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International Journal of Pharmaceutics 332 (2007) 38–44
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Effects of drying technique on extrusion–spheronisation granules and tablet properties

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Received 8 May 2006; received in revised form 23 August 2006; accepted 12 September 2006
Available online 4 October 2006

Abstract

Extrusion–spheronisation was used to generate smooth, highly spherical granules of a microcrystalline cellulose/propyl gallate/water paste. Freeze-drying retained the shape and size of the granules, whereas oven-drying produced roughened granules due to the uneven shrinkage of the wet powders. Compaction of one size fraction indicated that the granule strength differed noticeably, with the oven-dried samples producing tablets of lower voidage for a given applied compaction pressure. There was a reasonable correlation between tablet crushing strength and voidage. Major differences were observed in tablet dissolution, with the freeze-dried material exhibiting a two-regime behaviour and an initial dissolution rate constant an order of magnitude greater than the oven-dried form. Both the voidage and dissolution characteristics are postulated to be determined by the microstructure established during drying.

Keywords: Dissolution; Extrusion–spheronisation; Freeze-drying; Microcrystalline cellulose; Propyl gallate; Tabletting

1. Introduction

Although the extrusion–spheronisation of pharmaceutical pastes has been studied extensively in terms of paste formulation and processing conditions (*e.g.* see Wilson and Rough (2007) for a review), relatively little work has been reported on the impact of drying of the subsequent granules. Bashaiwoldu et al. (2004) present a summary of such studies, which include microwave-drying (Bataille et al., 1993), fluidised bed- and tray-drying (Dyer et al., 1994), conventional hot air oven- and freeze-drying (Kleinebudde, 1994a,b) and drying to the open atmosphere (Johansson et al., 1995).

The drying studies that have been reported to date mostly involve water-based pastes containing some form of microcrystalline cellulose (MCC). The fibrous structure of MCC allows water to be trapped in fine capillaries and internal pores (Bashaiwoldu et al., 2004), and the method of water removal (thermal or non-thermal) has been shown to have a significant effect upon the shrinkage and hence porosity of the resulting dried granules, and thus also upon their mechanical properties. So-called 'fast' removal of water, either by microwave-drying (Bataille et al., 1993) or by freeze-drying (Kleinebudde, 1994a; Bashaiwoldu et al., 2004), suppresses the granule shrinkage and hence produces granules of larger mean diameter, higher porosity and thus lower strength (higher deformability) than those dried by 'slow' means, such as hot air oven-drying or desiccation using silica-gel (Bashaiwoldu et al., 2004). The differences in porosity can also affect the dissolution rates, and hence drug-release characteristics, of the granules (Dyer et al., 1994; Kleinebudde, 1994b), with granules of higher porosity generally exhibiting a larger rate of dissolution.

The current study compares the effect of freeze-drying and conventional hot air oven-drying on the physical characteristics and dissolution behaviour of extrusion–spheronisation granules, *viz*. appearance, compaction behaviour, tablet voidage, crushing strength and dissolution behaviour. The excipient used is MCC, and the model drug chosen for detection in the dissolution tests is propyl gallate. The chosen paste formulation has been shown to extrude and spheronise in a well-behaved manner (Tomer et al., 2002). A main finding is that tablets generated from freeze-dried granules exhibit a previously unreported two-regime dissolution behaviour, which may or may not be desirable in a controlled-release product.

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doi:10.1016/j.ijpharm.2006.09.050

Nomenclature

a	a constant in Eq. (2) ($kg\,m^{-3}\,s^{-1}$)
A	surface area of propyl gallate dissolving in solution (m^2)
C	instantaneous concentration of propyl gallate in solution ($kg\,m^{-3}$)
C_0	final concentration of propyl gallate in solution ($kg\,m^{-3}$)
C^*	equilibrium solubility of propyl gallate in solution ($kg\,m^{-3}$)
D	diameter of tablet (m)
F	maximum crushing force (N)
h	height of tablet (m)
k	mass transfer constant for dissolution ($m\,s^{-1}$)
K	dissolution rate constant, as defined in Eq. (2) (s^{-1})
t	time (s)
V	volume of solution (m^3)
Greek letter	
σ	radial tensile crushing strength (Pa)

