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Effect of preparation method on compactability of paracetamol granules and agglomerates

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Abstract

The objective of this study was to investigate the effect of fracture strength of paracetamol particles on their compactability. For this purpose two series of paracetamol particles were prepared by crystal agglomeration and by granulation using different solvents. A free flowing particle size fraction of all types of particles was characterized with respect to their shape, degree of agglomeration and single fracture strength. The powders were compressed to tablets and the compression mechanism of the particles and the evolution in tablet micro-structure were assessed by compression parameters derived from the Heckel and Kawakita equations and by a tablet permeabililty coefficient. Tablet tensile strength and porosity were determined. The degree of deformation and fragmentation during compression varied between agglomerates and granules and was dependent on their failure strength. The granules varied in compactability with particle failure strength while the agglomerates showed limited variation. It is proposed that, the dominant mechanism of compression for the granules was permanent deformation while for the agglomerates it was fragmentation. It was thus found that the compression mechanism of the particles was dependent on both the degree of agglomeration and the particle failure strength.
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Keywords: Wet granulation; Crystal agglomeration; Particle fracture strength; Degree of agglomeration; Tablet tensile strength

1. Introduction

Fine particulate drugs are often processed into granules before tableting to preserve the fineness of the drug while a powder that is suitable for a tableting operation is accomplished. In the preparation of such granular solids, the most common procedures used in pharmaceutical production are based on the reprocessing of fine particles into secondary particles by wet granulation, i.e. granule formation with a liquid, and roller compaction. An alternative approach is obviously to control the crystallization of the drug in such a way that agglomerates of fine drug particles are formed during precipitation from solution.

The steps involved in the crystallization of organic and other compounds, including agglomeration and parameters influencing agglomeration during crystallization, have been subjects of interest in the literature (Ålander et al., 2004). Also regarding active pharmaceutical ingredients, several studies are reported in which agglomerates are formed during precipitation from solutions, e.g. paracetamol (Fachaux et al., 1995a, 1995b), acebutolol hydrochloride (Kawashima et al., 1995), ibuprofen (Rasenack and Müller, 2002), lobenzarit disodium (Amaro-Gonzalez and Biscans, 2002), and ascorbic acid (Kawashima et al., 2003). By agglomeration, downstream processing and handling of the powder in terms of flow properties and packing behavior can be improved. The question if the compactability is improved for the agglomerates compared to the original particles used in the preparation of the crystallization solution has also been addressed in some studies. It is reported that the agglomerates showed improved compactability (Kawashima et al., 1994; Fachaux et al., 1995b) and reduced capping propensity (Kawashima et al., 2003) compared to the original unagglomerated particles.

Ålander and co-workers (Ålander et al., 2003) have shown that paracetamol agglomerates crystallized from different solvents differ in physical properties in terms of size and number of primary particles and nominal fracture strength. The degree

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Nomenclature

a	compression parameter
a_m	cross-sectional area of the manometer arm
A	cross-sectional area of the compact
A_p	particle projected area
AR	particle aspect ratio
$1/b$	compression parameter
C	degree of compression
$C_{at\ pressure}$	degree of compression at 300 MPa
$C_{remaining}$	degree of compression at the time upper punch detaches from the powder bed
D	tablet diameter
ER	elastic recovery
F	force needed to cause particle breakage
F_t	compression force needed to fracture a tablet
FF	particle form factor
g	standard acceleration of gravity
h_1	stop point an the manometer arm
h_2	start point on the manometer arm
h_{2N}	tablet height at 2N after compaction
$h_{at\ pressure}$	tablet height at maximum pressure
h_t	tablet height
L	height of the compact
P	pressure
P_c	permeability coefficient
P_p	particle perimeter length
P_y	yield pressure
r	particle radius
t	time for airflow
w	tablet weight

Greek letters

δ	density of the manometer liquid
ε	porosity
ε_t	tablet porosity
$\rho_{300\ MPa}$	density of the powder bed at 300 MPa
ρ_{app}	apparent particle density
ρ_{bulk}	bulk density
σ_N	nominal particle fracture strength
σ_t	tablet tensile strength

of agglomeration, expressed as the number of crystals forming the agglomerate, were of an order of magnitude of 2–10 which is considerably lower than obtained when granules are formed from primary particles by wet granulation.

For paracetamol agglomerates formed by crystallization in water it is reported (Fichtner et al., 2005) that the distribution in agglomerate size, obtained by varying the conditions during the crystallization process, had no effect on the compactability of the agglomerates. However, there are hitherto no papers addressing the question if agglomerates of different nominal fracture strength behave differently while processed by confined compression. The aim of this work was to study the effect of the fracture strength of paracetamol agglomerates, prepared by precipitation form different solvents, on their compactability. As a comparison, granules of paracetamol were formed by wet granulation using the same solvents. Two sets of secondary particles with different degrees of agglomeration were thus prepared.

2. Material and methods

2.1. Nomenclature

In this study, two types of secondary particles of paracetamol were prepared: Firstly, cluster formation during precipitation and secondly, cluster formation during convective mixing with a required proportion of liquid. The first procedure is often referred to as crystal agglomeration and the latter as wet granulation. Thus, the first type of secondary particle is hereafter referred to as agglomerate (A) and the latter type as granule (G).

2.2. Preparation of powders

Micronised paracetamol (AstraZeneca, Sweden) with an estimated particle size of 12 μm was used for the preparation of all particles. The particle size was assessed from the powder surface area, experimentally determined according to Blaine (Blaine, 1943) and corrected for slip-flow (Carman and Malherbe, 1950), and an assumed surface to volume shape coefficient of 10 (Heywood, 1954).

