Effect of drying technique and disintegrant on physical properties and drug release behavior of microcrystalline cellulose-based pellets prepared by extrusion/spheronization

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\textbf{A B S T R A C T}

The aim of this study was to investigate the influence of drying technique and disintegrant on physical properties and drug release behavior of microcrystalline cellulose-based pellets prepared by extrusion/spheronization. Formulations of paracetamol (6.7\%, w/w), microcrystalline cellulose (66.7\%, w/w) and different disintegrants, alginic acid, calcium carbonate, \( \beta \)-mannitol, croscarmellose sodium, sodium starch glycolate, crospovidone, in concentrations of 10\% or 20\% (w/w) were made and processed to pellets by extrusion/spheronization. Different drying techniques, i.e. hot-air drying, microwave drying and freeze-drying, were applied to each formulation. Physical properties, such as particle size distribution, moisture content, apparent density, pellet morphology, were evaluated. The mechanical properties and drug release behavior of the pellets were also examined. Only small difference in crushing strength between hot-air dried and microwave-dried pellets were found. Freeze-drying process resulted in pellets with larger diameter, weaker and more porous than pellets dried with the other processes. The porous structure promoted a faster drug release while the drug release from hot-air dried, microwave drying and freeze-drying, were applied to each formulation. Physical properties, such as particle size distribution, moisture content, apparent density, pellet morphology, were evaluated. The mechanical properties and drug release behavior of the pellets were also examined. Only small difference in crushing strength between hot-air dried and microwave-dried pellets were found. Freeze-drying process resulted in pellets with larger diameter, weaker and more porous than pellets dried with the other processes. The porous structure promoted a faster drug release while the drug release from hot-air dried pellets and microwave-dried pellets was insignificantly different. Different disintegrants were incorporated in the pellets but none of the pellets disintegrated within 90 min. However, the drug release from pellets containing disintegrant was faster than that of pellets with no disintegrant. The results suggested that the type and amount of disintegrant is less influenced than the drying technique.

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Keywords: Pellets; Microcrystalline cellulose; Disintegrant; Drying; Extrusion; Spheronization

1. Introduction

The extrusion/spheronization process has become an important technique for the production of pharmaceutical pellets. Most drugs do not possess the properties required for successful pelletization by extrusion/spheronization. Addition of an aiding excipient is therefore required to produce formulations with the necessary rigidity, plasticity and water absorbing capacity to allow production of spheres. Microcrystalline cellulose (MCC) has been regarded as an essential component for successful extrusion/spheronization, possibly by favorably altering the rheological properties of the wet mass (Gandi et al., 1999). MCC pellets were reported not to retain their swelling potential after the manufacturing process and only disintegrated when the amount of drug was larger than the capacity of the MCC for keeping the structure together (Tho et al., 2003). At this point, when the drug has been dissolved, the structure will collapse and this could be observed as fragmentation, but it is not a true disintegration. In MCC pellets with higher amounts of excipient, water-soluble drug is washed out of the pellets leaving pores in the structure. For poorly water-soluble drug, the drug slowly dissolved from MCC pellets.
prepared by extrusion/spheronization. This slow dissolution rate derived from the pronounced contraction of the pellet during the drying phase, leading to reduced porosity which hindered an ingress of the dissolution medium into the pellet (Souto et al., 2005).