2. Materials and methods

2.1. Paste preparation

The paste consisted of 24.4 wt.% microcrystalline cellulose (MCC), 34.4 wt.% propyl gallate (PG) and 41.2 wt.% deionised water. The MCC powder (Avicel PH101, FMC Corp., Philadelphia, PA) had a particle size volume mean and Sauter mean of 79 and 45 μm, respectively (obtained using a Beckman Coulter LS 230 laser diffraction analyser), and the PG powder (Acros Organics, Fisher Scientific, UK) had a particle size volume mean and Sauter mean of 570 and 53 μm, respectively.

A 'Kenwood Chef' domestic planetary mixer (Kenwood Ltd., UK) with 'K'-beater attachment was used to prepare the paste. The MCC and PG powders were dry-mixed at the lowest speed setting for 5 min, and the water was slowly added within a further 1 min. The paste was then wet-mixed at the highest speed setting for 5 min, pausing every 1 min to disrupt any material caked on the sides and bottom of the mixing bowl with a plastic spatula. The freshly mixed paste was stored for 2 h in a sealed plastic bag prior to extrusion, in order to allow the water to equilibrate throughout.

2.2. Extrusion and spheronisation

The paste was ram extruded using a computer-controlled Dartec A100 screw strain frame (Stourbridge, UK) incorporating a cylindrical 25 mm internal diameter stainless steel barrel of height 180 mm, and a concentric cylindrical 1 mm diameter square-entry stainless steel die of length 4 mm. Approximately 90 g of the paste was loaded into the barrel and tamped down by hand to produce a plug ≈ 170 mm in height. The ram was positioned on top of the paste and was set to travel 100 mm at 1 $mm\,s^{-1}$ (corresponding to an extrudate velocity of 625 $mm\,s^{-1}$).

Approximately 50 g of slightly shark-skinned extrudate were collected in a plastic beaker during the extrusion process. The extrudate was loaded into a bench-top 120 mm diameter crosshatched plate spheroniser (Caleva Process Solutions Ltd., Dorset, UK) and spheronised for 5 min at 1600 rpm.

2.3. Granule drying

After spheronisation, the granules were divided into two batches and spread out on two PTFE-coated metal baking trays. One batch was dried at atmospheric pressure in an oven at 60 °C for 19 h, and the other batch was freeze-dried using a Virtis Advantage bench-top freeze dryer (SP Industries Inc., PA). For the freeze-drying, the granules were frozen at −20 °C for 4 h, after which a vacuum of 80 mTorr was applied for 28 h in order to sublime off the water. The sample tray was initially covered with "Cling-film" to prevent the granules from leaving the chamber when the vacuum was applied.

2.4. Granule characterisation

The granules (wet and dried) were viewed optically using an Intel® Play™ QX3™ computer microscope (Mattel, CA, USA). The wet granules were viewed as soon as possible after spheronisation to minimise shrinkage due to drying.

The size distributions of the dried granules were obtained by hand-sieving using a $2^{1/4}$ progression of apertures ranging from 0.6 to 1.7 mm. In some cases, a soft-haired brush was applied over the granules in the sieves to break up any agglomerates produced during the drying process. The granules in each fraction were weighed using an electronic balance to within ±0.01 g. Tapping analyses of the granules provided no evidence of granule breakage.

2.5. Tablet formation

Both oven-dried and freeze-dried granules of size fraction 1.40–1.70 mm were compacted into tablets using the strain frame incorporating a cylindrical 10 mm diameter compaction die. 0.25 g of dried granules were poured into the die. A stainless steel piston was used to compact the granules at a speed of 0.1 $mm\,s^{-1}$ to applied loads of 1.5, 3.0 or 7.0 kN (corresponding to applied compaction stresses of 19, 38, or 89 MPa). The piston load and displacement were recorded during the compaction process, and the data were corrected in order to compensate for the elastic compliance of the apparatus. The tablets were ejected from the compaction die using a constant load of 0.5 kN.

