Production and characterization of pellets using Avicel CL611 as spheronization aid

Sin Yee Puah, Hsiu Ni Yap, and Cheng Shu Chaw

Department of Pharmacy, Health and Well Being, University of Sunderland, Sunderland, UK

Keywords Disintegration, extrusion, shape, size distribution, tensile strength

Abstract

Purpose: The study looked into the feasibility of producing pellet using Avicel CL611 as spheronization aid by the extrusion/spheronization technique.

Methods: Pellets were formulated to contain either 20% or 40% Avicel CL611 and lactose monohydrate as the other sole ingredient. Water is used as liquid binder. Quality of pellets and extrudates were analyzed for size distribution, shape, surface tensile strength and disintegration profile.

Results: More water was needed when higher Avicel CL611 fraction was used during the production of pellets. The pellets of larger size were obtained by increasing the water content. Pellets with aspect ratios of ~1.1 were produced with high spheronization speed at short residence time. Higher tensile strength was achieved when increasing the water content and the fraction of Avicel CL611 during pellet production. These pellets also took longer time to disintegrate, nonetheless all the pellets disintegrated within 15 minutes. A positive linear relationship was obtained between the tensile strength and time for pellets to disintegrate.

Conclusion: Strong but round pellets that disintegrate rapidly could be produced with Avicel CL611 as spheronization aid using moderately soluble compounds such as lactose.

Introduction

Pelletization involves processing of fine powder into free flowing, spherical or semi-spherical pharmaceutical agglomerates known as pellets. Pellets manufactured in pharmaceutical industries normally range in size from 500 to 1500 μm1. Pellets are an attractive solid dosage form as they provide not only the therapeutic advantages but also the technological benefits2,3.

Pellets can be prepared using several techniques2,3. Extrusion/ spheronization is commonly used to produce pellets due to the ability to form pellets with high drug content while maintaining narrow size distribution. Low friability of the pellets also allow for the production of controlled release formulation that can withstand coating process. Production of pellets by extrusion/spheronization involves several stages, which include powder mixing, wet massing, shaping of wet mass and cutting into extrudate and rolling of extrudates into pellet which is followed by drying and screening if necessary3. There are many factors that may affect the property of wet mass and extrudates and hence the quality of pellets. Some of the factors that were investigated included the quantity and type of liquid binder; physical properties of starting materials which include particle size and solubility of drug and excipients; type of extruder, extrusion speed and temperature; speed, residence time and loading of spheronizer as well as drying techniques3–8.

Spheronization aid is usually incorporated to maintain the balance between plasticity and brittleness of the wet mass and extrudates. Due to its hygroscopic property, microcrystalline cellulose (MCC) has the ability to absorb water molecules and adsorb moisture from the surrounding. It can also retain a significant amount of water, thus provides the appropriate rheological properties to the wet mass for further processing9,10. Two models, which are ‘‘sponge’’ and ‘‘crystallite gel’’, have been proposed to explain how MCC may aid the extrusion/spheronization process11,12.

MCC remains one of the most commonly used spheronization aid and many studies were based upon the application of the conventional MCC to produce pellets with ideal properties. However, the use of MCC is associated with some limitations. Prolonged or incomplete drug release profile due to the lack of disintegration has been reported, especially when combining drug with poor solubility at high level2,5. The slow release of drug will pose a problem if an immediate effect is required. Adsorption of active ingredients onto the surface of MCC fibers13 and decomposition of sensitive drugs prior to release have also been reported14. To overcome these disadvantages, several strategies have been implemented such as using water/ethanol mixture instead of water alone as liquid binder; balancing the ratio of MCC and drug with the inclusion of the water-soluble diluents such as solubilizers and disintegrants in the formulation; replacing MCC with other possible alternatives such as powdered cellulose,

hydroxyethylcellulose, pectinic acid, k-carrageenan, crospovidone, chitosan and starch derivatives2,5,10,15.

MCC is available in various brands and grades in the market. Different physical properties of MCC could affect the quality of the pellets16–18. Compared to Avicel PH-series, Avicel CL or RC series are seldom used in manufacturing pellets but are commonly incorporated in suspension due to their ability to form thixotropic gel. These types of Avicel consist of MCC and sodium carboxymethylcellulose (NaCMC)19. Earlier work by Newton et al.20 reported that formulations with equal amount of colloidal MCC and lactose could produce extrudates with smooth surfaces, yet the pellets formed were classified as ''rounded'' instead of round. The colloidal grades MCC failed to produce satisfactory pellets due to its inelasticity21. Accordingly, the coprocessed NaCMC in the colloidal grades MCC could result in sticky granules18. Recently, studies have shown that the colloidal grades MCC could produce pellets with high drug loadings (90–95%) using 5-aminosalicylic acid22,23. This was due to their abilities to better retain water, thus preventing liquid phase migration (LPM) under applied pressure22. High yield could be obtained depending on the physicochemical properties of the model drug23. Therefore, colloidal grade MCC such as Avicel CL611 has demonstrated its potential as a spheronization aid. The ability of Avicel CL611 to produce pellets of satisfactory qualities with water-soluble materials remains to be explored. This study aims to investigate the quality of pellets prepared with Avicel CL611 at 60 and 80% with lactose as the other sole ingredient. Parameters such as quantity of liquid binder, extrusion speed and spheronization speed and residence time during spheronization were adjusted during manufacture of pellets. Physical properties of pellets such as size distribution, morphology and mechanical properties were investigated.

