets	Feret diameter, average equivalent diameter, aspect ratio and circularity/Leica Qwin	Ghanam, Hassan, Kleinebudde, 2010
Pellets	Aspect ratio/200/Leica Quantimet 500	Hamedelniel, Bajdik, Pintye-Hódi, 2010
Pellets	Feret diameter and aspect ratio/Leica Qwin	Hiorth *et al*., 2013
Pellets	Average diameter, aspect and sphericity/Image-Pro® Plus 4.5.0.29	Issa *et al*., 2012b
Pellets	Feret diameter, aspect ratio and sphericity/300/AnalySIS®	Mehta *et al*., 2012
Pellets	Feret diameter, aspect ratio and sphericity/Windox 5.0	Omwancha *et al*., 2013
Pellets	Aspect ratio, form factor and Feret diameter/100/Sonata Seescan	Podczeck, Newton, 2014
Pellets	Sphericity/200/Leco IA	Rabišková *et al*., 2012
Pellets	Feret diameter, aspect ratio and sphericity/Seescan Solitaire 512	Santos *et al*., 2005
Pellets	Sphericity/50/Size Meter®	Sonaglio *et al*., 2012
Pellets	Sphericity/40/Seescan Solitaire 512	Sousa *et al*., 2002a
Minitablets	Feret diameter/~300/ Leica QWin Lite v. 3.2	Czajkowska, Sznitowska, Kleinebudde, 2015

*Melt granulation

parameters, while the latter is most commonly used for surface display of external and internal particles. Pellet and granule sizes can also be determined, however, this task is somewhat laborious, given the need for individual evaluation of various particles to extrapolate particle size distribution throughout the batch. It is possible, however, to evaluate the presence of agglomerates not detected in sieve analysis (Mehta, 1989).

For the analysis of SEM, samples should be prepared to facilitate the capture of signals and image building. Thus, samples are placed in an aluminum support containing a carbon tape and conductivity of the material is increased by depositing a thin layer of metallic ions such as gold, gold-palladium or platinum in an inert atmosphere of argon. Carbon deposition may also be used. The accelerating voltage, angle of inclination and working distance are example parameters that must be adjusted when carrying out this type of assay (Mehta, 1989). Descriptions found in the literature for conducting these analyses are given in Table III.

Specific surface area

Particle size, shape, porosity and roughness of particulate materials are factors influenced by the conditions employed in the core production step (pellets, granules and minitablets) and, according to the variation, can result in different surface areas (Mehta, 1989; Lowell *et al*., 2004). A high surface area usually requires additional amounts of coating and establishes better contact of the dosage form with gastrointestinal fluids, thus promoting the dissolution process (Lehmann, 1994; Mehta, 1989).

Among the techniques available for determination of specific surface area, gas adsorption is widely employed,

TABLE III - Example descriptions of parameters used in SEM

Multiparticulate system	Sample preparation/Assaying condition	Reference
Granules	Deposition of gold ions (thickness of coating 200–400 Å)/acceleration voltage of 20 keV	Auriemma *et al*., 2013
Granules	Deposition of gold ions (thickness of coating 200–400 Å)/acceleration voltage of 20 keV	Del Gaudio *et al*., 2015
Granules (HME)*	Deposition of Platinum ions/increases of 60x and 70x	Dierickx *et al*., 2012
Granules (HME)*	Carbon deposition/acceleration voltage of 1-2 kV, working distance of 3 and 5 mm at room temperature, and increases of 500x and 5000x	Dong *et al*., 2008
Granules	Deposition of gold-palladium ions/accelerating voltage of 10 kV	Grassi *et al*., 2003
Granules (HME)*	Deposition of chromium ions under vacuum/accelerating voltage of 5 kV	Jedinger *et al*., 2015
Granules (HME)*	Carbon deposition/1kV acceleration voltage and increases of 150x and 2000x	Mašić *et al*., 2012
Pellets	Deposition of gold-palladium ions in an inert atmosphere of argon/acceleration voltage of 20 kV and increases of 45x to 65x	Amrutkar, Chaudari, Patil, 2012
Pellets	Deposition of gold ions/acceleration voltage of 10 kV and increases of 60x to 300x	Beringhs *et al*., 2012
Pellets	Deposition of gold ions (thickness of coating of 10 nm)/acceleration voltage of 15 kV and increases of 50x to 750x	Burke *et al*., 2013
Pellets	Deposition of gold ions (coating time – 2 minutes)/acceleration voltage of 3 kV and increases of 100x and 200x	Chopra, Venkatesan, Betageri, 2013
Pellets	Deposition of gold ions under vacuum/acceleration voltage of 10 kV	Lu *et al*., 2009
Pellets	Deposition of gold ions under vacuum (thickness of coating of 6 nm)/acceleration voltage of 1.5 kV and working distance of 10 mm and increases of 500x to 2500x	Marković *et al*., 2014
Pellets	Deposition of carbon/acceleration voltage of 10 kV and working distance of 7.5-7.8 mm at room temperature, beam diameter of 3 and increases of 1000x and 5000x	Omwancha *et al*., 2013
Pellets	Deposition of gold-palladium ions under vacuum/acceleration voltage of 10 kV and increase of 60x	Pund *et al*., 2010
Pellets	Deposition of gold ions under vacuum/acceleration voltage of 20 kV	Sabin *et al*., 2011