2.6. Tablet characterisation

The height of each tablet was measured using micrometers (±0.01 mm), the mass was determined using an electronic balance (±0.1 mg), and the true density of each tablet was determined using helium pycnometry (±4 $kg\,m^{-3}$). The data were

Fig. 1. Granules obtained from the spheronisation of MCC/PG paste extruded at 625 mm s^{-1} through a 1 mm diameter die of length 4 mm: (a) wet; (b) oven-dried; (c) freeze-dried granules. The scale shows 0.5 mm divisions.

used to calculate the tablet apparent density to within ±1%, and the tablet voidage to within ±5%.

The tablet crushing strength was determined by performing a standard compression test (Kuentz and Leuenberger, 2000), where a diametrical force was applied to the tablet using the strain frame. The tablet was placed between two 50 mm diameter stainless steel platens and held vertically in place on the bottom platen by a small piece of 'Blu Tack' (Bostik). The top platen was moved at 0.1 mm s^{-1} to a maximum displacement of 4 mm, and the upper platen force and displacement were recorded.

The dissolution behaviour of the tablets was investigated using an in-house apparatus. A tablet was suspended in a wire cage (orifice size <0.5 mm) and immersed in 1 l of 30 vol.% solution of ethanol in water. The liquid was well-stirred and maintained at a constant temperature of 20 °C using a water bath. Prior work had established that MCC did not dissolve in this solution, and the solubility of PG in this solution was greater than the maximum loading expected from complete dissolution of one tablet. A peristaltic pump circulated liquid from the system through a Unicam 8625 UV spectrometer (Unicam Ltd., England), which measured absorption at three wavelengths (240, 245 and 250 nm). These wavelengths were chosen since they have an extinction coefficient appropriate for the expected concentration of PG in solution. The data were recorded at 10 s intervals and were averaged across the three wavelengths to generate a single absorption curve. The absorption was linear in concentration across the range of interest, and a calibration chart allowed the concentration of PG in solution to be determined over time.

3. Results and discussion

3.1. Granule characterisation

Micrographs of the wet and dried granules are displayed in Fig. 1. Both the wet and freeze-dried granules demonstrate a high apparent sphericity and have relatively smooth surfaces, whereas the oven-dried granules are irregular in shape with rough surfaces. Since MCC absorbs more water than PG, the MCC shrinks more during oven-drying, resulting in the relatively large PG particles lying proud to the surface of the granule. Further experiments (not reported here) demonstrated that this roughness could be eliminated by using a paste consisting of a smaller proportion of PG powder of reduced particle size (less than 250 μm), thus producing a more homogeneous paste in terms of moisture distribution. Despite the large size of the PG particles and high proportion of PG used in the current paste formulation, freeze-drying allowed the granules to retain their original spherical shape and smooth surface structure.

Fig. 2 shows the size distribution of the dried granule batches in terms of sieved mass fractions. The oven-dried batch yields a broader size distribution than the freeze-dried one, with many fines formed due to asperities breaking off the granules. The modal fraction of the freeze-dried granules lies between 1.18 and 1.40 mm, while that of the oven-dried granules is between 1.40 and 1.70 mm, which may be due to their irregularity in shape.

3.2. Tablet formation

Fig. 3 shows the appearance of tablets, formed from the 1.40–1.70 mm size fraction of oven-dried and freeze-dried granules, compacted to different final pressures. For a given compaction pressure, the tablets produced using oven-dried granules feature much smoother surfaces than those produced using freeze-dried granules. For the lowest compaction pressure of 19 MPa, the outlines of the individual oven-dried granules are barely distinguishable, whereas the freeze-dried granules are clearly visible, with relatively large intergranular pores present on the tablet surface. For both the oven-dried and freeze-dried granules, as the compaction pressure increases, the granules merge, thus decreasing the tablet surface porosity and increasing its apparent smoothness.