There are different approaches to obtain disintegrating MCC-based pellets. For instance, powdered cellulose was used as a substitute for MCC but a binder had to be added in order to obtain pellets (Dukić-Ött et al., 2009). Pellet disintegration of MCC pellets can also be obtained using alcohol/water mixtures as granulating liquid instead of water as this reduced the mechanical strength of the pellets (Schröder and Kleinebudde, 1995). Another approach that has been proposed for overcoming the limitation of MCC is the inclusion of superdisintegrants, which has received relatively little attention. The information that is available does not allow general conclusions to be reached regarding the efficacy of this approach. It was reported that the effect of superdisintegrants on the rate of dissolution of furosemide from extrusion/spheronization pellets was moderate, and that the magnitude of the effect was dependent on the solubility of the filler that accompanies the microcrystalline cellulose (Lövgren, 1984). It was found that crospovidone was inefficient for accelerating the dissolution of propyphenazone from extrusion/spheronization pellets. In contrast, it was found that croscarmellose sodium markedly accelerated the dissolution of theophylline from pellets prepared in a rotary processor. Another study evaluated and compared the efficiency of two superdisintegrants with different swelling capacities, namely croscarmellose sodium and sodium starch glycylate, for increasing the dissolution rate of hydrochlorothiazide (here used as a model of poorly water-soluble drugs) from extrusion/spheronization pellets with MCC as a base excipient (Souto et al., 2005). In that report, pellets were prepared with either water or water/ethanol as a wetting agent, resulting in different porosities, with the aim of establishing whether disintegration efficiency depends on the micropore structure of pellet.

Drying is the final step of extrusion/spheronization process. Pellets can be dried at room temperature or at elevated temperature (Vervaet et al., 1995). Conventional ovens, forced circulation ovens or microwave ovens can also be used (Bataille et al., 1993; Song et al., 2007). Another technique is the freeze-drying process. The influence of the drying methods (i.e. hot-air oven or microwave oven) on the pellet quality was shown by comparing a formulation, containing MCC and lactose (Bataille et al., 1993). The pellets dried with microwave oven differed from those dried in a hot-air oven as their surfaces were rougher and those pellets were more porous and had lower hardness. Pellets dried by a freeze-drying were more porous than those dried by conventional oven (Bashaiwoldt et al., 2004; Gomez-Carracedo et al., 2007). It was shown that the drying conditions have an impact of the physico-mechanical properties of pellets, but they did not lead to disintegration of the pellets.

The reported results up to now, however, do not give an overview about the effect of different drying techniques and types of disintegrate. There were only some examples dealing with these parameters. Therefore, this study was performed in order to demonstrate systematically the impact of different drying techniques (i.e. hot-air drying, microwave drying, and freeze-drying) and different disintegrants or superdisintegrants on the physical properties, such as particle size distribution, surface morphology, mechanical properties and drug release behavior of MCC-based pellets prepared by extrusion/spheronization process. Paracetamol was chosen as a model drug because of its ready availability, relatively low cost, ease of assay, and chemical stability.

2. Materials and methods

2.1. Materials

Paracetamol was obtained from Rhodia Organique (Roussillon, France). Microcrystalline cellulose (MCC) (Ceolus® PH-101) was purchased from Asahi Kasai Chemicals Corporation, Japan). Dicalcium phosphate and crospovidone (cross-linked polyvinyl pyrrolidone or Polyplasdone® XL) were a generous gift from Maxway Company Limited (Bangkok, Thailand). Algicin acid (Kelaclid®) was a generous gift from ISP (Thailand). Croscarmellose sodium (cross-linked sodium carboxymethylcellulose or Ac-Di-Sol®) and sodium starch glycylate (Explotab®) were purchased from Rama Production Co., Ltd. (Bangkok, Thailand). All other chemicals were of reagent or food grade and used as supplied. Deionized water was used throughout all experiments.

2.2. Manufacture of pellets by extrusion/spheronization

One hundred and fifty grams of paracetamol (6.7%, w/w), microcrystalline cellulose (MCC) (66.7%, w/w), and dicalcium phosphate (DCP) (26.6%, w/w) were thoroughly mixed in a plastic container for 10 min. Various amounts of deionized water were added slowly to the powder blend, which was then mixed until a homogenous, cohesive, plastic mass was obtained. The resulting wet mass was extruded at a speed of 18 rpm (Model 25, Caleva, England), through perforations 2 mm in diameter and 1.5 mm in thickness. Spheronization was performed in a spherizer (Model 250, Caleva, England) with a rotating plate of regular crosshatch geometry, at a speed of 500 rpm for 20 min. Pellets were then dried by three different techniques, i.e. hot-air oven (Heraeus Instruments, Germany) at 50 °C for 2.5 h, microwave oven (Model MS1922E, LG Electronics, South Korea) at low energy level (360 W) for 7 min, and freeze dryer (Model FreeZone 2.5, Labconco, USA) by freezing at –80 °C and then applying the vacuum to a level of 0.04 mbar at the condenser temperature of –50 °C for 2 days.

