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Abrupt disintegration of highly porous particles in early stage dissolution

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1   **Abstract**

2   Dissolution of highly porous particles is a ubiquitous process in formulation chemistry. Scientific

3   challenges remain unsolved due to the complex of interfacial properties and physical interactions

4   between solid, liquid and gas phases. Two spray-dried powders consisting of sodium sulphate

5   and linear alkylbenzene sulfonate (LAS) were used to investigate the abrupt disintegration

6   mechanism focusing on the residual air in the highly porous particle during wetting stage. Four

7   typical dissolution phenomena were identified through individual particle dissolution

8   experiments using optical microscopy. The images suggest for the first time a link between

9   abrupt disintegration phenomenon and air behaviour. We have examined the hypothesis that, as

10 well as chemical changes occurring during wetting, physical processes can lead to disintegration.

11 Tensile tests of individual particles in both dry and hydrated conditions show significant

12 weakening of the particle strength during hydration. Mathematical simulation shows that fast

13 penetration of water through the open-ended pores compresses entrapped air and increases the

14 internal pressure. Hoop stresses generated by internal pressure are of the same magnitude as

15 breaking forces, suggesting that abrupt disintegration in the early stage of dissolution is driven

16 by air compression.

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1. Introduction

Physical and mechanical properties of spray-dried particles are a result of their porous structure. Controlled release of active ingredients in solid dosage forms is one of the key targets in pharmaceutical and biopharmaceutical industry[1]. Similarly in foods[2, 3] and detergents[4], quick dissolution is desired for these porous particles. The dissolution phenomenon of them can be summarised as: i) wetting - water penetrates into the pores due to capillary force; ii) immersion - powder sinks into water; iii) disintegration - solid bridges between primary particles dissolve; and iv) dissolution - soluble primary particles dissolve[5]. Heavy study in orally disintegrating tablet in pharmaceutics points out that disintegration is one of the effective paths to accelerate the whole dissolution process[6-11]. It could be realised through adding superdisintegrant into the tablets[12-16]. Other approaches include creating a variety of extra channels within the tablet for fast release using 3D printing technology[17].

On the controversy, very few papers have reported the study of disintegration of porous powders[18, 19], especially the mechanism. Researchers tried to define disintegration according to their scenarios. From the macroscopic point of view, Forny et at. defined disintegration as solid bridges dissolving resulting in powder breakage, and illustrated this mechanism schematically in the paper using spray-dried milk powder as research subject [20]. From the molecular point of view, Smrčka et al. defined three mechanisms: (i) *leaching*- the Active Pharmaceutical Ingredient (API) diffuse to solvent; (ii) *surface erosion* -solid bridges dissolve and individual primary particles detach from the granule surface; and (iii) *break-up* - granule breaks into various smaller particles abruptly[19, 21]. The reason behind the vague definition is the diverse particle shape, size, surface area, pore structure, composition and strength. All these factors contribute to the complex dissolution process.

1   The dissolution phenomena of porous powders is related to their physical and chemical

2   properties (e.g., particle size, density, porosity, and chemical composition) and the surrounding

3   liquid (e.g., liquid surface tension, viscosity, density, temperature, and diffusion/convection).

4   Hence, disintegration can be described differently. In this paper, we focus on the disintegration

5   defined by Forny et al. which is similar to the third mechanism of Smrčka et al. In particular, we

6   study the abruptly disintegration of porous particle in its early stage dissolution. This study has

7   been limited in literature due to the existence of bubbles in the surrounding liquid, which affects

8   the accuracy of optical observation and laser detection in bulk particle dissolution. Therefore, it

9   is necessary to investigate through single particle approach using statistic study of individual

10   particle mechanical strength and the force breaking them.

11   The mechanical strength of particles in both dry and wet powders has been reviewed by a

12   number of researchers, including measurement methods and theoretical considerations[22, 23].

13   However, given the inherent heterogeneity of particles, mechanical properties cannot be

14   described by continuum properties. In most cases, the mechanical strength of a porous particle is

15   affected by its tensile strength, yield strength, fracture toughness etc., and can be obtained using

16   different loading conditions for example tensile, shear and compression[23]. Sophisticated

17   analysis regarding the fracture of agglomerated powder mainly concerns the size and shape of

18   primary particles[24, 25], moisture in agglomerate[26, 27], and the strength of connecting points

19   between primary particles[25, 27-29].