The variation of tablet apparent density with final applied compaction pressure is illustrated in Fig. 4. The apparent

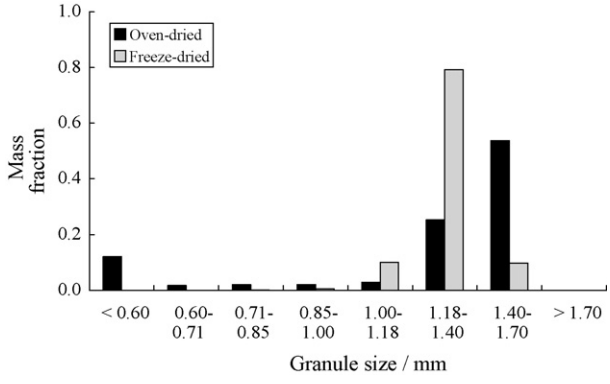

Fig. 2. Size distributions in terms of sieved mass fractions of oven-dried and freeze-dried granules obtained from the spheronisation of MCC/PG paste.

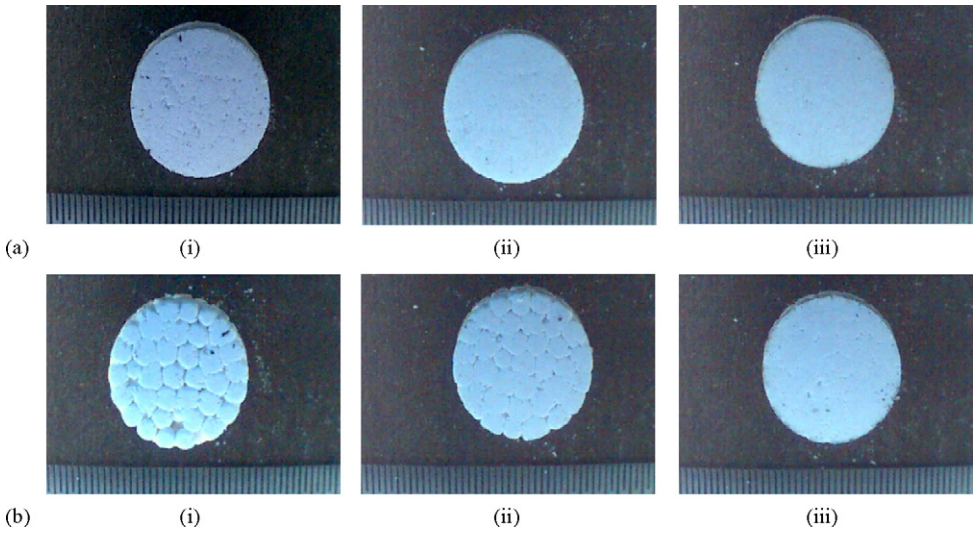

Fig. 3. Tablets generated from (a) oven-dried and (b) freeze-dried granules (1.40–1.70 mm sieve fraction), compacted to final pressures of (i) 19 MPa, (ii) 38 MPa and (iii) 89 MPa. The scale shows 0.5 mm divisions. Tablet diameter 10 mm.

densities of tablets prepared from freeze-dried granules are 8–14% lower than those of tablets prepared from oven-dried granules at a given compaction pressure, a difference which is beyond the experimental variation of ±1%. This implies that the oven-dried granules are easier to deform and/or break during part or all of the compaction process, thus generating tablets of lower voidage and hence of higher density as confirmed visually in Fig. 3. Both types of tablets increase in apparent density by approximately 33% over the compaction pressure range studied (i.e. 19–89 MPa).

The data for the tablet voidage (closed pores), obtained *via* helium pycnometry measurements, are shown in Fig. 5. The voidages for both types of tablet at the lowest compaction pressure are around 0.35, which may be expected for a random packing of spheres. The voidage of tablets produced from freeze-dried granules decreases by 52% over the compaction pressure range studied, whereas that of the tablets produced from oven-dried granules decreases by 68%, indicating that the true volume of the freeze-dried granules changes less with compaction pressure than that of the oven-dried granules. This was not evident from the apparent density data.