To study the effect of disintegrant in the pellet formulations on the pellet characteristics, the formulations of powder blends were modified. Some portions of DCP in the formulations were substituted by different amounts (10% or 20%, w/w) of various disintegrants (i.e. alginic acid, calcium carbonate, and β-manninitol) and superdisintegrants (i.e. croscarmellose sodium, sodium starch glycylate, and crospovidone). The amounts of paracetamol and MCC were kept constant.

2.3. Characterization of pellets

2.3.1. Particle size distribution

The particle size distribution of spherical pellets was determined using a set of the British standard test sieves (600–1700 μm with 20/25 progression) and a sieve shaker (Model Vibro, Retsch, Germany) operated for 10 min at an amplitude of 1.5 mm. The percentage of weight retained in each fraction was determined.
2.3.2. Pellet morphology
Morphological examination of the surface and internal structure of the dried pellets was carried out using a scanning electron microscope (Model Maxim-2000, CamScan Analytical, Cambridge, England) equipped with secondary electron detector at an accelerating voltage of 15 keV. The samples were coated with gold to a thickness of about 30 nm in a vacuum evaporator. The internal structure of the pellets was examined by cutting them in half with a steel blade.

The appearance of pellets were also observed using a digital camera (Model S602Zoom, Fujifilm, Japan) equipped with Super-EBC Fuji Nonlens (6×) optical zoom. Pellet imaging was performed on each batch of pellets. The pellets were spread over a flat surface by spatula and were photographed by digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate.

2.3.3. Moisture analysis
The moisture content of the dried pellets was analyzed with a moisture balance (Model YTC01L, Sartorius, Germany). Two grams of pellets were used for the test. The percentage of moisture loss during the procedure was calculated. The results are expressed as mean value of three measurements.

2.3.4. Apparent density of the pellets
The apparent density of pellet formulation without any disintegrant (6.7%, w/w, paracetamol, 66.7%, w/w, MCC, 26.6%, w/w, DCP) was estimated. Fifty pellets from each pellet formulation (size fraction of 1.18–1.40 mm), oven dried and freeze-dried, were counted and weighed. The measurement was done in triplicate.

2.3.5. Mechanical properties
Pellets of the size fraction of 1.00–1.18 mm were used to investigate the mechanical properties with a texture analyzer (Model TA-XPlus, Stable Micro Systems, UK). Twenty pellets were sampling from each formulation. The pellets were strained until pellet crushing occurred and the load applied at that time was detected.

The maximum crushing strength (\(\sigma_m\)) is calculated from the maximum applied load and the cross-sectional area of a pellet as described in Eq. (1),

\[
\sigma_m = \frac{0.4P_{m}}{\pi r^2}
\]

where \(P_{m}\) is the maximum load at failure (N) and \(r\) is the average radius of the spherical pellet in meters (Sriamornsak et al., 2006a).

2.4. Measurement of the drug content
About 100 mg pellets were weighed and added in a 100-ml volumetric flask, which was filled with simulated gastric fluid USP without pepsin (SGF). After 2 h of stirring with magnetic stirrer, the samples were filtered through 11-μm cellulose filters (Whatman, England) and diluted at 1:9 with SGF before measurement with the UV/vis-spectrophotometer (Model Lambda 2, PerkinElmer, USA) at 243 nm which is the maximum absorption of paracetamol. The tests were done in duplicate.