2.2.1. Granulation

An amount of 400 g paracetamol (AstraZeneca, Sweden) was poured into a planetary mixer (Kenwood Major, UK) and mixed with a relative mixing speed of 2. 100 g ethanol 99.5% (LS/Ph.Eur. Solveco Chemicals AB, Täby, Sweden), methanol 99.8% (LiChrosolv, Merck, Germany), acetone 99.8% (LiChrosolv, Merck, Germany), or 150 g of a mixture of acetone and deionised water (30/70 w/w) were pumped (Watson Marlow 505s, USA, flow rate: 100 ml/min) to the powder. The mixer was stopped after 2 min of mixing. The granules were dried at room temperature for at least 2 days. The particle size fraction 500–710 μm was obtained by dry sieving using stainless steel laboratory sieves (ASTM test sieves, Retsch, Germany) and a mechanical sieve shaker (Retsch, type RV, Germany). Portions of about 70 g were sampled and sieved for 9 min at a relative vibration intensity of 50. The particle size fraction 500–710 μm was stored at 40% r.h. for at least 7 days before further experiments.

2.2.2. Agglomeration

Four batches of paracetamol were prepared by precipitation from a saturated solution of ethanol 99.7% (Solveco chemicals AB, Sweden), methanol 99.8% (Anala R BDH Laboratory Suppliers Poole, England), acetone 99.5% (Anala R BDH Laboratory Suppliers Poole, England) and acetone/water (30/70 w/w) at 50 °C. Saturated solutions were obtained by dissolving 341.6, 551.2, 172.9, and 308.4 g paracetamol per kilogram ethanol, methanol, acetone and acetone/water, respectively. A 2-l double-walled glass beaker with circulating water between the walls was

used to cool down the solutions from 50 to 10 °C using cooling rates of 0.50 °C/min for methanol, 0.56 °C/min for ethanol and acetone (Julabo FP45, Germany) and 1.11 °C/min for acetone/water (Julabo FP50, Germany). The beaker was equipped with baffles and a propeller shaped impeller was used for stirring. In all cases, the agitation rate was 400 rpm (RW 20 DZW Janke & Kunkel, Germany). At 10 °C, the agglomerates were separated from the solution by filtration and dried at room temperature. The particle size fraction 500–710 μm was obtained by dry sieving and stored at 40% r.h. for at least 7 days before further experiments.

2.3. Bulk density and apparent density

A variable amount of powder (0.7–4.8 g) was poured into a graduated 10 ml cylinder (20 °C, scale: 0.1 ml) and the bulk density (ρ_{bulk}) ($n = 6$) was calculated from the volume and the weight of the powder.

The apparent particle density (ρ_{app}) of each powder was determined using a helium pycnometer (AccuPyc 1330, Micromeritics, USA) ($n = 3$).

2.4. Single particle characterization

2.4.1. Particle dimensions

Pictures of at least 30 particles of each powder were taken using a CCD camera (Olympus DP 50 CCD, Japan) connected to a light microscope (Olympus Vanox, Japan). Digital images with a pixel resolution of 1.8 μm/pixel were acquired at 5× magnification. For each particle the projected area (A_p), the perimeter length (P_p), the form factor (FF) and the aspect ratio (AR) were determined by using the non-commercial software ImageJ 1.31v and its plug-in "Shape Descriptors" (both available at http://rsb.info.nih.gov/ij/, National Institutes of Health, USA). A steel sphere (SKF, Sweden) with a diameter of 1 mm and an assumed circularity of 1.00 was used as reference (Eriksson et al., 1993). According to the software specification the form factor and the aspect ratio were calculated using the following equations (Cox, 1927):

$$FF = \frac{4\pi A_p}{P_p^2}$$

and

$$AR = \frac{\text{Major axis}}{\text{Minor axis}}$$

Additionally, the radius (r) of a circle of corresponding area was calculated in the following way:

$$r = \sqrt{\frac{A_p}{\pi}}$$

2.4.2. Nominal particle fracture strength

Single particles were fractured in a materials testing machine (Texture analyzer TA-HDi, Stable Micro Systems Ltd., UK), using a 5 kg load cell (0.98 mN display resolution) and a flat faced cylindrical 6 mm steel punch. Measurements were made on about 50 particles one by one from each batch at a loading rate of 3 mm/min (0.05 mm/s). The recorded force value increased until the first major breakdown of the agglomerate occurred. At that point, a drop in the force value was obtained resulting in a peak. The agglomerate strength was determined as the force required to cause the first particle breakage (first peak). Particle breakage was considered to have occurred when the force dropped below the threshold value which was set to 9.8 mN. The program "Texturexpert exceed 2.16" was used to analyze collected data.

From the mean projected area and the mean force (F) needed to cause breakage the nominal particle fracture strength (σ_N) was calculated as follows:

$$\sigma_N = \frac{F}{A_p}$$

2.4.3. Degree of agglomeration

For the agglomerates the number of crystals per agglomerate designated as C/A number was estimated as reported earlier by Ålander and co-workers (Ålander et al., 2004). For single crystals the C/A number is equal to 1. Agglomerates consisting of two or more crystals are characterized by C/A numbers higher than 1.

The number fraction of particles consisting of less than two crystals per particle, i.e. the number fraction of unagglomerated crystals, was used to derive the degree of agglomeration. The degree of agglomeration is high for agglomerates with a low number fraction unagglomerated crystals and low for agglomerates with a high number fraction unagglomerated particles. For the granules the number of crystals per particle was roughly estimated from the relation of the dimensions of the raw material and the produced granules.