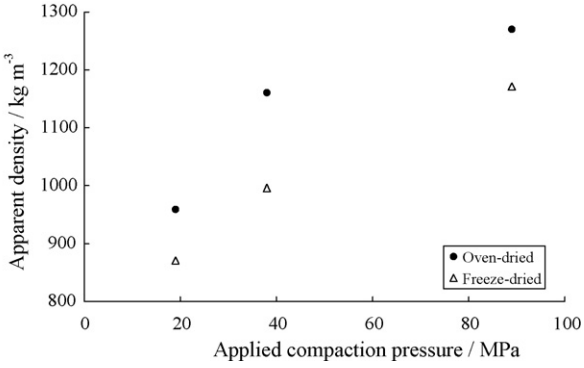

Fig. 4. Effect of compaction pressure on apparent density of tablets generated from (●) oven-dried and (△) freeze-dried granules. Error bars due to experimental measurements too small to be shown clearly.

Examples of continuous compaction profiles for tablets produced from oven-dried and freeze-dried granules are given in Fig. 6. At relatively low compaction pressures (less than 2 MPa), the apparent density of the freeze-dried granule tablet is ≈5%

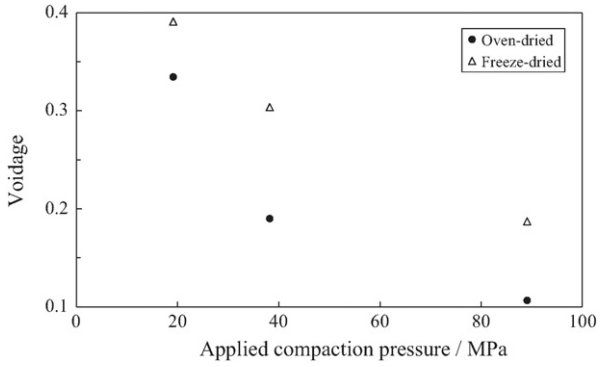

Fig. 5. Effect of compaction pressure on voidage of tablets generated from (●) oven-dried and (△) freeze-dried granules. Error bars due to experimental measurements too small to be shown clearly.

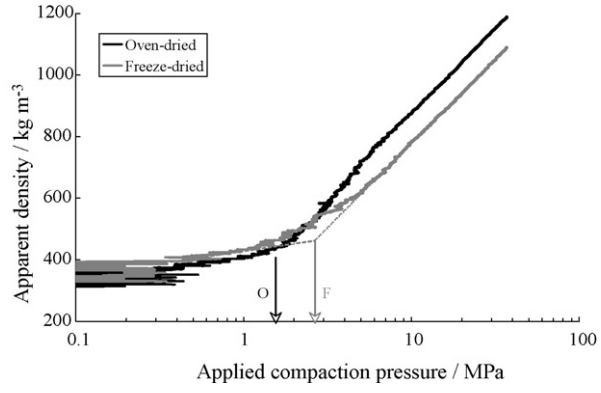

Fig. 6. Compaction curves showing apparent density against applied compaction pressure for tablets generated from oven-dried and freeze-dried granules, compacted to a final pressure of 38 MPa. Note logarithmic scale for applied compaction pressure. The arrows indicate the granule yield points for compaction of (O) oven-dried and (F) freeze-dried granules.

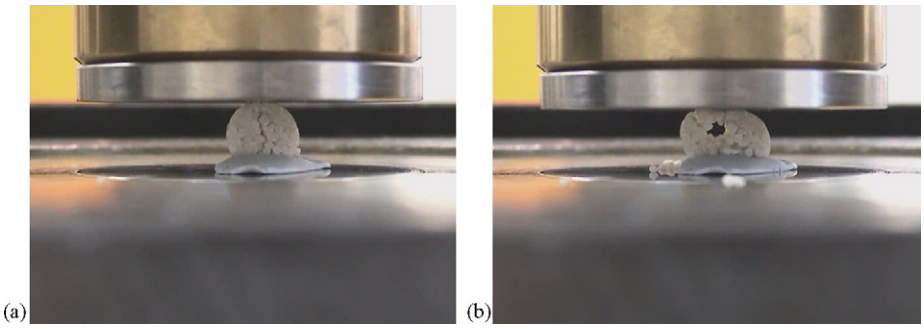

Fig. 7. Progressive images of the crushing process for a tablet generated from freeze-dried granules (1.40–1.70 mm sieve fraction) compacted to a final pressure of 38 MPa.