2.5. Dissolution studies
To examine the effects of investigated factors on the drug release, the dissolution studies were carried out using a USP dissolution apparatus II (Erweka, Germany) equipped with a paddle which was operated at the speed of 50 rpm. Nine hundred milliliters of SGF, as the dissolution medium, was placed into the glass vessel, assembled the apparatus. The dissolution medium was equilibrated to 37 ± 0.5°C. The amount of the drug release from pellets (200 mg of pellets) was measured at the suitable time interval and was then determined spectrophotometrically at 243 nm. Each dissolution study was performed in triplicate.

Higuchi model was used for the analysis of the drug release mechanism of matrix-typed pellets, as previously described (Sriamornsak et al., 2008). The release of a drug from the matrix pellets can be analyzed by release kinetics theories (Higuchi, 1963), as follows:

\[
\frac{M_t}{M_f} = k t^{1/2}
\]

where \(M_t\) is the amount of drug release at time \(t\); \(M_f\) is the amount of drug release after infinite time and \(K\) is the Higuchi release rate constant which reflects the shape and the internal structure of the matrix as well as the drug concentration and solubility.

2.6. Statistical analysis
Analysis of variance (ANOVA) and Levene’s test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, USA). Post hoc testing (\(p < 0.05\)) of the multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene’s test was insignificant or significant, respectively.

3. Results and discussion

3.1. Pelletization
Spherical pellets containing paracetamol, MCC and DCP were produced by extrusion/spheronization. MCC obtained from different sources/manufacturers, which differed significantly in the physical properties, influenced the water requirement for extrusion/spheronization as well as the size and roundness of the resulting pellets (Newton et al., 1992; May and Heng, 2001). Sinha et al. (2005) also studied a range of grades of MCC, and showed that the MCC (grade PH101) produced good quality pellets. Variables that may influence the quality of the final pellets, including the starting materials (e.g. active drug and other excipients), type of binder, type of extruder, extrusion speed, extrusion temperature, spheronization speed as well as spheronization time, were kept constant. In our previous studies, it was shown that the amount and concentration of binder affected the appearance of the resulting pellets (Sriamornsak et al., 2006b). Increasing the volume of binder solution increased the mean size of pellets but decreased the yield in the desirable pellet size range. The use of an excess amount of binder gave rod-shaped pellets. The spheronization speed and spheronization time were also optimized to achieve a good quality (round and smooth) of pellets in the preliminary study. The pellets obtained from the higher spheronization speeds were more spherical than those from the lower speeds.
Different techniques was shown in Table 1. Sieve analysis showed

<table>
<thead>
<tr>
<th>Size fraction (mm)</th>
<th>Weight retained in each fraction, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hot-air oven</td>
</tr>
<tr>
<td>&gt;1.70</td>
<td>0.9</td>
</tr>
<tr>
<td>1.40–1.70</td>
<td>5.5</td>
</tr>
<tr>
<td>1.18–1.40</td>
<td>57.1</td>
</tr>
<tr>
<td>1.00–1.18</td>
<td>23.3</td>
</tr>
<tr>
<td>0.85–1.00</td>
<td>8.4</td>
</tr>
<tr>
<td>0.60–0.85</td>
<td>4.6</td>
</tr>
<tr>
<td>&lt;0.60</td>
<td>0.2</td>
</tr>
</tbody>
</table>

(Sriamornsak et al., 2006a). The spheronization time of 20 min
(at a speed of 600 rpm) was not used in the present work as it
increase hardness of the pellets and thus decrease the
Disintegration time.