2.5. Powder compression

A materials testing machine (Zwick//Roell Z100, Germany) equipped with flat-faced circular punches (diameter of 11.3 mm) was used to apply a maximum pressure of 300 MPa to 300 mg powder beds ($n = 3$ for each batch). The movable upper punch was connected to a 100 kN load cell and an external extensometer was used to record the upper punch position. The lower punch and the die were stationary mounted to the lower grip. At a pre-load of 2 N compression speed was set to 25 mm/min. Data collection started at a force of 100 N. Upper punch position and pressure data were monitored and collected by the software "testXpert V11.0" and saved in intervals of 10 N. To assess the elastic deformation of the punches and the punch holder punch deformation curves were recorded by pressing the punches against each other at the compression speed used in the experiments. System deformation data ($n = 3$) was recorded and force-displacement curves were plotted. Except for the initial part at low pressures the force-displacement curves showed linearity. The equation $y = k_a x + l_a + l_b e^{(-k_b x)}$ where the exponential term accounts for the initial curvature was fitted to the deformation data and values for k_a, k_b, l_a and l_b were obtained. The punch displacement data obtained from powder compres-

sion was corrected for the system deformation error, calculated with the above equation, to assess the correct compact height. The system deformation was approximately 0.5 μm/MPa.

2.5.1. Heckel parameter

The in die compression parameter P_y reflecting the particle deformability during compression was derived from the Heckel equation (Heckel, 1961b, 1961a):

$$\ln\left(\frac{1}{\varepsilon}\right) = \frac{P}{P_y} + \text{intercept}$$

where ε is the porosity of the compressed powder bed at applied pressure P and P_y the yield pressure. P_y was determined by linear regression for pressures between 50 and 150 MPa. This interval corresponds to the linear region of the plot and spans 1000 data points.

2.5.2. Kawakita parameters

The compression parameters, $1/b$ and a, were derived from the Kawakita equation (Kawakita and Lüdde, 1971):

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

where C is the degree of compression of the powder bed at applied pressure P. The compression parameter a reflects the total degree of compression at infinite pressure and the reciprocal of the compression parameter b, $1/b$, is considered as an indication of deformation or failure stress of the particles (Kawakita et al., 1977; Adams and McKeown, 1996; Nicklasson and Alderborn, 2000). The parameters a and $1/b$ were determined from the equation obtained by linear regression in the pressure interval 1 to 300 MPa. This interval corresponds to the linear region of the plot and spans 3000 data points.

2.5.3. Degree of compression

The degree of compression of the powder beds at a load of 300 MPa ($C_{\text{at pressure}}$) was calculated by the following equation:

$$C_{\text{at pressure}} = \frac{\rho_{300\,\text{MPa}} - \rho_{\text{bulk}}}{\rho_{300\,\text{MPa}}}$$

where $\rho_{300\,\text{MPa}}$ is the density of the powder bed at 300 MPa calculated from the dimensions of the powder bed at that pressure and the apparent density of the material.

2.5.4. Elastic recovery

The elastic recovery (ER), which describes the percentage of axial expansion of a compact, was calculated from the tablet height at 2 N (h_{2N}), the pressure at which the punch is considered to lose contact to the powder bed surface and the height at maximum pressure ($h_{\text{at pressure}}$) according to following equation:

$$ER(\%) = \frac{h_{2N} - h_{\text{at pressure}}}{h_{\text{at pressure}}} 100$$

The degree of compression at the time the upper punch detached from the compact will be referred to as $C_{\text{remaining}}$ and used as an indicator for the permanent deformation of the particles.

2.5.5. Permeability coefficient

The materials testing machine (Zwick//Roell Z100, Ulm Germany) used as described above, was used to apply a pressure of 20 MPa to a powder bed poured into a die that could be connected to a Blaine apparatus as described earlier (Alderborn et al., 1985). The permeability coefficient (P_c) was calculated using the following equation:

$$P_c = \frac{\ln(h_2/h_1) L a_m}{A t 2 \delta g}$$

where h_2 and h_1 are the start and stop points on the manometer arm, L is the height of the compact, a_m the cross-sectional area of the manometer, A the cross-sectional area of the compact, t the time for air flow, δ density of the manometer liquid and g the standard acceleration of gravity. The distance between the punches at 2 N during the upward movement of the upper punch was chosen as compact height L.

2.6. Powder compaction and tablet characteristics

Tablets of 300 mg (granulated powders) and 400 mg (agglomerated powders) were prepared with an instrumented single punch press (Korsch EK 0, Germany) equipped with circular (diameter of 11.3 mm) flat-faced punches at applied pressures between 30 and 150 MPa. For each tablet, the powder was poured manually into the die, which was pre-lubricated by spreading magnesium stearate powder (Kebo, Sweden) on the punch and die surfaces with the aid of a small paint brush in-between every powder compression. The lower punch was stationary during compression and the upper punch machine driven, i.e. the machine was started when the upper punch was in its upper most position relative to the die. The compaction pressure was recorded for each tablet and a variation in compaction pressure of ±3% of the nominal value was accepted.

The porosity of the tablets (ε_t) was calculated from the apparent particle density (ρ_{app}) and the diameter (D), height (h_t) and weight (w) of each tablet in the following way:

$$\varepsilon_t = 1 - \frac{4w}{\pi h_t D^2 \rho_{app}}$$

The compression force (F_t) needed to fracture the tablets along their diameter was determined in a materials testing instrument (Holland C50, UK) at a loading rate of 1 mm/min. The tablets generally failed in tension and the tensile strength of the tablets (σ_t) was thereafter derived according to (Fell and Newton, 1970), i.e.:

$$\sigma_t = \frac{2F_t}{\pi h_t D}$$

Some of the tablets formed at the highest compaction pressure tended to laminate during strength testing and the transformation into a tensile strength is not correct. Nevertheless, to simplify the comparison, all data are presented as a tensile strength.