*Hot melt extrusion

and the surface analysis methodology and porosity of solid materials by the BET equation are commonly used approaches (Lowell *et al*., 2004).

As this calculation takes into consideration the volume of gas adsorbed in the sample, different materials may be used as adsorbates. Nitrogen is the most commonly used adsorbate due to the properties of the molecules, which enable interaction with the surface of many materials, and because the gas is readily available in liquid state (Lowell *et al*., 2004). In relation to the parameters used in this technique, these often include, in addition to type of gas, the sample preparation time, corresponding to the removal of air from the surface of the material under vacuum and at the appropriate temperature, freezing and the number of points collected (multipoint or single point) to obtain the adsorption-desorption isotherms.

As depicted in Table IV, the analysis is usually performed on a surface analyzer device using nitrogen gas due to its availability and low cost. The use of krypton was cited in some cases, probably due to its intrinsic characteristic of capturing small surface areas (Dong *et al*., 2008; Schrank *et al*., 2015; Sousa *et al*., 2002b).

Grassi *et al*. (2003) described surface area analysis performed using a mercury porosimeter, although this technique has the limitation of measuring closed pores (Giesche, 2006).

TABLE IV - Examples descriptions of parameters employed in specific surface area analysis

Multiparticulate system	Assay conditions/ Equation	Reference
Granules	Degassing of samples for 72 hours at room temperature and under 50 mTorr vacuum. Nitrogen adsorbate/multipoint BET	Chevalier *et al*., 2010
Granules (HME)*	Krypton adsorbate and nitrogen/multipoint BET	Dong *et al*., 2008
Granules (MG)**	Mercury porosimeter – 0.75 g sample and 30 minutes prior degassing/ Rootare-Prenzlow	Grassi *et al*., 2003
Pellets (HME)*	Degassing of samples for 24 hours and freezing with liquid nitrogen for 20 minutes. Nitrogen adsorbate/multipoint BET	Bialleck, Rein, 2011
Pellets	Degassing of samples for 24 hours under vacuum. Nitrogen adsorbate – pressure of 0.05-0.30 psi/ multipoint BET and single point BET	Santos *et al*., 2004
Pellets	Degassing of samples under vacuum and freezing in liquid nitrogen. Nitrogen or krypton adsorbate – pressure of 0.05 and 0.2 psi/ BET	Schrank *et al*., 2015
Pellets	Degassing of samples under vacuum and freezing with liquid nitrogen. Krypton or nitrogen adsorbate/multipoint BET and single point BET	Sousa *et al*., 2002b

*Hot-melt extrusion; **Melt granulation

Density and flow behavior

The knowledge of the density of a batch of multiparticulates is of great importance in the final stages of processing, such as in the mixture of different pellet formulations or granules, the coating step on a fluidized bed, and in capsule filling or tableting (Mehta, 1989; Santos *et al*., 2006).