The drying conditions can influence the physical appearance
of the produced pellets. The color of the pellets dried by a hot-air oven and a freeze dryer was almost white while
that of the pellets dried by a microwave oven turned slightly beige with some light brown. Despite the low energy input,
short drying time and regular stirring were applied; some pel-
lets got heat up more than others. The primary drawback of
microwave heating is its inability to heat materials in a uni-
form manner, leaving hot spots that damage the item being
heated and cold spots where the item is unheated or unpro-
cessed. As a result, the use of microwave oven may not be
suitable for a uniform drying process because the pellets were
not stirred during the time of energy input. However, the
microwave heating technology such as microwave fluidiza-
tion technique (Chen et al., 2001) may be the solution of this
problem. During the freeze-drying operation, all the free and
bound water have been removed, resulting in a residual mois-
ture level that assures desired structural integrity and stability
of the pellets. Since the physical structure of the pellets is not
altered during the freeze-drying process, the pellets retained
much of their color, shape, and texture. One of the major
disadvantages of freeze-drying process is its cost. The equip-
ment used for this process requires a substantial investment,
and the process itself is time consuming. Compared to other
pharmaceutical processes, freeze-drying is intrinsically more
complex which requires a careful balancing of product, equip-
ment, and processing techniques.

### 3.2. Physical properties of pellets

The particle size distribution of the pellets dried by three dif-
erent techniques was shown in Table 1. Sieve analysis showed
that the size distribution was narrow for most formulations.

Drying conditions influenced the mean size of the pellets.
The modal size fractions usually were 1.18–1.40 mm for hot-
air dried and microwave-dried pellets and 1.40–1.70 mm for
freeze-dried pellets. The average pellet size of the hot-air dried
pellets and microwave-dried pellets was significantly smaller
than that of the freeze-dried pellets (p < 0.05) due to the shrinking
during the drying process at higher temperatures. However,
the freeze-drying almost prevented shrinking of the pellets.

Size distribution of the hot-air dried pellets was similar to
that of the microwave-dried pellets, with 57.1% and 61.7%
in the modal size fraction, respectively. The freeze-dried pel-
lets showed a more narrow size distribution with 69.6% in the
modal size fraction (1.40–1.70 mm). Pellets formulations with
croscarmellose sodium, sodium starch glycolate and crospro-
done showed a smaller mean size because they were more
difficult to produce. Their size distributions were broader and
the modal size fraction was significantly different from the
above mentioned.

The drying conditions influenced the pellet density, which
increased with an increase in drying temperature, indicating
the formation of more dense structures, i.e. shrinking of the
pellets upon drying at higher temperatures (Sinha et al., 2007).
The apparent density of hot-air dried and freeze-dried pel-
lets (size fraction of 1.18–1.40 mm) was 1.54 and 1.02 g/cm³,
respectively. The freeze-dried pellets demonstrated a signifi-
cant smaller apparent density because they are more porous
than the hot-air dried pellets, with most of the pores open to
the atmosphere and had a higher surface area than pellets
dried by the other methods (Bashaiwoldu et al., 2004; Gomez-
Carracedo et al., 2007).

### 3.3. Pellet morphology

The photographs of MCC-based pellets containing paracetam-
ol (6.7%, w/w), microcrystalline cellulose (66.7%, w/w), and
dicalcium phosphate (26.6%, w/w), which dried by different
techniques, are shown in Fig. 1. They are fairly similar in term
of shape. The surfaces of freeze-dried pellets were rougher
than those dried by hot-air and microwave oven. According to
the SEM images (taken at magnitude of 45× and 500×), a
smooth surface for the hot-air dried and microwave-dried pel-
lets (Fig. 2a and b) and some pores or crevices on the surface
of the freeze-dried pellets (Fig. 2c) were observed. Fig. 3 shows
the cross-sectional images of the hot-air dried and freeze-
dried pellets. It is obvious that the freeze-dried pellets were
porous while the hot-air dried pellets were more compact.

The influence of drying is mainly related to the smaller vol-
umetric contraction that the freeze-dried pellets underwent,
which also caused the pellets to be larger and more spherical.
A similar tendency in morphology was recently reported for
MCC-Carbopol pellets (Gomez-Carracedo et al., 2007). Addi-
tionally, the internal structure of the extruded/spheronized
pellets, dried with hot-air oven and freeze dryer, revealed the
cavity inside the pellets (Fig. 3). This is likely due to the rota-
tional and the frictional forces involved in the spheronization
process, the edges of the flat side fold together like a flower
forming the cavity observed in the pellets (Sriamornsak et al.,
2008).