Table 1
Results of the ANOVA analysis

	D.f.	Sum Sq.	Mean Sq.	*F* value	Pr (>*F*)
a. Bulk density					
Solvent	3	0.0101	0.0034	27.76	<0.001
Method	1	0.1165	0.1165	957.67	<0.001
Solvent:method	3	0.0313	0.0104	85.67	<0.001
Residuals	39	0.0047	0.0001		
b. Fracture force					
Solvent	3	0.0033	0.0011	3.73	0.011
Method	1	0.0457	0.0458	153.50	<0.001
Solvent:method	3	0.0119	0.0040	13.26	<0.001
Residuals	445	0.1327	0.0003		
c. 1/*b*					
Solvent	3	0.8631	0.28770	875.08	<0.001
Method	1	0.3799	0.37989	1155.51	<0.001
Solvent:method	3	1.1758	0.39194	1192.16	<0.001
Residuals	16	0.0053	0.00033		
d. $C_{remainig}$					
Solvent	3	0.0037	0.0012	87.20	<0.001
Method	1	0.0393	0.0393	2804.24	<0.001
Solvent:method	3	0.0111	0.0037	263.36	<0.001
Residuals	16	0.0002	0.0000		
e. Permeability coefficient					
Solvent	3	2.13×10^{-5}	7.11×10^{-6}	33.47	<0.001
Method	1	6.87×10^{-5}	6.88×10^{-5}	323.48	<0.001
Solvent:method	2	1.80×10^{-5}	8.99×10^{-6}	42.27	<0.001
Residuals	14	2.98×10^{-6}	2.13×10^{-7}		

3. Results

For this study particles were prepared by two different particle preparation methods: wet granulation and crystal agglomeration from a saturated solution by cooling. As granulation and agglomeration liquids four different organic solvents were used: ethanol, methanol, acetone and a mixture of acetone and water. After particle preparation, a consistent particle size fraction showing good powder flow properties was chosen.

3.1. Bulk density

ANOVA analysis showed that the preparation method as well as the choice of solvent had a statistically highly significant effect on the bulk density of the powders (Table 1a). By wet granulation powders of lower bulk density were obtained than by crystal agglomeration. The lowest and highest bulk densities were observed for granules made of the acetone/water mixture (0.344 g/cm^3) and agglomerates crystallized from acetone (0.512 g/cm^3), respectively (Table 2).

3.2. Single particle characteristics

3.2.1. Particle dimensions

The particle preparation procedures used gave granules and agglomerates of similar size but of some variation in shape. Analysis of the two-dimensional images of the particles with ImageJ showed that variation within the parameters projected area (A_p), perimeter length (P_p), form factor (*FF*), and aspect ratio (*AR*) was slightly higher for the agglomerates than for the granules. Generally, the form factors obtained for the granules were higher than those obtained for the agglomerates but for all particles they were much lower than one. Therefore, the particles could not be described as spherical. No clear relationship between perimeter length or aspect ratio and the particle preparation procedure could be observed.

3.2.2. Nominal particle fracture strength

By crystallization agglomerates of higher nominal particle fracture strength were obtained than by wet granulation. ANOVA analysis confirmed the significant effect of the particle preparation method on the force needed to break a particle and at the same time the limited effect of the chosen solvent was shown (Table 1b). The highest and lowest nominal particle fracture strength values were observed for agglomerates crystallized from acetone (0.118 MPa) and granules made of the acetone/water mixture (0.022 MPa), respectively.

3.2.3. Degree of agglomeration

For the agglomerates the mean number of crystals per particle ranged between 2.0 and 6.9 while the mean number of crystals per particle of the granules was estimated to be about 100 times larger. Thus, the degree of agglomeration distinguishes clearly between granules with a high degree of agglomeration and agglomerates with a low degree of agglomeration. The SEM pictures (Fig. 1) which show particles of each batch at 50-fold magnification confirm this statement. Within the agglomerates the particles produced from the acetone/water mixture are

Table 2
Characteristics of individual particles and powders

	Projected area (A_p)[a] (mm^2)	Perimeter (P_p)[a] (mm)	Radius of a circle of corresponding area (r)[b] (mm)	Form factor (FF)[a] (mm)	Aspect ratio (AR)[a] (–)	Fracture force (F) (N)	Nominal fracture strength (σ_N)[c] (MPa)	Apparent particle density (ρ_{app}) (g/cm^3)	Bulk density (ρ_{bulk}) (g/cm^3)
$G_{Ethanol}$	0.461 (0.091)	3.31 (0.464)	0.381 (0.036)	0.533 (0.078)	1.37 (0.189)	0.021 (0.014)	0.045	1291 (0,002)	0.400 (0.018)
$G_{Methanol}$	0.445 (0.090)	3.01 (0.364)	0.375 (0.038)	0.620 (0.070)	1.33 (0.223)	0.020 (0.013)	0.046	1292 (0,000)	0.382 (0.006)
$G_{Acetone}$	0.395 (0.106)	2.83 (0.471)	0.352 (0.047)	0.622 (0.072)	1.34 (0.144)	0.014 (0.010)	0.036	1292 (0,001)	0.387 (0.009)
$G_{Acetone/water}$	0.413 (0.112)	3.02 (0.417)	0.360 (0.047)	0.567 (0.087)	1.40 (0.220)	0.009 (0.006)	0.022	1292 (0,000)	0.344 (0.007)
$A_{Ethanol}$	0.428 (0.126)	3.42 (0.556)	0.366 (0.053)	0.462 (0.087)	1.45 (0.240)	0.027 (0.016)	0.062	1289 (0,001)	0.420 (0.007)
$A_{Methanol}$	0.463 (0.102)	3.42 (0.426)	0.382 (0.043)	0.499 (0.071)	1.49 (0.315)	0.035 (0.022)	0.076	1293 (0,000)	0.477 (0.009)
$A_{Acetone}$	0.385 (0.091)	3.05 (0.492)	0.347 (0.042)	0.524 (0.074)	1.37 (0.217)	0.045 (0.025)	0.118	1291 (0,000)	0.512 (0.014)
$A_{Acetone/water}$	0.397 (0.099)	2.86 (0.405)	0.353 (0.043)	0.619 (0.115)	1.31 (0.190)	0.038 (0.020)	0.095	1292 (0,000)	0.502 (0.011)

Mean values, standard deviation in parenthesis.
[a] Determined by ImageJ.
[b] Calculated from the projected area.
[c] Calculated from the projected area and the force needed for breakage.