higher than that of the oven-dried one, which suggests that the smooth freeze-dried granules are more efficient at rearranging at these low pressures than the rough oven-dried granules due to the lower intergranular friction. There is a crossover in tablet densities at a compaction pressure of approximately 3 MPa, and from around 6 MPa onwards both densities are directly proportional to the logarithm of the applied pressure. The gradients of both compaction curves are similar, with the apparent density of the oven-dried granule tablet remaining $\approx$100 kg m^{-3} higher than that of the freeze-dried one, implying that the efficiency of compaction is the same for both types of tablet at these higher pressures. An indication of the granule yield point can be attained from the intersection of the tangents to the low and high pressure regions of the compaction curve, and values of 1.5 and 2.7 MPa are thus obtained for oven-dried and freeze-dried granules, respectively. This result further demonstrates that the oven-dried granules are less strong than the freeze-dried ones, and are therefore deformed more readily during the early stages of the compaction process.

3.3. Tablet strength

An example of a typical tablet crushing test is displayed in Fig. 7. For all the tablets tested, a central crack was formed shortly after the upper platen contacted the tablet. In some cases, granules became dislodged from the tablet and fell away from the structure. As the upper platen continued to move down, secondary cracks were created, which weakened the tablet further and caused complete breakage. This behaviour was reflected in the crushing force–displacement profiles (not reported here), which showed an initial elastic response, a peak in the force corresponding to the formation of the central crack, and a reduced resistance thereafter. The maximum force (F) was used to determine a radial tensile crushing strength (σ) (Kuentz and Leuenberger, 2000):

$$\sigma = \frac{2F}{\pi Dh} \quad (1)$$

where D and h are the diameter and height of the tablet, respectively. The subsequent crushing strength data are summarised in Fig. 8, and show that for a given final tabletting pressure, tablets produced from oven-dried granules are stronger than the ones produced from freeze-dried granules. For both types of tablet, the crushing strength increases linearly with applied compaction (tabletting) pressure.

Further insight into the crushing strength behaviour may be obtained by analysing the data as a function of tablet voidage, as illustrated in Fig. 9. At relatively high voidages of between 0.3 and 0.4, the crushing strength of both tablet types decreases linearly with increasing voidage. At a lower tablet voidage (around 0.19), the data sets diverge, with the freeze-dried granule tablet exhibiting a strength $\approx$70% higher than the oven-dried analogue, since a larger tabletting pressure is required to achieve the given voidage for the freeze-dried granules.

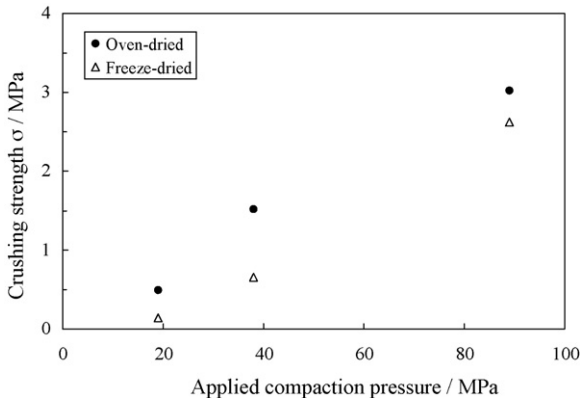

Fig. 8. Effect of compaction (tabletting) pressure on crushing strength σ (determined using Eq. (1)) for tablets generated from (●) oven-dried and (△) freeze-dried granules.