### 3.4. Mechanical properties of the pellets

In order to investigate the mechanical properties of the pel-
lets, compression tests were performed. The most significant
parameter is the displacement of the probe from the initial
contact to rupture of the pellet. From this data, the apparent
crushing strength was calculated. The resistance of individ-
ual pellets to the crushing is related to the cohesive and
adhesive properties of the excipients, their size and shape
as well as other properties that are specific to the manufac-
turing process (Dyer et al., 1994). The crushing strengths of
hot-air dried, microwave-dried and freeze-dried pellets were
14.5, 9.5 and 2.9 N/m², respectively. The results suggested that
hot-air dried pellets were stronger than the microwave-dried
the freeze-dried pellets, respectively. A reduction in mechanical strength of the microwave-dried pellets, compared to hot-air dried pellets, was obtained owing to slightly more porous pellets produced during a quick drying when using a microwave oven. Bataille et al. (1993) has also found that the less porous pellets produced by hot-air drying have a higher crushing strength than the porous microwave-dried pellets. The increase in porosity of the freeze-dried pellets, resulting in a low crushing strength, can be explained by the consequence of a weakening in the interparticular links inside the pellets (Bashaivoldu et al., 2004). A further factor that could be associated with the mechanical properties of the pellets is the amount of water in the pellet structure. The higher moisture content of the microwave-dried pellets (3.9%), compared to 2.6% for the hot-air dried pellets, could lead to a softening of the structure.

The effect of type and concentration of the disintegrant on the crushing strength of pellets is shown in Table 2. For both pellets without and with disintegrant, the crushing strength of the freeze-dried pellets was apparently lower than that of the hot-air dried pellets. The type of disintegrant insignificantly affected the crushing strength of pellets. However, hot-air dried pellet formulations with sodium starch glycolate or D-mannitol showed a slightly decreased crushing strength compared to the reference formulation with no disintegrant. However, for most disintegrants, there is only small or no significant difference ($p > 0.05$) between the pellet formulations with 10% and 20% (w/w) disintegrant.

### 3.5. Drug release studies

Fig. 4 shows the results of dissolution tests of MCC-based pellets using different drying techniques. The fastest drug release was observed with the freeze-dried pellets. This behavior has been also reported in the literatures (Bataille et al., 1993; Song et al., 2007). The hot-air dried and microwave-dried pellets showed an insignificant difference in drug release profiles ($p > 0.05$). After 10 min, 80% of paracetamol (based on the determined drug content) were released from the freeze-dried pellets, while only 58% were released from the hot-air dried and microwave-dried pellets. However, for all formulations, the drug release was complete within 30 min. The release of