Materials and methods

Materials

Avicel CL611 was obtained from FMC Corporation (Philadelphia, PA) and Granulac 230 (lactose monohydrate) was supplied by Meggle GmbH (Wasserburg, Germany). Freshly distilled water was used as liquid binder.

Production of pellets

In this study, different batches of pellets with the ratios of 2:8 and 4:6 of Avicel CL611: lactose were produced by using water as liquid binder. The appropriate amount of lactose and Avicel CL611 to produce 100 g of product were weighed out using Precisa 400M balance (Precisa Balance Ltd., Dietikon, Switzerland). The raw materials were premixed in a planetary mixer (Model A901E; Kenwood Chef, UK) for 2 minutes at a speed setting of 3. Then an appropriate amount of distilled water was added gradually into the powder mixture that underwent mixing for a further 10 minutes. A spatula was used to scrap off the sides of the bowl of the mixer to ensure homogenous mixing. The wet mass was then transferred immediately into the radial extruder (Model 10 Extruder, G.B. Caleva Ltd., Sturminster Newton, UK) fitted with a screen of 150mm in diameter and die holes of 1.0 mm. The extrudates produced were then spheronized immediately in a spheronizer (Model 120; G.B. Caleva Ltd., UK) fitted with a 125mm cross hatch plate. The pellets were collected and left to air dried under room temperature for 48 h before performing further tests. The process conditions and actual amount of water used in each preparation are stated in Table 1.

Size distribution of pellets and powder

The size distribution of pellets was determined with a sieve analyzer. A stack of British Standard Sieves (Endecotts) of a root-2 progression from 250 to 2000 μm was set up and pre-weighed. Approximately 50 g of pellets were transferred to the top sieve and subject to 10 minutes vibration with mechanical shaker (EFL 2000; Endecotts Ltd., London, UK). The final weight of each sieve was recorded and the weight of pellet retained on each sieve was calculated. The median diameter (D50) and the interquartile range (IQR) were determined after plotting the cumulative undersize distribution curves. The fine and coarse fractions were determined as those pellets less than 0.5 mm and over 1.4 mm, respectively. The yield is defined as pellets ranged between 0.71 and 1.4mm as this range is collected for further processing in to a tablet or a capsule. The percentage of pellets found in the sieve fraction of 1–1.4mm was also determined.

Pellet shape

The image analysis system consisting of the image analyser software KS 400 version 3.0 (Carl Zeiss Vision GmbH, Aalen, Germany) was connected to a digital camera (AxioCam MRc5 Carl Zeiss, Go¨ttingen, Germany) and microscope (Ernest Leitz Wetzlar GmbH,

Wetzlar, Germany). The equipment was calibrated with 1mm graticule (Macro Systems, London, UK). Thirty pellets were randomly chosen from the 1–1.4mm sieve fraction of each formulation. Shape factors including circularity and aspect ratio were determined. Aspect ratio was calculated after determining the Feret diameters, while the circularity was obtained from using projected area and projected perimeter directly derived from the software by applying relevant formulas described in Podczeck et al.24.

Morphology of pellets

Scanning electron microscopy (SEM) (Hitachi S3000N, Hitachi High Technologies America Inc., Pleasanton, CA) was performed to inspect the morphology of the pellets. Approximately 10–15 pellets in the 1–1.4mm sieve fraction from each formulation were placed on a 15mm double-sided carbon adhesive aluminium specimen stubs (Agar Scientific, Essex, UK). The specimen was then coated by exposing to an argon atmosphere for 2 x 10^5 s (turning through 180^o in between) under the process current of 18–20 mA using Polaron range SC760 coater (Quorum Technologies Inc., Guelph, Canada) before capturing the images.

Surface tensile strength of pellets

A physical testing instrument (CT-5 Engineering System, Nottingham, UK) with a 5 kN load cell with speed of the upper platen of 1 mm/min was used to determine the tensile strength of 30 pellets, which were in the range of 1–1.4 mm sieve fraction. Each pellet was placed between the flat plate and the load cell. The force obtained was used to calculate the surface tensile strength as described by Shipway and Hutchings25.

Disintegration profile of pellets

Fifty milligrams of pellets in the 1–1.4mm sieve fractions were weighed using Mettler AM100 balance (Mettler Instruments Ltd., Greifensee, Switzerland). The pellets were transferred to the disintegration instrument (Model: Erweka ZT4T; Apparatebau GMBH, Heusenstamm, Germany) fitted with a basket rack and mesh aperture of 0.42 mm. Seven hundred and fifty millilitres of distilled water was used as medium. The basket rack was immersed in the medium at 30 dips/min at 37^oC. The time for the pellets to disintegrate was recorded. Test was repeated thrice for each batch.

Results

The pellets were successfully produced by extrusion/spheronization. The quantity of liquid binder increased with higher Avicel CL611 fraction in the formulations (Table 1). The liquid binder used to produce pellets consisting of 40% Avicel CL611 was almost doubled when comparing with those with only 20% Avicel CL611 and this observation was also reported earlier with standard MCC26,27.