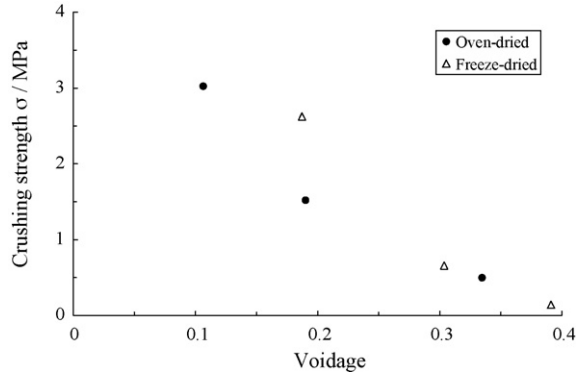

Fig. 9. Effect of voidage on crushing strength σ (determined using Eq. (1)) for tablets generated from (●) oven-dried and (△) freeze-dried granules.

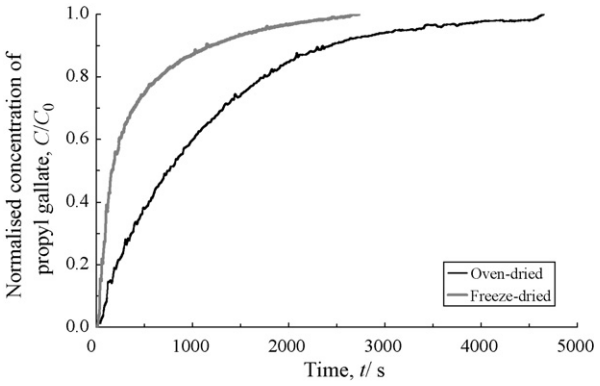

Fig. 10. Dissolution profiles showing normalised concentration of propyl gallate (C/C_0) in 30 vol.% ethanol solution against dissolution time (t) for tablets made from oven-dried and freeze-dried granules, compacted to a final pressure of 19 MPa.

3.4. Tablet dissolution

Fig. 10 shows an example of the change in concentration of PG in solution during a dissolution test for tablets formed from oven-dried and freeze-dried granules, both compacted to a final pressure of 19 MPa. The concentration variable is normalised by dividing the instantaneous concentration of PG in solution, C, by the final concentration, C_0. Both data sets show a continuous profile, with the freeze-dried granule tablet reaching complete dissolution markedly faster than the oven-dried form.

These dissolution data sets were analysed in terms of the following kinetic expression:

$$\frac{dC}{dt} = \frac{kA}{V}(C^* - C) = a - KC \quad (2)$$

where t is the time, k the mass transfer constant for dissolution, A the surface area of solid PG dissolving, V the volume of solution, C^* the equilibrium solubility of PG in solution, a is a constant and K is the dissolution rate constant.

Fig. 11 shows a plot of the dissolution rate dC/dt against C for the data sets in Fig. 10, and the difference in dissolution behaviour is marked. For both tablets, there is an initial increase in dissolution rate with increasing concentration, corresponding to the liquid media penetrating the tablets. This transient response was evident in tablets formed under low compaction stresses, suggesting that it is associated with relatively high or uneven voidage distributions. The peak in both transients occurs at a concentration of approximately 0.01 g dm^{-3}, with the freeze-dried granule tablet attaining a maximum dissolution rate of more than twice that of the oven-dried form. The oven-dried granule tablet exhibits dissolution kinetics described by Eq. (2) for concentrations greater than 0.02 g dm^{-3}. The freeze-dried granule tablet also exhibits dissolution kinetics following Eq. (2) for concentrations between 0.04 and 0.10 g dm^{-3}. In this concentration range, the freeze-dried granule tablet dissolves markedly faster than the oven-dried one (the gradient of the plot in Fig. 11, which corresponds to the dissolution rate constant K in Eq. (2), is an order of magnitude greater). In the final stages of dissolution, i.e. $C > 0.10$ g dm^{-3}, the dissolution rate approaches that of the oven-dried sample. Thus, the PG appears to be available in two forms in the freeze-dried granule tablets—about half in readily soluble form, and the remainder in a more tightly bound form.