<table>
<thead>
<tr>
<th>Disintegrant</th>
<th>Crushing strength of pellets (N/m²), n = 20</th>
<th>Drug release at 10 min after dissolution test (Q_{10min}) (%)</th>
<th>n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hot-air dried pellets</td>
<td>Freeze-dried pellets</td>
<td>Hot-air dried pellets</td>
</tr>
<tr>
<td>No disintegrant</td>
<td>13.04 ± 2.07</td>
<td>1.46 ± 0.54</td>
<td>54.78 ± 0.55</td>
</tr>
<tr>
<td>10% (w/w) Alginic acid</td>
<td>12.20 ± 1.33</td>
<td>1.19 ± 0.25</td>
<td>57.01 ± 0.30</td>
</tr>
<tr>
<td>20% (w/w) Alginic acid</td>
<td>13.80 ± 1.23</td>
<td>1.33 ± 0.16</td>
<td>46.89 ± 0.36</td>
</tr>
<tr>
<td>10% (w/w) Calcium carbonate</td>
<td>11.25 ± 1.19</td>
<td>1.82 ± 0.77</td>
<td>56.84 ± 0.51</td>
</tr>
<tr>
<td>20% (w/w) Calcium carbonate</td>
<td>10.35 ± 1.01</td>
<td>2.05 ± 0.82</td>
<td>60.83 ± 1.02</td>
</tr>
<tr>
<td>10% (w/w) D-mannitol</td>
<td>9.87 ± 1.00</td>
<td>2.41 ± 0.30</td>
<td>55.59 ± 0.17</td>
</tr>
<tr>
<td>20% (w/w) D-mannitol</td>
<td>7.57 ± 1.19</td>
<td>2.67 ± 0.40</td>
<td>61.15 ± 0.07</td>
</tr>
<tr>
<td>10% (w/w) Sodium starch glycolate</td>
<td>6.79 ± 1.00</td>
<td>2.35 ± 0.44</td>
<td>58.88 ± 0.17</td>
</tr>
<tr>
<td>20% (w/w) Sodium starch glycolate</td>
<td>9.47 ± 2.11</td>
<td>6.11 ± 0.89</td>
<td>78.78 ± 0.34</td>
</tr>
<tr>
<td>10% (w/w) Croscarmellose sodium</td>
<td>13.28 ± 1.13</td>
<td>1.19 ± 0.22</td>
<td>56.91 ± 0.65</td>
</tr>
<tr>
<td>20% (w/w) Croscarmellose sodium</td>
<td>12.55 ± 1.55</td>
<td>1.14 ± 0.05</td>
<td>58.15 ± 0.62</td>
</tr>
<tr>
<td>10% (w/w) Crospovidone</td>
<td>12.55 ± 1.55</td>
<td>1.14 ± 0.05</td>
<td>53.61 ± 0.34</td>
</tr>
<tr>
<td>20% (w/w) Crospovidone</td>
<td>14.38 ± 1.94</td>
<td>1.37 ± 0.22</td>
<td>62.47 ± 0.69</td>
</tr>
</tbody>
</table>
drug from a porous insoluble matrix may be described by Higuchi's equation. It is applicable if the release of drug is largely governed by the diffusion through water-filled pores in the matrix (Sriamornsak et al., 1997). Fig. 5 shows that the release of paracetamol from the MCC-based pellets, which conforms to Higuchi's equation with $r^2 > 0.981$, is primarily influenced by the different porosity resulting from the different drying techniques. It is considered that the effective release channel should be affected by the void space, i.e. porosity, and the high surface area. Therefore, a higher release rate constant, which reflected a faster drug release, was observed from the freeze-dried pellets.

The influence of incorporated disintegrant in the pellet formulation on drug release was investigated. Most of the disintegrants used in this study are hydrophilic materials comprising a hydrophilic colloid matrix that is insoluble at the pH of the stomach. In addition, to being hydrophilic, several of the disintegrants have a high affinity for water, and some, e.g. sodium starch glycolate, are hygroscopic. The drug release from hot-air dried pellets containing different disintegrants (20%, w/w) is shown in Fig. 6. The faster drug release was observed for MCC-pellets containing disintegrant except that containing 20% alginic acid. The release parameter, percentage of drug release at 10 min after dissolution test ($Q_{10\text{min}}$), obtained from different pellet formulations are shown in Table 2. The $Q_{10\text{min}}$ values of the pellets with no disintegrant were $54.78 \pm 0.55$ and $72.87 \pm 0.56$ for hot-air dried and freeze-dried pellets, respectively. The higher $Q_{10\text{min}}$ values were observed in freeze-dried pellets than in hot-air dried pellets, indicating a faster drug release from freeze-dried pellets. The $Q_{10\text{min}}$ values of formulations with 10% disintegrant were the same or slightly higher than that of the formulation with no disintegrant except for the freeze-dried formulation with 10% croscarmellose sodium which showed a markedly higher $Q_{10\text{min}}$ value (15% increase). When 20% disintegrant were used, $Q_{10\text{min}}$ values were slightly higher than