Size distribution and morphology of pellets

Determining size distribution and morphology are essential in optimizing the manufacturing process for pellets. Measuring pellet shape is challenging as various shape factors and techniques to determine shape have shown different sensitivity toward small variation in shape24,28. Aspect ratio is one of the earliest shape factors described; though not considered as the most sensitive parameter, it remains to be widely used in determining the shape of the pellet24. Pellets with the aspect ratio below 1.2 are usually accepted for capsule filling, nonetheless the upper limit for aspect ratio should be reduced to 1.1 for pellets with smooth surfaces24. Circularity is another popular shape factor to evaluate the pellet shape. The value of 1 corresponds to a perfect sphere. The size and morphology of pellets are listed in Table 2. In general, the pellets possessed low percentage (<10%) of fine fraction and at least 90% of pellets formed were under the sieve size of 1.4mm with the exception of A13. The overall yield was high. The percentage of coarse fraction was higher with pellets consisting of 40% Avicel CL611. The median diameters of at least 1mm were seen in all pellets consisting of 40% Avicel CL611 but not in pellets consisting of 20% Avicel CL611. The highest amount of pellets collected in the sieve fraction of 1–1.4mm was around 60% regardless of the formulation compositions. Pellets consisting of 40% Avicel CL611 conformed better to the upper limit of aspect ratio of 1.1, while some of the formulations prepared with 20% Avicel CL611 were outside of this limit. These results were also confirmed by examining the morphology of the pellets using high resolution SEM (Figure 1). For instance, A10 and A13 which were produced with 20 and 40% Avicel CL611, respectively, were considered ‘‘round’’ with aspect ratios less than 1.1 and circularity of over 0.9 (Figure 1a and b) while pellets such as A2 and A7 produced with 20% Avicel CL611 and low quantity of water were ‘‘rounded’’ (Figure 1c and d). For pellets produced with 20% Avicel CL611, increasing the liquid binder tends to increase the size and yield of the pellets and the largest median

diameter was obtained when 28.5% w/w of water was used, which was over 1 mm (Figure 2 and Table 2). Batch A1 that was produced by using the lowest amount of liquid binder showed the highest cumulative size fraction below 1mm (90.8%) and gave the lowest percentage of pellets at 1–1.4mm sieve fraction (9.2%). The speed and residence time applied during the spheronization process governed the overall force and energy experienced by the extrudates, thus affecting the shape and size of the pellets. From the result, high spheronization speed produced pellets with an aspect ratio of ~1.1.

Mechanical properties of pellets

The mechanical properties of pellets in the sieve fraction of 1–1.4mm were determined in terms of crushing force and surface tensile strength, and in addition, disintegration time of pellets was also measured (Table 3). Tensile strength of above 1 MPa is ideal if further processing is necessary29 and this was observed in all the pellets. The pellets produced with Avicel CL611 showed rapid disintegration in water. Typical disintegration time was less than 15 minutes. For the pellets consisting of 20% Avicel CL611, it was found that the tensile strength increased with an increasing level of liquid binder. The mean surface tensile strength values of A1, A2, A3 and A4 produced with 20.0, 22.5, 25.0 and 28.5% w/w of water were 2.31, 2.91, 3.98 and 4.55 MPa, respectively, and A4 also took the longest time to disintegrate (Table 3). Pellets consisting of 40% Avicel CL611 gave a higher tensile strength than those produced with 20% Avicel CL611. The tensile strength of pellets prepared with 40% and 20% Avicel CL611 ranged from 4.04 to 5.72 and 2.31 to 4.55 MPa, respectively.

Discussion

Size distribution and morphology of pellets

Liquid binder is a key variable in pellet production via extrusion/spheronization. During the wet massing, liquid binder is filled in between the particles to form the liquid bridges to hold the particles together. The optimum binder level in the formulation should reach the upper limit of the funicular state30, 31. Apart from aiding the formation of appropriate wet mass, liquid binder acts as lubricant and plasticizer to assist the wet mass to pass through extrusion screen and aid shape deformation during extrusion and spheronization. In this study water was used as liquid binder, and the effect of the quantity of water on the pellets was determined for formulation consisting of 20% Avicel CL611. Higher amount of liquid binder led to greater yield and median diameter but smaller aspect ratio (Figure 2). The wet mass produced with 20%w/w of water was quite dry resulting in extrudates, which were easily fragmented into fine. This is supported by the earlier study using Avicel PH101, indicating that ‘‘dry’’ formulation had led to uneven water content in the extrudates32. Fine fraction was high in A1. Hence, the 22.5% w/w of water was considered as the lower threshold for preparing pellets consisting of 20% Avicel CL611.