Although the density calculation is fairly simple, obtained by dividing the mass of the material by the volume it occupies, there are several approaches for this parameter (Table V), all of which convey different information that can be used in any step of production or even in elucidating the release profile of the formulation (He, 2009; Santos *et al*., 2006).

True density is a characteristic of the material derived from its manufacturing process and related to particle size. In this case, the volume adopted for calculation takes into account only the solid material, discounting the volume occupied by internal or external pores and spaces between particles (He, 2009; Lowell *et al*., 2004; Santos *et al*., 2006).

Helium pycnometry is the preferred method for determining true density, given the small size of the gas molecule, which has greater ability to penetrate very small pores. If the porosity of the multiparticulate form is very low or it possesses pores which may be filled by mercury or another liquid in which the material does not disintegrate, mercury porosimetry or liquid displacement method may also be used (Lowell *et al*., 2004).

For apparent density, sometimes called effective density, the volume is considered the volume occupied by the solid material plus internal pores, which are inaccessible. In most cases, mercury porosimetry is the method of choice for determining apparent density (Lowell *et al*., 2004). With the true density and apparent density

TABLE V - Types of densities used in the evaluation of multiparticulate systems (Lowell *et al*., 2004; Santos *et al*., 2006)

Density	Definition	Method of determination
True	Volume of material excluding pores (external/internal) and space between particles	✓ He pycnometry Hg porosimetry Fluid displacement
Apparent/ effective	Volume of material excluding only external pores and space between particles	✓ Hg porosimetry Fluid displacement
Bulk	Volume of material with pores (external/internal) and spaces between particles	✓ Beaker Scott volumeter
Tapped	Volume of material excluding spaces between particles	✓ Voluminometer – compacted density equipment

data, the percentage porosity of the multiparticulate form can be calculated (Ghanam, Hassan, Kleinebudde, 2010; Santos *et al*., 2005), as outlined below.

Bulk and compacted density provide information on the space occupied by the formulation and may be used, for example, to define batch sizes and equipment used in production and selection of capsule size. Furthermore, these parameters can indicate the flow of material when the compressibility index and Hausner ratio are calculated (He, 2009; Mehta, 1989; United States Pharmacopeia, 2015).

As shown in Table VI, density is a frequently studied property in multiparticulate systems.

Angle of repose and flow rate are also extensively used to evaluate the rheology of multiparticulate formulations. Several methods are available although, in most cases, these properties are determined as described in U.S. Pharmacopeia, i.e. by using a hopper in which the material passes and forms a cone, whereby the inclination angle is calculated (United States Pharmacopeia, 2015).

The flow of a material is dependent on several factors, such as humidity and the degree of particle consolidation, and hence the result may vary according to the conditions used for analyses. Thus, different devices have emerged for determining flow more accurately, which are based on the use of shear forces on the quantity

TABLE VI - Densities evaluated in multiparticulate systems

Multiparticulate system	Properties evaluated	Reference
Granules	Flow	Cai *et al*., 2013
Granules	Bulk, tapped and true densities	Chevalier *et al*., 2010
Granules (HME)*	True density	Dong *et al*., 2008; Yeung, Rein, 2015
Granules	Bulk and tapped densities; Hausner ratio	Eckert, Pein; Breitkreutz, 2014
Granules (HME)*	Bulk and tapped densities; compressibility index	Grycze *et al*., 2011
Granules	Bulk and tapped densities; compressibility index and angle of repose	Roohulaah *et al*., 2014
Granules	Bulk and tapped densities	Issa *et al*., 2012a
Granules	Bulk and tapped densities, compressibility index, Hausner ratio, angle of repose and flow rate	Lamolha, Serra, 2007
Granules (MG)**	Bulk and tapped densities and compressibility index	Mašić *et al*., 2012
Granules (MG)**	Bulk and tapped densities, angle of repose and compressibility index	Tran *et al*., 2011
Pellets	Bulk and tapped densities, angle of repose and Hausner ratio	Amrutkar, Chaudari, Patil, 2012
Pellets	Bulk and tapped densities, Hausner ratio and compressibility index	Beringhs *et al*., 2012
Pellets	Bulk and tapped densities, angle of repose, Hausner ratio and compressibility index	Chopra, Venkatesan, Betageri, 2013; Franc *et al*., 2015; Pagariya, Patil, 2013
Pellets	Bulk and apparent densities	Costa, Pais, Sousa, 2004
Pellets	Bulk, tapped and apparent densities	Ghanam, Hassan, Kleinebudde, 2010
Pellets	True density	Grassi *et al*., 2003; Hiorth *et al*., 2013; Issa *et al*., 2012b
Pellets	Bulk and tapped densities, compressibility index and angle of repose	Peng *et al*., 2015
Pellets	Bulk, tapped and true densities, compressibility index, angle of repose and Hausner ratio	Rabišková *et al*., 2012
Pellets	True and effective densities	Santos *et al*., 2005
Pellets	Bulk and tapped densities	Sonaglio *et al*., 2012
Minitablets	True density	Lopes *et al*., 2006