![Fig. 2 – Scanning electron micrographs of the surface of pellets dried by (a) hot-air oven, (b) microwave oven, and (c) freeze dryer. The composition of pellets was paracetamol (6.7%, w/w), microcrystalline cellulose (66.7%, w/w), and dicalcium phosphate (26.6%, w/w). Scale bars are shown on the individual photographs.](image-url)
Fig. 3 – Scanning electron micrographs of the internal structure (cross-section) of pellets dried by (a) hot-air oven and (b) freeze dryer. The composition of pellets was paracetamol (6.7%), microcrystalline cellulose (66.7%), and dicalcium phosphate (26.6%). Scale bars are shown on the individual photographs.

10% disintegrant, particularly the pellet formulation with calcium carbonate, α-mannitol and crospovidone (both hot-air dried and freeze-dried pellets). The formulations with 20% croscarmellose sodium (freeze-dried) and sodium starch glycolate (hot-air dried and freeze-dried) showed a substantial increase in the \( Q_{10\text{min}} \) value. The increase in drug release may be due to the mechanism of disintegrants that (i) promote capillary action, absorb moisture and swell, (ii) release gas when getting in contact with moisture (i.e. in case of calcium carbonate), or (iii) increase the wettability (Moreton, 2008). Furthermore, the increase in drug release in the formulations with 20% (w/w) disintegrants (or superdisintegrants) might be due to the less bonding between the MCC particles.

Although the disintegrant (especially superdisintegrant) can promote capillary action, absorb moisture rapidly and swell, none of the pellets disintegrated within 90 min. These may be also due to the fact that water that added was absorbed by the disintegrant and caused the partial swelling of disintegrant during pelletization so that it cannot act as a swelling

Fig. 4 – Drug release from pellets prepared by three different drying techniques. The composition of pellets was paracetamol (6.7%, w/w), microcrystalline cellulose (66.7%, w/w), and dicalcium phosphate (26.6%, w/w). The means of triplicate data are plotted; the standard deviation of the data is within the point size.

Fig. 5 – Drug release from pellets prepared by three different drying techniques, plotted as the cumulative percentage released versus the square root of time. The means of triplicate data are plotted; the standard deviation of the data is within the point size.
agent during the dissolution test. With partially soluble matrix components, the matrix could be dissolving and thus the disintegrant is deprived of some of what it might push against, thus reducing the disintegrant effect. However, Schröder and Kleinebudde (1995) reported that the pellets could disintegrate when a high amount of soluble component (e.g. 40%, w/w, d-mannitol) combined with 20% (w/w) MCC were used in the formulations. The high amount of soluble d-mannitol led to lower water contents during extrusion compared to the insoluble DCP (without disintegrant). Moreover, the penetration of water is somehow retarded, e.g. by a high agglomeration or compaction of pellets during spherization induced by centrifugal force, disintegration is prevented and this may in turn reduce the rate of the dissolution of the drug (Moreton, 2008). Increasing amount of disintegrant (from 10% to 20%) led to a greater $Q_{10\text{min}}$ value for both hot-air dried and freeze-dried pellets, resulting in the faster drug release pattern.

4. Conclusion

Three drying techniques, i.e. hot-air drying, microwave drying, freeze-drying, were compared. No difference in drug release and only small difference in hardness between hot-air dried and microwave-dried pellets were found. Freeze-drying process resulted in pellets with larger diameter, softer and more porous than pellets dried with the other processes. The porous structure promoted a faster drug release rate. Although different disintegrants were incorporated in the pellets, none of the pellets disintegrated within 90 min but the drug release quickly. It was shown that the type and amount of disintegrant have a smaller influence than the drying technique. The freeze-dried pellets containing croscarmellose sodium are recommended if the fast drug release is required.

Acknowledgements

The authors wish to thank Maxway Company Ltd. (Thailand) who kindly provided the samples of dicalcium phosphate and Polyplasdone® XL, and ISP (Thailand) who provided a sample of Kelacid®.

References