The forces exerted on the extrudates during spheronization, which was governed by the applied residence time and spheronization speed affected the morphology of the pellets33. The medium spheronization speed employed in this study was insufficient to produce adequate frictional and rotational forces to round off the extrudates, and consequently the pellets produced were elongated with high aspect ratio except for pellets produced with 28.5% w/w of water (Figure 1). According to Ek and Newton11, water molecules were squeezed and they moved toward the external surface of the MCC sponge during extrusion; the sponge structure expanded after the extrusion that led to the extrudates that could deform adequately. Soft but tacky extrudates were observed in this study, when more than 28.5% and 45% w/w of water was used to produce pellets consisting of 20% and 40% Avicel CL611, respectively. Without allowing these extrudates to rest and water within samples re-equilibrate before spheronization, these extrudates led to larger quantity of coarse fraction and ball formation. This was partly due to the presence of excess water on surfaces when subject to the applied pressure. LPM occurs when there is an excessive water movement34, 35 and this phenomenon is more pronounced when there is limited amount of MCC available to hold the water molecules23 or once the quantity of water exceeded the retention limit of MCC. Di Pretoro et al. 22 proposed that 1 g of colloidal MCC required 1.5 g water to produce a wet mass with appropriate plasticity. This recommendation is close to the upper limit of 28.5% w/w water for formulations consisting of 20% colloidal MCC without equilibration of the wet mass or extrudates. Nonetheless, for pellets consisting of 40% Avicel CL611, less water was required than anticipated. The other ingredients in the formulation such as the coprocessed NaCMC with its gel-forming property19 and use of lactose, a moderately water-soluble excipient, can also affect the water holding capacity of the wet mass 8, 23, 27,36, 37. Therefore, an appropriate quantity of water should be added in order to reach the acceptable consistency and plasticity for extrusion and spheronization.

In this study, extrudates with smooth surface were produced with the exception when extruded slowly. When applying high spheronization speed, the pellets produced with low extrusion speed were associated with large quantity of fine fraction and larger IQR while the median diameter was smaller as seen with A5 (Table 2). Harrison et al.38 indicated that the surface defect of extrudates could lead to uneven fragmentation during the early stage of spheronization and as a result, the amount of fines increased and pellets with wide size distribution were obtained. Tomer and Newton34 and Rough et al.39 reported that the water molecules had enough time to find a least resistance pathway to move to the bottom paste in the barrel of a ram extruder at low extrusion speed, thus leading to greater LPM. The explanation may be less applicable when using a radial screen extruder. Hasznos et al.40 recommended that high speed should be used when extruding wet mass with an axial screen extruder to avoid decrease in moisture content of the intermediate products. When low extrusion speed was employed, water evaporation was more prominent because the overall process took longer to complete. Therefore, higher water loss was anticipated, which could reduce plasticity of extrudates.

Spheronization of pellets occurs via several stages that involve breaking up the rod shape extrudates into shorter cylinders, agglomeration of the shorter cylinders and smoothing the surface to form pellets. Applying high spheronization speed produced pellets with the aspect ratio ┐ 1.1 and circularity closer to 1 regardless of the surface texture of the extrudates (Table 2). Baert et al.41 demonstrated that rounder pellet was produced with longer residence time. However, residence time has little effect on the shape of the pellet produced in our study when sufficient quantity of liquid binder is used but smaller yield is obtained in pellets consisting of 40% Avicel CL611 due to the production of coarse fractions (Table 2). The result is supported by earlier work where increasing residence time up to 10 minutes could increase the pellet size due to agglomeration while exceeding the limits could decrease the size and yield of pellets27. Newton et al.42 stated that the rounding process normally completed in 5 minutes and there was only little improvement in shape when increasing residence time to 20 minutes in our samples. It is worth to investigate the effect of shorter residence time on size, shape and yield in the future.

Mechanical properties of pellets

Higher mechanical strength and longer disintegration time were observed as the amount of liquid binder increased for pellets consisting of 20% Avicel CL611 (Figure 3). A p value of 0.001 was obtained from the ANOVA test (SPSS software, ver. 18, Chicago, IL) indicating that the influence of water was significant to the tensile strength of Avicel CL611 pellets. Water plays a critical role by acting as a medium to enhance the inter-particulates binding through the formation of ‘‘water bridges’’43. The higher the amount of water added to the powder blend, the more binding amongst particles could occur, thereby giving the pellet a stronger structure. In the study by Di Pretoro et al.23, minimum friability was observed when more water was added during pellet production. As the amount of water used increased with higher content of Avicel CL611, pellets with 40% Avicel CL611 could create a higher amount of water bridges that constituted a stronger structure, which contributed to a higher mechanical strength.

Debunne et al.44 indicated that the presence of co-processed NaCMC in Avicel CL611 increased the water uptake into the pellet matrix and thus Avicel CL611 possessed a greater swelling capacity. Nonetheless, disintegration of the pellets was not observed when the Avicel CL611 pellets were loaded with low level of poorly water-soluble drug, piroxicam (2.5 %w/w) at the ratio of 1:3 of Avicel PH101:Avicel CL61142. In contrast, in our study when lactose, which is moderately water soluble, was used as the model drug, complete disintegration of the pellets was observed. A decrease in lactose level in pellets with 40% Avicel CL611 in our study also retarded the disintegration process (Table 3). The mean disintegration time was almost doubled by increasing the proportion of Avicel CL611 (4.3 versus 7.3 minutes). Therefore, the disintegration profile of the Avicel CL611 pellet depends on the drug property as well as its composition in the final pellet formulation.