20   The force breaking particles comes from various states. In a compressed tablet, disintegration

21   force comes from the interaction between water and disintegrant[30]. Detailed study shows that

22   disintegration only happens when a certain amount of disintegration force is developed[31] and

23   this force linearly depends on the amount of water absorbed by the tablet[30]. In a flow regime,

1   particles experience numerous forces such as the collisional force between particles, the drag

2   force from the frictional interaction between fluid and particles, and the shear force from viscous

3   liquid moving around particle surface[32]. Among all these, only the shear stress has been

4   related to particle disintegration[33].

5   The dissolution of a porous particle involves gas, liquid and solid, and capillary action plays a

6   critical role in particle wetting. The generated capillary pressure across the meniscus caused by

7   immiscible fluids (including liquid and gas) has been found to be highly related to pore size,

8   liquid surface tension and pore surface energy[34-40]. And such an pressure can deform the

9   walls of nano- and micro-channels[41, 42]. In the present work, the mechanism of abrupt

10   disintegration has been investigated using two spray-dried powders, focusing on the driving

11   force and particle tensile strength. The sample powders were manufactured and provided by our

12   industrial partner aiming at developing future detergent powders in developing countries. The

13   investigated two samples have identical composition with only structural difference (e.g.

14   porosity, pore size distribution, undissolved salt in the void space), so the effect of particle

15   structure on dissolution can be distinguished from their composition. In this paper, particle

16   structure was characterized by microscopic techniques and mercury porosimetry. Disintegration

17   phenomena were identified by observing individual particle dissolving using optical microscopy.

18   Numerical simulation of the particle internal force caused by compressed air during wetting

19   stage was made, and compared to experimental results of the breaking force of both dry and

20   hydrated particles measured by micromanipulation. The relationship between the calculated hoop

21   stress and the measured tensile strength supports the hypothesis that the Young-Laplace pressure

22   from the gas phase is a major factor for the abrupt disintegration of porous powders during

23   dissolution.

2. Experimental methods

2.1 Materials

Two spray-dried powders (Batch code IM-14-000848 and IM-14-000849) supplied by Procter & Gamble were used. Sample 1 was made by mixing 29.1 % of 45 % linear alkylbenzene sulfonate (LAS) paste (LAS in water), 51.9 % of sodium sulphate and 35 % of water (including water from LAS paste); this mix was then pumped to spray-dry tower to form agglomerates at 220 °C using co-current hot air. Sample 2 was made by the same procedure but different formulation which was 16.9 % of the 45 % LAS paste, 30.4 % of sodium sulphate and 62 % of water (including water from LAS paste). This resulted in an identical composition ratio in the two dry powders but different porosities.

2.2 Particle characterization

Particle surface morphology was analysed using a scanning electron microscope (SEM) equipped with a backscatter detector (Hitachi TM3030, U.S.A) operated at 15 kV in low vacuum mode. Two magnifications (50 and 200 times) were used. Internal structure was analysed using an X-ray Microtomography (XRT) system (Skyscan 1275, Bruker microCT, Belgium). Particles were scanned at 60 kV and 80 μA. Scanning was performed by 180° rotation around the vertical axis with a rotation step of 0.2°. Images were reconstructed to provide axial cross-sections of their inner structure and pore size distribution on a single particle. Bulk density and porosity were measured using a mercury porosimeter (Micromeritics Autopore IV, GA) using intrusion pressures from 0.1 psi to 60,000 psi.

2.3 Experimental set up of dissolution test

1 Particles were first sieved into size ranges, <200, 200-500, 500-800 and 800-1000 μm. 50

2 individual particles from each size range were put into water at 20 °C and monitored using the

3 microscope (Leica Microsystem Z16, Germany) for the dissolution test. Dissolution temperature

4 was controlled while the water container (a glass slide with a cavity) sat on a Peltier stage

5 (Linkam Scientific Instruments Ltd. LTS120, United Kingdom). Image sequences were recorded

6 at 5 frames per second and analysed using open source software ImageJ.