*Hot-melt extrusion. **Melt granulation

of sample and application time, as well as the interactions between the particles of the material and the cell used for analysis (Amidon, Secreast, Mudie, 2009).

Porosity

Porosity is a property that relates to the release of drug from the dosage form, directly influencing the steps of disintegration and dissolution. High material porosity can lead to low density particles improving the dissolution process (D'Arcy, Persoons, 2011). It is determined by processing conditions and formulation, especially in the case of pellets and granules, due to the volume of liquid used in kneading and removal in the drying step (Farber, Tardos, Michaels, 2003; Mehta, 1989; Pund *et al*., 2010).

The size and distribution of pores can facilitate the penetration of gastrointestinal fluid in multiparticulate systems but these are not the only parameters. Another important issue associated with the surface of these units is the composition of the formulation, which can affect their wettability (Riippi *et al*., 1998). Furthermore, the presence of pores on the surface of the cores may influence coating quality, and hence lead to variation in the performance of the product (Mehta, 1989; Santos *et al*., 2006).

Techniques for determining the porosity of multiparticulate systems reported in the literature include porosimetry by mercury intrusion, determination of density by helium pycnometer or deposition of solid material, gas adsorption, scanning electron microscopy and X-ray computed tomography (XCT) (Table VII). The most used of these techniques are mercury porosimetry and helium pycnometer. Mercury porosimetry , can provide results such as pore size and its distribution volume and percentage porosity of the material, as illustrated using the densities in Equation 3 (Ghanam, Hassan, Kleinebudde, 2010; Mehta *et al*., 2012; Santos *et al*., 2005).

$$\varepsilon = 1 - \frac{\rho_a}{\rho_h} \qquad \text{(Equation 3)}$$

ε = porosity, ρ_a = effective/apparent density, ρ_h = true density

Since porosimetry is dependent on the pressure applied and mercury contact angle with the surface of the sample, there is a limitation for the evaluation of materials having pores of very small size (below 1.5 nm). In these cases, nitrogen adsorption technique using the BET equation may provide better results (Lowell *et al*., 2004; Santos *et al*., 2006).

TABLE VII – Example methods used to determine the porosity of multiparticulate systems

Multiparticulate system	Method/parameters calculated	Reference
Granules (HME)*	X-ray tomography/porosity and equivalent pore diameter	Almeida *et al*., 2011
Granules	Coating density analyzer/porosity	Ansari, Stepanek, 2008
Granules	Hg porosimeter/porosity	Chevalier *et al*., 2010
Granules	Hg porosimeter and coating density analyzer/porosity	Rahmanian *et al*., 2009
Granules (HME)*	He pycnometer/porosity	Verhoeven, Vervaet, Remon, 2006
Pellets (HME)*	He pycnometer and Hg porosimeter/relative density	Bialleck, Rein, 2011
Pellets	He pycnometer/porosity	Cespi *et al*., 2007; Pund *et al*., 2010; Rabišková *et al*., 2012; Santos *et al*., 2002
Pellets	He pycnometer and Hg porosimeter/porosity and average pore radius	Ghanam, Hassan, Kleinebudde, 2010
Pellets	Hg porosimeter/pore volume distribution, average pore diameter and porosity	Nordström *et al*., 2013
Pellets	Fluid displacement method/porosity	Patel *et al*., 2016
Pellets	He pycnometer and Hg porosimeter/porosity	Santos *et al*., *2004*
Pellets	He pycnometer and Hg porosimeter/porosity, total pore volume, total pore area and average pore diameter	Santos *et al*., 2005
Pellets	Hg porosimeter/average pore diameter	Sonaglio *et al*., 2012
Minitablets	He pycnometer/porosity	Weyenberg *et al*., 2003