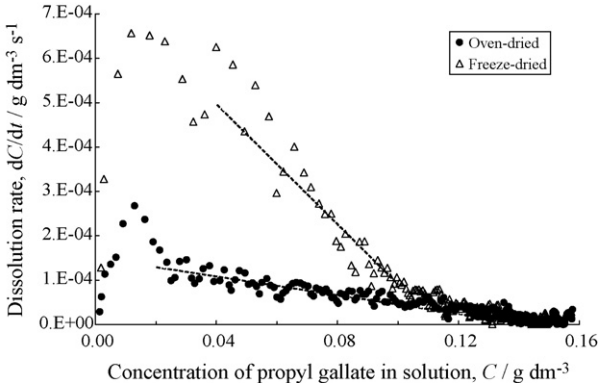

Fig. 11. Dissolution rate (dC/dt) against concentration of propyl gallate (C) in 30 vol.% ethanol solution for tablets made from oven-dried and freeze-dried granules, compacted to a final pressure of 19 MPa. The dashed lines represent best-fit linear trendlines through the data for a given concentration range.

Table 1
Dissolution rate constants (K, as defined in Eq. (2)) for tablets made from oven-dried and freeze-dried granules of MCC/PG paste (1.40–1.70 mm sieve fraction), compacted to final pressures of 19, 38 and 89 MPa, and dissolved in 30 vol.% ethanol solution

Final applied compaction pressure (MPa)	Dissolution rate constant, K ($\times 10^{-4}$ s^{-1})
Oven-dried	
19	8.2
38	2.4
89	1.7
Freeze-dried	
19	70
38	70
89	70

The timescales observed here are likely to be solvent-dependent and thereby subject to change when controlled-release studies are performed in other media, such as simulated intestinal fluid.

The dissolution data generated for tablets compacted to final pressures of 38 and 89 MPa were also analysed as described above, and in each case a dissolution rate constant was determined. The values obtained are listed in Table 1 and show that the tabletting pressure did not affect the dissolution kinetics for the freeze-dried samples, whereas K decreased as pressure increased for the oven-dried ones, as might be expected for decreasing tablet voidage.

4. Conclusions

The mode of drying had a noticeable effect upon the physical appearance and compaction characteristics of the extrusion–spheronisation granules. Freeze-drying allowed the granules to maintain their smooth surface and highly spherical shape, whilst oven-drying produced irregularly shaped, roughened granules due to non-uniform shrinkage of the MCC and

PG powders. The freeze-dried granules were more deformable in compaction, producing tablets of lower voidage for a given compaction pressure. Analysis of compaction data suggested granule yield points of approximately 1.5 and 2.7 MPa for the oven-dried and freeze-dried material, respectively. The trends in tablet crushing strength could be related to voidage, with stronger tablets being produced at higher compaction pressures, although the correlations differed between the two drying modes.

The dissolution kinetics of the two forms of tablet also showed marked differences. The freeze-dried granule tablets exhibited two-regime dissolution behaviour, with the first regime having a markedly larger dissolution rate constant, and the second regime having a rate constant approaching that of the oven-dried material. This may be a desirable feature or not, depending on the active ingredient and the type of controlled release profile sought. The two-stage behaviour could be a factor against the use of freeze-drying with MCC/water-based formulations when other factors would indicate that freeze-drying is desirable, such as the use of a thermally labile active that would undergo a polymorphic transformation or degrade at the temperatures involved in conventional oven-drying. Oven-dried granule tablets compacted at higher pressures showed a reduction in dissolution rate associated with a low-voidage structure, whereas a decrease in voidage did not affect the dissolution kinetics of the freeze-dried material. These different dissolution behaviours may be an important issue when designing tablets for controlled drug-release systems.

Acknowledgements

The authors wish to thank the following for their advice and assistance: Mr. Ruben Mercadé-Prieto (dissolution testing); Mr. Zlatko Saracevic (helium pycnometry); Mr. Richard Taylor (freeze-drying). The MCC powder was kindly supplied by Merck, Sharp and Dohme (Hoddesdon, UK). This work was carried out under a Merck, Sharp and Dohme Research Experience Grant 2005.

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