7 *2.4 Experimental set up of tensile breaking*

8 The breaking force of a single particle was determined by micromanipulation technique[43]. A

9 glass probe with a diameter of 300 μm mounted on a force transducer (Aurora Scientific Inc.

10 400A, 402A, Canada) was glued to one side of a particle by superglue (Loctite®, Ethy 1 2-

11 cyanoacrylate). The transducer was fixed to a fine micromanipulator driven horizontally by a

12 step motor. The other side of the particle was glued to another glass probe fixed on a manual

13 micromanipulator. After the superglue dried, the particle was pulled apart with the glass probe

14 travelling at 2.85 μm/s and the signal from the transducer was recorded to a computer (process

15 (a) (b) (c) in Figure 1). 20 individual particles from each size range 200, 500 and 800 μm, were

16 tested in this set up when particles were dry. In a second approach, shown in Figure 1(a) (b) (d)

17 (c), a 0.3 μL water droplet was pre-loaded on a hydrophobic substrate and moved upwards to

18 contact the particle for 3 s. The micromanipulation method was then used again to measure the

19 breakage force, using same probe travelling speed. A room environment of 35 % humidity and

20 20 °C temperature was presented. Further details of this technique are described elsewhere[43].

21 **Figure 1.**Schematic of tensile strength experiment set up. Process (a) (b) (c) refers to tensile test

22 for a dry particle. Process (a) (b) (d) (c) refers to tensile test for hydrated particle in which a

1 water droplet was pre-loaded on a hydrophobic substrate and moved upwards the particle, and

2 the particle was pulled apart by the probes after being wetted for 3 s.

3. Results and Discussion

3.1 Particle structure characterization

5 Spray-dried powders normally have hollow or semi hollow structures consisting of shell or film

6 regions with different physical and chemical properties and a large central void space[44]. In

7 Figure 2, SEM images of powder samples 1 and 2 at lower magnification (Fig. 2 (a) and (c))

8 show that both two samples have a wide particle size distribution, from tens to hundreds of

9 micrometres. Particles over 200 μm are often agglomerates of smaller ones; this is a typical size

10 range when spray-dried powders start to agglomerate[44]. Higher magnification (Fig. 2 (b) and

11 (d)) reveals that different sized holes appear on particle surfaces, from several micrometres to up

12 to 200 μm. Small spherical particles (< 100 μm) can be seen attached to the surface of sample 2,

13 whereas significantly fewer attach to sample 1, resulting in different surface roughness.

14 In Figure 2 (e) and (f), XRT results of bulk particles cross-sections reveal that the particles have

15 a hollow-shell structure (in agreement with literature[44]). In the images, white is solid and black

16 is air. Higher magnifications of sample 1 show that a thin shell of about 10 to 50 μm thickness

17 wraps around pebble-looking undissolved salt crystals (Na_2SO_4), while in sample 2 a much

18 thicker (about 10 to 100 μm) shell forms a foam structure with almost no undissolved salts

19 inside. Mercury porosimetry confirms that the porosity of sample 1 is 78 ± 2 %, and sample 2 is

20 85 ± 3 %. The structure of particles is highly related to their composition and manufacturing

21 process. The two samples differ only in water concentration (62 wt % in sample 2, 35 wt % in

22 sample 1). Higher water content gives higher porosity, less undissolved salt and thicker shell

1 structures in the dry powders. In addition, the ratio of salts (Na_2SO_4) to surfactant (LAS) within

2 the shell matrix could be significantly lower in sample 1 than sample 2, which might affect the

3 release rate during dissolution and also the mechanical strength.

4 **Figure 2.** Particle structure characterization: (a) (b) are SEM images of sample 1 at low and high

5 magnification, (c) (d) are sample 2; (e) and (f) are XRT cross-sections of bulk particles from

6 sample 1 and 2, the three images on the right side are different cross-sections of the particle

7 circled in (e) and (f) respectively.

8 *3.2 Disintegration phenomenon*

9 Four different types of dissolution process have been observed, summarised in Figure 3. Each

10 row represents one type.