Table 3
Degree of agglomeration

	C/A < 2 %	C/A number median
A_{EtOH}	7.9	6.9
A_{MeOH}	11.0	5.7
$A_{Acetone}$	9.2	6.6
$A_{Acetone/water}$	50.5	2.0

remarkable for their low number of crystals per particle and thus for their low degree of agglomeration (Table 3).

3.3. Compression mechanisms

The values obtained from the compression experiments are compiled in Table 4 and described in the following.

3.3.1. Heckel parameter

Yield pressure values (P_y) were obtained for both granules and agglomerates within the pressure range 50–150 MPa. The values can easily be grouped according to the particle preparation procedure. By wet granulation particles of clearly higher yield pressure were obtained than by crystal agglomeration.

3.3.2. Kawakita parameters

The compression parameters a and $1/b$ were derived from equations obtained by linear regression of the Kawakita profiles. For both granules and agglomerates the values of the compression parameter $1/b$ were in the same order of magnitude but nevertheless, ANOVA analysis showed a highly significant effect of the solvent choice and the preparation method on this parameter (Table 1c). Generally, higher values were obtained for granules than for agglomerates with the exception of $G_{Acetone/water}$ for which the lowest value was obtained and $A_{Acetone}$ for which the highest value was found.

3.3.3. Degree of compression

For all powders the degree of compression at 300 MPa ($C_{at\ pressure}$) equals the values for a, which reflect the degree of compression at infinite pressure. For the granules a higher degree of compression was observed than for the agglomerates.

3.3.4. Elastic recovery

The elastic in die recovery during the period of maximum pressure and the last measurable pressure (2 N) before the upper punch detached from the powder bed surface was approximately 7%. Generally, elastic recovery was higher for agglomerates than for granules and highest for the powders prepared with the acetone/water mixture. The only exceptions were the powders prepared with ethanol. They showed an equal ability to elastic recovery. ANOVA analysis indicated a highly significant effect of the solvent choice and the preparation method on the permanent deformation ($C_{remaining}$) of the particles (Table 1d).

3.3.5. Permeability coefficient

The air permeability of powder beds that were exposed to a pressure of 20 MPa was measured and the air permeability coef-

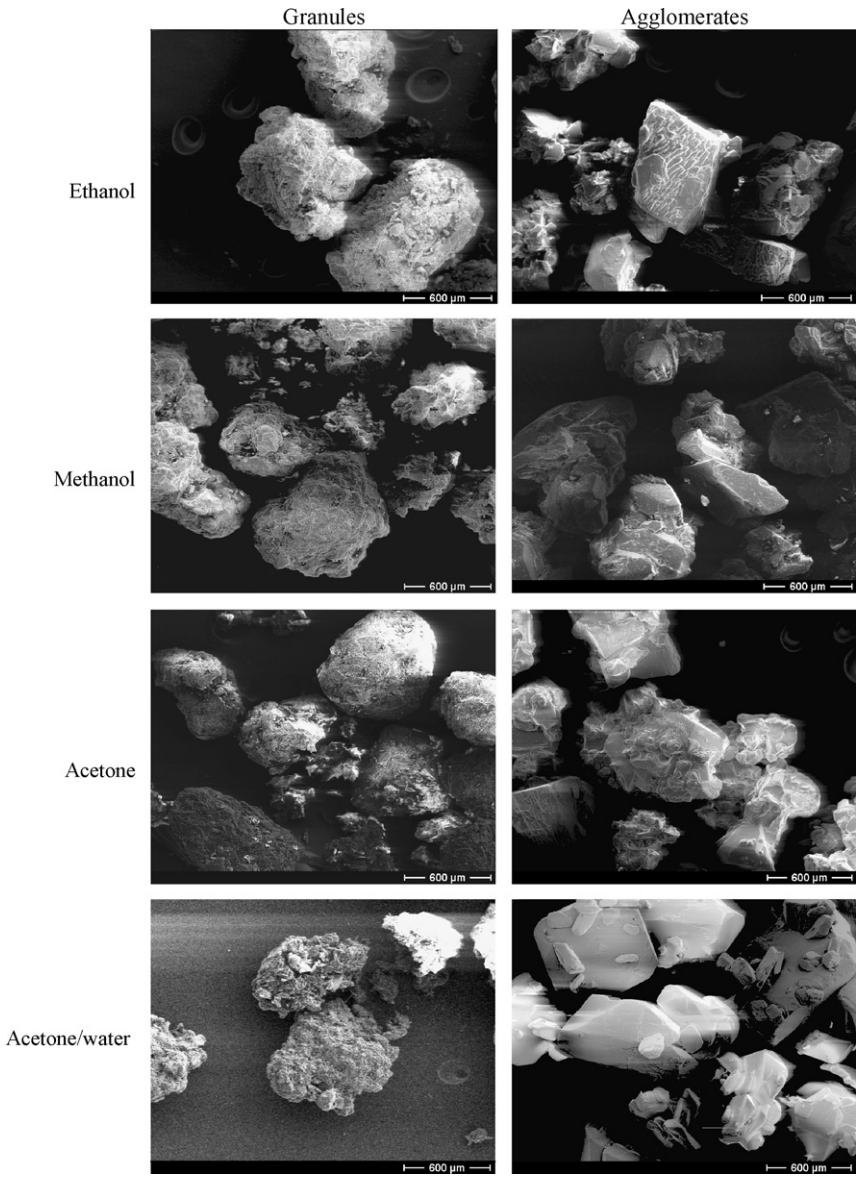

Fig. 1. SEM pictures of paracetamol granules and agglomerates.

ficient was calculated. The mean resistance to gas flow through the powder bed was clearly higher for the powder beds made of agglomerates than for the powder beds made of granules. At 20 MPa it was impossible to form a coherent powder bed of the acetone/water granules. ANOVA analysis demonstrated the highly significant effect of the used solvent as well as the chosen preparation method on the permeability coefficient (Table 1e).