*Hot melt extrusion

SEM and XCT are options for viewing the pore distribution in the multiparticulates. SEM is intended for only qualitative determination while XCT also provides quantification of pore size and porosity (Farber, Tardos, Michaels, 2003; Mehta, 1989).

Mechanical strength

The various unit operations to which the multiparticulate forms are subjected require a certain mechanical strength of these small units, particularly when steps such as fluidized bed coating and compression are involved. Advantageous from an economic standpoint as a way of reducing production costs, incorporation into tablet is a strategy adopted. However, it is important that the drug release properties are maintained after compression, for example, the coating film integrity (Cespi *et al*., 2007; Santos *et al*., 2004; Santos *et al*., 2006).

As can be seen in Table VIII, mechanical strength is constantly evaluated in multiparticulate forms. In the case of minitablets, the most common tests already used in tablets, such as hardness and friability, are employed (Lopes *et al*., 2006; Tomuta, Leucuta, 2007; Weyenberg *et al*., 2006). For granules and pellets, tensile strength (Equation 4) and Young's elastic modulus, related to the stiffness and crushing strength (hardness) of the material, are the most frequently determined. For this purpose, a strain chart can be obtained by using a texture analyzer device, in which the material is exposed to a given load against time (Santos *et al*., 2006; Šibanc *et al*., 2013; Yeung, Rein, 2015).

$$\delta = \frac{0.4F}{\pi r^2} \qquad \text{(Equation 4)}$$

δ = tensile strength; F = intensity of the force required to break; r^2 = radius of the particle obtained by Feret´s diameter

For friability, different adjustments are performed (Table IX), typically using glass or steel balls, in order to increase the material´s abrasion and improve the sensitivity of the method (Chopra, Venkatesan, Betageri, 2013; Issa *et al*., 2012b; Santos *et al*., 2006). A friabilometer is the equipment used in most cases, where sometimes a stirring system is used instead (Chevalier *et al*., 2010; Stoltenberg, Breitkreutz, 2011). Alternatively, the approach used by Li *et al*. (2014) can be adopted, in which the material is subjected to drastic conditions in the coating equipment.

The result is obtained by determination of the percentage mass of the material lost when exposed to abrasion, requiring the use of a sieve to separate the fraction formed as powder which is weighed during the assay. The study of Issa *et al*. (2012b) reported an alternative in which the mass loss is measured by comparing the amounts retained in the sieves, where the particle size distribution is carried out before and after the assay.

TABLE VIII - Strength properties evaluated in multiparticulate systems

Multiparticulate system	Parameters calculated	Reference
Granules	Tensile strength	Cai *et al*., 2013
Granules	Hardness	Chevalier *et al*., 2010
Granules (HME)*	Tensile strength	Yeung, Rein, 2015
Pellets	Elastic limit and elastic modulus	Abbaspour, Sadeghi, Garekani, 2008
Pellets	Tensile strength	Bialleck, Rein, 2011; Podczeck, Newton, 2014; Santos *et al*., 2005
Pellets	Hardness, tensile strength and relaxation module	Cespi *et al*., 2007
Pellets	Hardness	Costa, Pais, Sousa, 2004; Ghanam, Hassan, Kleinebudde, 2010; Hamedelniel, Bajdik, Pintye-Hódi, 2010; Rabišková *et al*., 2012; Rahmaniam, Naji, Ghadiri, 2011
Pellets	Tensile strength and elastic modulus	Šibanc *et al*., 2013
Minitablets	Hardness	Aleksovski *et al*., 2015; Lopes *et al*., 2006; Stoltenberg, Breitkreutz, 2011; Tomuta, Leucuta, 2007; Weyenberg *et al*., 2006
Minitablets	Tensile strength	Tissen *et al*., 2011