11 • Type I: Early disintegration: the particle breaks up abruptly after immersion in water for

12 2.2 s; meanwhile a large bubble (bubble size greater than one fourth of particle size)

13 appears and attaches to it. Then, particle dissolves and shrinks until dissolution is

14 complete. Disintegration can be categorised to Forny et al.'s definition of

15 disintegration[20] and also the third definition from Smrčka et al.[19].

16 • type II: particle dissolves without immediate disintegration: a large bubble appears in the

17 middle of the process (here 103.8 s) but without abrupt disintegration.

18 • type III: particle swells and then continuously dissolves: a large bubble appears at the end

19 of the process (here at 248.2 s).

20 • type IV: gradual dissolution without any large bubble formation or abrupt disintegration.

21 The observed phenomena suggest that early stage abrupt disintegration is strongly related to the

22 formation of the large bubbles. They always appear with obvious particle disintegration in the

1   early stage, indicating that gas plays an important role in the wetting stage. Our hypothesis is that

2   water is absorbed into the particle through the open-ended pores, compressing the residual air,

3   and forming an internal stress in a very small time scale. Meanwhile, the solid bridges between

4   the primary particles weaken continuously by chemical action, so the particle breaks abruptly.

5   **Figure 3.** Four typical dissolution phenomena summarized in image sequences of which

6   particles dissolve in water at 20 °C. First row A ~ E type I, sample 1 particle breaks abruptly at

7   2.2 s; Second row (a) ~ (d) type II, sample 2 particle dissolves without abrupt disintegration;

8   Third row I ~ V type III, sample 2 particle swells slightly instead of breaking abruptly; Fourth

9   row (i) ~ (v) type IV, sample 1 particle dissolves without breaking or swelling.

10   Figure 4 summaries the early stage abrupt disintegration time versus the total dissolution time as

11   a function of particle size. Clearly no disintegration was detected for samples smaller than 300

12   μm in diameter. When particles are larger than 300 μm, both sample 1 and 2 show abrupt

13   disintegration in the early stage, and they happen in the very short period time, less than 7% of

14   the total dissolution time. Sample 1 particles disintegrated more often than sample 2 particles at

15   all size ranges, which might be due to the differences of particle structure, ingredients dispersion,

16   porosity, and pore size between these two samples.

17   **Figure 4.** Ratio of abrupt disintegration time t_d to total dissolution time t_t as a function of

18   particle size for the two samples. Solid dots represent sample 1 and hollow dots represent sample

19   2.

20   *3.3 Tensile strength*

21   Whether internal forces due to water imbibition can break the particle depends on the particle

22   mechanical properties. The micromanipulation technique was first used to test the particle tensile

1 strength under dry conditions. Figure 5(a) is the optical image sequences of a particle breaking

2 under the test. In the middle of each image is the dry particle, diameter ca. 500 μm, glued to two

3 probes horizontally. The images clearly show the development of the fracture, starting from the

4 edge of the visible hole in the middle, developing a second fracture on the other side of the hole,

5 and eventually fully breaking (fractures are shown by the dashed circles in the images).

6 **Figure 5.**Tensile testing results: (a) image sequences of particle breaking, (b) and (c) plots of

7 particles 1 and 2 breaking forces in dry condition at different size ranges. The embedded pictures

8 are typical breaking force versus displacement curve.

9 Figure 5(b) and (c) show sample 1 and 2 particle breaking forces in dry condition for different

10 sizes. Typical examples of breaking force changes versus probe displacement are embedded. The

11 force on sample 1 increases sharply to the peak value and immediately decreases to zero, while

12 on sample 2 it continuously remains on the top and then slowly decreases to zero. This different

13 breaking behaviour may be related to particle shell structure, and similar behaviour has been

14 reported in the literature[22]. The breaking force of particles will be determined by the peak

15 value, and Figure 5 shows that the force increases with particle size for both samples. A wide

16 distribution of breaking force was detected at each size range. For sample 1, the breaking force is

17 distributed between 9-25 mN at 200 μm, 15-40mN at 500 μm, and 25-41 mN at 800 μm. While