3.4. Tablet characteristics

For all powders tablet porosity decreased with increasing compaction pressure. The porosity-compaction pressure profiles discriminated between the two types of particles while in-between each group the profiles coincided with higher porosity for tablets made of granules (Fig. 2).

Tablet tensile strength of ejected tablets made of granules or agglomerates was generally very low. The highest

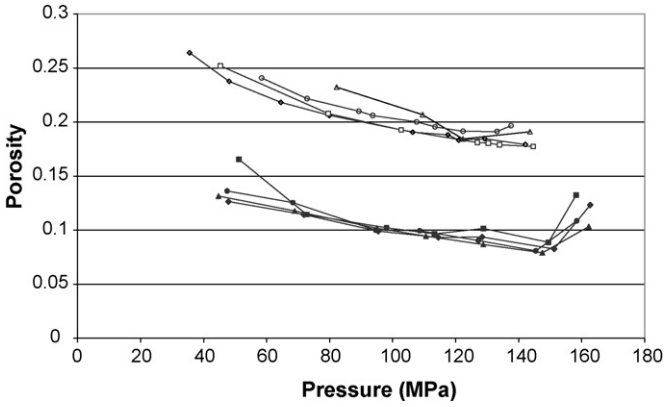

Fig. 2. Porosity of tablets made of granules (◊ ethanol, □ methanol, △ acetone, ○ acetone/water) and agglomerates (♦ ethanol, ■ methanol, ▲ acetone, ● acetone/water) as a function of applied compaction pressure.

Table 4
Characteristics of powder compression properties

	P_y [a] (MPa)	R^2 Heckel plot (–)	1/b [b] (MPa)	R^2 Kawakita plot (–)	ER [c] (%)	P_e [d] (Ns^2/m) × 10^5	a (–)	$C_{at\ pressure}$ (–)	$C_{remaining}$ (–)
$G_{Ethanol}$	100.9 (1.413)	0.9997	3.072 (0.015)	0.9997	6.599 (0.667)	3.46 (1.3 × 10^{-1})	0.690 (7.632 × 10^{-4})	0.691 (4.118 × 10^{-4})	0.671 (1.856 × 10^{-03})
$G_{Methanol}$	101.0 (0.715)	0.9997	3.052 (0.007)	0.9997	6.220 (0.149)	3.60 (2.4 × 10^{-02})	0.705 (2.355 × 10^{-4})	0.705 (2.450 × 10^{-4})	0.687 (3.198 × 10^{-04})
$G_{Acetone}$	104.8 (1.387)	0.9997	3.026 (0.026)	0.9997	6.350 (0.300)	2.49 (2.7 × 10^{-02})	0.700 (6.107 × 10^{-4})	0.701 (4.054 × 10^{-4})	0.682 (1.079 × 10^{-03})
$G_{Acetone/water}$	102.6 (0.940)	0.9998	2.669 (0.004)	0.9997	7.429 (0.356)	[e]	0.734 (3.943 × 10^{-4})	0.734 (2.698 × 10^{-4})	0.714 (1.221 × 10^{-03})
$A_{Ethanol}$	85.6 (7.499)	0.9997	2.094 (0.009)	0.9999	6.543 (0.759)	5.03 (1.4 × 10^{-1})	0.677 (1.671 × 10^{-3})	0.678 (1.662 × 10^{-3})	0.657 (1.965 × 10^{-03})
$A_{Methanol}$	85.6 (1.097)	0.9998	2.811 (0.011)	0.9998	7.047 (0.285)	7.32 (1.5 × 10^{-1})	0.635 (3.282 × 10^{-4})	0.636 (3.464 × 10^{-4})	0.610 (1.358 × 10^{-03})
$A_{Acetone}$	83.5 (3.260)	0.9997	3.129 (0.034)	0.9997	7.442 (2.590)	8.94 (1.16)	0.609 (8.799 × 10^{-4})	0.609 (8.476 × 10^{-4})	0.576 (7.527 × 10^{-03})
$A_{Acetone/water}$	82.2 (3.107)	0.9997	2.778 (0.015)	0.9997	8.035 (1.506)	7.47 (2.8 × 10^{-1})	0.616 (9.714 × 10^{-4})	0.617 (7.608 × 10^{-4})	0.587 (6.596 × 10^{-03})

[a] Yield pressure determined in the pressure interval 50–150 MPa.
[b] Kawakita parameter determined in the interval 1–300 MPa.
[c] Elastic recovery.
[d] Permeability coefficient at 20 MPa.
[e] Not determined due to capping.

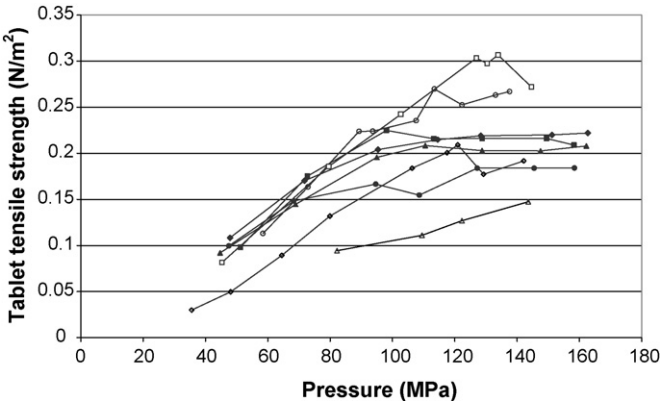

Fig. 3. Tensile strength of tablets made of granules (◊ ethanol, □ methanol, △ acetone, ◯ acetone/water) and agglomerates (♦ ethanol, ■ methanol, ▲ acetone, ● acetone/water) plotted as a function of applied compaction pressure.

tablet tensile strength values obtained for tablets made of the methanol granules were just above 0.3 N/m^2. Coherent compacts were generally obtained although of lower strength than is normally required for tablets. Thus, the focus is on relative effects of the agglomerate and granule properties on tablets strength. With increasing compaction pressure, tablet tensile strength rose to a critical compaction pressure and then decreased or leveled off with further pressure increase. Variation in the evolution of tablet tensile strength with increasing compaction pressure was only observed for tablets made of granules (Fig. 3).