Disintegration property of solid compact and powder agglomerates is thought to be affected by the formulary (e.g. nature of materials) and process (e.g. applied pressure on particle–particle interactions). For pellets, it has been determined using disintegration equipment or during the dissolution study. A range of mesh apertures of the disintegration basket typically ranging between 0.4 and 0.8mm have been described and the choice depends on the sieve fraction of the pellets. This has made the comparison less direct. The disintegration profiles of Avicel CL611 pellets produced in this study were found to be similar to those pellets loaded with poorly water soluble drug using carrengeena as sphronization aid but slower than

those produced using crospovidone as aid45,46. The nature of the materials thus plays a critical role in the disintegration process of the pellets. In addition, a polymorphic form of conventional MCC or MCC II has shown rapid disintegration profile overcoming the slow release of poorly water-soluble drug when formulated with conventional MCC47. No relationship was reported in terms of disintegration times with physical properties of pellets in the aforementioned works. In Figure 4, a positive linear relationship between the crushing force and the disintegration time of the pellets was obtained with a correlation coefficient of 0.87. A stronger relationship was also observed between tensile strength and disintegration time with a r value of 0.94. Dreu et al.4 showed that both tensile strength and disintegration times of MCC pellets increased, while the apparent pore diameter, porosity and friability decreased via a common factor derived from the specific properties (product of surface tension, relative permittivity and cosine of contact angle) of the granulating fluids. Thus, choice of the binder is another critical property affecting the disintegration profile of the pellets. Since only water was used as binding liquid in this study, other factors affecting the mechanical property of pellets such as density and porosity of the pellets need to be studied in the future to further elucidate its relation with disintegration times. Nonetheless, taking the size into account provides a better relationship to mechanical property and disintegration of pellets, as disintegration of the pellet depends on the total surface exposed to the medium for disintegration.

Conclusion

Liquid binder was one of the most important parameters that must be established to produce pellets with good quality. The quality of pellets with 20% Avicel CL611 was sensitive to the quantity of liquid binder. An increase in the quantity of liquid binder resulted in larger pellets and higher percentage of yield. As expected, more water was required for successful pellet production as the fraction of Avicel CL611 increased. Nonetheless, to avoid the formation of sticky product18,44, the threshold level of the binding liquid was less than that proposed earlier22. Generally speaking, production of ‘‘round’’ pellets has been associated with increasing spheronization speed and short residence time. When lactose was used as model drug, the disintegration times of the pellets were rapid. The mechanical property of the pellets was also influenced by the amount of water used as liquid binder where a higher amount of water formed pellets with a higher tensile strength. Pellet formulation with the higher amount of Avicel CL611 also gave a higher tensile strength and took longer to disintegrate. A positive linear relationship was seen between pellet’s disintegration time and mechanical strength.

Declaration of interest

All the authors of this manuscript report no declaration of conflict of interest.

References

1. Ghebre-Sellassie I. A general overview. In: Ghebre-Sellasie I, ed.Pharmaceutical pelletization technology. New York: Marcel Dekker;1989:1–14.
2. Dukic-Ott A, Thommes M, Remon JP, et al. Production of pellets via extrusion-spheronisation without the incorporation of microcrystalline cellulose: a critical review. Eur J Pharm Biopharm 2009;71:38–46.
3. Vervaet C, Baert L, Remon JP. Extrusion-spheronisation. A literature review. Int J Pharm 1995;116:131–46.
4. Dreu R, Sirca J, Pintye-Hodi K, et al. Physicochemical properties of granulating liquids and their influence on microcrystalline cellulose pellets obtained by extrusion-spheronisation technology. Int J Pharm 2005;291:99–111.
5. Dukic-Ott A, Remon JP, Foreman P, Vervaet C. Immediate release of poorly soluble drugs from starch based pellets via extrusion/spheronisation. Eur J Pharm Biopharm 2007;67:715–24.
6. Lustig-Gustafsson C, Johal K, Podczeck F, Newton JM. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation. Eur J Pharm Sci 1999;8:147–52.
7. Song B, Rough SL, Wilson DI. Effects of drying technique on extrusion–spheronisation granules and tablet properties. Int J Pharm 2007;332:38–44.
8. Sousa JJ, Sousa A, Podczeck F, Newton JM. Factors influencing the physical characteristics of pellets obtained by extrusionspheronisation. Int J Pharm 2002;232:91–106.
9. Chitu TM, Oulahna D, Hemati M. Rheology, granule growth and granule strength: application to the wet granulation of lactose–MCC mixtures. Powder Technol 2011;208:441–53.