18 for sample 2, the distribution is between 3-22 mN at 200 μm, 18-40 mN at 500 μm, and 55-126

19 mN at 800 μm. In many cases in agglomerated powders, the strength is transmitted by forces at

20 the points of contact between the primary particles[22]. The detected breaking force is highly

21 related to the angle between fracture plane and the tensile force. The maximum tensile stress is

22 developed normal to the loaded diameter and tends to pull the powder in half[45]. As fracture

23 occurs by crack extension at the flaw with the most unstable orientation towards the surface[46],

1 and the agglomerate tensile strength could be the sum of all inter-particulate forces across the

2 failure surface[25, 47], it has been pointed out that large standard deviations would be

3 expected[48, 49]. The wide distribution detected for our samples thus agrees with the literature.

4 Sample 2 has a higher strength than sample 1. At 200 µm, sample 2 has similar shell structure to

5 sample 1 but without undissolved salt attaching to the inner surface. For particles larger than 200

6 µm, agglomeration occurred and more complex and random structures were formed which could

7 strengthen the connecting point in the shell. The Breaking force nearly doubled from size 200 to

8 500 µm for both samples. The foam shell structure in sample 2 dominates the particle strength,

9 breaking force increases significantly at size 800 µm, almost three times higher than sample 1.

10 The results indicate that particle strength strongly depends on its shell structure and size. Large

11 agglomerated particles need higher forces to break.

12 In Type I dissolution, abrupt disintegration happens after the particle contacts water and is

13 hydrated for a very short period of time. The bridges of spray-dried powders are built of partially

14 dehydrated amorphous substances and their tensile strength depends on the temperature and

15 moisture content of the material as well as the strain rate applied during the mechanical property

16 measurement[20]. Mechanical strength of hydrated particles can be much weaker than in dry

17 condition depending on the water saturation in the agglomerate[26]. For example, Figure 6

18 shows an 800 µm sized particle breaks after being hydrated for 3 s. Quite different from the dry

19 test, multiple peaks were detected throughout the breakage. For sample 1, a maximum breaking

20 force of 9 mN was observed, which is approximately 22 ~ 36 % of the dry ones at this size. The

21 breaking force of sample 2 reduced even further. A maximum of 18 mN was detected which is

22 only 14 % of the highest value and 33 % of the lowest value in dry condition. Such a significant

23 reduction (more than 60 % in average) provides strong evidence that after particle being wetted

1   by water, their mechanical strength reduced drastically, so particles can be broken by a much

2   lower internal force.

3   **Figure 6.** Hydrated particle tensile breaking force of (a) sample 1 and (b) sample 2. Particle size

4   is 800 μm in both graphs.

5   4. **Type I breakage mechanism**

6   *4.1 Calculation of internal pressure generated by capillary penetration*

7   To explain the abrupt disintegration in the early stage of dissolution, a simple mathematical

8   model was built to estimate the internal pressure increase due to water imbibition.

9   Particles have a hollow-shell structure with a variety of non-uniformly sized pores (see pore size

10   distribution in Figure 1 in supplementary material). The schematic is illustrated in Figure 7 (a)

11   for sample 1 and (b) for sample 2. To study particles with such structures, a simplified spherical

12   geometry is built in Figure 7 (c), including a shell, a hollow core and a number of uniformly

13   open-ended pores. A few assumptions have been made to further simply the simulation, e.g.

14   water penetrating through all the pores evenly in Figure 7(d), the internal pressure increasing and

15   creating stress on the wall in Figure 7(e). These assumptions will be discussed later in the section

16   *limitations of the model*. Neglecting gravity force (water penetrating from all directions), and

17   including the compression forces, the dynamics of capillary penetration can be described using

18   the Newton dynamic equation[50]:

19
$$\rho \cdot \left[h \cdot \frac{\partial^2 h}{\partial t^2} + \left(\frac{\partial h}{\partial t} \right)^2 \right] = \frac{2}{r} \cdot \gamma \cdot \cos\theta - \frac{8}{r^2} \cdot \mu \cdot h \cdot \frac{\partial h}{\partial t} - P_A \cdot \left(\frac{V_{air,0}}{V_{air,t}} - 1 \right) \tag{1}$$