4. Discussion

4.1. Particle characteristics

A consistent sieve fraction of all particles was used in this study and the values derived from the two-dimensional particle projections supported that the particles generally were of the same size. Although the degree of agglomeration was considerably lower for the agglomerates than for the granules, their relative dimensions were similar. It can thus be expected that the bulk voidage should generally be similar but nevertheless, powders of the agglomerates had a higher bulk density than powders of the granules. This difference in bulk density can thus be explained by the assumption that the intra-granular porosity of the agglomerates was lower than for the granules. The nominal particle fracture strength was nearly linearly related to the bulk density (Fig. 4) of the powders and the differences obtained in nominal particle fracture strength could thus at least partly be explained by a variation in intra-granular porosity of the particles. Albeit the particles were generally of similar dimensions, and could be categorized into two groups dependent on their method of preparation. Generally the agglomerates had a lower degree of agglomeration and porosity but were of higher single particle fracture strength than the granules. The relative variation in bulk density and particle fracture strength was similar within the two groups of particles.

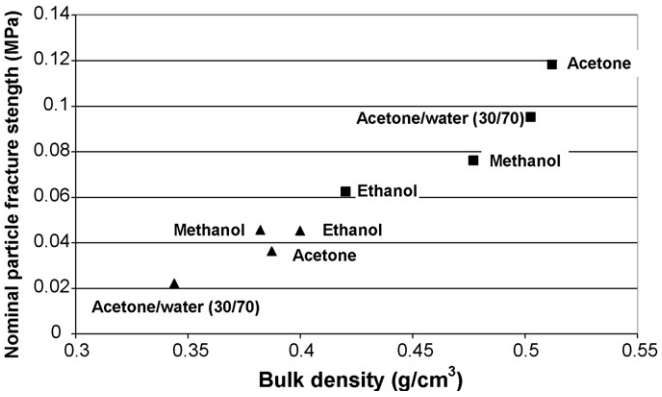

Fig. 4. Nominal particle fracture strength of granules (▲) and agglomerates (■) plotted as a function of bulk density.

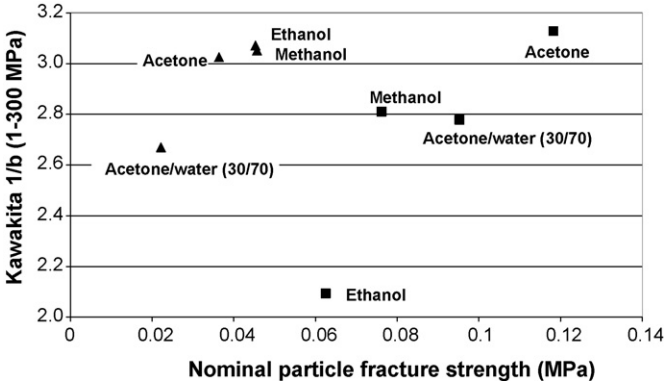

Fig. 5. Kawakita 1/*b* of compacts prepared from granules (▲) and agglomerates (■) plotted as a function of nominal particle fracture strength.

4.2. Compression mechanisms

In earlier studies on the compression of different types of granules, characterized by a good ability to form tablets, it has been proposed that granules tend to keep their integrity while compressed as a powder and permanent granule deformation is to be the single most critical factor for the evolution in tablet micro-structure during compression (Johansson et al., 1995). However, for weak and irregular granules, fragmentation or attrition may also be significant mechanisms in the compression process.

A common approach to derive an indication of the compressibility of a powder is to describe how global tablet properties, such as porosity and volume, depend on the applied pressure during compression. A concentrated way to describe such a relationship is to calculate compression parameters. Two common parameters in this context are the Heckel (P_y) and the Kawakita 1/*b* parameters, both suggested to indicate the failure strength of particles during confined compression.

The relationship between tablet porosity and applied pressure grouped the particles in accordance to their method of preparation but in-between each group, the relationships more or less coincided. The Heckel parameter grouped the particles in the same way and in-between each group, the parameter did not discriminate between particles of different nominal fracture strength.

For the Kawakita parameter 1/*b*, a larger spread in values than for the P_y parameter was obtained and for each type of particle, a positive correlation with the nominal particle fracture strength was obtained (Fig. 5). It seems thus for granules and agglomerates, the Kawakita parameter discriminated between the particles dependent on their nominal fracture strength.

The variation in Kawakita parameter 1/*b* indicated that a variation in failure strength between the agglomerates and granules existed although the final tablet porosity within each group was similar. However, the absolute values for the Kawakita parameter 1/*b* were not of the same order of magnitude as the nominal particle fracture strength values and the interpretation of the parameter is thus difficult. To further investigate the degree of deformation or fragmentation that was expressed during compression, the degree of compression of the powders and the permeability of the tablets formed from them were determined.

Since paracetamol is considered to show an elastic expansion (Malamataris et al., 1996) during unloading, both the degree of deformation during loading ($C_{\text{at pressure}}$) and the remaining degree of deformation ($C_{\text{remaining}}$) were determined. As another indicator of the evolution in tablet micro-structure during compression, the tablet permeability (P_c) was used. $C_{\text{remaining}}$ and P_c are thus used as indicators of the permanent degree of deformation or fragmentation of the particles occurring during compression while the tablet elastic recovery is used as an indication of the elastic particle deformation.