10. Alvarez L, Concheiro A, Gomez-Amoza JL, et al. Powdered cellulose as excipient for extrusion-spheronization pellets of a cohesive hydrophobic drug. Eur J Pharm Biopharm 2003;55:291–5.
11. Ek R, Newton JM. Microcrystalline cellulose as a sponge as an alternative concept to the crystallite-gel model for extrusion and spheronisation. Pharm Res 1998;15:509–11.
12. Kleinebudde P. The crystallite-gel-model for microcrystalline cellulose in wet-granulation, extrusion, and spheronization. Pharm Res 1997;14:804–9.
13. Al-Nimry SS, Assaf SM, Jalal IM, Najib NM. Adsorption of ketotifen onto some pharmaceutical excipients. Int J Pharm 1997; 149:115–21.
14. Jain SP, Singh PP, Amin PD. Alternative extrusion-spheronization aids. Drug Dev Ind Pharm 2010; 36:1364–76.
15. Liew CV, Gu L, Soh JLP, Heng PWS. Functionality of crosslinked polyvinylpyrrolidone as a spheronization aid: a promising alternative to microcrystalline cellulose. Pharm Res 2005;22: 1387–98.
16. Alvarez L, Concheiro A, Gomez-Amoza JL, et al. Effect of microcrystalline cellulose grade and process variables on pellets prepared by extrusion-spheronisation. Drug Dev Ind Pharm 2002;28:451–6.
17. Heng PWS, Koo OMY. A study of the effects of the physical characteristics of microcrystalline cellulose on performance in extrusion spheronisation. Pharm Res 2001;18:480–7.
18. Podczeck F, Knight P E, Newton JM. The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization. Int J Pharm 2008;350:145–54.
19. Rowe RC, Sheskey PJ, Owen SC. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press; 2006.
20. Newton JM, Chow AK, Jeewa KB. The effect of excipient source on spherical granules made by extrusion/spheronisation. Pharm Tech Intl 1992;4:52–8.
21. Chohan RK, Newton JM. Analysis of extrusion of some wet powder masses used in extrusion/spheronisation. Int J Pharm 1996;131: 201–7.
22. Di Pretoro G, Zema L, Gazzaniga A, et al. Extrusion–spheronisation of highly loaded 5-ASA multiparticulate dosage forms. Int J Pharm 2010;402:153–64.
23. Di Pretoro G, Zema L, Palugan L, et al. Optimisation and scale-up of a highly loaded 5-ASA multi-particulate dosage form using a factorial approach. Eur J Pharm Sci 2012;45:158–68.
24. Podczeck F, Rahman SR, Newton JM. Evaluation of a standardised procedure to assess the shape of pellets using image analysis. Int J Pharm 1999;192:123–38.
25. Shipway PH, Hutchings IM. Attrition of brittle spheres by fracture under compression and impact loading. Powder Technol 1993;76:23–30.
26. Kleinebudde P, Schoroder M, Schultz P, et al. Importance of the fraction of microcrystalline cellulose and spheronisation speed on the properties of extruded pellets made from binary mixtures. Pharm Dev Technol 1999;4:397–404.
27. Wan LSC, Heng PWS, Liew CV. Spheronization conditions on spheroid shape and size. Int J Pharm 1993;96:59–65.
28. Almeida-Prieto S, Blanco-Me´ndez J, Otero-Espinar FJ. Microscopic image analysis techniques for the morphological characterization of pharmaceutical particles: influence of the software, and the factor algorithms used in the shape factor estimation. Eur J Pharm Biopharm 2007;67:766–76.
29. Kranz H, Jurgens K, Pinier M, Siepmann J. Drug release from MCC and carrageenan-based pellets: experiment and theory. Eur J Pharm Biopharm 2009;73:302–9.
30. Luenburger H. Moist agglomeration in pharmaceutical powders. In: Chulia D, Deleuil M, Pourcelot Y, eds. Powder technology and pharmaceutical processes. Amsterdam: Elservier; 1994:377–89.
31. Podczeck F, Wood AV. The relationship between granule growth mechanism, amount of liquid binder added and properties of the wet powder mass determined using a split bed shear tester. Int J Pharm 2003;257:57–67.
32. Boutell S, Newton JM, Bloor JR, Hayes G. The influence of liquid binder on the liquid mobility and preparation of spherical granules by the process of extrusion/spheronization. Int J Pharm 2002; 238:61–76.
33. Umprayn K, Chitropas P, Amarekajorn S. Influence of process variables on physical properties of the pellets using extruder and spheronizer. Drug Dev Ind Pharm 1999;25:45–61.
34. Tomer G, Newton JM. Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions. Int J Pharm 1999;182:71–7.
35. Mascia S, Patel MJ, Rough SL, et al. Liquid phase migration in the extrusion and squeezing of microcrystalline cellulose pastes. Eur J Pharm Sci 2006;29:22–34.
36. Fielden KE, Newton JM, Rowe RC. The influence of lactose particle size on spheronisation of extrudate processed by a ram extruder. Int J Pharm 1992;81:205–24.
37. O'Connor RE, Schwartz JB. Spheronisation II: Drug Release from drug diluent mixtures. Drug Dev Ind Pharm 1985;11:1837–57.

38. Harrison PJ, Newton JM, Rowe RC. The characterisation of wet powder masses suitable for extrusion/spheronisation. J Pharm Pharmacol 1985;37:686–91.
39. Rough SL, Wilson DI, Bridgwater J. A model describing liquid phase migration within an extruding microcrystalline cellulose paste. Chem Eng Res Des 2002;80:701–14.
40. Hasznos L, Langer I, Gyarmathy M. Some factors influencing pellet characteristics made by an extrusion/spheronisation process. Part I: effects on size characteristics and moisture content decrease of pellets. Drug Dev Ind Pharm 1992;18:409–37.
41. Baert L, Vermeersch H, Remon JP, et al. Study of parameters important in the spheronisation process. Int J Pharm 1993;96:225–9.
42. Newton JM, Chapman SR, Rowe RC. The influence of process variables on the preparation and properties of spherical granules by the process of extrusion and spheronisation. Int J Pharm 1995;190:101–9.
43. Sousa JJ, Podczeck F, Newton JM. Influence of process conditions on drug release from pellets. Int J Pharm 1996;144:159–69.
44. Debunne A, Vervaet C, Remon JP. Development and in vitro evaluation of an enteric-coated multiparticulate drug delivery system for the administration of piroxicam to dogs. Eur J Pharm Biopharm 2002;54:343–8.
45. Thommes M, Kleinebudde P. Use of kappa-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. I. Influence of type and fraction of filler. Eur J Pharm Biopharm 2006;63:59–67.
46. Verheyen P, Steffens KJ, Kleinebudde P. Use of crospovidone as pelletization aid as alternative to microcrystalline cellulose: effects on pellet properties. Drug Dev Ind Pharm 2009;35:1325–32.
47. Krueger C, Thommes M, Kleinebudde P. MCC SANAQ burst—a new type of cellulose and its suitability to prepare fast disintegrating pellets. J Pharm Innov 2010;5:45–57.