20   where ρ is liquid density (kg m^{-3}), h is penetrating depth (m), t is penetrating time (s), r is

21   pore radius (m), γ is liquid surface tension (N m^{-1}), μ is liquid viscosity (Pa s), P_A is

1   atmospheric pressure (Pa), $V_{air,0}$ is the initial air volume in a particle (m³), and $V_{air,t}$ is the

2   compressed air volume (m³) at time t, calculated by subtracting invaded water volume $V_{water,t}$

3   (m³) from the initial air volume. $V_{water,t}$ depends on the number of pores and the penetrating

4   velocity, hence

5    $$V_{air,t} = V_{air,0} - V_{water,t} = V_{air,0} - n \cdot \pi \cdot r^2 \cdot \int_0^t \frac{\partial h}{\partial t} \cdot t \qquad (2)$$

6   where n is the number of pores. Equations (1) and (2) were solved numerically by commercial

7   software package (MATLAB 7.1, The MathWorks Inc., Natick, MA, 2000) with initial and

8   boundary condition as $h'(0) = \sqrt{2\gamma \cos\theta / \rho r}$ and no-slip at walls respectively[51]. The

9   differential air pressure in the centre of the spheres is calculated by

10   $$P_{air,t} = \frac{V_{air,0}}{V_{air,t}} \cdot P_A \qquad (3)$$

11   where $P_{air,t}$ is air pressure (Pa) at time t. The internal force is calculated by multiplying $P_{air,t}$ by

12   the particle internal surface area, or, as discussed later, the hoop stress in the shell can also be

13   calculated.

14   **Figure 7.** Simulation model description: schematic of (a) sample 1 and (b) sample 2, (c) hollow-

15   shell geometry representing particle with (a) and (b) structures, (d) water penetrating through the

16   pores and (e) water filling pores and internal surface of shell, generating internal force on the

17   shell as air pressure increases.

18   A series of simulations were carried out using different combinations of particle size, shell

19   thickness, pore size and number. Some results are shown in Figure 8. Figure 8(a) (b) and (c)

1 respectively show for a fixed 10 µm pore size, where pore number and shell thickness were set

2 accordingly to achieve porosities of 50, 78 and 85 % when particle diameter is 200, 500 and 800

3 µm. The internal pressure first increases and then slowly approaches equilibrium; pressure

4 stabilises as the Young-Laplace pressure resulting from the surface tension at the interface

5 between water and air[52, 53]. The time to achieve this pressure varies, but is always on the

6 order of milliseconds. As the particle porosity increases from 50 to 85 %, the time to equilibrium

7 decreases from 0.06 to 0.04 ms, 2.48 to 0.07 ms and 96.8 to 0.35 ms for 200, 500 and 800 µm

8 particles, yielding a reduction of 33.3, 97.2 and 99.6 %, respectively, as a result of changes in

9 pore number (between 30 and 700 pores are simulated).

10 The second simulation case focuses on pore size. The real porous particle has poly-disperse pore

11 sizes. Figure 8(d) shows the differential air pressure versus time when particle has a size of 800

12 µm, shell thickness of 40 µm and porosity of 78 %. With the change of pore size from 20 to 50

13 µm, the equilibrium pressure reduces by more than 50 %. Oscillation occurs when the pore size

14 is larger than 30 µm, indicating a critical value in the system[50] which is strongly related to

15 liquid surface tension, contact angle, viscosity and density[50, 54-56]. Pore size effect were

16 further studied with a much wider pore size distribution from 5 to 100 µm. Results show that

17 when pore number changes over four orders of magnitude, the equilibrium time remains in

18 milliseconds (see Table 1 in supplementary material).

19 **Figure 8.** Simulation results: differential air pressure increase as a function of penetrating time

20 for different sized particles (a) 200 µm, (b) 500 µm and (c) 800 µm with 10 µm pore diameter,

21 and shell thickness and pore number modified to achieve 50, 78 and 85 % porosities; (d)

22 different sized pores when particle size is 800 µm, shell thickness is 40 µm and porosity is 78 %;

23 (e) internal force versus particles size with different porosities.