*Hot melt extrusion

TABLE IX - Conditions employed for determination of the friability of multiparticulate systems

Multiparticulate system	Conditions employed	Reference
Granules	10 g of material in a glass container subjected to 240 oscillations for 4 min.	Chevalier *et al*., 2010
Granules	10 g of material, 200 spheres of 4 mm, at 25 rpm for 10 min.	Mehta *et al*., 2012
Pellets	10 g of material, 10 spheres of 5 mm, at 25 rpm for 10 min.	Adbdalla, Mäder, 2007
Pellets	10 g of material, at 200 rpm	Amrutkar, Chaudari, Patil, 2012
Pellets	6 g of material, 25 spheres of 2 mm, at 25 rpm for 4 min.	Chopra, Venkatesan,Betageri, 2013
Pellets	10 g of material, 200 spheres of 4.3 mm, at 25 rpm for 4 min.	Issa *et al*., 2012b
Pellets	5 g of material, atomization pressure of 0.2 bar, air flow of 45 Hz for 20 min.	Li *et al*., 2014
Pellets	6 g of material, 25 spheres of 2 mm, at 100 rpm	Pund *et al*., 2010
Minitablets	1 g of material in a glass container, at 25 rpm for 4 min.	Eckert, Pein, Breitkreutz, 2014
Minitablets	1 g of material, 20 spheres of 5 mm, at 25 rpm for 4 min.	Gaber, Nafee, Abdallah, 2015
Minitablets	10 g of material, at 100 rpm	Katakam *et al*., 2014
Minitablets	20 units, at 25 rpm for 4 min.	Lopes *et al*., 2006
Minitablets	1 g of material in a glass container subjected to agitation in a shaker and 200 vibrations per minute for 1 hour	Stoltenberg, Breitkreutz, 2011
Minitablets	10 units, 100 spheres of 4 mm, at 25 rpm for 10 min.	Weyenberg *et al*., 2006

Disintegration

Given the tendency of the incorporation of multiparticulate systems in the form of tablets, for example, in the case of a multiple unit pellet system (MUPS), disintegration should occur quickly so that each unit can operate independently. Thus, this step in the release process becomes a key feature and can improve the selection of excipients to be used in the formulation, as well as the conditions employed in compression (Abbaspour, Sadegni, Garekani, 2008; Ghanam, Kleinebudde, 2011; Mehta *et al*., 2012).

For immediate release multiparticulate systems, the disintegration process of each subunit is vital because this step occurs prior to the dissolution process. The occurrence of disintegration problems can affect drug release and consequently drug absorption (Mahato, 2007).

When in tablet form, the assay method is the conventional one, evaluating six units using the apparatus described in the pharmacopoeias (Abbaspour, Sadeghi, Garekani, 2008; Chopra, Venkatesan, Betageri, 2013; Mehta *et al*., 2012). However, assays with small units are also described in the literature and, therefore, adjustments can be made either by using narrower mesh to ensure that the material is stirred and/or by employing down-sized sample holders (Abdalla, Mader, 2007; Ghanam, Kleinebudde, 2011), as well as other devices, such as the roller bottle equipment used by Ghosh and Chakraborty (2013).

CONCLUSION

The fact that pharmaceutical dosage forms can be delivered in small functional unities, makes multiparticulates an attractive option for the development of new formulations. On the other hand, given the small size of these units, physical characterization tests become fundamental to understand the process variables and to assist the formulator in the selection of excipients and parameters used in the various unit operations involved in production. Tests are now well known. However, as multiparticulates are relatively new compared to traditional tablets, some adjustments are needed to improve the sensitivity of the techniques used. Adequate physical characterization is achieved by combining different assays. The most used tests are granulometric distribution by the sieving method, morphology by determining shape parameters based on microscopy images derived, surface

area analysis by the gas adsorption technique, density and porosity by combining pycnometry and porosimetry techniques, as well as mechanical strength, especially for obtaining breakdown tension, hardness, friability and disintegration.

ACKNOWLEDGEMENTS

The authors would like to thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/ Brazil).

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Received for publication on 28th November 2016
Accepted for publication on 28th March 2017