Since the total and permanent degree of compression as well as the permeability of the tablets varied with bulk density and nominal single particle fracture strength (Figs. 6 and 7), it is concluded that a variation in fracture strength of the particles gave a variation in the degree of deformation or fragmentation that was expressed during compression and is also remaining after the compression.

4.3. Compactability

The compactability of a powder is commonly assessed by the relationship between tablet tensile strength and applied compaction pressure. Over a wide range of compaction pressures,

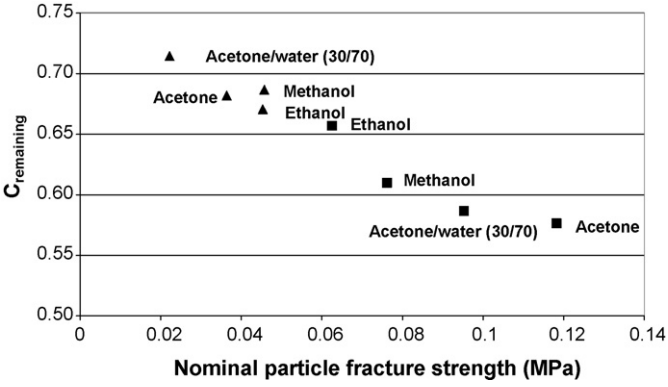

Fig. 6. Kawakita C at 2 N after compaction ($C_{\text{remaining}}$) for compacts prepared from granules (▲) and agglomerates (■) plotted as a function of nominal particle fracture strength.

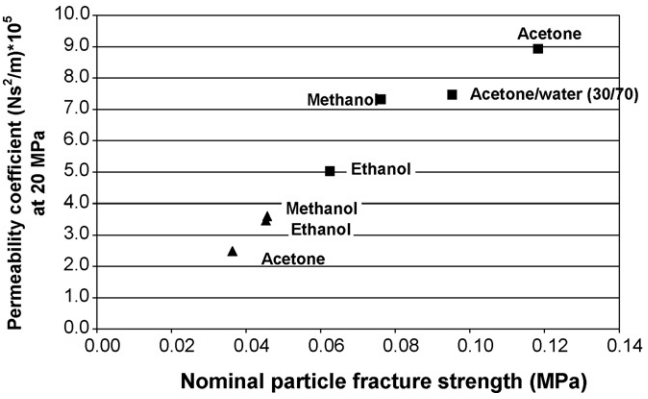

Fig. 7. Permeability coefficient at 20 MPa for compacts prepared from granules (▲) and agglomerates (■) plotted as a function of nominal particle fracture strength.

this relationship is often described as sigmoidal or tri-phasic. Since paracetamol shows poor compacatability and is prone to laminate or cap (Malamataris et al., 1996), the tablet strength levelled off and the tablets subsequently capped at relatively low applied pressures and complete compactability sigmoidal or tri-phasic profiles could not be obtained. The tablets formed were generally of low tensile strength. In the pressure range in which apparently flawless tablets were formed, the granules gave a clearly different evolution in tablet tensile strength dependent on their failure strength while the agglomerates gave similar compactability profiles. Thus, although similar variations in bulk density and failure strength were obtained for the respective type of particles, reflected also in variations in deformation or fragmentation as discussed above, a variation in compactability was obtained only for the granules.

Due to the weak and variable tablet tensile strength and the limited range of increasing tablet tensile strength with pressure, it is difficult to derive measures of the compactability. For the granules, the variation in compactability tended to vary with the particle strength of the granules, i.e. an increased compactability with a decreased bulk density. This conclusion is thus consistent with earlier experiences on the compactability of granular solids (Zuurman et al., 1994). It can thus be hypothesized that the variation in compactability is related to a variation in the degree of deformation that is expressed during compression due to a variation in failure strength of the granules. Thus, permanent deformation is proposed to be the dominant compression mechanism for the granules. The relatively poor correlation between compactability and bulk density may be due to both a difficulty in deriving an indication of compactability and to an effect of the elastic behavior of the particles.

An explanation for the limited variation in compactability obtained for the agglomerates is that the dominant compression mechanism for this type of particles was fragmentation. A variation in the degree of fragmentation affects the evolution in the inter-granular pore system and the number of inter-particulate junctions in the tablet. However, it has been proposed that a variation in the degree of fragmentation has a limited effect on the total area of contact at the inter-particulate junctions and thus on the tablet tensile strength (assuming that some proportionality exists between total inter-particulate contact area and tablet tensile strength) (Eriksson and Alderborn, 1995). A consequence of this discussion is that the dominant compression mechanism differs between agglomerates and granules. A possible explanation is that the degree of agglomeration differs considerably between these two types of particles and that the degree of agglomeration is a factor affecting their compression mechanism.

4.4. Effect of nominal particle strength on the evolution in tablet micro-structure and tensile strength

Two series of powders in the form of clusters of particles were prepared with different physical characters in terms of degree of agglomeration, nominal fracture strength and intragranular porosity. The tableting behavior of the particles was analyzed and an overall interpretation of the data in terms of evolution in micro-structure and tablet tensile strength as a function of applied pressure can be summarized in the following way:

The global tablet porosity reduction during compression and the final tablet porosity of the ejected tablets were independent of the variation in failure strength of both the agglomerates and granules, which indicated that also a reduction in porosity of the granules and agglomerates affected their compressibility. Nevertheless, the evolution in tablet micro-structure was correlated to the particle failure strength, indicating that the degree of deformation and fragmentation that was expressed during the compression phase varied between agglomerates and granules dependent on their failure strength. The evolution in tablet tensile strength was for the granules dependent on their porosity while the compactability of the agglomerates was less affected by their failure strength. Thus, permanent deformation is proposed to be the dominant compression mechanism for the granules while fragmentation is proposed to be the dominant mechanism for the agglomerates. The compression mechanism of granular solids thus depends on both the degree of agglomeration and the particle failure strength.

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