1   Simulation results suggest that the equilibrium time is in the order of milliseconds and is far less

2   than the total dissolution time. It also does not vary significantly with pore size, suggesting that

3   this order of magnitude change will occur for poly-disperse porosity of the type studied here.

4   Equilibrium pressure can be used to calculate the internal force by multiplying by particle

5   internal surface area. The force values are plotted in Figure 8(e). Data show that the internal

6   force increases with particle size increasing when the pore size is fixed at 10 μm. Although for

7   different sized particles, the Young-Laplace pressure is the same here, the internal surface area

8   changes significantly when particle size changes from 100 to 1000 μm, resulting in a much

9   higher internal force for larger particles. Such results agree with the dissolution experiment,

10   where disintegration rarely happens when particles are smaller than 300 μm.

11   *4.2 Abrupt disintegration mechanism*

12   Simulation results show that capillary action of water can generate an internal force from

13   entrapped air. This force ranges from 0.4 mN (the lowest value in Figure 8 (e), particle size 100

14   μm, pore size 10 μm) to 77 mN (the highest value inFigure 8(e), particle size 1000 μm, pore size

15   10 μm). Such an internal force strongly depends on particle size, pore size and particle porosity

16   but increases with particle size, suggesting that larger particles experience higher internal forces

17   during dissolution. These results agree with the dissolution experiments that abrupt disintegration

18   happens only when the particle is larger than 300 μm. The calculated internal forces are in the

19   same order as the particle breaking forces measured in tensile strength experiment.

20   Early stage disintegration is a function of two key factors, the force breaking the particle and the

21   particle tensile strength. A simplified model can be used to calculate the tensile strength of a

22   porous powder:

1 $$\sigma_t = \frac{2F}{\pi r_p^2} \qquad (4)$$

2 where F is the breaking force (N)[57]. As an example, we study particle size of 800 μm with a

3 porosity of 78 %. The mean breaking forces measured in both dry and hydrated conditions were

4 used in Equation 4, and all the peak values in Figure 6 were selected for the hydration case.

5 Results are listed in Table 1. Meanwhile, for a thin-walled sphere (wall thickness no more than

6 about one-tenth of its radius), the internal gauge pressure can be related with the hoop stress

7 exerted circumferentially in the sphere wall:

8 $$\sigma_h = \frac{P \cdot r_p}{2\delta} \qquad (5)$$

9 where σ_h is the hoop stress (N m^{-2}), P is the differential air pressure (Pa)[58]. When the hoop

10 stress is larger than the tensile strength, failure happens; here, the particle breaks and

11 disintegration happens. The simulated differential air pressure was used in Equation (5) to

12 calculate the hoop stress. The same particle geometry as Equation (4) was used. Results are also

13 shown in Table 1. When pore size changes from 5 to 100 μm, the hoop stress decreases from

14 0.29 to 0.01 MPa. The tensile strength calculated from mean breaking force is 0.13 ± 0.02 MPa

15 and 0.02 ± 0.01 MPa in dry and hydrated conditions respectively, indicating an early 6 times

16 reduction after being hydrated for 3 s. The hoop stress is larger than the tensile strength in most

17 of the cases. This suggests that the effect of the strength decay along with the hoop stress

18 generated from the entrapped air is the main reason for abrupt disintegration in the early stage of

19 dissolution.

20 **Table 1.** The Hoop stress compares with the mean tensile strength of particles in dry and

21 hydrated conditions. Particle size is 800 μm, shell thickness is 40 μm, and porosity is 78 %.