Table 1 Formulation composition and process parameters of pellets. [a] Mass of water per dry powder mass in percentage.

Batch	Ratio of Avicel CL611 : Granulac 230	Liquid binder (% w/w)[a]	Extrusion speed (rpm)	Spheronization speed (rpm)	Residence time (min)
A1	2:8	20.0	medium	medium	10
A2	2:8	22.5	medium	medium	10
A3	2:8	25.0	medium	medium	10
A4	2:8	28.5	medium	medium	10
.0A5	2:8	22.5	low	high	10
A6	2:8	22.5	medium	high	10
A7	2:8	22.5	medium	medium	20
A8	2:8	25.0	medium	high	10
A9	2:8	25.0	medium	high	20
A10	2:8	28.5	medium	high	10
A11	2:8	28.5	high	medium	10
A12	4:6	45.0	medium	high	10
A13	4:6	45.0	medium	high	15
A14	4:6	45.0	medium	high	17.5

Table 2 Size distribution and shape factors of pellets.

Batch	Median diameter (mm)	IQR (mm)	Yield (%)	1-1.4 mm sieve fraction (%)	Fine fraction (%)	Coarse fraction (%)	Aspect ratio	Circularity
A1	0.85	0.18	95.1	9.2	4.5	0.3	1.49 (0.20)	0.82 (0.15)
A2	0.88	0.19	96.9	19.3	2.1	1.0	1.21 (0.11)	0.90 (0.15)
A3	0.94	0.24	96.1	35.9	0.8	3.1	1.14 (0.05)	0.94 (0.02)
A4	1.05	0.21	96.1	60.7	0.4	3.6	1.13 (0.07)	0.92 (0.08)
A5	0.89	0.32	90.3	32.4	9.1	0.6	1.16 (0.06)	0.93 (0.06)
A6	0.99	0.28	95.2	48	2.0	2.8	1.10 (0.04)	0.94 (0.03)
A7	0.94	0.24	97.4	37.8	1.7	0.9	1.36 (0.17)	0.89 (0.06)
A8	0.99	0.27	95.2	47.2	2.5	2.3	1.13 (0.04)	0.94 (0.04)
A9	1.00	0.28	94.2	49	4.3	1.5	1.06 (0.03)	0.89 (0.06)
A10	1.02	0.26	96.8	53.6	0.5	2.8	1.08 (0.03)	0.93 (0.03)
A11	1.05	0.24	95.3	58.9	0.4	4.3	1.15 (0.06)	0.92 (0.03)
A12	1.05	0.24	97.2	59	0.0	2.8	1.08 (0.03)	0.94 (0.03)
A13	1.01	0.30	87.6	46.5	0.4	12.0	1.08 (0.03)	0.94 (0.03)
A14	1.00	0.29	91.0	47	0.5	8.6	1.08 (0.05)	0.92 (0.10)

*Values expressed as mean (Standard deviation).

Table 3 Mechanical properties of pellets. Values expressed as Mean (standard deviation).

Batch	Crushing force (N)	Surface tensile strength (MPa)	Disintegration time (min)
A1	8.05 (2.8)	2.31 (0.9)	3.17 (0.29)
A2	8.27 (2.9)	2.91 (0.9)	3.83 (0.29)
A3	15.18 (4.4)	3.98 (1.4)	4.11 (0.0)
A4	14.87 (3.6)	4.55 (1.3)	5.96 (0.42)
A5	7.40 (1.6)	2.77 (0.8)	2.55 (0.0)
A6	11.82 (2.7)	3.95 (0.9)	5.01 (0.0)
A7	10.25 (5.0)	2.85 (1.7)	3.08 (0.0)
A8	12.68 (4.3)	3.97 (1.2)	4.33 (0.0)
A9	13.96 (2.9)	3.54 (0.8)	5.41 (0.05)
A10	12.59 (3.6)	3.83 (1.5)	5.17 (0.14)
A11	12.30 (3.6)	3.88 (0.9)	4.76 (0.31)
A12	12.34 (2.5)	4.04 (1.0)	5.13 (0.06)
A13	17.84 (6.8)	5.72 (1.7)	8.31 (0.71)
A14	17.19 (4.5)	5.68 (1.1)	8.38 (0.05)