Pore size (μm)	Hoop stress (MPa)	Mean tensile strength in dry condition (MPa)	Mean tensile strength in wet condition (MPa)
5	0.29		
10	0.15		
20	0.07		
30	0.05	0.13±0.02	0.02±0.01
40	0.04		
50	0.03		
100	0.01		

1

4.3 Discussion: limitations of the model

3 The core of the model begins from the observation of the rapid breakage of some particles in the

4 first few seconds of contact with water. Pore size has a significant effect on internal pressure

5 increase. Smaller pores have higher capillary pressure. The model is simplistic in that and all the

6 pores on the wall were assumed the same diameter. The capillary pressure calculated as well as

7 the internal force is thus probably the largest possible values in each case. In reality, the porous

8 particle has different sized pores that are distributed non-evenly in the shell, and are either open-

9 ended or closed-ended. The open-ended ones create flow channels for water to the cavity, while

10 the close-ended ones do not contribute to the solid release in the early stage. With a large open-

11 ended pore, internal pressure can easily build up due to water imbibition to the point where the

12 particle breaks, and this provides a physical mechanism for type I dissolution phenomenon where

13 the particle breaks up abruptly and perhaps for some of the swelling seen in the type III

14 behaviour. It is also possible that with different sized open-ended pores, the higher capillary

15 pressure in the smaller ones will overcome the lower capillary pressure in the larger pores, and

16 air will be pushed out through the larger pores. This may explain dissolution phenomena without

1 early stage disintegration, for example type II where a large bubble is formed on the particle

2 surface but breakage does not occur, and type IV where no large bubble is found.

3 Computational dissolution models have been developed by researchers using particle size

4 distributions[19, 59, 60], porosity[61, 62], and real particle geometries scanned from XRT[63,

5 64]. A few enable the simulation of particle disintegration in their codes, for example Štěpánek

6 and his group simulated dissolution process of pharmaceutical particles focusing on API release

7 while abrupt break-upof particle was least investigated[19]. To our best knowledge, so far there

8 is no direct proof of the kinetic study for porous particles breaking abruptly in the early stage of

9 dissolution in the literature. The relationship between particle internal structure and their

10 dissolution rate has been subject to a few experimental and theoretical studies in the past,

11 especially for highly porous particles. Although it cannot predict the whole dissolution behavior,

12 the mathematical model in this work suggests a mechanism to understand abrupt disintegration

13 in the early stage dissolution, where the effect of the capillary action on residual air has been

14 modeled, explaining for the first time the physics behind this phenomenon.

5. Conclusions

16 A study of the dissolution of highly-porous spray-dried particles has been conducted, and four

17 mechanisms identified. Some particles disintegrate very quickly, with associated evolution of air

18 bubbles. The hypothesis that gas compression contributes to breakup has been tested, combining

19 numerical simulation of internal forces generated by air bubbles due to capillary action and

20 experimental measurement of breaking force using micromanipulation. Results suggest that gas

21 pressure could be the key factor for porous particle disintegration in the early stage of

22 dissolution. Conclusions from the present study suggest a new mechanism of disintegration,

23 involving a role for the trapped air in porous particles. This could have significant impact in the

1 development of strategies to speed up porous particle disintegration by controlling particle shell

2 properties (pore size and size distribution) as well as particle size, in addition to other properties.

3 The results can be applied in smaller scales where visualisation is limited, in that case, it will

4 benefit a wider research community for designing structured functional materials.

5 **Keywords:** Abrupt disintegration, Capillary action, X-ray microtomography, Tensile strength

Acknowledgment

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9

1 Nomenclature and Units

2 F breaking force, N

3 P internal pressure, Pa

4 P_A atmosphere pressure, Pa

5 $P_{air,t}$ air pressure at time t, Pa

6 V_{agglo} initial volume of the agglomerate, m^3

7 $V_{air,0}$ initial air volume in a particle, m^3

8 $V_{air,t}$ the compressed air volume at time t, m^3

9 V_{diss} dissolved solid volume, m^3

10 $V_{water,t}$ invaded water volume, m^3

11 g gravity acceleration, m s^{-2}

12 h penetrating depth, m

13 n number of pores

14 r pore radius, m

15 r_p particle radius, m

16 t penetrating time, s

17 δ shell thickness, m

18 ε agglomerate porosity, %

1   γ liquid surface tension, N m^{-1}

2   μ liquid viscosity, Pa s

3   ρ liquid density, kg/m^3

4   σ_h hoop stress, N m^{-2}

5   σ_s tensile strength of the solid substance, N m^{-2}

6   σ_t dynamic tensile strength, N m^{-2}