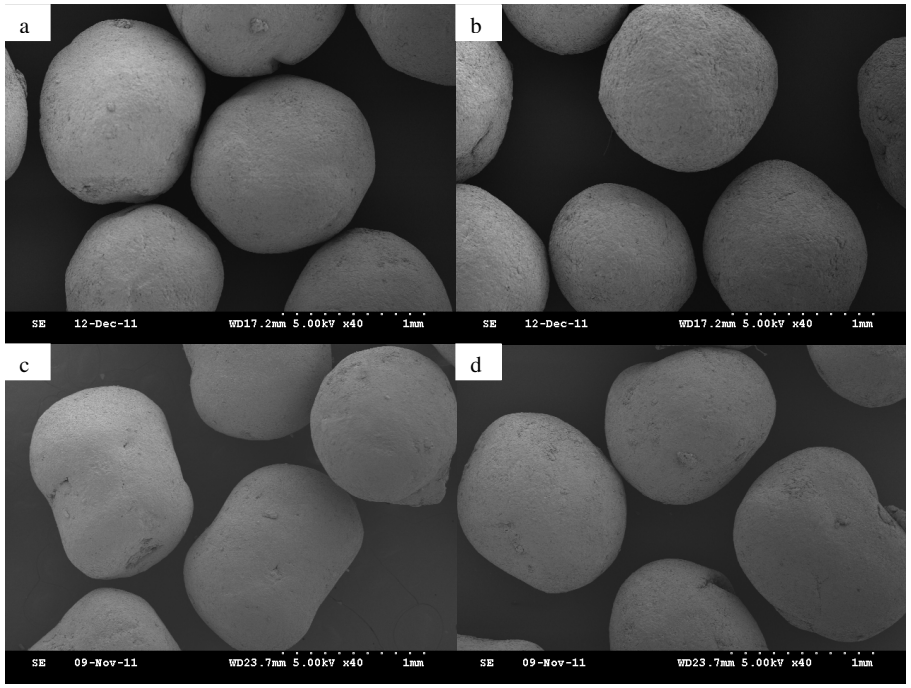

Figure 1 Scanning electron micrographs of pellets at magnification ×40. (a) A10, (b) A13, (c) A2, (d) A7.

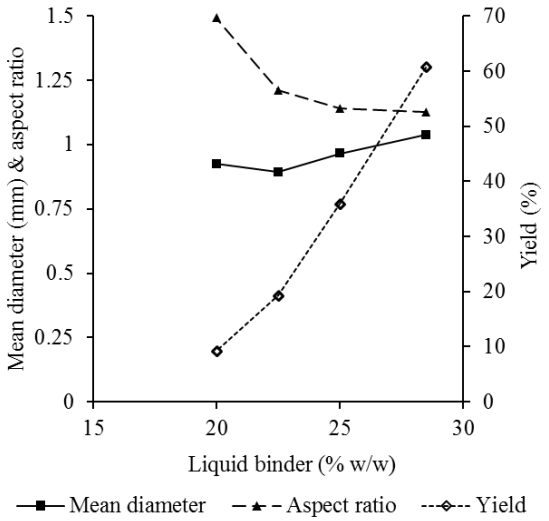

Figure 2 Effect of liquid binder on mean diameter, aspect ratio and yield of pellets consisiting of 20% Avicel CL611. The extrusion speed is 30rpm (medium) and spheronisation speed and residence time were 900 rpm (medium) and 10 minutes, respectively.

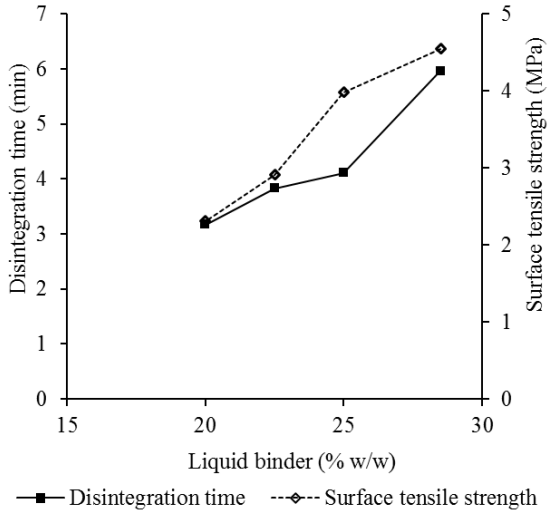

Figure 3 Effect of liquid binder on surface tensile strength and disintegration time of pellets consisiting of 20% Avicel CL611. The extrusion speed is 30rpm and spheronisation speed and residence time were 900 rpm and 10 minutes, respectively.

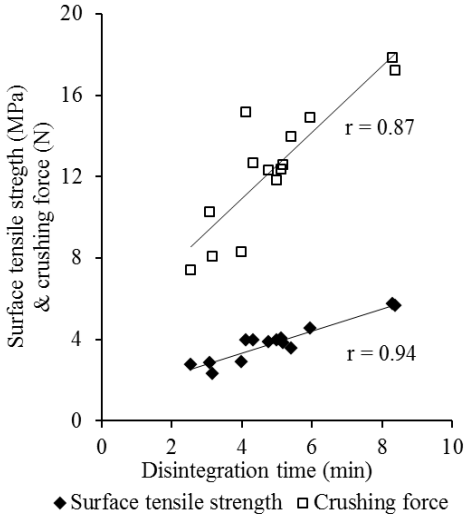

Figure 4 Mean disintegration time versus mean tensile strength and crushing force of pellets.